# Research to Practice Implications of High-Risk Genotypes for Beryllium Sensitization and Disease

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**Objective:** Beryllium workers may better understand their genetic susceptibility to chronic beryllium disease (CBD) expressed as population-based prevalence, rather than odds ratios from case-control studies. **Methods:** We calculated CBD prevalences from allele-specific DNA sequences of 853 workers for *Human Leukocyte Antigen (HLA)-DPB1* genotypes and groups characterized by number of E69-containing alleles and by calculated surface electronegativity of HLA-DPB1. **Results:** Of 18 groups of at least 10 workers with specific genotypes, CBD prevalence was highest, 72.7%, for the *HLA-DPB1*02:01:02/DPB1*17:01* genotype. Population-based grouped genotypes with two E69 alleles wherein one allele had −9 surface charge had a beryllium sensitization (BeS) of 52.6% and a CBD prevalence of 42.1%. **Conclusions:** The high CBD and BeS prevalences associated with −9-charged E69 alleles and two E69s suggest that workers may benefit from knowing their genetic susceptibility in deciding whether to avoid future beryllium exposure.

Chronic beryllium disease (CBD) has a well-characterized immunologic mechanism requiring cell-mediated sensitization to the metal antigen. Beryllium sensitization (BeS) is affected by both exposure and genetic characteristics. Since 1993, six research groups, studying a number of beryllium-exposed populations, have confirmed that workers with a glutamic acid (E) in the 69th position of the Human Leukocyte Antigen (HLA)-DPB1 molecule, involved in antigen presentation, have increased susceptibility for BeS and CBD.[1–10] However, this supra-allelic *E69* marker of genetic risk is present in more than one-third of the U.S. population and far exceeds the prevalence of BeS and CBD in worker populations. For those reasons, *E69* genetic testing was not pursued as a good predictor of who might develop CBD in a beryllium workplace,[11] especially in light of concerns for employment and insurance discrimination.

In 2008, the Genetic Information Nondiscrimination Act (GINA)[12] prohibited genetic discrimination in employment and health insurance and precluded employers from using individually identifiable genetic testing in employment decisions. However, genetic studies have identified very high-risk subsets of E69 variants (Table 1).[13–15] Workers may benefit from genetic testing to understand their susceptibility to CBD and to consider whether to avoid future beryllium exposure.

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This paper was funded as an employee work product by the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

No authors declared conflicts of interest.

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DOI: 10.1097/JOM.0000000000000805

Worker genotypes pertinent to the immune response gene associated with BeS consist of two alleles. As of January 2016, there were 630 known DNA sequence variants of *HLA-DPB1*, of which 204 are *HLA-DPB1*E69* (coding for E69, a glutamic acid in the 69th position of the protein), 380 are *HLA-DPB1*K69* (lysine), 38 are *HLA-DPB1*R69* (arginine), and 8 had uncharacterized amino acids in the 69th position.[16] Presence of one copy of the most common E69 allele, *HLA-DPB1*02:01*, confers an odds ratio of 2 for CBD compared with workers having no E69 alleles.[13]

Mechanistic work enabled through computational chemistry modeling[14,17] and crystallization of the product of the most common *HLA-DPB1*E69* allele in a heterodimer[18] suggests that the beryllium cation binds deep in a pocket of the peptide molecule's binding groove on the antigen-presenting cell that contains negatively charged amino acids. Diverse self-peptides can then cover the bound beryllium ion without haptenization, changing the conformation of the HLA-DP heterodimer molecule such that the T-cell receptor binds to the antigen-presenting molecule in a manner common to auto-immune mechanisms.[19,20] The morphometry and electronegativity of specific amino acids in the binding groove explain the shape and energy required for stable bonding of a positive beryllium cation and differing self-peptides recognized by the T-cell receptor as an antigen.[21]

This mechanistic work provides biologic plausibility for the odds ratio observations of E69 allelic risk of BeS and CBD. Having any two E69 alleles or having one of the E69 alleles with a −9 (most electronegative) charge on the surface of the molecule is associated with much higher odds ratios, up to 30.8 for CBD, compared with workers with no E69 allele.[13] The subset of *HLA-DPB1*E69* alleles with −9 surface charge includes *93:01, *37:01, *29:01, *17:01, *16:01, *10:01, *09:01, *08:01, and *06:01. The most common E69 allele, *02:01, has a −7 surface charge, and having a single *02:01 allele has an odds ratio of 2.4 for CBD compared with workers with no E69 allele.[13] Most of the non-E69 alleles have surface charges of −3, −5, −6, and −7.[15]

