

# Low Prevalence of Chronic Beryllium Disease Among Workers at a Nuclear Weapons Research and Development Facility

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**Objective:** To study the prevalence of beryllium sensitization (BeS) and chronic beryllium disease (CBD) in a cohort of workers from a nuclear weapons research and development facility. **Methods:** We evaluated 50 workers with BeS with medical and occupational histories, physical examination, chest imaging with high-resolution computed tomography ( $N = 49$ ), and pulmonary function testing. Forty of these workers also underwent bronchoscopy for bronchoalveolar lavage and transbronchial biopsies. **Results:** The mean duration of employment at the facility was 18 years and the mean latency (from first possible exposure) to time of evaluation was 32 years. Five of the workers had CBD at the time of evaluation (based on histology or high-resolution computed tomography); three others had evidence of probable CBD. **Conclusions:** These workers with BeS, characterized by a long duration of potential Be exposure and a long latency, had a low prevalence of CBD.

Chronic beryllium disease (CBD) is a granulomatous inflammatory disorder that is characterized by a specific cell-mediated immune response to beryllium and a clinical-pathological presentation similar to sarcoidosis.<sup>1,2</sup> The diagnosis of CBD is usually made on the basis of confirmation of sensitization to beryllium through the use of the lymphocyte proliferation test (BeLPT) and histopathological evidence of epithelioid granulomas and/or mononuclear cell infiltrates on lung biopsy.<sup>3,4</sup>

The exact exposure-response relationship for the development of sensitization and disease is unclear. Genetic susceptibility, dose, and duration of beryllium exposure seem to be important risk factors for sensitization and disease. CBD has been viewed as a progressive disorder with a poor prognosis<sup>5,6</sup>; however, there is evidence that some cases of CBD remain mild for a prolonged time.<sup>7</sup> In addition, there is evidence that some beryllium-sensitized individuals have not progressed to CBD over considerable follow-up periods.<sup>8</sup>

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Cross-sectional epidemiological studies using the BeLPT have been used to identify beryllium-sensitized individuals in settings with historically high occupational exposures to beryllium (eg, beryllium machinists, ceramics workers, and nuclear weapons production workers). In this setting, it has been shown that a large proportion of sensitized workers will have CBD at the time of documentation of sensitization.<sup>9-14</sup> Recently, Newman et al<sup>15</sup> reported that in the longitudinal follow-up of beryllium-sensitized individuals without CBD at the time of identification, more than 30% of such individuals progressed to CBD (based on lung histology) during a mean follow-up time of 3.8 years. Interestingly, the severity of the CBD in this study appeared to be mild, in contrast to historical cases from earlier decades before use of the BeLPT for case identification.<sup>16</sup> These findings have raised concerns that the widespread use of the BeLPT to screen populations of exposed workers may result in the identification of individuals with beryllium sensitization (BeS) who will never develop clinical disease.<sup>16</sup> In addition, it is unclear how often sensitization and disease occur in workers with lower levels of Be exposure.

We had the opportunity to evaluate currently employed or retired beryllium-sensitized workers from a nuclear weapons research and development facility where the occupational exposures were probably, in general, much lower than in production facilities. In this study, we sought to determine the risk for development of CBD in these workers.

## METHODS

### Study Population

As part of a national U.S. Department of Energy (DOE)-sponsored medical surveillance program current or former employees of Lawrence Livermore National Laboratory (LLNL) were screened for beryllium sensitization based on at least two positive BeLPTs (ie, beryllium-stimulated proliferation of lymphocytes from peripheral blood samples drawn on two separate occasions or on split samples tested in two different DOE-approved laboratories). Workers found to have positive BeLPTs were evaluated in the Occupational Medicine Clinic at San Francisco General Hospital between 1999 through 2005. Although the individuals were initially evaluated for clinical purposes, a protocol for aggregating the clinical data to prepare this report was approved by the Committee on Human Research of the University of California, San Francisco.

