

1) Consent form: Why is CDC giving an option to receive genetic information that does not have a clinical interpretation? The standard across HHS for all of the studies that we've reviewed seems to be NOT to offer genetic results that do not have a clinical relevance. If you delete the last two sentences of item '2) genetic result', you will be able to delete the entire paragraph about the possible implications of sharing personal genetic information. We feel very uncomfortable about the accusations in the latter language. If NIOSH really thinks insurance companies are using study data in this way, CDC needs to have a policy-level discussion within the context of its 'Beyond Gene Discovery' initiative.

NIOSH has enabled participants in the beryllium research program to obtain limited personal genetic information since the late 1990s, when the program began. Those who have participated in the genetic component of our research were (and are) able to request information on whether they carry one specific genetic marker (*HLA-DPB1<sup>Glu69</sup>*). The decision to make this information available to those who desired to learn it was made with the approval of the NIOSH Human Subjects Review Board (HSRB), and was based, in part, on the number of studies that had replicated the relationship between that marker and chronic beryllium disease (CBD), and the strength of that relationship across different research populations. We believe it is appropriate to continue to offer the same limited information to upcoming participants, as we believe they have a right to know and to use that information as they see fit when making decisions regarding current and future employment.

Your comment concerning “genetic results that do not have clinical relevance” is well taken. However, when this study was planned, we worked closely with the NIOSH HSRB and consulted with the CDC Office of Genomics and Disease Prevention to develop an appropriate protocol. The protocol was further scrutinized in 2002 by a special sub-committee of the NIOSH Board of Scientific Counselors that reviewed NIOSH studies on beryllium sensitization and CBD. An early observation was that the positive predictive value of the *HLA-DPB1<sup>Glu69</sup>* marker was in the range of 7-14% (but only in the presence of beryllium exposure). This is important because, although this is much lower than positive predictive values for markers of diseases like cystic fibrosis, phenylketonuria, and other inborn errors of metabolism, it is actually much higher than those for the multitude of single nucleotide polymorphisms that may or may not confer a significant risk of adverse health outcomes. In addition, about 15% of CBD-affected beryllium workers do not have the *HLA-DPB1<sup>Glu69</sup>* marker.

We do not encourage workers to obtain their results because of the current absence of legislation to protect their rights. Until laws are passed that protect the individual who learns about an inherited risk factor, the possibility exists for discrimination by employers and/or insurance companies (among others). We are not aware of specific incidents in which this has occurred for beryllium workers, but it has certainly occurred for other predisposing genes outside of the workplace setting. When participants first request information regarding their genetic status, we send them a letter restating the possible risks/benefits, as covered in the consent form, of having their genetic results. If participants still wish to receive the results of genetic testing, they may make a second

request, at which point we send them their results. We do not feel the language used to describe the possible implications of sharing genetic information to be accusatory or inflammatory in any way, but it does address a valid issue of concern about which these participants deserve to be aware. To date, among almost 1200 participants in our ongoing longitudinal beryllium genetic research, <5% have initiated the request procedure, and <3% have pursued the second step.

2) Questionnaire, page 1: Given the certificate of confidentiality, we question the language in caps and bold that says "DATA WILL BE TREATED IN A CONFIDENTIAL MANNER UNLESS OTHERWISE COMPELLED BY LAW. We suggest deleting this language as it is not specific enough to be completely accurate. The language in the consent form is more specific and includes discussion of the certificate of confidentiality; the consent form is a more appropriate place for the participant to be made aware of the issue.

To clarify, the 308(d) certificate of confidentiality obtained for our beryllium research program, which includes the participants in this study, only covers participants' genetic information. The survey questionnaire and lymphocyte proliferation blood test results are still covered by the standard Public Health Service confidentiality language. However, we have no objections to removing the language from the questionnaire.

3) Questionnaire, page 1: re: bold language 'and authorized for collection under the public health service act'. We suggest that the co-location of this clause diminishes the power of the first part of the statement - that provision of the SS number is voluntary. The PHS Act authorizes more than just the SS number. Again, this info is in the consent form and it is not necessary here, and indeed detracts from the point being made. We have not seen CDC use the sentence about the SS number as the vehicle for conveying the authorization for the study before.

We have deleted "and authorized for collection under the public health service act."

4) Questionnaire: Please consider asking the health status questions first (before the work place exposure questions), especially now that the questions about perception of the effectiveness of the program have been added. We think that asking the health questions first will avoid coloring the response to the health questions with any peeve about program effectiveness.

The questionnaire will be presented to the participants in electronic form with NIOSH staff reading each question and recording each answer into the computer. The questionnaire is set up in modules and we can switch the order of those modules to ask the health questions first.