Although estimation of odds ratios for CBD and BeS from case-control studies is well established,[3,4,6,7,10,15,22,23] translation of these results into prevalence of CBD and BeS for specific genotypes requires population-based data. Here, we reexamine the National Institute for Occupational Safety and Health (NIOSH) data, some of which we contributed to a multi-institutional case-control study.[13] Unlike the other contributed studies, we have population-based denominator data with which to calculate prevalence of CBD and BeS for aggregated genotypes. Prevalence, in contrast to odds ratios, is a more understandable concept and might motivate workers to avoid beryllium exposure if they have a rare −9-charged genotype or two E69 alleles with extremely high susceptibility to immune sensitization and CBD. For example, knowing whether his or her allelic genotype is more likely than not to result in CBD may be more meaningful to beryllium workers than knowing that a risk is 30-fold that of a genetically different group of workers without E69.

## METHODS

### Study Population

The genetic study population consisted of current and former beryllium workers who participated in cross-sectional studies in

**TABLE 1.** Prior Findings Regarding Genetic Susceptibility to CBD by Author and Year

| Genetic Characteristic | Finding in CBD Cases vs All Beryllium-Exposed Controls (Unless Otherwise Stated) | Author and Year |
|---|---|---|
| E69 homozygosity, all charges | OR 31.7 (CI 3.5–284.0) | Wang et al, 1999[3] |
| | OR 19.4 (CI 4.4–84.5) | Maier et al, 2003[7] |
| | OR 24.3 (CI 10.8–54.6) | McCanlies et al, 2004[8] |
| | OR 2.90 (CI 1.16–7.14) | Rosenman et al, 2011[10] |
| | OR 30.8 (CI 16.6–57.2) | Silveira et al, 2012[13] |
| Non-*02:01 E69 (all charges) | OR 14.4 (CI 2.4–21.1) | Wang et al, 1999[3] |
| | OR 12.2 (CI 6.1–24.4) | Maier et al, 2003[7] |
| | OR 1.95 (CI 0.97–3.91, $P = 0.041$) vs E69 controls | Rosenman et al, 2011[10] |
| | OR 2.4 (CI 1.8–3.3) vs no E69 controls | Silveira et al, 2012[13] |
| −9 charge E69 alleles | OR 18.3 (CI in Fig. 1) | Snyder et al, 2008[14] |
| | OR 6.8 (CI 4.2–11.1) vs non-E69 controls | Weston et al, 2005[15] |
| | OR 43.2 (CI 17.33–110.41) vs E69 controls | Rosenman et al, 2011[10] |
| −9 charge E69 alleles vs −7 E69 alleles | OR 2.8 (CI 1.6–5.0) | Weston et al, 2005[15] |
| | OR 2.8 (CI 1.6–4.9) | Snyder et al, 2008[14] |
| | OR 3.22 (CI 1.55–6.72) | Rosenman et al, 2011[10] |
| | OR 5.6 (CI 3.6–8.8) | Silveira et al, 2012[13] |
| *09:01, *10:01, or *17:01 (all −9 charge) | OR 14 (CI 4.0–49.4) vs E69 controls | Wang et al, 1999[3] |
| *06:01 (−9 charge) | Higher frequency, no statistics given | Wang et al, 1999[3] |
| | Statistically associated with combined BeS and CBD | Rossman et al, 2002[6] |
| | 12.8% vs 0.0%, $P < 0.0001$ | Maier et al, 2003[7] |
| | Higher frequency, no statistics given | Rosenman et al, 2011[10] |
| | OR 10.8 (CI 5.5–21.3) vs no E69 in controls | Silveira et al, 2012[13] |
| *09:01 (−9 charge) | 4.5% vs 0.0%, not significant | Saltini et al, 2001[5] |
| | 9.6% vs 0.9%, $P = 0.004$ | Maier et al, 2003[7] |
| | Higher frequency, no statistics given | Rosenman et al, 2011[10] |
| | OR 4.4 (CI 1.9–10.1) vs no E69 in controls | Silveira et al, 2012[13] |
| *10:01 (−9 charge) | 13.6% vs 5.4%, not significant | Saltini et al, 2001[5] |
| | 16.0% vs 4.0%, $P = 0.005$ | Maier et al, 2003[7] |
| | Higher frequency, no statistics given | Rosenman et al, 2011[10] |
| | OR 4.5 (CI 2.6–4.5) vs no E69 | Silveira et al, 2012[13] |
| *17:01 (−9 charge) | 9.1% vs 0.0%, not significant | Saltini et al, 2001[5] |
| | 12.4% vs 4.3%, $P = 0.03$ | Maier et al, 2003[7] |
| | Higher frequency, no statistics given | Rosenman et al, 2011[10] |
| | 4.9% vs 0.6%, no statistics given | Silveira et al, 2012[13] |

