Medical Evaluation of Workforces at Risk of CBD

A Review of the Relevant Literature and other Considerations

Medical and Epidemiological Subcommittee
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Contents

Appendices

Figures

Tables

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Foreword

This white paper describes the medical tests used to evaluate workers at risk for chronic beryllium disease (CBD) with emphasis on the beryllium lymphocyte proliferation test (BeLPT). This white paper is meant to provide information to those who oversee or perform medical testing in the workplace. The rights of workers to make fully informed decisions regarding their own health need to be balanced with the responsibility of employers to operate risk management programs. The authors of this white paper reviewed the literature for publications on the legal and ethical factors on the decision to provide preventive medicine services and the published attributes of an ethical informed consent process. This white paper attempts to provide useful information to aid decision making; it is not meant to recommend or promote a specific test.

The need for recommendations on medical testing may be triggered by beryllium in the workplace, an initial case of CBD, or other compelling evidence that workers may be at risk of developing CBD. Occupational health programs often struggle with balancing the potential benefits and harms of testing for work related disease. Most people exposed to beryllium may not get the disease due to the amount of airborne dust present in the workplace. For some, it can be a relatively minor condition, while for others it can become a very serious, disabling disease.

Testing must be of benefit to the individual being tested and not just a benefit to the workforce as a whole. For CBD, striking the right balance is difficult due to the combination of individual susceptibility, workplace exposure characterization, and the uncertainty surrounding CBD prognosis for an individual. As with other lung diseases, CBD may go undetected if individuals delay seeking medical attention for symptoms they attribute to aging or deconditioning. When combined with reports of CBD cases among individuals with seemingly trivial exposures, there is uncertainty that CBD cases will be identified through the provision of medical care to individuals with symptoms and raises the question of whether a more active approach is beneficial. The value of early detection and/or intervention will depend on a particular individual's health and life circumstances. The potentially progressive nature of the lung damage which can occur with CBD may create opportunities for individuals to delay or possibly prevent disability.

1.0 Background

1.1 Chronic Beryllium Disease (CBD)

CBD is an immune-mediated, granulomatous lung disease caused by exposure to airborne beryllium (Be) particulate.[1] Its pathology is similar to a more common disease called sarcoidosis with the exception that sarcoidosis usually resolves during its normal course, whereas clinically evident CBD generally does not resolve but may reach a steady state condition and may worsen over time. Granulomas are abnormal tissues that form due to a proliferation of immune-system cells known as lymphocytes. In the lung, accumulations of granuloma can interfere with gas exchange between the blood and the lungs. If inflammation persists, scar tissue forms (fibrosis) resulting in permanent lung damage. This beryllium-induced proliferative and granulomatous response is specific to CBD. Neither blood nor lung T cells from sarcoidosis patients proliferate in the presence of beryllium salts in culture.

1.2 Immunopathogenesis

Activation of beryllium-specific CD4+ T cells requires presentation of the antigen by a major histocompatibility complex (MHC) class II molecule on the surface of antigen-presenting cells (APCs) such as a macrophage or B-cell. In persons capable of mounting a beryllium-specific immune response, CD4+ T cells proliferate and secrete cytokines, such as interleukin-2, interferon-γ and tumor necrosis factor-ά (Figure 1). The release of cytokines promotes the accumulation, activation, and aggregation of immune-system cells, which may result in the development of inflammation and eventual lung damage.

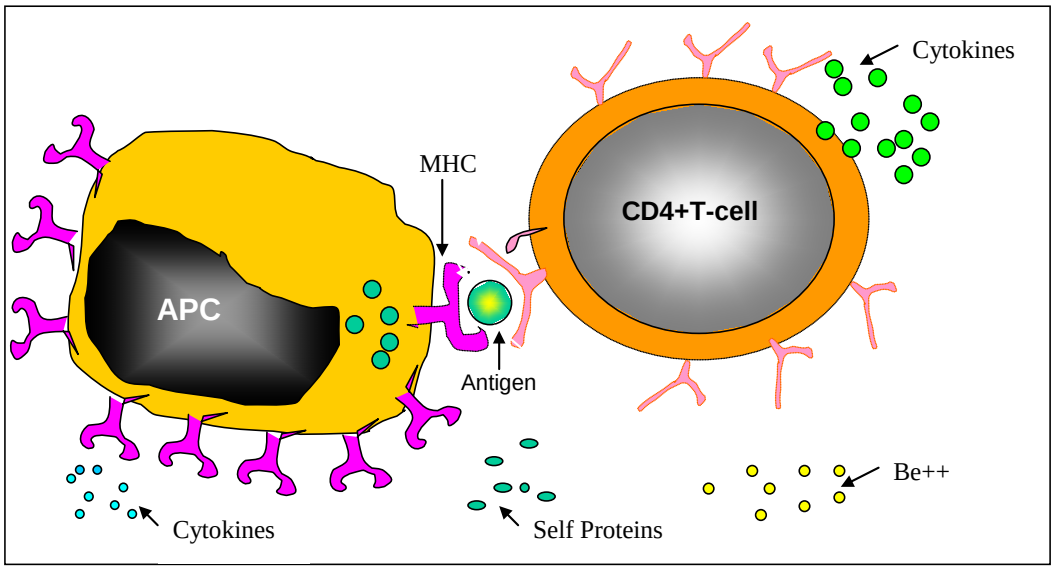

Figure 1. Cell Mediated Immune Response

Caption: Beryllium plus 2 ions (Be++) combine with a self protein or the major histocompatibility complex (MHC) protein on antigen presenting cells (APC) to present antigen to CD4+ T-cell lymphocytes. The lymphocytes emit signaling molecules called cytokines that cause a proliferation of immune-system cells and inflammation. It is hypothesized that the continuing presence of Be++ from the slow dissolution of the less soluble forms of beryllium sustains the inflammation, which may lead to CBD.

1.3 Natural History

The natural history of CBD is marked by the wide variability in individual susceptibility, rate of progression and severity. The spectrum of clinical findings may include the detection of beryllium sensitization (BeS) with granulomas, a lymphocytic process in the lung, and other abnormalities on biopsy (e.g., granulomas), visible evidence of lung damage with x-ray, and evidence of loss of lung function in pulmonary function and exercise tolerance testing. BeS precedes CBD and is the demonstration of the beryllium-specific, cell-mediated immune response. It is usually detected by using the beryllium lymphocyte proliferation test (BeLPT). Detection of BeS has been used as a marker of occupational exposure to beryllium and of the immune system's ability to respond to beryllium.

BeS alone does not cause physical impairment. Studies have shown that some persons who are confirmed abnormal have never been occupationally exposed to beryllium and some persons with CBD have never tested positive, though this is thought to be very low and may range from 0% to 1%.[2,3] Studies have also noted that some individuals with BeS may never develop CBD.[4] Persons who only have evidence of BeS and granulomas

(asymptomatic CBD) may or may not progress to a symptomatic form of CBD. Observational data indicate that the rate of progression from BeS to CBD may be related to the level of exposure and the form of beryllium.[5] Individual differences in cytokine production triggered by cell mediated immune response are also reported to be a risk factor in determining who will progress from BeS to CBD.[6]

BeS and CBD are known to have a genetic susceptibility component so that only a few percent of exposed individuals will develop CBD.[7] There is currently no medical therapy to prevent progression from BeS to CBD. Physicians generally recommend removal from future beryllium exposure to reduce the risk of progression based on experience with other immunologically mediated diseases and evidence that exposure is a risk factor for development of CBD. There are no published clinical trials of whether the general practice of recommending removal is beneficial. Diagnostic evaluations are required to determine whether a BeS individual has progressed to CBD. Workers are counseled to seek medical attention if they develop new or worsening respiratory symptoms.

