



California
Department of
Health Services

SANDRA SHEWRY
Director

State of California—Health and Human Services Agency
Department of Health Services



ARNOLD SCHWARZENEGGER
Governor

February 15, 2006

Brad Therrell, PhD
National Newborn Screening Genetic Resource Center
1912 W. Anderson Lane, Ste. 210
Austin, TX 78757

Dear Dr. Therrell:

We wish to thank you and the site review team for your efforts in conducting the California Newborn Screening Program Review which took place on February 25-26, 2005. We are pleased with the overall findings of the review. The positive tone of the report clearly reflects the success of our program and the commitment of our staff. There were, however, some areas of constructive comment or suggestion where the site review team felt we could improve. Per your request, we have formulated a response to these items for your review.

Formulation of Response

In addition to extensive internal discussion of these issues within the Department of Health Services (DHS) Genetic Disease Branch (GDB), we developed a plan for obtaining additional input from external stakeholders. We sent copies of the report to our health care partners, including our contract laboratories, follow-up centers, confirmatory laboratories, and state endocrinologists, hematologists, and metabolic specialists. We also posted the report on our web site for any public input. Further, we notified the 16 California Children's Services (CCS) Endocrine Care centers, the 21 CCS Sickle Cell Centers, the 16 Metabolic Care Centers, the PKU parents of California, Keith Nash of the March of Dimes, Tera Mize of Save the Babies Foundation, Trish Mullaley of the National Coalition for PKU and Allied Disorders, and Kelly Light of the CARES Foundation. For input from other state programs, we contacted Dr. Ken Pass of the New York Newborn Screening Program, and Dr. Neil Buist of the Oregon Newborn Screening Program. Finally, we contacted non-Health Care partners such as Senator Deborah Ortiz, Chair of the Senate Health Committee, and several other members of the State legislature from both parties. All of these names can be provided upon request.

Although we did not receive responses from everyone, we did incorporate any feedback we received into our consolidated response which follows.

Response – Summary

Both the GDB staff and stakeholders were pleased with the positive tone of the review. Regarding the suggestion that contract laboratories could be consolidated, the overall opinion was that although this may have some benefits, it may not be the best direction for California, given both its geographic size and high birth rate, and the fact that we operate both a Newborn Screening Program and a Prenatal Screening Program. Nevertheless, this suggestion is still under active consideration. A limited consolidation may be valuable. (Discussion of our specific thinking follows in the next section.) Overwhelmingly the respondents agreed that an external advisory committee is advisable. Contributors commented that it is very important that this committee be external to DHS. It was suggested that in some ways a de facto committee is already functioning in a limited capacity and should be formalized and expanded in scope.

Detailed Response – Item by Item

Advisory Committee and Education of Policy Makers (e.g. Legislators,) pages 3, 18, 37-39

The report indicates that a formal external advisory committee is important and that fact is reinforced in several published guidelines. Furthermore, it indicates that California is one of only two states in the country which does not have such a formal committee. GDB agrees with this assessment as do our partners and consultants. Currently we meet with the state's endocrine, hematological, and metabolic specialists on a regular basis and solicit input from them regarding such matters as which disorders should be screened, appropriateness of cutoffs and positive rates, and treatment guidelines. We appreciate the committee's recognition that in large states such as ours, multiple committees or multiple sub-committees are often necessary (p 38). However, we agree this informal arrangement should be formalized and expanded. Although a formal committee could not realistically include all of the specialists with whom we currently meet, it should include representatives from each group. We also agree that additional input is needed, including representatives from parents' groups, Medi-Cal, the Women, Infants and Children Nutritional Program (WIC), and the Birth Defects Monitoring Program. Currently Newborn Hearing Screening is not part of GDB, but this will be addressed elsewhere in this document. We will work with the leadership in Primary Care and Family Health and the state legislature to help realize this goal of formalizing an external, multi-disciplinary advisory committee. We agree with the statement on page 18 that the advisory committee would and should be useful in helping to determine when fee increases are necessary to fund program expansion.

Multiple Contract Laboratories for Screening. pages 4, 19-21

We appreciate the committee's recognition that several factors unique to California have resulted in a screening model that employs multiple laboratories. These factors include California's high birth rate and business practice of contracting with private laboratories. However, the committee suggests that some consolidation might save costs or improve

efficiencies. For example, the current configuration required at least two tandem mass spectrometry (MS/MS) machines per laboratory to allow for down time in the larger laboratories. It is suggested that fewer laboratories with more machines per laboratory would have satisfied this requirement. Theoretically this is true, and we are considering some moderate consolidation, such as merging the two Kaiser Permanente laboratories into one, and a possible private merger of two of the other existing contract laboratories into one. This would decrease the total laboratories from eight to six and might gain some efficiency. However, before proceeding toward consolidation, it is important to consider the following: First, California is different than other states in that, in addition to conducting newborn screening for approximately 550,000 babies annually, California also does prenatal screening for over 380,000 women per year. This coupled with California's requirement for backup capability in the event of a disaster, such as an earthquake, makes it impractical for California to rely on a single, central laboratory as other states do. Second, the existence of the two Kaiser HMO organizations is mandated in California law and regulation, so elimination or consolidation of them into the other labs would require both regulatory *and statutory* change. The report indicates that each laboratory should perform at least 50,000 tests per year, which the two Kaisers do not do individually. Moreover, any attempt to merge the two Kaiser laboratories into one would necessitate significant programming and billing changes, as the two organizations currently function as separate entities from that perspective.

