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Issues in Newborn Screening

From the Editor and Authors:

There is much public attention surrounding the use of DNA for genetic testing. What the lay public fails to realize is that genetic testing in the form of newborn screening has been in use for two to three decades. While newborn screening is not considered as fancy as the polymerase chain reaction amplification or allelic-specific oligonucleotide hybridization, the testing of protein products of genes or metabolites of metabolic pathways is an indirect genetic test.

Newborn screening has clearly proved quite effective for selected disorders. For example, cretinism from untreated hypothyroidism is now a medical rarity, and patients with late or untreated phenylketonuria no longer populate residential treatment programs. While early identification of patients with hypothyroidism or phenylketonuria has not eliminated all of the problems associated with these disorders, there is no argument that newborn screening is particularly effective for these two disorders and has been implemented in all fifty states. Thus, hypothyroidism and phenylketonuria are good examples of the success of newborn screening as a public health measure.

In This Issue

All is not stagnant in the newborn screening universe, however, and controversies abound. This issue of the Genetic Drift presents a number of the problems facing newborn screening - from alternative uses of newborn screening blood spots, to dilemmas arising from carrier detection for some of the disorders. While we have certainly not covered all of the issues facing newborn screening, we hope that the information in this volume will be both useful and thought provoking. Please visit the MSRGSNet WebSite at http://ahsc.arizona.edu/msrgsn/publicat.htm for the 1996 Newborn Screening Practitioners Manual.

This issue was spearheaded by Randall A. Heidenreich, MD (AZ), with additional contributions from David Mills, Ph.D. (NM), Holly Nyerges, MSN, CPNP (NM), Benjamin Wilfond, MD (AZ), Peter A. Lane, MD (CO), and Carol Greene, MD (CO).

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Alternative Uses of Guthrie Spots from Newborn Screening Programs

Increased Demand for DNA Specimens

The rapid pace of genetic research which has accompanied the undertaking of the Human Genome Project has led to an unending stream of new insights concerning genetic contributions to human disease, as well as impressive methodological advances in genetic analysis. For example, buoyed by early success in the identification of the gene for cystic fibrosis, researchers have more recently focused their attention on searching for genetic factors involved in more complex disorders afflicting modern society.

Examples include cancer, alcoholism, obesity, diabetes, cardiovascular disease, and psychiatric disorders. The driving force for such studies is more than the academic quest for knowledge. Rather, answers are being sought for the individual and public health problems most affecting morbidity, mortality, and health care costs in our society, and for which traditional approaches seem to have yielded limited success.

Studies of complex disorders require large numbers of DNA samples for analysis. As a consequence, many of the advances made to date in genetic research, particularly those relating to public health issues, have relied upon the use of tissue specimens originally obtained for other purposes. In many cases, the individuals providing the specimens may have had no knowledge that the specimen would be used for any purpose other than testing relevant to their immediate medical care. As researchers seek to delineate the genetic contribution to multifactorial chronic conditions, such as the question of the degree of penetrance of an allele of the breast cancer susceptibility gene in the population, they require large numbers of DNA specimens from a broad spectrum of the general population. This increased demand for tissue samples has led to searches for suitable sources of DNA in nontraditional areas, including the specimen repositories of newborn metabolic screening programs. Such demand is reflected in the increased request by public and private agencies for access to samples and in some of the larger states, more than 100 requests were received in 1994.

Attractiveness of Newborn Screening Specimen Repositories

Several aspects of the newborn metabolic screening programs make the blood spots (named Guthrie spots after their inventor) attractive for use in genetic research, population-based epidemiological studies, and other DNA-based testing activities, such as forensic investigation. First, newborn screening programs are found in all of the states and territories of the U.S. Within these programs, tissue samples (blood) are collected from essentially all live born infants, providing what is potentially the largest and most complete genetic bank and library available in the country. Secondly, when stored properly, these specimens are stable for a long period of time. Recently, a 20 year-old newborn screening specimen was used as a critical link in the identification of a body in a forensic investigation. Presently, however, the retention of Guthrie spots by newborn screening programs varies greatly among programs. According to the 1991 CORN (Council of Regional Genetics Networks) report, of the 53 newborn screening programs in the U.S., 27 store their specimens less than one year following completion of analysis, 15 store them from 1-15 years, 6 store them 20-30 years, and 5 store them indefinitely.

