Use of Beryllium Lymphocyte Proliferation Testing for Screening of Asymptomatic Individuals: An Evidence-Based Assessment

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*Objective: We reviewed published data describing use of beryllium lymphocyte proliferation testing (BeLPT) to determine the appropriateness of BeLPT for screening asymptomatic individuals. **Methods:** Published studies were identified by computerized literature searches and hand searches of relevant bibliographies and cited references. Critical assessment of evidence focused on five elements essential to judging effectiveness of preventive services: 1) burden of suffering, 2) accuracy and reliability of screening tests, 3) effectiveness of early detection, 4) harms of screening, and 5) benefits outweighing harms. **Results:** Important gaps and deficiencies in the evidence were found. The prevalence of beryllium sensitization and chronic beryllium disease in asymptomatic individuals are unknown. The accuracy and reliability of BeLPT are uncertain. Marked intra- and interlaboratory variability has been reported. The clinical benefits of early intervention have not been confirmed or quantified in asymptomatic individuals. **Conclusions:** There is currently insufficient scientific evidence to support the use of BeLPT for routine screening of asymptomatic individuals.* (J Occup Environ Med. 2006;48:937–947)

T he use of the beryllium lymphocyte proliferation test (BeLPT) as a screening test for persons without signs or symptoms of disease has been proposed as a means of identifying individuals with chronic beryllium disease (CBD) at an early stage based on the presumption that early therapeutic interventions might prove more effective. The logic of adopting BeLPT for screening purposes is that it serves to identify a subgroup in whom the likelihood of a diagnosis of CBD is substantially increased. In other words, BeLPT might usefully identify asymptomatic individuals at increased risk of developing clinically significant disease.

Although intuitively attractive, the correctness of that testing logic has not been established. Concerns have been raised as to whether the BeLPT is an accurate and reliable screening tool for CBD or beryllium sensitization (BeS), whether identified asymptomatic cases are likely to progress to clinical disease, and whether earlier diagnosis yields clinical benefits. It is therefore unclear whether screening for BeS and CBD is appropriate in persons without symptoms or physical findings suspicious for pulmonary disease or CBD.

In the following discussion, *screening* refers to the early detection of preclinical disease in persons without signs or symptoms suggestive of the target condition. Screening tests are distinguished from surveillance and diagnostic testing on the basis of whether the individuals undergoing testing have signs or symptoms of the target

condition. *Diagnostic testing* refers to the evaluation of patients with signs or symptoms associated with the disease. *Surveillance testing* refers to follow-up monitoring for recurrences or complications in patients who have already been diagnosed with and treated for the condition.

The fundamental tenet of screening is that finding the disease before symptoms develop enables detection at a less advanced stage and that instituting treatment at that time leads ultimately to improved health outcomes.[1] Although the value of early detection seems intuitive, current scientific evidence indicates that implementation of some screening tests (eg, screening for phenylketonuria[2,3] or cervical cancer[4]) yields overwhelmingly positive benefits, whereas the benefits of other screening tests (eg, prostate,[5] lung,[6] or ovarian cancer) are less readily apparent. To properly evaluate the effectiveness of a screening test requires an approach that is explicit and consistent with the tenets of *evidence-based medicine*. The latter refers to the effort to link clinical and public health practices to the quality of supporting evidence, to examine that evidence systematically, and to judge its quality with systematic standards for critical appraisal.[7] This scientific approach has been used by the U.S. Preventive Services Task Force (USPSTF) in its expansion and refinement of the guidelines for screening[1,8,9] first adopted by the World Health Organization.[10]

To objectively evaluate the effectiveness of the BeLPT test as a screening tool, we have applied the USPSTF methodology for the critical appraisal of evidence[1] with specific focus on the five key elements that are essential in judging the effectiveness of a preventive service: 1) burden of suffering, 2) accuracy and reliability of the screening test, 3) effectiveness of early detection, 4) harms of screening, and 5) benefits outweighing harms.[1,9] The preceding analytical steps are necessary to address the pivotal question of whether patients and populations experience better outcomes with screening than without it.

Appropriateness Criteria for Screening

Burden of Suffering

The first consideration in assessing the effectiveness of screening is the frequency with which the condition occurs in the population and its attendant health effects. The health condition to be averted must be sufficiently common in the screened population and pose a substantial threat to health to justify routine screening.[1,9,10] The prevalence rate determines the pretest probability of disease or the average likelihood that a person in the screened population will have the disease. The lower this value, the lower the *yield* (ie, a larger number of tests must be performed to detect one case of the disease).