BeS, beryllium sensitization alone without CBD; CBD, chronic beryllium disease; CI, 95% confidence interval; E69, HLA-DPB1 allele with a glutamic acid (E) in 69th position of protein encoded by gene; OR, odds ratio.

Weston et al, 2005,[15] is a meta-analysis (with some assumptions) of Saltini et al, 2001,[5] Rossman et al, 2002,[6] and Maier et al, 2003,[7] each an independent beryllium-exposed cohort. He showed that the log OR for CBD was linearly associated with increasing electronegativity of surface of antigen-binding site.

either 1992 through 1994 or 1998 through 2001 at three industrial plants of the largest producer of beryllium and beryllium-containing products in the United States.[8] Current workers were recruited between August 1999 and December 2001, and contact of former workers continued through 2005. Although previous publications concerning the NIOSH genetic studies[8,14] were described as population-based, the number of CBD and BeS cases had been augmented by 19 historical cases that, though employed by the company, had not participated in previous cross-sectional studies. Therefore, we omitted these 19 from analyses of aggregated genotypes. We included two previously excluded employees who had no medical questionnaire regarding symptoms and job histories. We also included eight employees who were excluded from earlier publications because of suspected false-positive BeLPT tests for BeS in one of two laboratories conducting split testing and follow-up testing[24]; none with clinical follow up ($N = 7$) or surveillance had BeS or CBD and were included in this study as nonsensitized. These exclusions and additions resulted in a population-based study population of 834. All workers gave written informed consent approved by the NIOSH Institutional Review Board. Widely varying beryllium air concentrations existed within and among plants, although the prevalence of BeS and CBD identified through company medical surveillance differed little by plant.[8,24–27]

The beryllium company conducted surveillance on current workers for BeS using the beryllium-specific lymphocyte proliferation test (BeLPT) on blood samples, and the results were released to NIOSH with worker consent. We defined BeS as a confirmed abnormal BeLPT. The company offered clinical evaluation including bronchoalveolar lavage and transbronchial biopsy to both current and former workers with abnormal BeLPTs to establish the presence of BeS alone (without CBD) or findings consistent with CBD (granulomas or lymphocytic infiltrates or the presence of abnormal bronchoalveolar lavage BeLPT). We classified those participants declining clinical evaluation as BeS alone. One worker with progressive granulomatous disease arising during employment with only one abnormal BeLPT was classified as having CBD. For most participants, BeS alone and CBD status were current as of 2002. Some former workers had BeLPT testing and clinical evaluations as late as 2005. The approved genetic study design did not include prospective updating of BeS and clinical status in ongoing company medical surveillance of current workers, and we censored data from follow-up surveillance or clinical evaluations for which we had no participant permission.

## Blood Samples and DNA Sequence Analysis

Participants gave a blood sample of approximately 7 mL that was analyzed at NIOSH for genotype during 2004 through 2006. We performed DNA-sequence determination using a set of seven allele-specific primers (four forward and three reverse). Details of DNA extraction and DNA-sequence analysis were described in detail previously.[28] The genetic results regarding E69 presence were protected under a 308(d) Assurance of Confidentiality provided by the Centers for Disease Control and Prevention that precluded sharing the identifiable results with anyone other than the individual participant.

## Statistical Analysis

We calculated prevalence of CBD, BeS without CBD (BeS alone), and total BeS (BeS with or without CBD) as the number of persons with the health outcome divided by the number of persons with the genotype or genotype group. We present prevalence analyses for groups of 10 or more participants with identical genotypes in the entire genotyped population. For further analyses by aggregated genotype groups, population-based prevalences are better reflective of risk, more stable with larger denominators, and pertinent to workers with rare genotypes with fewer than 10 individuals. We used the two proportions *z*-test to determine whether the aggregated genotype proportions were statistically significantly different at *P* value 0.05 or less.