Ethical and Legal Issues Surrounding Alternative Uses of Guthrie Spots

Technological developments in the field of genetic testing have outpaced societal development of ethical and legal guidelines for testing. While several states have passed laws attempting to protect the privacy of genetic information, no Federal laws yet exist, despite a recent congressional attempt to pass a Genetic Privacy Act. Without such protections for genetic research and information derived from it, the enthusiasm over the potential benefits to be gained from access to this vast genetic bank are counterbalanced by the following concerns: the ownership of tissue samples and the genetic information contained therein; requirements for informed consent for genetic testing; and the right to privacy of both the individuals providing the specimens as well as sub-populations of society potentially affected by genetic information revealed.

The issues surrounding ownership of genetic specimens and informed consent for genetic testing are not entirely independent of each other. As previously mentioned, many tissue samples used in genetic studies are originally collected for other purposes, in which case informed consent for the genetic testing would not have been obtained. This is the case with Guthrie blood spots used in state-run newborn screening programs, which are collected for specific testing purposes (thyroid function, PKU, galactosemia, cystic fibrosis, hemoglobinopathies, etc.). Collection and testing in these programs is mandatory and performed under authority of state law or health department regulation. As such, there is no informed consent in the strictest sense and any additional analyses conducted beyond those mandated by state law or regulation should not be conducted without obtaining informed consent from the provider of the specimen, which is quite impractical in most instances. This issue gained national attention, and subsequent debates ultimately led to a nationwide moratorium on the eight-year CDC-sponsored maternal serum prevalence study. In this study, Guthrie spots from newborn screening programs were stripped of identifiers and universally tested for HIV. Some states have attempted to address the limitations of informed consent by including in the description of uses allowed for newborn screening specimens the phrase "other research purposes." Whether this vague clause will withstand legal challenges for all analytical applications is questionable and remains to be seen.

In the end, questions of ownership and informed consent come back to the concern over the privacy of genetic information and the ability of the individual to limit what genetic information is available to third parties. Fears of discrimination, based upon revelations from genetic testing, which could lead to denial or limitation of health and/or life insurance, educational and employment opportunities are not without foundation. There are unique privacy issues as well, since genetic analyses performed on a tissue specimen could reveal not only information about the individual providing the specimen, but may also reveal genetic information of siblings, parents, and offspring of the individual. Even if privacy laws can be written to protect the individual being tested from adverse repercussions, can they be written to protect relatives of the individual who are unaware that the testing is done, or who may not even yet be born? Should a parent or guardian be allowed to provide informed consent on behalf of a newborn for testing which is not of medical necessity, given the potential ramifications of the testing?

One final concern is that most of the discussion concerning the protection of genetic privacy has focused only on the individual. Similarly, all of the established and proposed legislation aimed at protection of genetic privacy has dealt with the topic by stipulating that all personal identifiers be removed from specimens, such as name, street address, and social security number. Such protections will not adequately protect all

individuals, as other non-personal demographic data required for the information to have any value in epidemiological research could be used to identify the individual providing the specimen. For example, in rural states with low population density and/or high racial/ethnic variation, providing as little information as ethnicity and county of collection will often allow the identification of the individual providing the specimen. Conversely, genetic profile and county of specimen origin could, in some cases, be used to determine race or ethnicity and, subsequently, the personal identification of the specimen source. The long-standing Federal laws governing informed consent in human research were not only established to protect the rights of the research subject (the individual), but also of the researcher (protection from litigation), and society as a whole. Genetic privacy laws must take into account the need to protect all members of society as well, in order to preclude ethnic, racial, or gender genetic discrimination.