Screening for chronic conditions tends to increase the detection of early-stage, preclinical diseases, leading to the identification of a much larger proportion of latent lesions that might otherwise go undetected for the life of the patient.[11] This phenomenon of screening, known as *overdiagnosis*, figures prominently in debates about the benefits of screening, because the net health benefit of screening is diluted by the degree to which latent conditions, which are not destined to progress, are represented among screen-detected cases. A common criticism of screening for prostate cancer, for example, is that many screen-detected cancers are latent carcinomas that, due to that disease's slow growth characteristics, are unlikely to progress or cause clinical symptoms.[12,13] Similar concerns have been raised about latent diseases detected by screening for cancers of the breast and lung.[14–16]

Accuracy and Reliability of the Screening Test

The second consideration in judging the effectiveness of screening is whether the available test(s) can detect the condition at an early stage without producing large numbers of false-positive or false-negative results. Of greatest concern is the test's *accuracy*, the degree to which it measures the true value of the attribute it is testing, and its *reliability*, the consistency of the result when it is repeated. The principal parameters for measuring accuracy are sensitivity, specificity, and predictive value.

A screening test must have sufficient *sensitivity* (the proportion of persons with the condition who correctly test positive) to find the condition earlier in its clinical course than if screening was not performed and sufficient *specificity* (the proportion of persons without the condition who correctly test negative) to avoid producing a large proportion of false-positive results (people without the condition who receive an abnormal test result).[17] An accepted reference standard ("gold standard") is essential to the empiric determination of sensitivity and specificity, because it defines when the disease is present and therefore provides the means for distinguishing between "true" and "false" test results.[18] A screening test must also have sufficient *reliability* (the ability to produce a similar result with consistency). For example, a reliable blood test should generate similar results, within and between testing laboratories, when the test is repeated on other samples from the same tube of blood.

Although the sensitivity and specificity of a screening test are generally constant across populations and settings, this is not true for the *positive predictive value* (PPV), which is the proportion of abnormal results in which the individual actually has the condition. The PPV depends on the pretest probability or likelihood that the condition is present at the time that the person is tested. For any screening test, the PPV is lower (and the chances of false-positive results are higher) when there is a lower prevalence of the condition.

This important principle, which underlies many concerns about screening, is best understood by example.

Suppose a test has a sensitivity and a specificity of 90% each. Clinicians might misinterpret these data to mean that a patient who has a positive result has a 90% likelihood of having the condition (ie, PPV = 90%). In actuality, the PPV is dependent on a third variable, the prevalence (pretest probability) of the condition. If the prevalence of the condition is 1% (1000 per 100,000 population), administering a screening test with 90% sensitivity means that positive results will be obtained for 900 of the 1000 individuals with the condition. The 90% specificity means that 89,100 of the 99,000 people without the condition will test negative. The probability that the condition is present in an individual with a positive test result (the PPV) would not be 90%, but 8%: the number of persons who tested positive who have the disease (900) divided by the total number who tested positive (900 + 9900 = 10,800). The seeming accuracy conveyed by the "90%" attribution for both sensitivity and specificity obscures the disturbing problem that the test would give false-positive information to 92% of those testing positive (11 people for every one person who truly had the condition). Regardless of the accuracy of a screening test, the administration of a test to populations or individuals with a low risk of having the condition can introduce major problems with false-positive results, leading to harms that can offset the benefits of screening.

Effectiveness of Early Detection

Screening is justified only if finding the condition earlier in its clinical course achieves better health outcomes than if screening was not performed. Implicit in this requirement is evidence that an effective treatment is available for persons found to have the condition as well as evidence that treatment of persons identified at an earlier stage through screening achieves superior outcomes than usual care.[1,11] The argument for screening is weakened when screening serves to identify the disease earlier in its course, but evidence is lacking that prognosis can be improved.