Newman et al. evaluated a group of patients with BeS, but no CBD at 2-year intervals.[4] Of the 55 patients, 17 (31%) progressed to CBD within an average of 3.8 years. It was noted in this study that some individuals with BeS may never develop CBD. Only 1 patient in this group was being treated for clinical symptoms of CBD. In this group, being a machinist conferred higher risk of progression to disease.

The group of 55 patients were a subset of patients described in a subsequent publication by Mroz et al., that examined 171 beryllium exposed workers with CBD and 229 with BeS to look at risk factors for and progression of surveillance-identified CBD over time.[5] In addition to being a machinist, those diagnosed with CBD were also more likely to have been exposed in the ceramics industry and less likely to have bystander exposures compared to those with BeS, suggesting that form and dose of beryllium may contribute to development of CBD. It was reported that 8.8% (22/251) of all workers, 12.6% (12/95) never smoking workers, and 6.4% ever smoking workers developed CBD over the course of the study and that 19.3% of CBD cases developed clinical abnormalities resulting in oral immunosuppressive therapy an average of 1.4 years after initial diagnosis and 22.8 years after first exposure. They found that 18.9% of CBD cases had an initial abnormal profusion score of 1/0 or greater compared to 5.5% of those with BeS. The study noted that physiologic changes can occur within 1 month of first exposure to beyond 30 years from first exposure. However, the authors note that clinical follow-up was incomplete for this larger cohort and only 48 of the 95 BeS never smokers had at least one or more subsequent evaluations to determine progression. Among never smokers with an opportunity for clinical follow-up, 25% (12/48) demonstrated progression from BeS to CBD.

Rosenman et al. studied 577 workers from a primary beryllium processing plant whose first exposure, on average, began in the 1960s.[8] This study is unique in that the subjects were tested over 20 years following their last exposure to beryllium. They identified 7%

to have CBD and another 7.6% with BeS at the time of their study. Those with BeS had a shorter duration of exposure to beryllium, began work later, last worked with beryllium longer ago, had lower measures of cumulative and peak exposure, and had lower non-soluble exposures than those with CBD, again suggesting that exposure variables may impact progression from BeS to CBD.

Two other studies have also reported that individuals with positive blood BeLPTs were less likely to have CBD at the time of their initial evaluation if they worked jobs in industries with low airborne beryllium exposures. Welch et al. tested 3,842 construction and craft workers who had intermittent opportunities for beryllium exposure while working at Department of Energy (DOE) sites.[9] They found 53 (1.4%) with BeS based on two or more abnormal BeLPT results. Only 5 (15%) of BeS cases who accepted the offer of a clinical evaluation were diagnosed as having CBD. Arjomandi et al. report similar results among current and former workers at Lawrence Livermore National Laboratory (LLNL).[10] Among the 1,875 participants tested, 59 (3.1%) were found with BeS. Of these, 50 accepted the offer of a clinical evaluation and 40 consented to bronchoscopy and bronchoalveolar lavage. Five of the 40 (12.5%) were diagnosed with CBD. The authors compared workroom air monitoring results from LLNL, which were much lower than those from the DOE Rocky Flats Plant, where 38% of BeS cases were diagnosed with CBD.

A recent National Academy of Science review states *"CBD has a clinical spectrum that can range from evidence of BeS and granulomas of the lung without clinically significant symptoms or deficits in lung function to end-stage lung disease."*[11] Treatment with a group of drugs called *corticosteroids* ("steroids"), such as *prednisone*, may be advised for those with symptoms of, or pulmonary function test results indicative of CBD. These steroids reduce inflammation and are believed to help keep the condition from progressing. Any decision to use drugs should be made by the employee after discussing possible side effects with her/his personal physician.

In his observations, Preuss divided a group of 26 patients being treated for CBD into three groups: 1) those whose initial symptoms improved and did not develop significant disability; 2) those whose symptoms stabilized with treatment, suffered permanent impairment but had near normal life expectancy; and 3) those that progressed despite treatment and had a shortened life expectancy.[12] The latency period, rate of progression and severity of the disease are highly variable, possibly due to variation in exposure amount, route and type, and genetic and other host susceptibility factors. The factors that affect progression are not understood well enough to allow physicians to provide patients with specific advice on their likely prognosis.

2.0 Reported Medical Evaluation Methods for CBD

Maier and Newman summarize the medical tests that have been used to evaluate both asymptomatic workers and individuals who have symptoms or clinical findings.[1] These tests may be categorized by the type of information gathered: signs and symptoms, pulmonary physiology, x-ray studies, and immunologic tests. Decisions on methods used will depend on the purpose of the evaluation, the data the method is expected to generate, and the ability to interpret data provided by the method.

2.1 Signs and Symptoms

The signs and symptoms of lung damage due to CBD are similar to other lung diseases such as asthma, bronchitis, and emphysema. The American Thoracic Society (ATS) publishes questions that have been validated for use in self-administered questionnaires to elicit responses on whether the signs and symptoms of lung disease are present.[13] Appendix A provides a link to the ATS-DLD-78 questions and subsets of these have been used to test for CBD. In addition to identifying individuals who have not sought medical aid for symptoms they already have, symptoms questionnaires are commonly used to establish a baseline of condition at the time of placement in a job with risk for lung disease and for health promotion since the presence of signs and symptoms of lung disease would be a reason for referral for a diagnostic evaluation whether or not the suspected cause is occupational.

Symptoms questionnaires are neither sensitive nor specific and have low predictive value for CBD. Kreiss et al. reported the predictive value of symptoms for a cohort of 505 ceramics workers and 895 DOE nuclear plant workers. Among the ceramics workers only unintended weight loss occurred more often among the 9 cases (22.2%) than among non-cases (3.4%).[14] For the nuclear workers, only unusual phlegm was significantly more prevalent among 18 sensitization cases (33.3%) than non-cases (13%).[15] Despite their limitations, symptoms questionnaires are commonly included in occupational medicine programs for beryllium workers as a non-invasive, low cost method of limiting potential harm from false negative results for other tests and because participants may benefit when undetected lung disease is identified.

2.2 X-ray Studies

Maier and Newman describe both chest x-ray and computed tomography (CT) scan radiographic imaging findings typical of CBD.1 While useful for diagnosis and guiding treatment decisions, they describe imaging as an insensitive tool for early identification of asymptomatic CBD. Kreiss et al. reported that among the 488 ceramics workers they studied, 31 had abnormal x-ray findings and 4 were diagnosed with CBD. This was 44% of 9 cases compared to 5.6% among non-cases.[14]

Among the 1,022 nuclear workers they studied 40 participants had abnormal chest x-ray findings of whom only 1 was diagnosed with CBD. The prevalence of abnormal findings among the 18 sensitization cases was 5.6% compared to 4.7% for others.[15] Rosenman et

al. studied the prevalence of CBD in a cohort of former beryllium production plant workers.[8] Among the 577 workers studied 57 had abnormal chest x-ray findings. Seven of the 57 also had abnormal BeLPT results and all 7 were diagnosed with CBD. Of the 50 with normal blood BeLPT results, 22 consented to clinical evaluations with bronchoscopy and 6 (27.3%) were diagnosed with CBD. There were abnormal x-ray finding in 13 of the 119 CBD and sensitization cases (11%) compared to 44 among the 458 other participants (10%).