### Clinical Evaluation

The standard clinical evaluation offered to these beryllium-sensitized individuals included a medical and occupational history, a routine physical examination, chest imaging (usually both plain chest radiographs and high-resolution computed tomographic [HRCT] scanning of the chest), pulmonary function testing (spirometry, lung volumes by plethysmography, and single-breath diffusing capacity), and fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsies.

## Beryllium Exposure

Occupational medicine physicians obtained a lifetime work history that included information on dates and duration of employment at the nuclear weapons research facility and other jobs with possible Be exposure. Historical information obtained from both the evaluated workers and occupational medicine physicians at the facility was used to generate a relative beryllium exposure index that had three categories of exposure: low (exposure to beryllium dust or fumes unlikely), moderate (occasional exposure to beryllium dust or fumes), and high (frequent exposure to beryllium dust or fumes). Each worker was assigned a level of beryllium exposure based on reported job title(s).

## High-Resolution Computed Tomography

HRCT scans were performed on a single-slice HighSpeed CT/i scanner (General Electric Medical Systems, Milwaukee, WI) using a standard interstitial lung disease (ILD) protocol.<sup>17</sup> Axial scans were obtained in full inspiration in both supine and prone positions at 2 cm intervals using 1 mm collimation using standard thoracic CT settings (120 kVp, 200–350 mA). Expiratory imaging following a forced vital capacity maneuver was performed at three levels: the aortic arch, the tracheal carina, and above the diaphragm. Postprocessing included reconstruction of the images using a high spatial frequency algorithm. HRCT images were viewed using hard copy format using image display parameters appropriate for lung (level = -700 HU, width = 1000 HU) and soft tissue (level = 40 HU, width = 400 HU) review. All scans were evaluated by a single chest radiologist experienced in ILD for findings consistent with CBD (eg, perilymphatic nodules, thickened septal lines, ground glass opacification, and hilar adenopathy).<sup>18</sup>

## Bronchoalveolar Lavage and Transbronchial Biopsy

Bronchoscopy was performed as follows. Intravenous access was established, supplemental O<sub>2</sub> was delivered, and the upper airways were anesthetized with topical lidocaine. Sedation with intravenous midazolam and fentanyl was used as needed for subject comfort. The bronchoscope was introduced through the mouth and vocal cords into the airways. The bronchoscope was then directed into the right middle lobe where BAL was performed with four 60-mL aliquots of 0.9% saline warmed to 37°C (two aliquots to each of the medial and lateral segments). Immediately after BAL, an attempt was made to obtain eight transbronchial biopsies of peripheral lung tissue from the right lower lobe. After bronchoscopy, each subject was observed for an approximate 2-hour recovery period.

Recovered lavage fluid was immediately put on ice. Total cells were counted on uncentrifuged aliquots of BAL using a hemocytometer. Differential cell counts were obtained from slides prepared using a cytocentrifuge, 25 g for 5 minutes, and stained with Diff-Quik (Dade Behring, Düringen, Switzerland). BAL fluids were then centrifuged at 234 g for 10 minutes, and the cells were resuspended in 10 to 15 mL of RPMI-1640 media with 10% fetal calf serum and 0.5% penicillin and streptomycin to obtain a final concentration of about 5 to 10 million cells per mL. The cells were subsequently shipped to National Jewish Medical and Research Center in Denver, Colorado, at room temperature by overnight delivery for performance of BAL BeLPT.

## Clinical-Radiographic-Pathological Review

A clinical-radiographic-pathological review of the data available for each of the evaluated individuals was done together by four of the authors (two pulmonologists—J.B., T.K.; a chest radiologist—M.G.; and a lung pathologist—S.N.) to determine by consensus whether or not there was sufficient evidence to make a diagnosis of CBD. CBD was defined as evidence of beryllium sensitization (all individuals evaluated) with epithelioid granulomas

and/or mononuclear cell infiltrates in lung tissue. In these beryllium-sensitized individuals, the combination of a positive BAL BeLPT and HRCT findings consistent with CBD was also accepted as diagnostic of CBD. Probable CBD was defined as follows: 1) HRCT evidence of CBD without histological evidence of CBD or BAL lymphocytosis; 2) non-specific HRCT and histological evidence of fibrosis with BAL lymphocytosis; and 3) abnormal BAL BeLPT with BAL lymphocytosis. The differential cell count criterion for BAL lymphocytosis was set at 30% of total leukocytes (the criterion used by the ongoing DOE-sponsored, multi-center Beryllium Biorepository project).