For participants with two E69 alleles (homozygous E69), we calculated prevalences for three groups: (1) those with both alleles regardless of surface charge; (2) those with only one allele of −9 surface charge, the other allele being any charge less negative than −9; and (3) those with both alleles having any surface charge less negative than −9.

For participants with only one E69 allele, we calculated prevalences for two groups: (1) those having an E69 allele with −9 surface charge; and (2) those with an E69 allele having any surface charge less negative than −9.

For participants with any E69 allele, we calculated prevalences for three groups: (1) those with at least one allele of any charge, (2) those with at least one −9-charged allele, and (3) those with at least one allele with any charge less negative than −9. We also calculated prevalences in the population-based group for all participants without any E69 alleles.

# RESULTS

Full DNA-sequence determinations were made for 853 of the 884 DNA samples obtained for the study; 41 samples (4.8%) either did not amplify or did not produce interpretable signals. In the population-based cohort of 834, 68 persons had a diagnosis of CBD and 57 had BeS alone.

## Specific Genotypes Associated With Highest CBD and BeS Prevalences

Among the 853 genotyped participants, the 18 groups of at least 10 with identical *HLA-DPB1* genotypes constituted 66.8% of the genotyped study population. The genotype associated with the highest CBD prevalence contained the most common E69 allele (−7-charged) paired with an E69 −9-charged allele, *HLA-DPB1*02:01:02/DPB1*17:01*, with 8 of the 11 individuals (72.7%) having CBD and none having BeS alone (Table 2). The genotype associated with the second highest CBD prevalence among these 18 groups was *HLA-DPB1*04:01/DPB1*10:01*—a non-E69 −3-charged allele paired with an E69 −9-charged allele, with 8 of the 15 individuals (53.3%) having BeS, and the majority of these (6 of 8) having CBD (40.0% CBD prevalence for the genotype). Of the 21 individuals with the genotype *HLA-DPB1*02:01:02/ HLA-DPB1*02:01:02* (homozygous for the most common E69 allele, which has −7 charge), 11 individuals (52.4%) had BeS, and 7 of these 11 had CBD (33.3% CBD prevalence for the genotype). With restriction of analyses to the population-based cohort, the highest risk genotype in Table 2 no longer met the criterion of having at least 10 participants, but two-thirds had CBD.

## Population-Based Grouped Genotypes With Two E69 Alleles and Various Numbers of −9 Charge

The group with two E69 alleles of any charge had a total BeS prevalence of 47.2% and a CBD prevalence of 28.3%. For genotypes that included an E69 allele with −9 charge, total BeS and CBD prevalences were higher than prevalences for genotype groups that did not include E69 alleles with −9 charge (Fig. 1). Groups with two

**TABLE 2.** Percent Prevalence of CBD and Total BeS by Genotype for 18 Groups of At Least 10 Persons With Identical HLA-DPB1 Genotype (66.8% of the Genotyped Population), With Specification of Number of E69 Alleles and Number of Alleles With Negative 9 Electronegativity for Each Genotype, in a Population of 853 Genotyped Beryllium Workers

| *HLA-DPB1* Genotype | Number of E69 Alleles | Number of −9 Charged Alleles | CBD % Prevalence | Total BeS % Prevalence | Percentage of Genotyped Population |
|---|---|---|---|---|---|
| **02:01:02/*17:01* | 2 | 1 | 72.7 | 72.7 | 1.3 |
| **04:01/*10:01* | 1 | 1 | 40.0 | 53.3 | 1.8 |
| **02:01:02/*02:01:02* | 2 | 0 | 33.3 | 52.4 | 2.5 |
| **02:01:02/*04:02* | 1 | 0 | 27.8 | 38.9 | 2.1 |
| **02:01:02/*03:01:01* | 1 | 0 | 16.7 | 38.9 | 2.1 |
| **02:01:02/*04:01* | 1 | 0 | 12.0 | 22.0 | 11.7 |
| **03:01:01/*05:01* | 0 | 0 | 10.0 | 20.0 | 1.2 |
| **04:01/*05:01* | 0 | 0 | 10.0 | 20.0 | 1.2 |
| **01:01:01/*02:01:02* | 1 | 0 | 10.0 | 10.0 | 1.2 |
| **04:01/*04:01* | 0 | 0 | 3.1 | 5.5 | 15.0 |
| **01:01:01/*04:01* | 0 | 0 | 3.1 | 3.1 | 3.8 |
| **04:01/*04:02* | 0 | 0 | 2.6 | 6.4 | 9.1 |
| **03:01:01/*04:01* | 0 | 0 | 2.0 | 4.1 | 5.7 |
| **04:01/*11:01:01* | 0 | 0 | 0.0 | 6.7 | 1.8 |
| **03:01:01/*04:02* | 0 | 0 | 0.0 | 0.0 | 2.1 |
| **01:01:01/*03:01:01* | 0 | 0 | 0.0 | 0.0 | 1.6 |
| **04:01/*13:01* | 1 | 0 | 0.0 | 0.0 | 1.4 |
| **03:01:01/*03:01:01* | 0 | 0 | 0.0 | 0.0 | 1.3 |