Summary

The rapid and extensive developments in genetic research have created an unprecedented demand for genetic specimens representing a broad spectrum of society. Such specimens are available in the repositories of newborn screening programs. In the foreseeable future, those individuals entrusted with the protection of these specimens, and delegated the responsibility of responding to requests for access to these specimens, can anticipate a growing demand for access to them for use in genetic research. As clear legal and ethical guidelines by which these requests can be evaluated do not currently exist, decisions will have to be based upon careful weighing of the potential benefit to be derived versus the potential harm to individuals and society which may result. Such decisions would best be made in consultation with individuals representing a broad range of backgrounds and perspectives. Toward this end, government agencies involved in newborn metabolic screening programs might be well advised to establish formal review panels for the purpose of evaluating requests to access specimens for research.

Contributed by David Mills, Ph.D. (NM)

Issues Relating to Early Hospital Discharge and the Impact on Newborn Genetic Screening Programs

Introduction

For more than three decades, newborn screening has been a successful example of a population-based screening program to detect and treat disorders which cause preventable mental retardation and morbidity. However, some trends in managed care and demand for cost containment are raising concerns for state newborn screening programs across the country, including our region. The greatest impact thus far relates to increasing frequency in early hospital discharge (i.e., hospital stays of 24 hours or less) of healthy infants after birth.

When newborn screening started in 1962, hospital stays allowed for the ideal timing of specimen collection between 48 and 96 hours following birth and for the infants to be monitored. Early newborn screening specimen collection (i.e., before 48 hours of age) is primarily a result of early discharge. This practice affects newborn genetic screening programs in two ways: (1) by decreasing the ability to detect infants with inborn errors of metabolism who have not had adequate nutritional intake, and (2) by not being able to minimize the impact on families that is generated by a high number of false positive test results requiring further testing and follow-up to reach a confirmed diagnosis.

The results of a 1994 study of the impact of early discharge on newborn screening in California showed the following:

Two-thirds of specimens were collected before 24 hours.

10% of specimens were collected before 12 hours.

50% of low birth weight (LBW) specimens were collected before 24 hours (7% before transfusions).

Larger hospitals had more early discharges than smaller hospitals.

The trend toward early hospital discharge in the Mountain States Region is similar to that of California.

Issues Related to Specific Screening Tests

Phenylketonuria. Screening tests for phenylketonuria (PKU) are affected by "too early" specimen collection because there is a physiological rise in phenylalanine levels for the first 10 hours following birth gradually falling back to the level one hour post birth at approximately 24 hours of age. At a cutoff level of 4 mg/dl, a significant number of normal results will be falsely positive if collected during the first 24 hours. California found a false positive rate as high as 11/1000 before 24 hours compared to 1.1/1000 between 24-48 hours. Lowering the cut-off level for specimens collected before 24 hours resulted in more false positives without an increase in confirmed cases. Early discharge can also result in false negative newborn screening results. For example, discharge of an infant with PKU may occur before blood phenylalanine levels have increased to sufficient levels to be detected by the newborn screen. Hence, the early screen would miss an infant with PKU. This scenario is particularly likely for infants with hyperphenylalaninemia, who do not have classical PKU, but still have an error of phenylalanine metabolism.

Hypothyroidism. The detection of primary hypothyroidism presents a similar problem because of a thyroid stimulating hormone (TSH) surge at birth which peaks at around six hours and then gradually declines to reach normal cut-off values by the fifth day of life. Since the majority of screening programs in the US take the lowest 10% of T4 results and run TSH analysis to determine a positive screening result for primary hypothyroidism, specimens collected during the first 24 hours will have a high false positive rate.

Maple syrup urine disease. Screening for maple syrup urine disease (MSUD), by detection of elevation of leucine, is optimal at 24-48 hours of age. This elevation is subject to the same considerations as PKU but the medical issues are more complex in that life-threatening symptoms may become evident before screening results are available.