Both the ceramics and production plant workers were cohorts that had previously worked with beryllium at operations that were no longer ongoing and who had not had opportunities to be evaluated for CBD for an extended period. The nuclear workers included many who currently worked with beryllium and participated in occupational medicine programs that included periodic chest x-rays. The nuclear workers study did not include individuals who had already been diagnosed with CBD as a result of their past participation in company occupational medicine programs.

Chest x-rays continue to be used by occupational medicine programs to establish a baseline of condition at the time of placement into beryllium work. In studies of cohorts that have not had opportunities for routine testing, chest x-rays have been used to limit the impact of false negative BeLPT results and because of the benefit they provide to participants in finding other lung diseases. Because chest x-rays are used in periodic evaluations for other occupational diseases, it is not uncommon for workers with access to occupational medicine services to have periodic chest x-rays for these other reasons. For clinical evaluations Maier and Newman report that thin section CT is more sensitive than chest x-rays. They state that *"In one study of biopsy proven CBD, abnormalities were noted in 10/13 of the patients with normal chest radiographs and 89% of the 28 patients studied."*[1]

2.3 Pulmonary Function Tests

Spirometry has had long standing use as a test for CBD. Maier and Newman note that pulmonary function abnormalities typical of CBD include mild obstructive patterns early in its progression and restrictive patterns of decreased lung volumes in more advanced disease.[1] The diffusing capacity for carbon monoxide (DLCO) has also been used as a test for CBD but Maier and Newman note that abnormal results would only be expected in more advanced disease cases. An exercise tolerance test, during which cardiopulmonary performance is actively monitored, is more sensitive to early changes but is too invasive and complex to use periodically for evaluating asymptomatic individuals. It has a role in diagnostic evaluations to determine severity and progression of disease.

Kreiss et al. report that among ceramics workers 14 participants had restrictive pulmonary results, 12 consented to clinical evaluation and of these 3 were diagnosed with CBD for a 33% prevalence of abnormal spirometry results among 9 new cases of

CBD.[14] The case rate for CBD included asymptomatic persons diagnosed via the detection of BeS and granuloma upon biopsy. The 9 with abnormal findings occurred among the 496 other participants for a CBD prevalence of 2%. In their paper on nuclear workers they provide information on the prevalence of abnormal spirometry results for 18 BeS cases and 877 other participants in Table 1.[15]

Table 1. Prevalence of Abnormal Spirometry Findings

Test	Prevalence Among Sensitization Cases	Prevalence Among Others
Forced Expiratory Volume (FEV)	12.5%	12.9%
Forced Vital Capacity (FVC)	6.3%	4.1%
FEV/FVC	12.5%	16.7%

Like symptoms questionnaires and x-ray imaging studies, spirometry tests lack the sensitivity needed to identify CBD in its asymptomatic stage and are not specific for CBD.

2.4 Immunological Tests

The body's immune response to beryllium can be measured with patch testing or with lymphocyte proliferation testing. Reports on the use of patch testing were first published in the 1950s; however its use fell out of favor because of its perceived potential to sensitize individuals and concern that it could possibly exacerbate disease. Patch testing continues to find limited use as a diagnostic test when other methods are producing indeterminate results.[16] The peripheral blood BeLPT is an in vitro test with minimal physical risk and has been widely used by the DOE and frequently used as part of epidemiology studies within the primary beryllium industry.[17] The BeLPT of bronchoalveolar lavage fluid is a diagnostic test that is considered to provide the best evidence of sensitization to beryllium but is invasive, has potentially serious medical risks, and is very expensive.[18] Sensitized peripheral blood or bronchoalveolar lavage (BAL) cells proliferate when stimulated in vitro by Be salts.[19] The BeLPT does not distinguish BeS from CBD. Initial abnormal BeLPT results are usually followed by confirmatory tests of a split blood sample sent to two laboratories. BeS is confirmed if results from either laboratory are positive. A recent review concluded that repeated borderline results can also be a basis for referral for diagnostic evaluations.[20]

2.4.1 BeLPT Test Method and Interpretation

There are disparate views with respect to use of the peripheral blood BeLPT. They range from not recommending the BeLPT, to requiring the offer of the blood BeLPT as part of beryllium medical surveillance.[21]

Frome et al. describe the test method and Borak et al. describe the variations in the methodologies among laboratories.[22,23]

Upon receipt of a blood sample, lymphocytes are separated by centrifugation, washed with buffered saline, counted and then medium is added to create a specified cell concentration. The cell suspension is distributed into micro-titer plates and incubated for two time periods ranging from 4 to 7 days. Twelve wells are untreated controls, 12 wells are treated with beryllium sulfate with 4 each at 3 concentrations, 12 wells are treated with mitogen known to stimulate lymphocytes and 12 wells are treated with a recall antigen as a second positive control. Six to 18 hours prior to harvest tritiated thymidine is added to the medium. Cells are harvested on glass fiber filters, washed to remove any media and placed in a beta counter. Six stimulation indices (SIs) are calculated from the ratio of mean counts from beryllium exposed wells divided by the mean counts in the unexposed control wells (or the mean of log transformed counts of exposed well minus the mean of log transformed counts of control wells).

The normal range of results and the cut-points for declaring a test abnormal, normal or borderline are established by testing unexposed volunteers. The 6 different days and doses are used to accommodate host variability in conditions that will create the strongest response. The normal range and cut-points are based on the distribution of the largest and second largest SIs. The pooled human sera added to the growth media to provide the proteins needed to support lymphocyte proliferation are a variable in the test system that must be controlled for and the normal range and cut-points have to be adjusted for each batch of serum.

Figure 2 is taken from Frome et al. and shows the distribution of log transformed maximum SIs [Ln(SImax)] from blood samples tested at a single laboratory in a single serum from 1,080 beryllium exposed workers and 33 unexposed volunteer donors.[22] The line is fitted to the results from the unexposed volunteers. The worker data have a multi-modal distribution with abnormal results that are outliers from the distribution of normal results. However, the SI is a continuous variable and includes results that are not clearly normal or abnormal. Establishing a cut point for declaring a BeLPT abnormal necessarily involves judgment based in part on the consequences of false positive versus false negative results. Results from 116 (11%) maximum SIs exceeded the cut point of 3.1 used to judge a test as abnormal or borderline. Of these, 80 also had a second high SI and were declared abnormal.