 

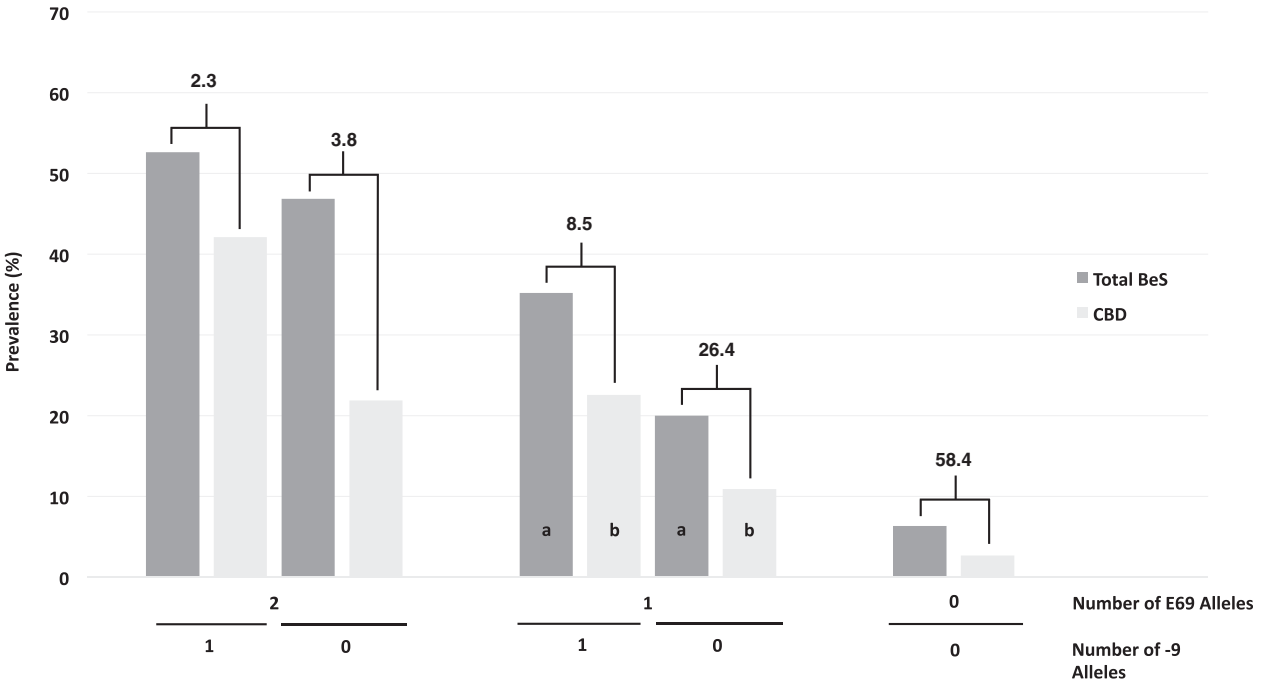


**FIGURE 1.** Percent prevalence of total BeS and CBD by number of E69 and −9 alleles, among population-based genotyped beryllium workers. Numbers above bars are percentage of population with that genotype group. Letters within bars indicate statistically significantly different comparisons from other bar with same letter. [a]$P = 0.009$; [b]$P = 0.014$.