## Statistical Analysis

Statistical analysis was limited to descriptive parameters of the distributions of various characteristics of the population.

## RESULTS

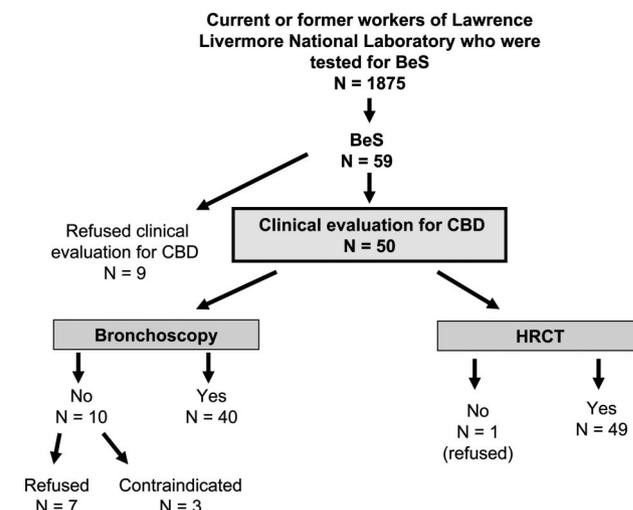
### Beryllium Sensitization

Of the 1875 current or former workers of LLNL who underwent BeLPT through 2005, 59 individuals had BeS based on the criterion described above, for a sensitization rate of 3.1%. Details of potential exposure to Be of the workers screened with BeLPT are not known.

### Chronic Beryllium Disease

Of these 59 individuals with BeS, nine refused any clinical evaluation for CBD and were not evaluated by us (Fig. 1). The mean age of the 50 beryllium-sensitized individuals we evaluated was 63 years (range, 39 to 81). Ten of the individuals were women. The mean duration of employment was 18 years (range, 0.5 to 41). The mean potential latent period between start of employment and time of clinical evaluation was 32 years (range, 12 to 48). Of the 50 individuals evaluated, 45 were no longer working at LLNL. None of the individuals who were still employed at the facility ( $n = 5$ ) was currently being exposed to beryllium at the time of his/her clinical evaluation.

The classification of the likely beryllium exposure of the individuals is shown in Table 1. Most of the beryllium-sensitized individuals had low or moderate exposures. Average annual area monitoring data for beryllium at LLNL were available for the years 1962–1984 and 1992–1993. Area monitoring data for the Rocky



**FIGURE 1.** Flow chart of surveillance for beryllium sensitization (BeS) and CBD among current and former workers from LLNL.

Flats nuclear weapons production facility were reviewed for the years 1961–1988 (see on-line Table A, <http://links.lww.com/JOM/A33>) as a comparison. The LLNL area beryllium levels are much lower than those at Rocky Flats for the years with available data (Fig. 2).

Of the 50 individuals who did undergo clinical evaluation for CBD, 10 did not undergo bronchoscopy (seven refusals and three

medical contraindications). Nine of the 10 individuals who did not undergo bronchoscopy had HRCT scans performed that showed no evidence of ILD. One individual refused HRCT.

Of the 40 individuals who had bronchoscopy, five were diagnosed to have CBD through the clinical-radiographic-pathologic review described above. Four had epithelioid granulomas on transbronchial biopsy. The fifth individual was given the diagnosis of CBD despite the lack of granulomas or mononuclear cell infiltrates on transbronchial biopsies because she had BAL lymphocytosis, a positive BAL BeLPT, and HRCT evidence of pulmonary nodules in a pattern suggestive of sarcoidosis. All five were ex-smokers.