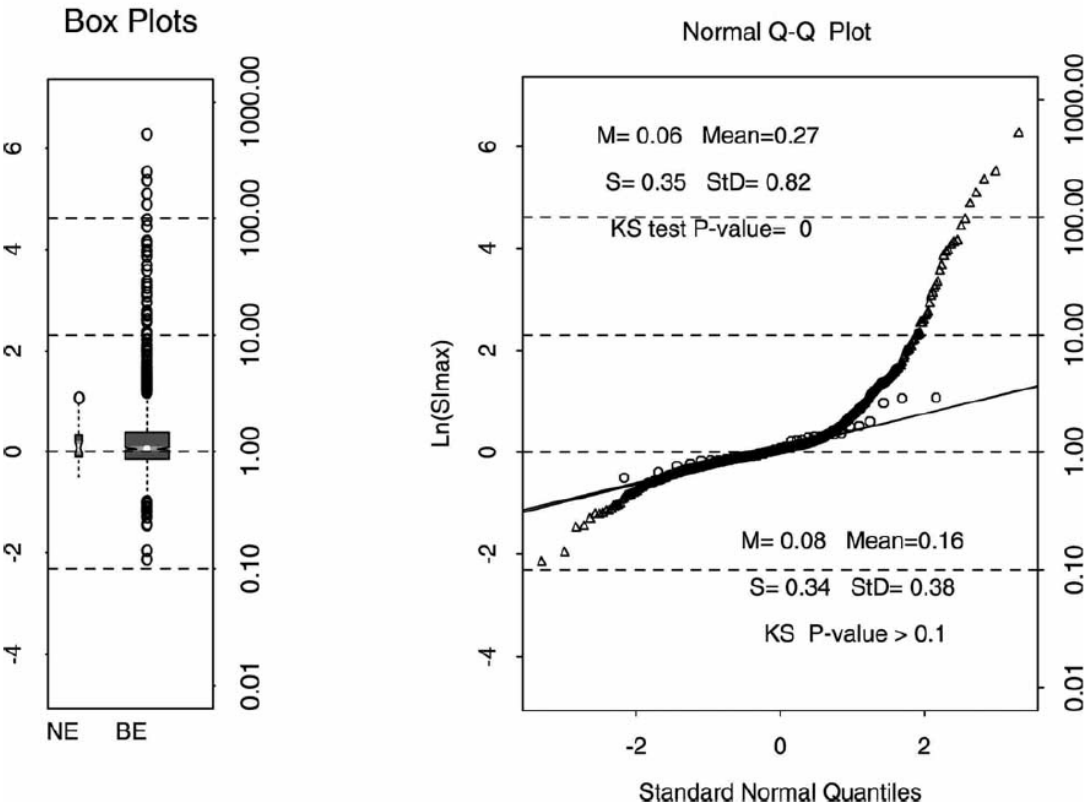

Figure 2. Maximum SIs for 1,080 Beryllium Workers and 33 Unexposed Volunteers

Caption: Box plots (left panel) and normal Q-Q plots (right panel) for Ln(SImax). In the right panel summary statistics for non-exposed controls (circles) are shown in lower right, and for beryllium workers (triangles) in upper left of Q-Q plot. M and S are outlier resistant estimates of the mean and standard deviation. A small P value for Kolmogorov -Smirnov (KS) goodness-of-fit test indicates departure from normal distribution for Ln(SImax). In the box plots, half the data are in the box, whiskers extend 1.5 times the inter-quartile range from the box and the circles beyond the whiskers are outliers.

Figure 3 is taken from a 1996 article by Stange et al. showing that the chances that an initial positive will be confirmed increase with increasing SI.[24] Individuals whose abnormal results were not confirmed were offered periodic testing at the same frequency as those who had normal test results.

Table 6. Positive BeLPT retest consistency, June 1991 to October 1994.

Positive BeLPT value range	No. positive on first BeLPT (*n*=222)	No. negative on first BeLPT retest (*n*=141)	% Reversion
1.6–2.9	61	54	88.5
3.0–4.9	62	52	83.9
5.0–9.9	40	21	52.5
10.0–19.9	26	9	34.6
20.0–49.9	17	5	29.4
≥50.0	16	0	0.0

Figure 3. Results of Confirmatory Tests[24]

Caption: Positive BeLPT value is the largest of 6 stimulation indices for the test.

In a study of 538 new employees over a 4-year period, Donovan found at least one reversion in blood BeLPT results (defined by positive-to-negative or positive-to-borderline results) was observed in 100% (9/9) of new employee program participants that underwent follow-up testing after they were previously classified as confirmed BeLPT-positive following workplace exposure to beryllium.[3]

2.4.2 Estimates of Sensitivity and Specificity for the BeLPT

Stange et al. provided estimates of the sensitivity and specificity of the BeLPT for BeS by evaluating paired results from different testing laboratories.[25] The authors examined 20,275 BeLPT results from medical evaluations of 7,820 current and former DOE workers over a 10-year period. The program led to the diagnosis of 117 cases of CBD and the confirmation of 184 cases of BeS without disease for a combined prevalence of 3.85% (301/7,820). The evaluation protocol called for split testing by two laboratories of some initial blood draws for quality assurance and administrative purposes and for all repeat tests of abnormal or borderline results. Estimates of sensitivity were based on the frequency of false-normal results among those diagnosed as sensitized based on two or more abnormal results and estimates of specificity were based on the frequency of false-abnormal results among those for whom a single abnormal result could not be confirmed with repeat testing. Table 2 shows parameters taken from Table VI of the Stange et al. publication.

Table 2. Calculated Parameters for BeLPT Results (n = 19,396)

False positive rate	1.1%
False negative rate	
Borderline-abnormal results included	27.7%
Borderline-abnormal results excluded	31.7%
Be-LPT sensitivity	68.3%
Be-LPT specificity	96.9%

Donovan et al. evaluated the performance of the BeLPT from general workforce survey data and a 5-year survey of new employee data.[3] More than 10,000 results, from nearly 2,400 participants over a 12- year period, were analyzed using consistent criteria to describe the performance characteristics of the BeLPT. Thirteen of the 538 participants (2.4%) had at least 1 positive BeLPT result when they started work at Brush Wellman. Nine of these individuals (1.7%) were confirmed to be positive during subsequent testing (2 positive tests). Three of these 9 new employees were identified as having a known occupational exposure or possible take-home exposures. Two of the 9 subjects tested borderline and negative (split testing) initially, then positive on repeat testing at 37 days and 50 days respectively. The background prevalence of initial BeLPT-positive responses among new hires with no known occupational exposure or possible take-home exposures to beryllium was 1.1% (6/535).

2.4.3 Positive Predictive Value

The positive predictive value (PPV) of a test is the number of true-positives divided by the number of all positive results (true-positive + false-positive). This rate will depend on the prevalence of the disease in the population being tested. Authors have reported PPVs of BeS for CBD that have ranged from 100% in a group of ceramics workers with a prevalence of CBD of 1.78% (9 of 505) to 9% in a group of construction workers with a prevalence of CBD of 0.13% (5 of 3,842).[14] Two of the cases counted among the 9 ceramics workers had normal or inconsistently abnormal tests.

Table 3 estimates PPV from prevalence of BeS and CBD by job category reported by Stange et al. for individuals who had worked at the DOE Rocky Flats Plant.[26] The cases were identified through use of the BeLPT within a medical testing protocol offered to all current and former workers and do not include cases identified through symptoms or other clinical findings. The authors collapsed job titles into categories and assigned individuals to the category judged to have had the highest opportunity for beryllium exposure. PPV is highest for job categories with the highest prevalence of CBD (Pearson correlation coefficient = 0.81).