Interestingly, GDB and our partners differ in response to the recommendation to consolidate the laboratories. Although GDB agrees some limited consolidation as described above might be of benefit and is still studying these options, our partners generally do not agree. They like the geographic specificity of the current model and fear that too few laboratories could jeopardize the timeliness of testing due to the increased time of transport of specimens. Timeliness of testing is crucial in many of the newborn screening disorders. They indicate that they prefer the existing scenario particularly as it relates to the very complex MS/MS testing program

In summary, we will continue to explore limited consolidation of laboratories.

“Refer all Strategy/Retesting of Initial Positives”, pages 5, 21-22, 26-7

This is an area of some controversy within the scientific community as a whole and within newborn screening programs in particular. GDB refers almost all positive results for follow-up. The report refers to this as a “refer-all” strategy. This only occurs after extensive quality control measures both at the contract laboratory and the Genetic Disease Laboratory (GDL). There are some exceptions to this policy, including in MS/MS testing, where approximately 5-10% of results are reviewed manually by a clinical chemist before they are reported. Many of these are not referred after consultation on other demographic factors which might affect the positive results. In some cases this reviewer may request a retest before the result is reported. In addition, the extensive quality control procedures at GDB often result in positives being retested prior to release.

We have discussed extensively the committee's recommendation that we should consider retesting all positives. However, we do not agree that routine retesting of positives is appropriate. Two scenarios result from this policy: A repeat of a positive will be positive, in which case no knowledge has been gained and the reporting of these often-times urgent disorders is delayed. Or, a repeat could be negative. If so, the program has two further choices. One is to not report based on the repeat negative. This is not a good policy because the positive result is technically just as accurate as the subsequent negative. This is a dangerous strategy. In fact, in another state, two cases of a serious metabolic disorder were missed due to this strategy. In fact, that program changed their policy (at least for that disorder) as a result of the missed cases. The other choice is to somehow average the two results. But this would produce a positive or negative averaged result and, again, the program is faced with the dilemma described above.

One of the reasons given for repeat testing is that it is important to keep false positives and parental anxiety down. However, because of our extensive quality control procedures both at the contract lab and GDL, our positive rates are quite low. On page 21, the committee notes that an appropriate positive rate for MS/MS is 0.3%. However despite our refer-all strategy, our positive rate is in fact lower, at approximately 0.2%. This improvement over the expected or acceptable rate more than compensates for what would have been gained by retesting and avoids the dangerous prospect of missing cases by not referring a case with a known and valid positive test result.

Another reason noted by the report for retesting is to eliminate the possibility of specimen mix-up. However we already have a system in place for follow-up of anomalous results. Extensive retesting and identity testing is performed whenever a confirmatory test and a screening test are widely discordant. The existence of "fliers" is always investigated. The cost savings of checking for specimen mix up this way is substantial over that of retesting all positives, as "fliers" are much rarer than positives in general.

On page 22, the committee correctly notes that GDB recently changed TSH recall testing procedure and should collect data on whether this is effective. Perhaps we did not adequately communicate *the specifics of this change* or the reasons for it. We did not change the refer-all strategy. Previously all positive TSH values were referred as they are now. However, we offered the option of retesting a filter paper at GDL for convenience, and it is this option which we discontinued. In both cases, all positives were referred before retesting. This was similar to the existing PKU recall system, where GDL offers retesting of all positive PKU results. It is still a refer-all procedure, as the positive has already been reported. The retest is part of the follow-up process. In these cases, virtually all specialists institute the diet immediately due to the severity of the consequences for PKU. If the recall is negative, the diet can be eliminated. Also, regarding data collection, previous to the TSH policy change we did an extensive survey of endocrine specialists and pediatricians, and found that most of them ordered a private confirmatory serum test anyway. Most felt the filter paper retest was not

particularly useful, particularly since newborns are slightly older at that time and, therefore, the appropriate cutoffs would be different than the initial screening test results. In short, all positive results still have a confirmatory test and GDL workload is decreased. We feel this was a positive and efficient policy change.

Consolidation of Newborn Screening Programs, page 6

For a variety of reasons, California's Newborn Hearing Screening Program (NHSP) is located in the Children's Medical Services Branch instead of the GDB. We realize this is atypical when compared to other states. However, at this time, placement of the NHSP is not being reconsidered.

Integrated Health Information Systems, page 6

We agree this would be a good idea. We have succeeded in adding a place for the NSP unique identifier number on the birth certificate. Our GDB scientific staff has made significant progress in developing matching algorithms to link to other state databases. We also have developed an annual matching and case registry ascertainment process with the Birth Defects Monitoring Program (BDMP), although currently the BDMP is only investigating birth defects detected prenatally. We welcome any data exchange and linkage with other state programs and have implemented some of these abilities in our new computer system.

Long-term tracking and follow-up, page 7

We agree that long-term tracking would be valuable and have already implemented the first step in California. Currently, we have vendor agreements with the metabolic centers to track outcomes for five years. This tracking of outcome data has been automated in the new computer system. The centers have online access to these forms. We hope to expand this to endocrine and hematological disorders in the future as funding becomes available.

Educational materials for patient and provider, page 24

We appreciate the positive feedback on educational materials and accessibility of translated materials. We agree that the website should be updated more frequently and that additional links such GeneHELP or other programs would be useful. We also agree that staff scientific publications can be made available in pdf format and more summary data should be made available. We will attempt to make these improvements quickly.

Again, we wish to thank you and the site review team for an insightful and constructive evaluation. Your findings will strengthen our ongoing efforts to continuously improve our Newborn Screening Program. It was a pleasure to work with you throughout the review process. Should you have any questions or comments about our response to the review findings, please contact me at the address below.

Sincerely,

A handwritten signature in blue ink that reads "John E. Sherwin". The signature is written in a cursive style with a large initial 'J' and 'S'.

John E. Sherwin, Ph.D., Acting Chief
Genetic Disease Branch
850 Marina Bay Parkway, F353
Richmond, CA 94804
Phone: 510-231-1728