None of the five patients with diagnosis of CBD had severe disease based on their symptoms, pulmonary function test results, and HRCT findings (Tables 2 and 3), and thus none were treated with immunosuppressive therapy. An additional three individuals had HRCT and/or BAL abnormalities consistent with probable CBD but did not meet our a priori criteria for a definitive diagnosis (Tables 2 and 3).

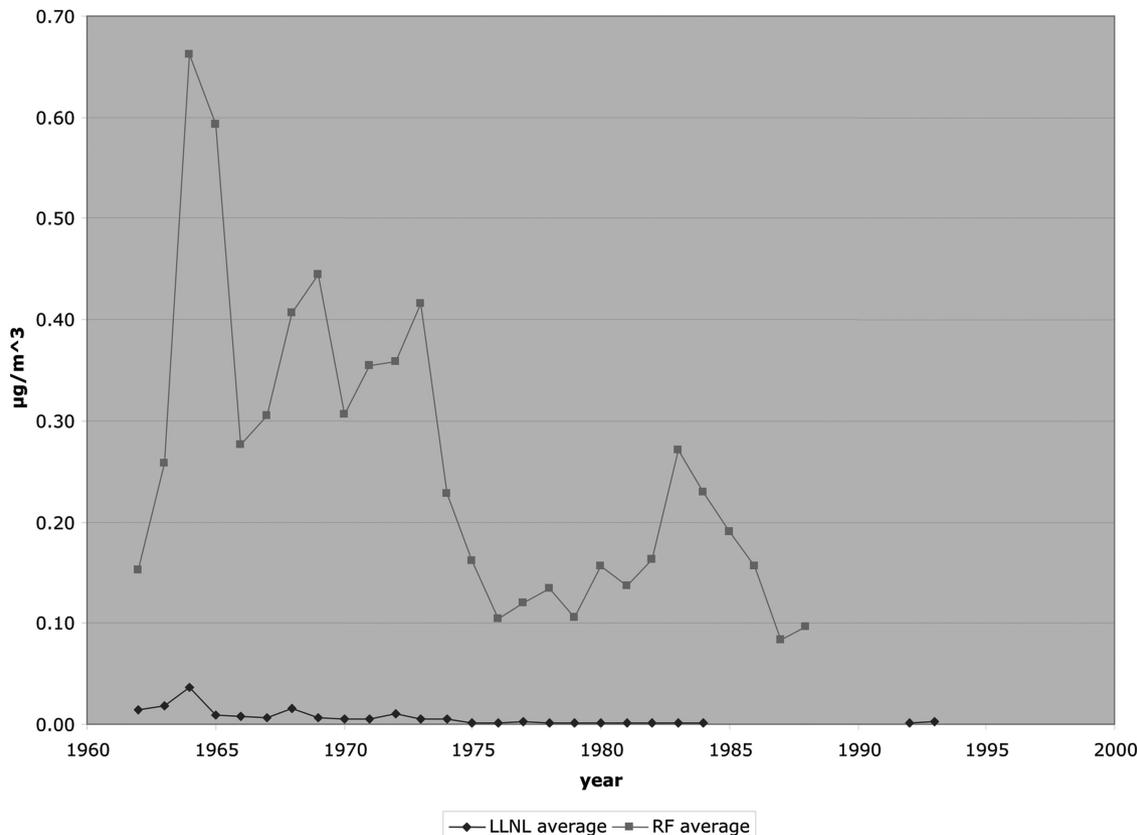
Thus, the CBD rate among sensitized individuals who underwent evaluation is either 5/40 (12.5%) or 5/49 (10.2%) depending on whether one requires pathological review of lung tissue or accepts HRCT as a surrogate. The CBD rate among the entire LLNL population tested for BeS is 5/1875 or 0.3%. If one includes the three individuals with some but not definitive evidence of CBD (Table 3), the rate of CBD is (0.4%).