Table 3.Positive Predictive Value by Job Category at Rocky Flats

Job Category	# Tested	BeS with CBD	BeS no CBD	PPV of BeS for CBD
Beryllium machinist	201	17	7	71%
Decontamination	157	7	5	58%
Custodial	709	21	19	52%
Chemical technician	859	20	21	49%
Laborer	483	13	14	48%
General machinist	1077	28	33	46%
Crafts & trades	632	13	17	43%
Environmental	255	3	4	43%
Facilities support	570	10	16	38%
Technician/inspection	1444	22	36	38%
Radiation technician	346	8	15	35%
Engineer	988	14	27	34%
Repair	167	3	7	30%
Administrative	2254	29	69	30%
Construction trades	191	5	14	26%
Scientist	329	1	10	9%
Security	288	0	4	0%
All subjects	5173	81	154	35%

2.4.4 Discrepant Inter- and Intra-Laboratory Results

Stange et al. analyzed discrepancies between split blood samples analyzed by the same or two different laboratories and used these discrepancies to estimate the sensitivity, specificity and PPV of the BeLPT as discussed above.[25]

The medical evaluation protocol included confirmatory testing of an abnormal result in which the second blood sample is split and sent to the laboratory that found the initial abnormal result and a second laboratory as well. Figure 4 reproduces the tables Stange et al. used to report percent agreement among individuals diagnosed BeS based on at least 2 abnormal BeLPT results.

TABLE VB. Inter-Laboratory Split-Specimen Agreement, Sensitized Cases Only,1992 - 2001

Laboratories	Number of test pairs	Number of abnormal-abnormal pairs	%Agreement for abnormal results
1and 2	93	34	36.6
1and 3	218	107	49.1
1and 4	34	22	64.7
2 and 3	159	65	40.9
2 and4	0	n/a	n/a
3 and 4	9	5	55.6
Total	513	233	45.4

TABLE VC. Intra-Laboratory Sequential-Specimen Agreement, Sensitized Cases Only,1992 - 2001

Laboratory	Number of tests	Number of abnormal tests	%Agreement for abnormal results
1	427	368	86.2
2	285	229	80.4
3	345	317	91.9
4	72	64	88.9

Figure 4. Agreement Tables from Stange et al.[25]

Deubner also analyzed data related to the variability of BeLPT results within and among various laboratories and the PPV of the BeBLPT for CBD.[27] Deubner reviewed the paired results of three laboratories that had analyzed over 5,000 blood samples collected since 1992 where every worker's blood sample was split and tested by two different laboratories using the BeLPT method. Figure 5 is a copy of the tables from Deubner's report showing intra- and inter-laboratory agreement for both BeS and normal cases. He found that the BeBLPT results varied significantly both within each laboratory and from one laboratory to another. Overall, the data showed that those laboratories which detected a positive result on the first blood test found a negative result 30% of the time on a second blood test on the same person. When two different labs (Labs A and B) tested the same blood sample, Lab A did not confirm 30% of Lab B positive results and Lab B did not confirm 30% of Lab A positive results. Deubner also observed a number of cases in which the BeLPT results changed from confirmed positive to confirmed negative upon re-testing.

These data are derived from a survey conducted at Brush Wellman's Elmore, Ohio facility. There, 10 of 18 persons (55%) who were confirmed BeLPT positive (2 positive tests) in the early 1990s and who continued to work in beryllium operations tested negative in 1999 based on a blood sample tested by two different laboratories. Deubner

concluded that *"substantial inter- and intra-laboratory disagreement exists among the laboratories that conduct this test."*

TABLE II
Comparison of BLPT results reported by three laboratories with the first and the second test performed on the same individual (intra-laboratory agreement)

First Test	Second test: Abnormal	Borderline	Normal	Total
Laboratory A				
Abnormal	7	0	4	11
Borderline	3	3	13	19
Normal	4	3	24	31
Total	14	6	41	61
		Kappa = 0.4		
Laboratory B				
Abnormal	41	4	16	61
Borderline	5	4	23	32
Normal	4	4	89	97
Total	50	12	128	190
		Kappa = 0.6		
Laboratory C				
Abnormal	30	3	19	52
Borderline	3	2	17	22
Normal	4	3	70	77
Total	37	8	106	151
		Kappa = 0.5		

TABLE III
Comparison of BLPT results on the same split sample as reported by three pairs of laboratories (inter-laboratory agreement)

		Lab B: Abnormal	Borderline	Normal	Total
Lab A	Abnormal	4	0	0	4
	Borderline	0	0	4	4
	Normal	4	6	113	123
	Total	8	6	117	131
			Kappa = 0.5		

		Lab C: Abnormal	Borderline	Normal	Total
Lab A	Abnormal	5	1	17	23
	Borderline	3	2	19	24
	Normal	23	16	482	521
	Total	31	19	518	568
			Kappa = 0.2		

		Lab B: Abnormal	Borderline	Normal	Total
Lab C	Abnormal	44	8	13	65
	Borderline	5	3	18	26
	Normal	38	33	945	1,016
	Total	87	44	976	1,107
			Kappa = 0.6		

Figure 5. Agreement Tables from Deubner et al.[27]

Caption: The kappa coefficient is a statistical measure of the degree to which inter-rater agreement is larger than agreement due to chance (can range from 0 to 1).

The relatively high false-negative rate tolerated to maintain a low false-positive rate means that discrepant results will be common. As noted above, the pooled human sera used in media are thought to be a major variable in the BeLPT. This provides a plausible explanation of why discrepant results are more common for split samples sent to two different laboratories which results in testing in two different sera than for sequential samples sent to the same laboratory and presumably tested in the same serum. A range of host specific variables are also thought to affect the responsiveness of lymphocytes to beryllium (i.e., infections).

Cher et al. used control charting methods to analyze the variation over time in the mean of SIs among participants found to be normal. [28] Results from a 10-year period were used to estimate a grand mean and variance that would be expected, and used these to identify months when laboratories were operating outside this expected range. In addition they analyzed the frequency of missing SIs (i.e., test in which fewer than 6 SIs

are reported) as an indicator of possible quality problems. During the 10-year period of this study, all laboratories displayed variation in test results that were beyond what would be expected due to chance alone. Patterns of test results suggested that variations were systematic. The authors offer the following 7 possible biological and testing methodology causes for the out-of-control periods they identified.

1. *Nonrandom distribution of individuals who are sensitized among the entire population tested.*
2. *Changes in cell reactivity in a given person over time (e.g., development of sensitization, resulting in increasing responses).*
3. *Changes in cell reactivity due to extraneous biological factors, such as viral illnesses or drugs that suppress immune responses.*
4. *Changes in laboratory conditions under which the test is performed. Such changes could include different technicians performing the test, day-to-day reliability of the technician, characteristics of test substances (e.g., changes in serum lots or degradation of serum over time, differences in reagents used), or laboratory errors (e.g., adding the test substance twice to a well or bacterial contamination). The fact that there is no positive control available to calibrate this test on a routine basis may contribute to laboratory variation.*
5. *Changes in workplace exposures, either levels of beryllium exposure or type of beryllium exposure (chemical form, particle size changes).*
6. *The size of control groups among laboratories varies and is generally small. In addition, laboratories tend to use the same people repeatedly to generate the baseline value for calculating the stimulation index. This procedure may contribute to the instability of the simulation index.*
7. *Some laboratories have a more stringent protocol for excluding extreme SI values, which may reduce laboratory variability relative to other labs.*

2.4.5 Testing Protocols

In a 2008 publication, Middleton et al. discussed testing protocols aimed at minimizing false positive results through confirmatory testing.[29] They estimate the performance of protocols in which the blood sample from an initial screening is sent to a single lab and abnormal results are either not confirmed by additional testing or confirmed by a second test that is split and sent to two laboratories with at least 1 abnormal result and confirmed by a second split test with at least 1 borderline result.