Homocystinuria. Early specimen collection affects screening for homocystinuria (HCU) by increasing the number of false negative results, since the measured metabolite methionine is often not elevated above normal levels during the first week of life. The optimal time to screen for homocystinuria is actually at 3 to 4 weeks of age.

Congenital adrenal hyperplasias. There are four different forms of congenital adrenal hyperplasia (CAH) that can be detected through newborn screening: salt-wasting, simple virilizing, non-classical late onset, and cryptic. The analyte tested is 17-hydroxy-progesterone (17-OHP). At birth, 17-OHP is normally elevated and undergoes a rapid decline to adult normal levels by one to three weeks of age. During the first week of life, the levels of 17-OHP show marked variation. Thus, early specimen collection is expected to result in an unacceptably high number of false positives.

Sickle cell disease, biotinidase deficiency, and galactosemia. Other conditions screened for; but not dependent on the time of specimen collection, include tests for sickle cell disease, biotinidase deficiency, and galactosemia. The screening tests for these conditions rely on red cell components. These test results are affected by blood transfusions and specimens must be collected before transfusion for valid results.

Potential Strategies and Solutions

It is evident from the above information that early discharge has the potential to adversely affect the accuracy of newborn screening for the majority of conditions included in the panels of most newborn screening programs. Several strategies are being implemented to remedy this problem. The most important of these may be the legislation signed last fall by President Clinton whereby health insurers must cover 48 hour hospital stays for mothers and babies for a normal delivery and 96 hours for Cesarean sections. This will hopefully decrease the number of specimens collected at less than 24 hours. This legislation will go into effect January 1998.

The 1992 AAP and ACOG Guidelines state that all newborns must be screened prior to discharge regardless of age or feeding status of the infant and that the optimal time to collect a sample is at 3 days of age. Most state programs have initiated a routine second screen if the newborn was screened before 24 hours of age. These second screens are collected between 1-2 weeks of age for some programs and 1-4 weeks for others. Some states are narrowing the period of time for the second screen to no later than two weeks of age because of the concern of delayed detection and treatment. There are seven states that have implemented a routine second screen on the entire screening panel as a safeguard. They include Delaware, Oregon, New Mexico, Nevada, Texas, Colorado, and Utah. All these states consider a routine second screen to be an effective means (both medically and economically) of detecting clinically significant disorders not detected on the original screen.

In the state of Oregon, the routine second screen has resulted in 38 confirmed cases in whom diagnosis would either have been missed or delayed. Since 1991, five PKU cases have been picked up on the second screen. Oregon has also found that the routine second screening enhances practitioners' involvement in the screening process since second screening specimens are collected in their offices. They receive copies of both screening results for all the infants in their care and hopefully discuss these with the parents.

Despite this apparent success in Oregon, there is much controversy in the newborn screening community concerning the effectiveness of the routine second screen. The following questions need to be considered in any discussion:

1) Is it effective in detecting treatable cases?
2) Is the comparative cost/benefit positive? (In comparison to improved testing sensitivity, liability costs, etc.)
3) What is the appropriate time of collection for a second screen? (1-2 weeks, 2-4 weeks, etc.)
4) What other factors may play a role in whether a second screening test is performed? (Are race and socioeconomic factors significant?)
5) Should the second screen be recommended or required? (Is there discrimination if not required?)

A standard process is needed to incorporate newborn genetic screening into early discharge planning and programmatic changes, including more precise analytical methods, to ensure the integrity of each state's newborn screening program.

For more in-depth discussion of the information presented in this article, consult the Conference Proceedings on "Early Hospital Discharge: Impact on Newborn Screening" held in Washington, D.C. on 3/31/95-4/1/95, available from the National Maternal and Child Health Clearinghouse, 8201 Greensboro Drive, Suite 600, McLean, VA 22102.