In evaluating the effectiveness of screening for chronic conditions, the analysis can be influenced by such factors as lead-time and length-time biases. *Lead-time bias* refers to the overestimation of survival time due to a backward shift in the starting point for the measurement of survival as a result of early detection.[19] The lengthened period of awareness of having "a condition" that results when screening identifies an otherwise asymptomatic condition does not necessarily translate into increased survival time. *Length bias* refers to the tendency of screening to detect slowly advancing conditions more readily than those that are aggressive. The effects of these biases on "calculated survival time of persons detected through screening could overestimate the actual effectiveness of screening."[1]

Harms of Screening

Screening is appropriate only if the attendant harms are acceptable. The harms can affect the large proportion of the screened population that is ultimately determined to not have the condition and the subset found to have disease.[11,17] The potential harms can include the adverse effects of the tests themselves, the psychologic and labeling effects (eg, anxiety) generated by positive results, and the morbidity associated with the cascade of follow-up tests and treatments triggered by initial screening. For a test with a low PPV, in which most persons who test positive do not have the condition, a much larger number of individuals in the screened population will face those risks, with no apparent benefit, than the number of people who do benefit.

The adverse societal harm resulting from ineffective screening tests includes the consumption of resources that would help patients more effectively if they were invested elsewhere.

Benefits Outweighing Harms

Screening is appropriate only if the tradeoff between benefits and harms is favorable. In most cases, this means that the harms incurred by the large proportion of the screened population without disease are small enough to be outweighed by the benefits obtained by the few who are found to have disease.[11] To assess whether benefits outweigh harms, one must know the likelihood and probable magnitude of benefits and harms to screened persons. The evaluation of the benefit versus potential harms of screening should be made using evidence that has been judged to be of *good* to *fair* (but not *poor*) quality.[8] The assessment of study quality involves considerations of internal validity (eg, study design, methods of sample recruitment, execution of the tests, and completeness of study report) and external validity (eg, generalizability to normal practice conditions).[17]

Evaluation of the Beryllium Lymphocyte Proliferation Test

Burden of Suffering

The clinical significance of most cases of CBD that are currently being diagnosed has not been established. Without doubt, CBD was historically a very serious disease. Formal criteria for its diagnosis were first established in the early 1950s by the Beryllium Registry founded at the Massachusetts Institute of Technology following reports of severe CBD in workers exposed to beryllium-containing phosphors in the fluorescent bulb industry.[20,21] Those criteria, which remained the principal basis for diagnosing CBD for nearly 40 years, addressed two concerns: "establishment of significant beryllium exposure" and "objective evidence of lower respiratory tract disease."[22] Clinically, "objective evidence" was defined as finding at least two of the following: 1) clinical symptoms

and course consistent with CBD, 2) characteristic histologic changes in lung tissue or lymph nodes, 3) chest x-ray evidence of interstitial fibronodular disease, or 4) abnormal pulmonary function (obstruction or restriction and diminished diffusing capacity).[23,24] Thus, for nearly 40 years, CBD was diagnosed only in patients with clinically symptomatic disease, and it was accordingly regarded as a disease of substantial morbidity and mortality. Reportedly during the 1950s, for example, one of three persons diagnosed with CBD died from the disease.[25] Such cases are rare in the modern era.

Today, most CBD is detected through workplace screening programs that have identified mainly asymptomatic individuals. The new case mix reflects technologic advances that changed the criteria for CBD and "revolutionized"[26] the diagnostic approach to beryllium disease. One advance was the refinement of analytical methods for detecting beryllium-sensitized lymphocytes, a laboratory technique that evolved over more than 30 years[27–32] and led to the BeLPT. Another was the popularization of fiberoptic bronchoscopy. These advances confirmed the immunologic nature of CBD[30] and provided a fundamentally different understanding of the natural history and epidemiology of beryllium-induced disease.

Beginning in 1989, an increasing number of beryllium workers who did not meet the Beryllium Registry criteria were diagnosed as CBD by means of BeLPT and fiberoptic bronchoscopy.[33,34] That led to a redefined "classification system" with three categories of beryllium effects: 1) "beryllium disease" (equivalent to clinically evident CBD); 2) "subclinical beryllium disease" (abnormal BeLPT and characteristic lung biopsy, but no "constellation" of clinical findings); and 3) "beryllium sensitization" (BeS) (abnormal BeLPT). Thereafter, beryllium was recognized as causing a spectrum of effects, from asymptomatic sensitization to clinically evident

CBD.[26] As discussed subsequently, these redefined criteria have sometimes been modified or inconsistently applied; nevertheless, the fact remains that individuals can meet these criteria and be labeled with disease despite the absence of clinical symptoms or functional deficits.