E69 alleles, only one of which was −9-charged (the other allele was most often −7-charged), had a total BeS prevalence of 52.6% and a CBD prevalence of 42.1%; of the 10 individuals with BeS, 8 (80.0%) had CBD. Groups with two E69 alleles wherein both alleles were any charge less negative than −9 had a total BeS prevalence of 46.9% and a CBD prevalence of 21.9%; of the 15 individuals with BeS, 7 (46.7%) had CBD.

### Population-Based Grouped Genotypes With One E69 Allele, with and without One −9-Charged Allele

Total BeS and CBD prevalences of persons with only one E69 allele (the other allele being non-E69) were higher when the single E69 allele was −9-charged, as opposed to any other charge less negative than −9 ($P = 0.009$ for total BeS; $P = 0.014$ for CBD) (Fig. 1). In the group wherein the single E69 allele was −9-charged, the total BeS prevalence was 35.2%, and the CBD prevalence was 22.5% [16 of 25 BeS individuals (64.0%) had CBD]. In the group wherein the single E69 allele had any charge less negative than −9, the total BeS prevalence was 20.0%, and the CBD prevalence was 10.9% [24 of 44 BeS individuals (54.5%) had CBD].

### Population-Based Grouped Genotypes With Any E69, With and Without Any −9-Charged Alleles; No E69 Alleles

For genotypes with at least one E69 allele, total BeS and CBD prevalences for grouped genotypes that included E69 alleles with −9 charge were higher than grouped genotype prevalences that did not include E69 alleles with −9 charge. In groups with any E69 allele regardless of charge, the total BeS prevalence was 27.3% and the CBD prevalence was 16.0% [55 (58.5%) of the 94 individuals with BeS had CBD]; this group includes individuals who had one or two E69 alleles of −9 charge. The group with any E69 allele wherein one or both of the alleles were −9-charged had a total BeS prevalence of 38.0% and a CBD prevalence of 26.1% [24 (68.6%) of the 35 individuals with BeS had CBD]. Groups with any E69 allele wherein one or both were any charge less negative than −9 had a total BeS prevalence of 23.4% and a CBD prevalence of 12.3%; of the 59 individuals with BeS, 31 (52.5%) had CBD. The group with no E69 alleles made up 58.8% of the genotyped population and had a total BeS prevalence of 6.3% and a CBD prevalence of 2.7% (Fig. 1).

## DISCUSSION

The high prevalences of BeS and CBD for rare E69 genotypes with −9 surface charge and E69 homozygotes raise reconsideration of genetic testing for prospective beryllium employees who might want to avoid occupational lung disease risk. In 2004, only 36 of 884 participants in the prior published study[8] obtained their personal E69 carrier status results (E69 positive or negative). However, they had to sign an additional consent acknowledging that there might be risks of genetic discrimination from health insurers and employers if this information were made known to them, either inadvertently or because of participant inability to protect personal results from subpoena. NIOSH's 308(d) protection precluded our releasing individuals' results to anyone but the individual. We did not ascertain reasons why personal results were (or were not) sought. With GINA protection, many prospective and current beryllium employees may have interest in their personal genotype results, particularly as the risk of the −9-charged E69 alleles or E69 homozygosity for BeS and CBD is high (population-based quantitative risk in Fig. 1). After conducting pre-GINA focus groups with 30 current and former beryllium workers at Department of Energy nuclear weapons sites, Silver et al[29] suggested a threshold of "more likely than not" for giving workers access to genotype testing that would predict who might get a disease.

Until recently, we thought that genetic screening during beryllium employment had little value to already-exposed workers because beryllium body burden appears to confer lifetime risk for

 

BeS and CBD. However, there is increasing evidence that CBD is associated with cumulative exposure,[22,27,30] but that BeS can occur within weeks of employment.[27,31] Thus, current employees sensitized early in employment may have personal interest in genotype testing; identification of high-risk −9-charged E69 alleles or homozygous E69 genotype might motivate self-protective limitation of further exposure to poorly soluble beryllium compounds that could accumulate in their lungs over time and result in CBD. In the 1940s, rash illness early in employment in beryllium metal extraction with soluble beryllium salt exposure had been cause for dismissal, because the medical providers associated it with risk of acute beryllium disease.[32,33] Acute beryllium disease differed from CBD in being slowly reversible over a period of months away from exposure. In retrospect, the clinical picture of rash and reversible lung disease is best explained by cell-mediated sensitization to a soluble beryllium antigen that did not persist in the lung to support irreversible CBD.[34] The cases of acute beryllium disease in the beryllium extraction part of the industry that later progressed to CBD may have reflected the lung accumulation of poorly soluble beryllium compounds. Both genotyping and reduced beryllium exposure may complement each other in prevention of CBD.