Contributed by Holly Nyerges, MSN, CPNP (NM)

Issues in Newborn Screening for Cystic Fibrosis

While newborn screening for cystic fibrosis (CF) has been feasible since 1979 using the IRT (immunoreactive trypsinogen test), and there have been slowly accumulating observational data regarding the potential benefits of such testing, it is not routinely performed in most states. In part, this is because CF is different from the classic model of PKU newborn screening in which a relatively simple intervention must be initiated within a short time frame (weeks) in order to avoid a significant complication (severe mental retardation). In contrast, cystic fibrosis is a chronic and gradually progressive disease and the potential benefit of newborn screening may be harder to discern.

There have also been concerns regarding the potential harms of newborn screening such as adverse effects on parental bonding in children diagnosed with cystic fibrosis, increased acquisition of pulmonary pathogens, and confusion and anxiety in families of children with false positive tests. In the early 1980's there were particular concerns about the sensitivity and positive predictive values of the IRT. At that time, two clinical research programs on neonatal screening were developed in the United States: an observational study in Colorado; and a randomized controlled trial in Wisconsin. The data from the Wisconsin trial continue to be analyzed and there is yet no published information regarding changes in pulmonary outcome during nine years of screening in

Wisconsin (1985-1994). Both the Colorado and Wisconsin trials have generated data suggesting that there is a short-term (less than five years) improvement in nutritional parameters, including height and weight, among individuals identified by newborn screening. While the pulmonary data from Wisconsin have not yet been analyzed, a number of observational studies in Europe and Australia suggest some pulmonary improvement compared to controls; certainly newborn screening does not result in lower pulmonary function compared to patients not screened. Additionally, qualitative studies in Wisconsin and Australia suggested that there are no significant negative psychosocial problems in children identified with CF through screening. There may also be a reduction in the parental anxiety since the time to diagnosis is less with newborn screening, but this is difficult to assess for methodological reasons.

The most significant risk of cystic fibrosis screening has been adverse effects in false positive patients. With either the repeat IRT approach (Colorado) or a single IRT approach (Wisconsin) there is some anxiety, stress, and anger in parents due to the sensitivity and specificity of the test. However, after more than ten years of screening in both Colorado and Wisconsin, these problems, while present, have been observed in only a small number of families. In the single IRT approach (Wisconsin), the positive predictive value was only 15%. For this reason, in 1991 a combined screening using the IRT and molecular mutation analysis of the CF gene was developed using a second tier test for DF508 (the most common CF gene mutation). This offered the benefit of improved positive predictive value. However, this has meant that many individuals identified as false positives are CF carriers. Thus this approach needs to include careful genetic counseling for all at-risk family members.

In January 1997, a conference sponsored by the NIH, CDC, and the CF Foundation was held to review the data from the Colorado and Wisconsin programs as well as information from Europe and Australia. The consensus of the meeting was that there was accumulating evidence of short-term nutritional benefits of cystic fibrosis newborn screening and lack of clear evidence of significant harms. The data were not sufficiently compelling to recommend neonatal screening for all infants, because of continued unanswered questions about the ideal approach to the implementation of statewide newborn screening programs, the appropriate handling of carrier families, and the value of early interventions. There was a consensus that these questions could not be answered by waiting for additional data from the Wisconsin trial, but it would be necessary to move to a further phase of observational research in the context of a statewide newborn screening program to answer these questions. There was discussion about the reasonableness of additional states adopting the statewide newborn screening programs. Ideally, hypothesis-driven research questions would be incorporated regarding the role of early interventions in cystic fibrosis. Such interventions could include use of anti-inflammatory drugs, antibiotics, or deoxyribonuclease. Other possible research questions could deal with the ideal approach to genetic counseling for the IRT/DNA method, and the logistics of statewide implementation. Additionally it was emphasized that newborn screening programs must be linked to the provision of standard of care treatment for cystic fibrosis. This would mean that patients identified would need to have access to cystic fibrosis centers and that such centers might require additional support in the current managed care environment to maintain the same quality of care provided previously. Finally, there was acknowledgment of the need to develop better approaches to informed consent for newborn screening.