Of interest, no evidence of an exposure gradient based on job classification is apparent for prevalence of CBD among the current

**TABLE 1.** Classification of Likely Level of Exposure to Beryllium Based on Worker Job Descriptions

| Level of Exposure | Job Description     | Number |
|-------------------|---------------------|--------|
| Low               | Clerical            | 13     |
|                   | Draftsman           |        |
|                   | Geologist           |        |
|                   | Data technician     |        |
|                   | Software engineer   |        |
| Moderate          | Physicist           | 28     |
|                   | Engineer            |        |
|                   | Custodian           |        |
|                   | Research technician |        |
|                   | Driver              |        |
|                   | Plumber             |        |
|                   | Sheet metal worker  |        |
|                   | Machinist           |        |
| High              |                     | 9      |

**Concentrations of Beryllium in Area Air Samples from LLNL and RF**



**FIGURE 2.** Annual average beryllium area air sampling concentrations (in  $\mu\text{g}/\text{m}^3$ ) from the LLNL and Rocky Flats nuclear weapons production facility (RF) for the years 1962–1993 where available. LLNL,  $\blacklozenge$ ; RF,  $\blacksquare$ .

**TABLE 2.** Exposure History and Clinical Features of the Workers With Definite and Probable CBD

| Subject      | Age (Years) | Sex    | Smoking History | Exposure | Years Employed at Facility | Latency (Years) | Dyspnea | Cough | Phlegm |
|--------------|-------------|--------|-----------------|----------|----------------------------|-----------------|---------|-------|--------|
| Definite CBD |             |        |                 |          |                            |                 |         |       |        |
| 1            | 66          | Male   | Ex-smoker       | Low      | 8                          | 16              | Yes     | No    | No     |
| 2            | 72          | Female | Ex-smoker       | Low      | 3                          | 23              | Yes     | Yes   | No     |
| 3            | 68          | Male   | Ex-smoker       | Low      | 6                          | 30              | No      | No    | No     |
| 4            | 68          | Male   | Ex-smoker       | Moderate | 7                          | 20              | No      | No    | No     |
| 5            | 78          | Male   | Ex-smoker       | Moderate | 28                         | 44              | Yes     | No    | No     |
| Probable CBD |             |        |                 |          |                            |                 |         |       |        |
| 6            | 63          | Male   | Non-smoker      | Low      | 9                          | 47              | No      | No    | No     |
| 7            | 63          | Female | Ex-smoker       | Low      | 22                         | 24              | No      | Yes   | No     |
| 8            | 73          | Male   | Ex-smoker       | Moderate | 41                         | 51              | No      | Yes   | Yes    |

**TABLE 3.** Laboratory Findings of Workers With Definite and Probable CBD

| Subject      | Pulmonary Function          |                |                |                 | HRCT Findings                       | Lung Biopsy Findings   | BAL BeLPT           | BAL Lymphocytes |
|--------------|-----------------------------|----------------|----------------|-----------------|-------------------------------------|------------------------|---------------------|-----------------|
|              | FEV <sub>1</sub> %predicted | FVC %predicted | TLC %predicted | DLco %predicted |                                     |                        |                     |                 |
| Definite CBD |                             |                |                |                 |                                     |                        |                     |                 |
| 1            | 83                          | 84             | 74             | 74              | Normal                              | Epithelioid granulomas | Negative            | 15              |
| 2            | 112                         | 113            | 116            | 103             | Perilymphatic nodules               | Normal lung tissue     | Positive            | 30              |
| 3            | 66                          | 77             | 88             | 58              | Normal                              | Epithelioid granulomas | Negative            | 23              |
| 4            | 74                          | 90             | 101            | 85              | Normal                              | Epithelioid granulomas | Negative            | 31              |
| 5            | 53                          | 95             | 124            | 58              | Emphysema                           | Epithelioid granulomas | Insufficient sample | Not done        |
| Probable CBD |                             |                |                |                 |                                     |                        |                     |                 |
| 6            | 102                         | 115            | 125            | 101             | Reticulation, centrilobular nodules | Refused                | Refused             | Refused         |
| 7            | 91                          | 92             | 96             | 67              | Septal thickening                   | Focal fibrosis         | Negative            | 35              |
| 8            | 93                          | 99             | 96             | 84              | Normal                              | Normal                 | Positive            | 51              |

FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; TLC, total lung capacity; DLco, diffusing capacity for carbon monoxide; BAL % lymphocytes, % lymphocytes in BAL.

and former LLNL employees we evaluated. In fact, there is a significant inverse trend. The percentages of definite or probable CBD cases were as follows: low exposure, 5/13 (38%); moderate exposure, 3/28 (11%); and high exposure, 0/9 (0%).

## DISCUSSION

The primary finding of this descriptive study of beryllium-exposed workers from a research and development facility of the U.S. nuclear weapons industry is that the rate of beryllium sensitization is low (3%). In general, the workers screened for beryllium sensitization from this facility were exposed to only low levels of beryllium. The proportion with CBD among the sensitized individuals is also relatively low (10% to 12%) compared with workers in high-risk production operations such as beryllium machining or ceramics manufacturing. Furthermore, among the individuals with confirmed or probable CBD, there were no cases of disease severe enough to require immunosuppressive therapy.

Several other studies of U.S. workers in the nuclear weapons industry have reported low rates of beryllium sensitization (Table 4). A study by Welch et al<sup>8</sup> of 3842 current and former construction workers at three DOE facilities (Hanford Nuclear Reservation, Oak Ridge Reservation, and the Savannah River Site) who participated in medical screening for beryllium sensitization showed that 53 (1.4%) of these workers had two positive BeLPTs; five workers were diagnosed to have CBD. Stange et al<sup>14</sup> studied current and

**TABLE 4.** Comparison of Beryllium Sensitization and CBD Rates At Several DOE Nuclear Facilities

| Facility                  | Rocky Flats <sup>14</sup> | Hanford/Oak Ridge/Savannah River <sup>8</sup> | LLNL      |
|---------------------------|---------------------------|---|-----------|
| Workers tested with BeLPT | 5173                      | 3842  | 1875      |
| Be sensitized workers     | 154 (3.0%)                | 53 (1.4%)                                     | 59 (3.1%) |
| Workers with CBD          | 81 (1.6%)                 | 5 (0.13%)                                     | 5 (0.3%)  |

Numbers in parentheses represent the percentages of all workers tested.

former workers at the Rocky Flats DOE facility, a nuclear weapons production plant with more workers potentially exposed to beryllium. Of the 5173 individuals from Rocky Flats who had BeLPTs done, 154 (3%) were sensitized (based on two positive BeLPTs) and 81 (1.6%) were diagnosed to have CBD.

The highest prevalence of BeS was among machinists (11.4%), but other groups of workers thought to have lower exposures such as custodial workers also had some increase in risk (5.6% prevalence of BeS). We compared data on area concentra-

tions of beryllium from Rocky Flats and LLNL as a rough guide to relative differences in potential exposures of workers to beryllium between the two facilities (Fig. 2 and on-line supplement, <http://links.lww.com/JOM/A33>). It is intriguing that while area concentrations at Rocky Flats were many times greater than at LLNL, the prevalence of beryllium sensitization is similar; however, the prevalence of CBD is approximately five times greater at Rocky Flats.

Within the LLNL population that likely had relatively lower exposures to beryllium than occurred at Rocky Flats, there was an inverse exposure-response gradient for progression from BeS to CBD based on job classification. None of the more highly exposed machinists at LLNL had evidence of CBD, whereas 38% of sensitized employees with low occupational exposure risk did progress. The higher percentage of CBD cases in the lower exposure category does not seem to be due to longer duration of exposure, as the mean work tenure of the five cases in this category, 16 years, is close to the overall mean of 18 years, and the mean latency of the five cases, 28 years, is close to the overall mean of 32 years. Unfortunately, personal beryllium exposure data from either monitoring or model estimates were not available for the workers we evaluated.