In a second 2011 publication the predictive value of borderline results in an initial test and in both confirmatory tests of a split sample conclude that this result also justifies referral for a clinical evaluation for CBD.[20]

From Stange et al., the probability of a truly sensitized individual having an abnormal BeLPT result is 59.7%, the probability of a borderline result 12.6% and the probability of a normal result is 27.7%.[25] Sensitivity = 1 – 27.7% = 72.7%. Stange et al. report a false

positive rate for a single abnormal BeLPT of 1.11%, which results in an estimated specificity of 98.89%. Middleton et al. use these values to estimate the PPV of screening protocols with and without confirmatory testing in populations with a prevalence of BeS ranging from 1% to 10%. Table 4 reproduces these estimates and also includes and estimates for a population with a prevalence of BeS of 0.1%.

Table 4. PPVs for Selected Population Prevalence of BeS

Criteria	Sensitivity/ Specificity	False Positives per 10,000	0.1%	1%	5%	10%
1 AB	0.682/0.9889	111	5.8%	38.3%	76.4%	87.2%
1 AB + 1 BL	0.657/0.9992	8	45.1%	89.2%	97.7%	98.9%
2 AB	0.612/0.9998	2	75.4%	96.9%	99.4%	99.7%

Confirmatory testing can be used to increase the PPV of the BeLPT in populations with a low prevalence of BeS. Serial or split testing can be used to increase the sensitivity of BeLPT screening (reduce the false negative rate.) If the false negative rate for a single BeLPT is 27.7%, the probability of having two false negative results is 7.7% and the probability of having 3 false negative results is 2.1%. In general, serial testing limits the impact of false negative results and may identify new BeS cases due to continued exposure risk. Split testing has been used to control the false negative rate in cohorts for whom retesting will be difficult and especially when the testing has been triggered by findings of index or clusters of CBD cases indicating the cohort is at high risk for the disease.

3.0 Feedback and Improvement

The analysis of health outcomes of groups of workers with similar exposure may help to direct future efforts to prevent exposure and subsequent disease. Sentinel events and unexpected patterns in findings have led to expansion of medical testing efforts. For example, in their study of machinists in a nuclear facility, Kreiss et al. found CBD cases in a control group that was assumed to be unexposed, but were in fact intermittently exposed.[15]

Over time this and other findings led to offering medical evaluations for CBD to the entire plant population and identification of CBD cases among professional, administrative, and other stand-by workers. In other settings, results may identify groups who are not at risk for CBD and can be safely dropped from continued periodic testing.

Harber et al. analyzed the published results of several medical surveillance projects that used the BeLPT as a medical test.[30] They note that the mathematical models that best fit

the data assume that the latency period for BeS after first exposure is generally less than 5 years while the latency period for CBD is commonly longer than 5 years. The best fit model also assumes the population is split between those who are susceptible to BeS and CBD and those who are not. The model predicts that the BeLPT is most effectively used in a cohort that has had long standing opportunities for exposure that has not been evaluated in the past. It also predicts that the number of cases identified by periodic testing will decline over time as the susceptible sub-group with sufficient exposure convert. The cost of an annual testing program relative to the number of cases identified increases rapidly after 10 years.

Research conducted by the Department of Medicine at the University of California San Francisco (UCSF) in collaboration with LLNL Health Services and Hazards Control staff (Arjomandi, et al.) suggest that because of lower average levels of beryllium exposure, a smaller proportion of sensitized workers at LLNL may go on to develop CBD when compared to other workers with higher exposures.[10] They describe the results of 50 LLNL Be affected workers' pulmonary evaluations and found that LLNL workers were exposed to generally low levels of beryllium and had a low prevalence of CBD when compared to other high-risk production operations such as beryllium ceramics manufacturing. Because of the low prevalence of CBD as well as the fact that none of the cases were severe enough to require immunosuppressive therapy, the UCSF group has modified their pulmonary evaluation of asymptomatic LLNL workers to included only pulmonary function and chest imaging instead of the more invasive bronchoscopy. The pattern of low exposure levels and sensitization prompts the hypothesis that very little exposure may be required to sensitize some individuals. If the conclusions of the Arjomandi et al. paper hold true over time, these individuals may be at relatively low risk of CBD.

The routine collection and analysis of data and the dissemination of information about risk allows for continued alignment of medical testing and work control efforts based on the risk profile of the cohort as it changes over time. Communication of the analysis provides opportunities for prevention and helps inform participants so that they can make better decisions.

4.0 Considerations Regarding the Informed Consent Process

Providing an informed consent to test with the BeLPT is a difficult prospect. Those engaged in decision making should have access to an understanding of technically complex mechanisms including the test itself, the human immune system, as well as an understanding of the natural history of BeS and CBD. There is not a definitive understanding of exposure mechanisms or pathways. There is presently limited understanding regarding the progression from sensitization to disease (including the probability of or the time progression after exposure to that of beryllium sensitization or the probability of or time progression from beryllium sensitization to chronic beryllium disease). Largely the interventions and treatment are empirical. Admitting uncertainty

may be uncomfortable and some individuals may be unprepared to cope with uncertainty. Greene and Smith use the BeLPT to illustrate some of the problems with attempting to obtain informed consent when *"the interpretation of screening results is complicated by their probabilistic nature and is clouded by empirical uncertainty."* [31] Green and Smith argue that, *"Only avoidable risk is relevant to rational decision-making and that the practical significance of a positive screening result is likely to be very different for different workers."*

The DOE via 10 CFR 850 requires a specified informed consent process and form.[21] Also included is a set of 'Frequently Asked Questions' that is used as part of the consent package. While medical surveillance is not human subjects research, an institutional review board can be a source of expert advice on informed consent materials.

Discussions of the risks and benefits associated with the BeLPT should be conducted as a two-step process: evaluations for sensitization and evaluations for those sensitized for CBD. To provide informed consent, the core elements of information necessary for individuals to engage meaningfully in this decision: a basic understanding of CBD, the potential benefits of early detection, the strengths and limitations of the BeLPT, and the risks of finding sensitization, the individual ramifications of being sensitized and that subsequent more invasive medical evaluations for CBD will be recommended if they are found to be sensitized.

4.1 Principles of Preventive Evaluations

The following principles are abstracted from the U.S. Preventive Services Task Force (USPSTF) Procedure Manual: 1) there must be scientific evidence that persons who receive the preventive service experience better health outcomes than those who do not, and that the benefits are large enough to outweigh the harms; 2) the outcomes that matter most in weighing the evidence and making recommendations are health benefits and harms; and 3) recommendations apply only to asymptomatic persons or to those with unrecognized signs or symptoms of the target condition for which the preventive service is intended.[32] The USPSTF Manual has an expanded discussion of methods for grading the level of scientific evidence and magnitude of the net benefit that it uses to reach a recommendation.