In summary, the accumulating data worldwide regarding newborn screening for cystic fibrosis suggest a potential benefit. Before CF screening can be fully implemented, however, new programs need to be developed to address the unanswered questions regarding ideal approaches to screening design and the opportunity for the enrollment of identified children into clinical trials.

Contributed by Benjamin Wilfond, MD (AZ)

Issues Regarding Identification of Hemoglobinopathy Carriers by Neonatal Screening

The primary purpose of neonatal screening for hemoglobinopathies is to identify infants with sickle cell disease, for whom early diagnosis, parental education, prophylactic penicillin, and comprehensive medical care markedly reduce morbidity and mortality. In 1987, an NIH consensus development panel concluded that "the benefits of screening (for sickle cell disease) are so compelling that universal screening should be provided. State law should mandate the availability of these services while permitting parental refusal." During the subsequent 10 years, the number of states that conduct newborn screening for hemoglobinopathies has increased dramatically. Currently, 43 states and the District of Columbia screen newborns for sickle cell disease. In the Mountain States Region, 4 of 6 states (Arizona, Colorado, New Mexico, and Wyoming) screen all newborns for sickle cell disease.

Each of the laboratory methods currently used to screen newborns for sickle cell disease (hemoglobin electrophoresis, isoelectric focusing, and high performance liquid chromatography) also detects infants who are heterozygous carriers for a wide variety of hemoglobin variants, including hemoglobins S (sickle cell trait), C, and E. In most instances, identification of a hemoglobinopathy carrier has no implications whatsoever for the health or medical care of the infant. Geneticists and ethicists generally agree that population screening for genetic disorders should be voluntary, preceded by informed consent, and strictly confidential. While newborn screening programs strive to protect the confidentiality of results, few are voluntary (many are mandated by state law), and meaningful informed consent is rarely obtained. Thus, the detection of hemoglobinopathy carriers by neonatal screening, an unavoidable byproduct of screening for sickle cell disease, presents newborn screening programs with a significant dilemma. How and under what circumstances should the information be conveyed to the infant's parents, many of whom were not aware that newborn screening might yield such genetic information, and at least some of whom might not have consented to such testing had it been voluntary?

There are a number of potential benefits to providing families with information, education, and counseling regarding the identification of an infant who is a hemoglobinopathy carrier. These include the education of families so that they will be more knowledgeable about hemoglobin variants (and not confuse benign carrier states with disease), the avoidance of redundant testing in the future, and the opportunity to offer testing of parents and other family members (and thus identify and counsel couples with sickle cell trait who are at risk for having future children with sickle cell disease). Many feel that a decision not to provide test results and offer education and counseling to such parents would be unethical and/or would place screening programs in legal jeopardy. In at least one instance, legal action (for wrongful birth) was pursued (and an out-of-court settlement achieved) by parents who were not notified that their child had sickle cell trait and who subsequently conceived a child with sickle cell disease.

The potential harm of identifying hemoglobinopathy carriers has also been articulated. Risks include the exposure of mistaken paternity and confusion between sickle cell trait and disease with consequent stigmatization, anxiety, and inappropriate parenting. Documentation that such harm may occur was provided over 20 years ago by a sickle cell screening program for older children in Seattle. Families were informed about the test results by a clinic pediatrician, yet 72% of parents erroneously anticipated significant symptoms in their child with sickle cell trait, and 49% inappropriately imposed some restriction of physical activity. The potential for similar problems is a real concern for those responsible for newborn screening programs. Discrimination by employers and/or health insurance organizations against carriers of serious genetic disorders is another potential risk of identifying hemoglobinopathy carriers.