Why a positive BeLPT has a lower positive predictive value for CBD at LLNL and Hanford than at Rocky Flats and why sensitized workers with low exposure to beryllium at LLNL were more likely to have CBD than workers with moderate or high exposure are questions that remain to be answered. Clear exposure-response relationships among DOE workers with BeS are not apparent from the existing literature. Further investigation of the exposure-response relationships for both BeS and CBD is needed, especially for DOE-screened populations with relatively low-level exposures.

A study of 2221 workers involved in the cleanup of a former DOE nuclear weapons production facility that manufactured beryllium-containing weapon parts (presumably Rocky Flats) by Sackett et al<sup>19</sup> showed that 19 (0.8%) were beryllium-sensitized based on two or more abnormal BeLPTs. These results taken together and extended by those we report here suggest that, in general, there is a relatively low risk of beryllium sensitization and CBD among workers in current or former nuclear weapons facilities and associated national weapons research laboratories, although some groups, such as production machinists, have much higher risk.

A diagnostic issue that our data touch on is the sensitivity of the BAL BeLPT, which has been suggested as being more sensitive than the peripheral blood BeLPT for predicting the presence of CBD.<sup>3,4</sup> We report here that in three out of four cases of CBD for which a BAL BeLPT was performed, the test did not show abnormal lymphocyte proliferation to beryllium. In all three of the cases for which the BAL BeLPT was negative, two peripheral blood BeLPTs were positive. Although this sample of cases is too small to properly assess the sensitivity of the BAL BeLPT, our results do suggest that it might not be that sensitive for the diagnosis of CBD. The test can be helpful in the diagnosis of CBD, however, if biopsied lung tissue shows no evidence of granulomatous inflammation and when combined with results of other tests (Table 3).

Another clinical decision for which our data have relevance is when to perform bronchoscopy for the diagnosis of CBD. Because of the low prevalence of CBD among LLNL workers with beryllium sensitization as well as the lack of progression to clinically severe disease among those workers who have been diagnosed to have CBD, we have become more comfortable with annual medical follow-up of asymptomatic beryllium-sensitized workers with normal baseline pulmonary function tests and chest imaging

instead of early bronchoscopy. It would be helpful if future research could provide more definitive evidence on which to base the important decision for a beryllium-sensitized patient about whether or not bronchoscopy with transbronchial biopsies should be performed. Because the procedure is invasive and carries serious risk, the decision ought to be based on evidence.

In conclusion, aggressive evaluation of beryllium-sensitized workers using bronchoscopy for multiple transbronchial biopsies of lung tissue as soon as two BeLPTs are positive may be warranted in some cases. However, in populations that have low rates of CBD among the sensitized and lack of progression to severe disease among those with CBD, noninvasive longitudinal follow up may be preferable. With the current state of knowledge, bronchoscopy might best be reserved for individuals with progressive symptoms, decrements in pulmonary function, or chest imaging findings.

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*Dr Arjomandi created the database that was used to write the manuscript, performed the bronchoscopies of the patients with Dr Balmes, and cowrote the manuscript with Dr Balmes. Dr Seward referred the patients to UCSF, provided the data on the number of Be-sensitized workers at LLNL, and suggested that we include LLNL and Rocky Flats (RF) environmental monitoring data for Be in the manuscript. Dr Gotway read all the HRCT scans and participated in the clinical-pathological-radiological review of the patients. Dr Nishimura reviewed all the histological material and participated in the clinical-pathological-radiological review of the patients. Mr Fulton prepared the report on the environmental monitoring data for Be at LLNL and RF. Dr Thundiyl reviewed the medical surveillance records regarding Be-sensitized workers at LLNL. Dr King participated in the clinical-pathological-radiological review of the patients. Dr Harber coconceived of the study with Dr Balmes. Dr Balmes initially evaluated all the patients in clinic, performed all the bronchoscopies with Dr Arjomandi, obtained institutional review board approval to aggregate the clinical data, and cowrote the manuscript with Dr Arjomandi. All the authors reviewed the manuscript before submission and made substantive contributions to the final wording.*

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