4.2 Ethical and Informed Consent Principles

A written medical ethics statement was first adopted by the American Medical Association in 1847, evolving in the years following the Nuremberg trials into modern medical ethics, which are based on the principle of personal autonomy as a basic human right.[33] Autonomy implies taking personal responsibility for the consequences of one's actions. Respect for the autonomy of individuals to make medical decisions requires providing them access to information on the consequences of their decisions. Medical providers usually meet their ethical responsibilities through both verbal and written informed consent processes. Traditionally, the term informed consent has been used to refer to patients informed decision making, particularly for invasive interventions. Informed consent may convey that the proper decision is that the patients agree to the physician's proposed plan of action, rather than a considered deliberate decision making based on the individual's unique situation and personal desires and values.

As an example of a rigorous informed consent process for medical treatment that may also serve to guide the physician with regard to medical testing is the current American Medical Association's Informed Consent. The guidance states, *"Informed consent is more than simply getting a patient to sign a written consent form. It is a process of communication between a patient and physician that results in the patient's authorization or agreement to undergo a specific medical intervention.*

In the communications process, you, as the physician providing or performing the treatment and/or procedure (not a delegated representative), should disclose and discuss with your patient:

- *The patient's diagnosis, if known;*
- *The nature and purpose of a proposed treatment or procedure;*
- *The risks and benefits of a proposed treatment of procedure;*
- *Alternatives (regardless of the cost or the extent to which the treatment options are covered by health insurance);*
- *The risks and benefits of the alternative treatment or procedure; and*
- *The risks and benefits of not receiving or undergoing a treatment or procedure.*

In turn, your patient should have an opportunity to ask questions to elicit a better understanding of the treatment or procedure, so that he or she can make an informed decision to proceed or to refuse a particular course of medical intervention. This communications process or a variation thereof, is both an ethical obligation and a legal requirement spelled out in statutes and case law in all 50 states."[34]

Appendix B discusses an analogy between the consent process for the BeLPT and the prostate specific antigen (PSA) test, another preventive service in which the value of the test to the person receiving it will depend on the individual's health and life circumstances.

An occupational setting creates special challenges for informed consent because medical evaluations and testing may potentially affect job placement decisions. Economic consequences will depend upon the individual's situation: mandatory pre-placement or as voluntary ongoing medical surveillance evaluation; early or late in career, other non-beryllium career options; and on the particular individual's life circumstances. An initial job offer may be contingent on the results of testing. For those already employed, the decision to consent to medical testing may have economic as well as health consequences because the results of such testing may limit future career choices. An individual's participation, or lack of participation, may have consequences for coworkers because results may be indicative of less than fully controlled working conditions. Also, providing removal benefits based on test results can increase the ultimate size of the exposed population without a defined benefit to either the individual or the population.

Federal and state laws may also bear on placement decisions. The Justice Department offers the following guidance on occupational medicine evaluations. *"The reason(s) for not hiring must be job-related and consistent, due to business necessity. . . A post-offer medical examination may disqualify an individual if the employer can demonstrate that the individual would pose a 'direct threat' in the workplace (a direct threat is defined as a significant risk of substantial harm to the health or safety of the individual or others) that cannot be eliminated or reduced below the direct threat level through reasonable accommodation."*[35] The Americans with Disabilities Act seeks to balance the right of the employee to accept risk for economic gain with the right of an employer to manage risk to prevent an economic loss, with *"significant risk of substantial harm to the health or safety of the individual or others"* as the criteria to be used in determining when the employer's rights predominate.

4.3 Risks of the BeLPT

- Venipuncture may cause pain and bruising.
- The test may need to be repeated due to:
  - Shipping/processing delays which may harm cells.
  - Failed tests that result in "un-interpretable" results.
  - Borderline or abnormal results that require confirmatory testing.
- False negative or false positive results may occur.

4.4 Risks/Benefits of Being Sensitized to Beryllium for the Worker's Consideration

- If current job duties create potential exposure to beryllium, it is likely physicians will recommend changes in these duties to reduce future exposure. It is hoped that removal from potential exposure will reduce the risk of developing disease.
  - — May change career path.
  - — May cause worry and anxiety (about health, about insurability, about job) in worker or loved ones.
- May result in additional and repeated invasive medical evaluation procedures risks, though infrequent, may result in injury related to diagnostic procedures.
- Eligibility for worker's compensation benefits for the cost of recommended medical care. For DOE workers, U.S. federal employees and in most U.S. states, diagnosis of an occupational disease provides access to worker's compensation insurance coverage with medical and disability benefits.
- Work cohort/public health benefits may result in identification of inadequate work controls thus resulting in prevention of future additional worker exposure.
- Secondary prevention: Early treatment of CBD may prevent progression of disease to permanent lung damage and disability. Although not providing definitive proof, authors of recent studies have concluded that the long standing standard of care for CBD has been shown to reduce the progression of disease.[36] [37] Marchand et al. conclude that *"corticosteroid treatment in patients suffering from serious chronic beryllium disease improved symptoms, pulmonary function tests and radiology by acting on inflammatory granulomas. The control of inflammatory granulomatosis limited the fibrotic evolution as long as doses were monitored under the control of clinical examination, serum angiotensin-converting enzyme and high resolution computed tomography scanning. However, corticosteroids seemed insufficient to stop this poor evolution for some patients."*

4.5 Genetic Information Nondiscrimination Act of 2008 (GINA)

GINA prohibits discrimination in health insurance and employment based on genetic information.[38] Since genetic susceptibility is an important determinant of who will get CBD, medical tests that identify individuals with BeS or CBD necessarily identify individuals who are presumed to be genetically susceptible. Since most diseases have at least some genetic susceptibility component, GINA distinguishes between "genetic information" on susceptibility and tests that detect disease but do not directly provide genetic information. The relevant section is 201(7)(A), which states "*The term 'genetic test' means an analysis of human DNA, RNA, chromosomes, proteins, or metabolites, that detects genotypes, mutations, or chromosomal changes:*" and 201(7)(B) that states "*The term 'genetic test' does not mean an analysis of proteins or metabolites that does*

not detect genotypes, mutations, or chromosomal changes." The BeLPT and other tests used in CBD occupational medicine programs do not detect genotypes, mutations or chromosomal changes and thus are not covered by GINA.

GINA also makes exceptions allowing employers to collect genetic information under certain circumstances. One of these exceptions is in section 202 (b)(5), which states: "*where the information involved is to be used for genetic monitoring of the biological effects of toxic substances in the workplace, but only if— (A) the employer provides written notice of the genetic monitoring to the employee; (B)(i) the employee provides prior, knowing, voluntary, and written authorization; or (ii) the genetic monitoring is required by Federal or State law.*" GINA provides further endorsement of informed consent as the process for assuring ethical use of medical tests.

5.0 Summary of Blood BeLPT Characteristics

The use of the BeLPT test is at the discretion of the clinician and employer. Analysis of potential socio-economic impacts of the BeLPT when used for screening, monitoring, or surveillance remains an industry specific challenge.