Logistically, the provision of appropriate education and counseling services to families of hemoglobinopathy carriers identified by newborn screening is a formidable and potentially costly task. Approximately 50 infants who are carriers for hemoglobin variants are identified for each individual with sickle cell disease. Thus, thousands of carrier infants are identified each year by neonatal screening programs in the United States. In many states, the large number of such cases far exceeds the capacity of clinical genetics programs and genetic counselors. Many states have long-standing contracts with community-based sickle cell organizations or with academic sickle cell centers to provide follow-up services. Frequently, but not always, education and counseling are provided by health care professionals (nurses, social workers, etc.) who have extensive knowledge of and experience with hemoglobinopathies. To help ensure the highest quality for the services, many have advocated that a national program be established to set minimum standards of education and training for hemoglobinopathy educators/counselors and to provide for a certification process.

A compromise between not reporting any carrier test results and attempting to notify, educate, and counsel all families with a carrier infant was briefly entertained in Oregon. The idea was to routinely report and follow-up only results indicative of clinically significant disease. An attempt would be made to inform parents of all infants that the newborn screening test might have revealed information about a genetic carrier state. Interested parents could then request the results and receive education and counseling. Parents who did not request results would not be informed of a child's carrier status. This plan for "informed request" was never implemented for a number of practical, legal, ethical, and political reasons.

In September 1995, a national symposium was held to address the legal, ethical, technical, and logistical issues concerning the follow-up of hemoglobinopathy carriers identified through neonatal screening. Participants included representatives from newborn screening programs and sickle cell organizations, geneticists, ethicists, hematologists, and consumers. There was a clear consensus that families of hemoglobinopathy carriers should be notified of the results and that appropriate education and counseling should be available. As a direct outgrowth of that conference, the CORN Sickle Cell, Thalassemia and Other Hemoglobin Variants Committee (with advice and support from the CORN Newborn Screening Committee) developed guidelines for the follow-up of hemoglobinopathy carriers detected by newborn screening. These guidelines (available through the Mountain States Regional Genetic Services Network coordinator) were recently endorsed by the Steering Committee of CORN and are summarized below:

Ideally, education about newborn screening, which usually includes testing for sickle cell disease, should be provided to families during prenatal care - well in advance of the time of delivery.

A mechanism should be in place in State Newborn Screening Programs so that all results of sickle cell newborn screening can be made available to parents of all infants who are tested.

Parents of all infants who are detected to be carriers of hemoglobin variants should be offered appropriate education, counseling, and testing.

Individuals who counsel should have appropriate training and credentialing in order to insure the highest quality of services for families of carriers detected by newborn screening.

Newborn screening programs should have a mechanism for monitoring and assessing the approaches to, responses to, and costs of providing carrier education and counseling services.

Meanwhile, the Sickle Cell Disease Association of America has initiated the lengthy process of developing a national certification program for hemoglobinopathy counselors.

Contributed by Peter A. Lane, MD (CO)

Top Ten Pitfalls in Newborn Screening

1. *Assuming that the result of the newborn screening test is negative (or normal) because you have not heard otherwise.*

There are many reasons why the primary care provider may not be notified about an abnormal newborn screening result: difficulty finding and notifying a provider, a test might have never been sent, or an error in delivery of the result to the primary health care provider. The primary care provider of record at the birth of an infant assumes the responsibility to

assure that a screen was obtained and that the results are duly recorded in the medical records. In light of the increasing complexity of the health care system, many newborn screening programs are working to facilitate proper dissemination of newborn screening results.

2. *Assuming that a negative (or normal) result of newborn screening definitively excludes the conditions screened for.*

"False negative" test results may occur for a wide variety of reasons including human error such as sample transposition and the statistically "built in" false negative tests. For example, approximately 30% of hypothyroidism is missed in babies who were tested before the second week of life. If the primary care provider observes symptoms, which could be the result of one of the disorders on the newborn screening panel in your state, it is appropriate to confirm the results. Any baby with symptoms which might be caused by PKU, hypothyroidism, sickle cell disease, galactosemia, cystic fibrosis, or any other disorder for which newborn screening was negative should have specific diagnostic testing performed by an appropriate diagnostic laboratory.