The clinical relationship among "beryllium disease," "subclinical beryllium disease," and "beryllium sensitization" is uncertain. In particular, the natural history of CBD, as currently diagnosed, is unknown.[35–38] Progression from BeS to subclinical beryllium disease has been documented in a number of cases,[39–41] but only one relatively small longitudinal study (55 subjects) has specifically addressed disease progression in beryllium-sensitized workers.[38] How often such progression leads to "clinically manifest disease" has yet to be determined.[42] In recent studies, the majority have been subclinical cases requiring no treatment. Among the 55 subjects in the sole longitudinal study of BeS, only one went on to be treated with corticosteroids.[38] Thus, the natural history and rate of progression from beryllium sensitization to clinically evident CBD is still unknown.

The prognosis of currently diagnosed cases of clinically evident CBD is also unknown. Recent reviews have suggested that one third or more of untreated patients progress to end-stage respiratory disease,[43] but such statements reflect the experience of mainly pre-1950s historical cases that were "severe and detected at a late stage."[41,44] The relevance of such historical observations to current cases is questionable. Today, the proportion of CBD cases that will eventually require treatment is unknown. Likewise unknown is the proportion that will die as a result of CBD, although clinical experience suggests that currently "most individuals with CBD die from other causes."[26] Based on recent clinical observations and the limited nature of existing evidence, it seems correct to say that the clinical course of CBD

is variable, that patients with CBD may remain clinically stable for many years, and that despite the possibility of progression, the prognosis of CBD has been only poorly characterized.[37,40,45] It is conceivable that large proportions of persons identified with subclinical CBD or BeS will live their entire lives without perceptible adverse health effects.

Finally, prevalence rates of BeS and CBD are not well documented. Among exposed workers, reported rates of positive BeLPT range from approximately 1% to 16%,[46–48] of whom a fraction (generally less than 50%) have subclinical beryllium disease and a much smaller fraction suffer clinically evident disease. Many reports do not provide the actual numbers of those with clinical versus subclinical disease. The reported fractions vary across studies, probably reflecting both the limited numbers of subjects in most reports and (as discussed subsequently) the variability across studies of criteria for CBD and for abnormal BeLPT.

The total number of individuals who have ever been diagnosed with CBD or documented as BeS is unknown. The number cannot be approximated by combining reports from individual studies, because the same workers appear to have been included in multiple published reports, eg, sequential cross-sectional studies at specific worksites, composite reports combining multiple worksites of a given company or agency, and reports from the individual laboratories that perform BeLPT. For example, results of BeLPT testing at a nuclear weapons facility were described in at least three sequential reports,[39,49,50] whereas results from a beryllium manufacturing facility were described in at least four reports.[46,48,51–53] In addition, BeLPT results from both facilities were probably included in reports published by researchers at the individual laboratories.[40] Moreover, because many BeLPT screening programs have used split samples sent to multiple laboratories, it is likely that many

workers have been included in reports from more than one laboratory.

Accuracy and Reliability of the Screening Test

The BeLPT lacks sufficient evidence of sensitivity, specificity, and acceptable PPV to meet current criteria for a good screening test. The true sensitivity and specificity of the test have not been properly calculated and will be difficult to properly calculate. The denominators needed for those calculations (the total number of individuals in the screened population with and without disease) are not determined in most reported CBD studies. Doing so would require subjecting the entire screened population to a definitive "reference test" for CBD, which (to satisfy current CBD criteria) would entail bronchoscopy. Understandably, most studies have offered bronchoscopy, biopsy, and bronchoalveolar lavage (BAL) only to screened workers with abnormal BeLPT.[26,50] In addition, some screened workers with abnormal BeLPT refuse bronchoscopy.[47] Thus, the database necessary to determine the sensitivity and specificity of BeLPT is incomplete.

In addition, there is no consensus reference standard for diagnosing CBD. That diagnosis is generally made on the basis of a history of beryllium exposure and a positive BeLPT in blood and/or BAL fluid along with lung biopsy findings, but specific criteria have varied across studies. Table 1 presents 10 different criteria sets used in 19 studies. Notably, some workers have been included in two or more studies that used different criteria, and the same research groups have used different criteria at various times. In a review of more than 12,000 Department of Energy (DOE) workers, CBD was diagnosed on the basis of four different sets of criteria, including one that required "only abnormal peripheral blood and BAL BeLPTs."[49] A source of further confusion has been the introduction of ambiguous categories such as "probable CBD" and "possible CBD" based on other clinical data and defined differently by each research group.[47,50,54] Some individuals are diagnosed as CBD by some, but not all of these criteria. No study has made a head-to-head comparison of the yield from each set of diagnostic criteria.