In a 2006 publication, Borak et al. reviewed the reliability and appropriateness of using the BeLPT using criteria established by the World Health Organization (WHO).[23] He found the accuracy and reliability of the BeLPT to be uncertain and that the clinical benefits of early intervention have not been confirmed or quantified in asymptomatic individuals. Borak concluded: *"There is currently insufficient scientific evidence to support the use of BeLPT for routine screening of asymptomatic individuals."* More recently, the National Research Council (2008) report [11] titled "Managing Health Effects of Beryllium Exposure" states, "*Screening of healthy exposed workers with the BeLPT, enabled the detection of BeS in such workers and has enabled earlier diagnosis of CBD. Despite some issues regarding the reproducibility, sensitivity and specificity of the BeLPT, the committee judged it to be an adequate assay for use in a surveillance program*." In addition, in February 2011, NIOSH released a NIOSH ALERT entitled, "Preventing Sensitization and Disease from Beryllium Exposure," in which they encourage workers who come in contact with beryllium dusts, fumes, mists, and beryllium-containing solutions and suspension to participate in workplace medical surveillance that includes the BeLPT so that risks related to job tasks can be identified and prevented. [39]

In 2010, *Schweizerische Unfallversicherungsanstalt* (SUVA) (German for *Swiss National Accident Insurance Fund)* the socialized workers insurance body in Switzerland, which is a financially independent body incorporated under public law evaluated the BeLPT and stated: *"In conclusion, we cannot yet - at present give clear and definitive answer to the question of the relevance of a screening systematically exposed workers using the BeLPT, survey data available is insufficient in this regard."* [40]

The difficult issues that surround the use of the BeLPT are summarized below.

- The test is not widely available and there exists intra- and inter-laboratory variability.
- The significance of intra-individual variability (reversals from positive to negative over time) is not well understood.
- The unexposed 'background' rate of sensitization is thought to be 0-1% of the unexposed population.
- Serial testing is recommended due to the possibility of false negatives associated with a single test.
- There remains a lack of standardization of what constitutes 'sensitized' (2 abnormal results[24], 1 abnormal, 1 borderline, 3 borderlines[3]).
- Benefits of the removal from future Be exposure after sensitization is argued by analogy to other pulmonary hypersensitivity responses, and remains unproven.
- There may be adverse effects, both physical and psychological, following the identification of sensitization.
- While not curable, early diagnoses of CBD create opportunities for treatment of the lung damage that causes disability. The evidence for the efficacy of treatments is limited.

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Appendix A

Links to Online Documents

Information about Medical Tests

1. Recommended Respiratory Disease Questionnaires for Use with Adults and Children in Epidemiological Research, American Thoracic Society: http://www.cdc.gov/niosh/atswww.txt

2. American Thoracic Society and European Respiratory Society Task Force, Standardization of Lung Function Testing: http://www.thoracic.org/statements/resources/pfet/PFT2.

3. National Institute for Occupational Safety and Health (NIOSH) Chest Radiography, B Reader Information for Medical Professionals: http://www.cdc.gov/niosh/topics/chestradiography/breader-info.html.

4. Department of Energy (DOE) Specification, Beryllium Lymphocyte Proliferation Testing (BeLPT), DOE-SPEC-1142-2001, April 2001: http://www.hss.doe.gov/HealthSafety/WSHP/be/belpt/spec11422001.pdf.

Information about CBD and Sensitization for Informed Consent

1. National Jewish Health Chronic Beryllium Disease Overview: http://www.nationaljewish.org/healthinfo/conditions/beryllium-disease/index.aspx.

2. DOE Beryllium Affected Workers Web Resources: http://www.hss.doe.gov/HealthSafety/berylliumaffectedworkers/.

3. DOE 10 CFR Part 850 Chronic Beryllium Disease Prevention Program; Final Rule: http://www.hss.doe.gov/healthsafety/wshp/be/docs/berule.pdf. See Appendix A to Part 850—Chronic Beryllium Disease Prevention Program Informed Consent Form on page 68913 and Appendix B to the Preamble - Questions and Answers Concerning the Beryllium-Induced Lymphocyte Proliferation Test (Be-LPT), Medical Records, and the Department of Energy (DOE) Beryllium Registry on page 68903.

Appendix B

An Analogy – Divergent Testing Recommendations for Prostate Cancer

An analogy can be made of the evolution of the science and subsequent testing that surrounded the use of the Prostate Specific Antigen (PSA) as a test from the early 1990s to 2010. The implementation of the PSA as a test is not without controversy. The natural history of the evolution of a localized prostate tumor to metastatic disease is not well understood. Similarly we do not understand the progression of beryllium sensitization to chronic beryllium disease. The psychological angst of knowing you have a non normal condition and whether or not to engage in an evaluation (prostate biopsy or bronchoscopy) or to engage in interventions (removal of the tumor or removal from work) for a condition that may or may not have health outcome consequences (prostate cancer/symptomatic CBD).

Prostate cancer testing which uses the PSA was first introduced in the early 1990s. Finding and treating cancer would on its surface appear to be an admirable goal; however our understanding of the disease is incomplete. Some prostate cancers grow very slowly and others are aggressive. The PSA is unable to distinguish between tumors that are aggressive and those that are indolent. Periodic PSA testing may not be frequent enough to detect the most aggressive tumors that can develop into untreatable cancer in a few months. Some men, having positive PSA tests, may remain asymptomatic throughout their lifetime. Several of the treatment decisions that may be made have side effects that may seriously affect the quality of life (e.g., urinary incontinence and sexual impotency). A positive PSA test may lead to anxiety associated with the diagnosis of cancer and a decision to treat it immediately when a watchful waiting approach might be better. There is no direct evidence that the early treatment of prostate cancer reduces mortality. Because PSA testing may detect cancers that never would have caused morbidity or mortality and miss those that do, the value of PSA testing remains unclear. There is no question that the PSA test can help spot many prostate cancers early but is the cancer likely to cause death. Given the risks inherent in both the test and the available treatment options the value of the PSA test remains unclear.

This uncertainty has led to divergent recommendations by nationally recognized bodies. The American Urological Association and the American College of Radiology continue to recommend annual PSA testing at prescribed ages and intervals. In contrast, the American College of Preventive Medicine, the American Cancer Society (ACS), the Canadian Task Force on the Periodic Health Examination, the United Kingdom, and the USPSTF do not recommend generalized testing.[1] Rather, these groups have recommended that men concerned about the risk of prostate cancer have individualized discussions with their physician to ensure that they receive clear and balanced information about the advantages and disadvantages of the PSA test.

The American Cancer Society[2] has summed the dilemma quite well:

"*Although there have been substantive advances in our understanding of prostate cancer screening since the last American Cancer Society (ACS) guideline update in 2001, there remain significant uncertainties regarding the overall value of detecting prostate cancer early. …When the evidence is not clear that the benefits of screening outweigh the risks, an individual's values and preferences must be factored into the screening decision. In light of the uncertain balance between the benefits and risks of prostate cancer screening, it is vital to involve men in the decision whether to screen. This ethical mandate to involve men in the decision-making process stems in part from the preventive nature of screening. By definition, screening involves performing a medical intervention on individuals who are otherwise healthy; i.e., they exhibit no symptoms or signs of the disease. This scenario confers a greater responsibility on the provider to uphold the doctrine of primum non nocere—first, do no harm—than in the case of interventions on symptomatic conditions. Although it is not clear how heavily the balance of benefit and risk must favor a benefit to obviate the need for informed decision making, it is clear that this point has not been reached for prostate cancer screening…."*

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[1] Screening for Prostate Cancer, Topic Page. August 2008. U.S. Preventive Services Task Force. http://www.uspreventiveservicestaskforce.org/uspstf/uspsprca.htm accessed 9/7/2010

[2] American Cancer Society Guideline for the Early Detection of Prostate Cancer: Update 2010, CA Cancer J Clin 2010; 0: caac.20066v1.