Longitudinal follow-up of this cohort will extend the current findings and improve the information that workers can use when deciding whether to limit accumulation of a persistent beryllium lung burden that could support CBD. For those with high genetic susceptibility to BeS, any beryllium exposure may be unwise, regardless of compliance with a potentially lower permissible exposure limit.[35] Although GINA was intended to prevent discrimination in employment based on genotype, prospective workers or current workers may choose to select out of jobs with the potential for beryllium exposure. Now that we have identified −9-charged E69 and homozygous E69 genotypes as conferring sensitization or CBD prevalence in about half of the population-based group, workers may have more interest in personally benefiting from this increased scientific knowledge. Whether potential beryllium workers or current workers have interest in limiting further beryllium exposure in the presence of a high-risk E69 genotype might be answered with further research. The potential application of the existing research to worker health is an appropriate practical application made possible by assuming legal protection from discrimination.

The setting of genetic testing of beryllium-exposed workers or potential workers, even as an employer-funded service, should be guided by ethical requirements governing the research to date: voluntary testing; a counseling context giving a basic understanding of risk factors and health consequences of beryllium exposure and genetic susceptibility if exposed; informed consent; and confidentiality. The American College of Occupational and Environmental Medicine published a position statement in 2015 expanding on good scientific practices.[36] Genetic counselors may benefit from additional training regarding work life genetic issues. The focus group findings before GINA still suggest that an Assurance of Confidentiality may be beneficial to preclude disclosure of genetic results to anyone other than the participant because of worker concerns over employers possibly having access to this information.[29] The public health system conducts genetic testing on newborns and might be a locus of extending scientific knowledge about occupational disease susceptibility to workers, independent of employers.

This study had the strength of large numbers of population-based genotyped participants from the primary beryllium production industry. The employer, who received no individual genetic results and would not reassign workers on the basis of genetic risk or sensitization status, cooperated by allowing worker education and participation on work time. A limitation of the study is that we had no systematic informed consent to receive longitudinal BeLPT results collected by the company in ongoing current worker screening or clinical evaluations of those who may have undergone subsequent diagnostic tests for CBD. In one of the three worker cohorts from this employer, we found that cross-sectional prevalence of BeS was one-third of the estimate of sensitization over 11 years of follow-up.[37] Accordingly, the prevalence of sensitization and CBD in this genetic study likely underestimates those who have since developed BeS or CBD over time in relation to their genotypes. Although the genotyped population was relatively large, one-third of the participants were omitted from groups of 10 or more in Table 2 because of small numbers with specific genotypes, and even fewer groups of 10 or more resulted from the population-based analyses. With research into CBD prevalences associated with high-risk genotypes, employers might be ethically obligated to ensure that workers have the option of confidential genetic testing for many alleles.[36] We do not think that these data are sufficient to address standard setting in relation to genotype,[38] although some small percentage of workers with high-risk genotypes may not be able to safely tolerate any beryllium exposure, despite proposed lowering of the permissible exposure limit.[35]

In summary, the study of genetic risk for BeS and CBD has allowed researchers to elucidate mechanisms of immune-mediated disease with a known antigen. This research also might benefit prospective and current beryllium workers given current legislation that protects them from employment and health insurance discrimination. Whether prospective and current beryllium workers may want to use E69 genotyping in decisions to avoid a cumulative burden of poorly soluble beryllium that supports CBD is a matter for further research. Neither proposed regulation to lower the beryllium permissible exposure limit nor genotyping is likely to prevent all CBD, some of which occurs in the absence of E69 genotypic risk (Fig. 1). However, workers, employers, and the public would benefit from further research that highlights what degree of genetic risk, coupled with the appropriate GINA-compliant settings of information exchange and counseling, may motivate highly susceptible workers to avoid beryllium exposure.

## ACKNOWLEDGMENT

*The authors thank the participating workers, current and former, and the company for their cooperation with this genetic research. The authors also acknowledge Bonnie Frye and James Ensey who performed the allele-specific DNA sequence determinations and RFLPs.*

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