The sensitivity and specificity of the BeLPT for BeS is also uncertain. Although widely adopted as the standard test for BeS,[57,61,62] its performance cannot be readily characterized because it is the "only practical means to determine BeS"[49]; there are no other standard tests to which BeLPT can be compared. However, perspective can be gained from test–retest confirmation of initial BeLPT results. In one study of 3842 workers, retesting confirmed only 62% of initially abnormal tests.[63] Another study of 4268 workers demonstrated that test–retest consistency was inversely proportional to BeLPT results (as measured by the "stimulation index" discussed subsequently). As shown in Table 2, for example, confirmatory retesting was negative in 83.9% of individuals with a stimulation index of 3.0 to 4.9 on initial BeLPT.[50] Such data suggest a high false-positive rate for the BeLPT.

Additional perspective derives from studies comparing BeLPT with beryllium patch testing, a test that predated BeLPT historically[64] but was rarely used in the United States. Patch testing has been proposed recently as an in vivo measure of BeS in contrast to the in vitro BeLPT. In a recent study, 11 patients with biopsy-proven CBD, but repeatedly equivocal or negative BeLPTs, were administered both BeLPT and beryllium patch testing; all 11 had positive patch tests, but only four had abnormal BeLPTs.[56] Others have reported that BeLPT results can fluctuate over time, even in patients with biopsy-proven CBD.[38,54] Despite the

TABLE 1

Diagnostic Criteria for Chronic Beryllium Disease in 19 Published Studies

Diagnostic Criteria	References
Abnormal BeLPT in blood *or* BAL fluid *plus* granulomas on lung biopsy	Barna et al[40] Culver and Dweik[37] Kreiss et al[39,46,51,55] Markham[48] Rosenman et al[47]
Abnormal BeLPT in blood *or* BAL fluid *plus* granulomas *or* mononuclear cell infiltrates on lung biopsy	Bobka et al[56] Newman et al[33,54]
Abnormal BeLPT in blood *or* BAL fluid *plus* granulomas *or* "other pathologic abnormalities consistent with that diagnosis"	Schuler et al[57]
Abnormal BeLPT in blood *and* BAL fluid *plus* granulomas on lung biopsy	Stange et al[50] Viet[58]
Abnormal BeLPT in blood *and* BAL fluid *plus* granulomas *or* mononuclear cell infiltrates on lung biopsy	Stange et al[49]
Abnormal BeLPT in BAL fluid *plus* granulomas *or* mononuclear cell infiltrates on lung biopsy	Mroz et al[59]
Abnormal BeLPT in blood *plus* granulomas *or* mononuclear cell infiltrates on lung biopsy *or* CT evidence of granulomas	Stange et al[49]
"Borderline *or* abnormal" BeLPT on BAL fluid *and/or* granulomas on lung biopsy	Hennenberger et al[52]
Abnormal BeLPT in blood *or* BAL fluid *plus* "compelling evidence of pulmonary disease"	Stange et al[49]
Abnormal BeLPT in blood and BAL fluid	Stange et al[49]; Stokes and Rossman[60]

BeLPT indicates beryllium lymphocyte proliferation testing; BAL, bronchoalveolar lavage; CT, computed tomography.

TABLE 2
Results of Confirmational Retesting for Positive Beryllium Lymphocyte Proliferation Tests (BeLPTs) in 4268 Workers*

Positive BeLPT: Range of Stimulation Index Values	No. Positive: Initial BeLPT	No. Negative: First Retest BeLPT	Percent 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	16	0	0.0

*Adapted from Stange AW, Furman FJ, Hilmas DE. Rocky flats beryllium health surveillance. *Environ Health Perspect*. 1996;104(suppl 5):981–986.

limited value of such small, uncontrolled studies, they suggest the possibility that BeLPT may yield numerous false-negative results for both BeS and CBD. Unfortunately, current data are insufficient to critically evaluate that possibility.

Methodological problems with the assay protocol also contribute to uncertainties about BeLPT. The test is performed by only five U.S. laboratories,* which follow generically similar protocols.[40,53,55,65,66] Lymphocytes are incubated with a soluble beryllium salt and tritiated thymidine is added before harvesting. The amount of thymidine taken up by the lymphocytes, reflecting cellular replication, is measured by scintillation counter. A "stimulation index" (SI), the ratio of the counts in treated cells to counts in unexposed cells, is then calculated. BeLPT results are judged abnormal or normal on the basis of the calculated SI.

Despite such nominal agreement, protocols differ across laboratories and have differed across time at individual laboratories. Lymphocytes have been incubated for "3, 5, and 7 days"[59] "3 to 7 days,"[60] "5 and either 6 or 7 days,"[57] "harvested on 2 separate days, from days 4 to 7,"[65] or for "3 days."[67] Such differences seem relevant because results have been

reported to differ according to duration of incubation.[60,68] Some studies used two or more laboratories using different protocols.[52,57] In others, analytical protocols were described by reference to an earlier report,[59] but the cited protocol was not followed.[38]

There is also disagreement about criteria for an abnormal BeLPT. Some reports defined abnormal as a peak SI exceeding the mean peak SI of unexposed controls plus two standard deviations.[51,59] Using that approach, the criterion SI varied from study to study: 1.9,[46] 2.0,[51] 2.42,[68] 2.5,[62,67] and 3.5.[39] Others used that approach but did not report the resulting criterion SI.[50,54,55] In 1995, a "consensus standard" established SI $\geq$3.0 as the criterion for an abnormal test[53] and some reports then adopted that criterion.[31,40,52,53,57] The use of alternative statistical approaches has resulted in still different criteria,[68] whereas some studies reported neither analytical protocol nor criteria for an abnormal BeLPT.[47]

Such inconsistencies raise concerns about the comparability of results across studies. They also discourage pooling of data (eg, meta-analysis), which might otherwise be helpful because sample sizes in many studies have been small (5–17 persons with positive test results in most reports of BeLPT testing at single worksites).[39,46,51,52,54,57,69] Such small sample sizes amplify the apparent effects of random error, making calculations of sensitivity and specificity necessarily less certain.

Similar issues impact efforts to determine PPV, which require knowledge of the true prevalence of CBD and BeS. As discussed previously, neither is known. It seems likely that use of variable criteria has tended to overestimate the prevalence of CBD in tested populations. The estimated prevalence of CBD in exposed workers has ranged from 1% to 16%, depending on the nature of exposure.[26,62] Nearly the same range has been estimated for the prevalence of BeS.[26,37,57] Such wide ranges raise questions about the validity of the reported data and make it difficult to determine the true prevalence of either CBD or BeS in beryllium-exposed workers. Even less clear are what prevalence rates to assume for those not occupationally exposed. Several reports have described positive BeLPTs in approximately 1% of persons said to have had no history of beryllium exposure (eg, newly hired workers),[69,70] but this has not been systematically studied. Accordingly, it is not surprising to find estimates of the PPV of BeLPT for CBD that range from 11% to 100%.[51,53,60,63] We are not aware of any systematic estimates of the PPV of BeLPT for BeS, a deficiency that partially reflects the lack of an accepted "gold standard" for BeS.

It is also noteworthy that "strikingly inconsistent results" within and between laboratories have long been recognized.[26,37,48,55,61,63,66] Because many BeLPT investigations use split samples and several laboratories, there are numerous interlaboratory comparisons. In a study of 627 workers, use of either one of two laboratories alone would have identified only 46.5% to 48.8% of BeS cases: "abnormal tests were often accompanied by normal tests in the same or different laboratory."[55] In more than 12,000 DOE workers, split blood samples were tested at two from among four different laboratories; interlaboratory agreement ranged from 26.2% to 61.8% for abnormal tests.[49] An earlier study of 4268 workers at one site reported interlaboratory

*BeLPT is currently performed at Oak Ridge Institute for Science and Education, Cleveland Clinic Foundation, Hospital of the University of Pennsylvania, National Jewish Center for Immunology and Respiratory Medicine, and Specialty Laboratories, Santa Monica, CA.

agreement of only 21% to 38% for abnormal tests.[50] Some studies used the kappa statistic to evaluate interlaboratory agreement. Analysis of 3081 blood samples obtained from 1510 employees of a beryllium manufacturer evaluated agreement between three laboratories; for pairs of laboratories, the kappa statistic ranged from 0.2 ("poor agreement") to 0.6 ("moderate agreement").[53] In a recent NIOSH study of 153 workers, agreement between two laboratories was "poor" (kappa = 0.20): one laboratory reported eight samples with abnormal BeLPT, whereas the second reported 17.[57] Moreover, that second laboratory was nearly five times more likely to report "borderline" or "uninterpretable" results. Such interlaboratory disagreements necessarily raise concerns about the accuracy and reliability of BeLPT.

Beyond the data deficiencies just described, many studies that evaluated BeLPT are limited by methodological issues and deficiencies. Sampling schemes were often poorly documented or ambiguous. In some studies, not all of the eligible workers chose to participate.[47,48,50,52,57] In others, results included workers diagnosed historically but who were not participants in the protocol study.[46,47,55,57] Only a few studies documented the characteristics of the nonparticipants; thus, it is often not possible to know whether participants and nonparticipants differed significantly. Such systematic differences could lead to selection bias that inflated the apparent prevalence of CBD, eg, if nonparticipants had had less beryllium exposure. That particular possibility was confirmed in studies that provided sufficient data on nonparticipants, revealing that they were younger and less likely to be exposed to beryllium than were the participants.[39,51] The reported prevalence of CBD may also have been overestimated because cases were sometimes classified as CBD even if they did not meet predetermined diagnostic criteria.[39]

One further methodological concern is the apparent lack of blinding in many of the studies. Little or no information has been provided about whether evaluation of bronchoscopic biopsies and chest x-rays was performed by pathologists and radiologists who were aware of the patients' BeLPT results. Knowledge of BeLPT results before evaluating such biopsies and x-rays could have potentially skewed their interpretation, an effect referred to as "review bias." Review bias can lead to falsely elevated indices of accuracy.[71,72]

Effectiveness of Early Detection

There is no valid evidence that early detection of CBD or BeS improves health outcomes. Even before demonstrating *incremental* benefit from early detection, there must be a foundation of evidence that treatment is of benefit, independent of stage. Although dramatic benefits from corticosteroid therapy for CBD have been reported in the literature and observed in clinical experience, most of these observations occurred 50 years ago, when advanced forms of CBD predominated. Even at that time, doubts were raised about the strength of evidence that corticosteroids were beneficial.[25,73] Such lack of evidence remains a concern today. The use of corticosteroids in CBD has never been tested in a randomized control trial,[26,37,45,66,74] and no standardized clinical regimen for such therapy has been adopted in patient care.[35]

Although corticosteroids are often regarded as "first-line therapy" for CBD,[45] it is generally agreed that they are primarily indicated only for patients with disabling symptoms, significant impairment, or progressive deterioration.[26,35,41] Most reports do not indicate the number of individuals identified by BeLPT who have been administered corticosteroids. On the basis of limited reports, however, that number may be very small. For example, in a recent longitudinal study of patients with BeS, of whom 17 subsequently were diagnosed with CBD,[38] only one patient was administered corticosteroids during postdiagnostic follow up (average follow up, 4.7 years; range, 1–10 years).

There is no evidence that corticosteroid treatment changes the course of subclinical CBD or BeS and the incremental benefit of corticosteroids in early disease management is unknown.[41,45] In a small study, steroid use did not affect BeLPT results.[56] More generally, there are currently no established interventions or treatment for BeS (other than recommendations for avoidance of further exposure and ongoing clinical monitoring).[26,52] Removal from further exposure to beryllium has been recommended as "prudent,"[41,52,74] but no study has determined whether such removal changes clinical outcome.[36,52,66,74] Accordingly, the benefits of treatment and intervention for subclinical CBD and BeS remain unknown.

Harms of Screening

The immediate physical harms of BeLPT screening are minor, although it might entail a modest degree of inconvenience. The poor reliability of the BeLPT imposes some inconvenience because of the frequent need for repeat testing. In one study, 3.6% of 505 screened beryllium ceramics workers had to return for repeat blood work because initial data were inadequate.[51] Among 7820 workers at one plant, 2.79% had positive BeLPTs that could not be confirmed with retesting.[49] In most of those who returned for repeat testing, BeLPT results were normal.

A much larger concern is the consequences of positive results, which may affect a substantial proportion of the screened population. Among those in whom the BeLPT is initially unconfirmed, indeterminate, or equivocal, expected adverse effects include anxiety over the possibility of having a disease, a phenomenon well documented in research with other screening tests. That research demonstrates that, even if the abnormality is eventually determined to be a false-positive, a subset of individuals

will continue to believe that they have something wrong with their health.[75–77] Other labeling effects such as decreased insurance and job eligibility have been documented with screening in general[78–81] and have also been reported in workplace beryllium screening programs, even when initial abnormal results are ultimately shown to be false-positive.[82] There are also potential costs from job disruption in those who change their work to avoid further exposures.

Adverse physical effects can also result from the diagnostic workups initiated in response to abnormal BeLPT. Individuals with confirmed abnormal BeLPT are commonly advised to undergo bronchoscopy with transbronchial biopsy and BAL.[26,47,49] In a report from a beryllium manufacturer, bronchoscopy was performed in 90% of workers with confirmed BeLPT.[53] Less often, medical referral and bronchoscopy are recommended to those with unconfirmed BeLPT. For example, the same manufacturer reported that bronchoscopy was performed in 45% of workers with an unconfirmed BeLPT.[53] The DOE refers workers for medical follow up on the basis of a single BeLPT.[83]

The sensitivity of bronchoscopy in diagnosing CBD is unknown.[37] The majority of bronchoscopies performed after BeLPT screening do not detect CBD,[40,48,50,55] and repeated bronchoscopy is sometimes advocated if samples are not diagnostic.[39,74] In the report from the beryllium manufacturer, 192 bronchoscopies were performed on 159 BeLPT-positive workers, but CBD was diagnosed in only 61 individuals.[53] An NIOSH study reported that bronchoscopy was performed in 16 BeLPT-positive workers, but only four had CBD.[57] Thus, even among workers with known beryllium exposure and confirmed abnormal BeLPT, the majority had normal pulmonary findings.

In addition, individuals with confirmed abnormal BeLPT are often encouraged to undergo periodic bronchoscopy, regardless of symptoms, to monitor "progression."[26,74] For example, among a group of 55 patients with BeS, 21 had two bronchoscopies, seven had three bronchoscopies, and two had four bronchoscopies each.[38] Most studies do not report the numbers of subjects who underwent repeat bronchoscopy or the numbers of patients thereby diagnosed. However, in studies that reported iterative screening, including BeLPT and bronchoscopy, yield rates declined with successive iterations.[49,54] Thus, only a minority undergoing bronchoscopy because of abnormal BeLPT will have CBD and that proportion is expected to decline when bronchoscopy is repeated. Accordingly, the adverse effects of screening bronchoscopy may impact disproportionately those who do not have CBD.

There are also harms resulting from the treatment of those found to have BeS or CBD, including the adverse effects of being removed from worksite exposure (eg, job transfer) and those from medical interventions. The side effects and complications of steroid therapy are widely recognized and depend on the regimen advocated. Two recommended regimens are 0.5 to 0.6 mg/kg prednisone daily or every other day[74] and 40 mg every other day for up to 6 months followed by gradual tapering ("no more than 10 mg every other month")[84] until patients show renewed disease activity. Once initiated, steroid therapy is usually continued for life.[26,74,84] Such doses and durations will induce side effects and complications in a proportion of the treated population that must be counterbalanced against their putative benefits.

Benefits Outweighing Harms

There is no currently available evidence that the presumed benefit of screening for BeS and CBD by use of the BeLPT outweighs its potential harms. To make this assessment, one must know, in at least approximate terms, the likelihood and probable magnitude of benefits and harms to screened persons. The dearth of evidence outlined here, including questions about the very existence of benefit, makes it impossible at this time to answer these fundamental questions. Lacking such information, one cannot conclude on scientific grounds that the benefits of using the BeLPT as a screening test (ie, for persons without signs or symptoms of disease) outweigh its harms. It is therefore inappropriate (and perhaps unethical) to recommend its use for routine screening.

Conclusion

Clinical and scientific advances have combined to illuminate the biochemical processes that underlie BeS and CBD. Originally regarded as an irritant pneumonitis[85] and first hypothesized to have an immunologic basis in 1951,[86] beryllium's mode of action is now increasingly understood at the genetic and molecular levels.[87–91] These advances, reflecting the benefits of longstanding research efforts, have led some to recommend wide adoption of BeLPT screening programs in asymptomatic individuals.[83,92,93] Notwithstanding the insights and understandings gained, those research efforts have not yet established a credible scientific basis to support such screening programs.

A variety of important questions remain unanswered. The prevalence of BeS and CBD are unknown for most worker groups and for the general population. The accuracy and reliability of BeLPT are uncertain, and the test itself has demonstrated marked intra- and interlaboratory variability. The prognosis of BeS and subclinical CBD is essentially unknown and the clinical benefits of early intervention have not been studied. It is therefore difficult to judge whether potential benefits outweigh the harms of testing and treatment.

Accordingly, there is currently insufficient scientific evidence to support recommendations that BeLPT be

adopted as a clinical screening tool in asymptomatic individuals. Beryllium-exposed workers may be eligible for worksite screening in the context of occupational health surveillance, although the clinical benefit of such testing has not been determined.

Acknowledgments

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