3. *Submitting a newborn screening sample with incomplete or illegible information.*

All states design the newborn screening forms to suit the specific panel of tests they perform and each piece of requested information is essential. Nevertheless, all newborn screening programs receive samples with inaccurate or incomplete information. The submitter of the sample cannot, of course, be responsible when families deliberately provide misinformation. The submitter is, however, responsible for providing legible information that is correct so far as she/he is aware. When the screening lab requires multiple copies, all copies must be legible (often a problem with hospital card stamps). When a newborn screening form asks for information about the use of antibiotics, history of transfusion, or prematurity - that information is necessary for accurate interpretation of test results. Date of birth is always necessary for proper identification of the newborn, and date of sample for test interpretations. Precise information on age in hours may be necessary for the increasingly complex interpretation of results for early screening.

4. *Ordering a solubility test (Sickledex, Sickleprep) as the follow-up in an infant with positive newborn screen for hemoglobinopathy.*

Diagnostic follow-up testing is required after a positive newborn screen to exclude a false positive result and to define the specific diagnosis. The false positive rate and the differential diagnosis varies with the disease for which screening is performed and with the nature of the test. Confirmatory testing for infants with abnormal hemoglobinopathy screening tests (hemoglobin Barts excepted) should always include hemoglobin electrophoresis. The solubility test (Sickledex, Sickleprep) should never be performed in this setting because it is often falsely negative in infants with sickle cell disease, does not define the specific hemoglobinopathy present, and fails to differentiate individuals with disease from those with hemoglobin traits. Similarly, for other conditions on a newborn screen, specific protocols and policies for confirmatory testing have been developed by each newborn screening program. For example, in Colorado, a result of 4 mg/dl on the screen for PKU should be followed by a repeat screen; while a baby with one level of more than 4 mg/dl or two levels of 4 mg/dl each should have diagnostic testing sent to a specific laboratory for phenylalanine and tyrosine levels. Consultants are available for each disorder and can assist with routine follow-up and with unusual circumstances in which follow-up might need to be tailored to a particular newborn's situation.

5. *Prescribing a PKU treatment formula before confirming the diagnosis of PKU.*

A significant number of babies with a positive screening test for PKU ultimately prove to be unaffected. After a positive screen, diagnostic test results can be completed in hours to days and treatment begun in a timely fashion, once the diagnosis is confirmed. If treatment is started after the screen only, this may interfere with subsequent diagnostic testing. Also, the PKU diet may be harmful to a child without PKU. The diet for PKU needs to be carefully calculated by a trained registered dietitian to give a precise amount of essential amino acids by combination of the metabolic formula with human milk or infant formula. In contrast, if a state screens for galactosemia using a test with a low rate of false-positive results, an immediate diet change might be required while diagnostic tests are pending. Each state has recommendations that take into consideration the specific tests performed in the screening laboratory and the nature of the population served. Guidance regarding any necessary treatment while follow-up screening or diagnostic testing is pursued (also see "pitfall 4") will be provided.

6. *Not collecting a newborn screening sample prior to blood transfusion because the baby is "too young" or has not yet been fed.*

Transfusion will alter the results of certain newborn screening tests. If a baby is transfused and then screened using an assay affected by transfusion of red cells, the transfusion will affect the test results. For example, when red cells are transfused prior to screening for hemoglobinopathy, the newborn screening laboratory will be testing donor hemoglobins. One test for galactosemia uses the Beutler Assay to measure in red blood cells the activity of galactose-1-phosphate uridyltransferase, the enzyme deficient in galactosemia. The enzyme is present in red cells and thus the transfused red cells will affect the test results. The appropriate strategy always is to collect a newborn screening sample immediately before transfusion in the very young newborn.

7. *Not collecting a newborn screening sample prior to transfer of the infant to another institution.*

Sick and premature babies, some of whom require transfer for more intensive/specialized care, are at no lower risk than healthy newborns for disorders detected by newborn screening. States may have explicit regulations about responsibility for screening when a baby is transferred from or to a nursery. Regardless of specific regulations, it is appropriate for a newborn screen to be sent by the hospital or institution from which the baby is transferred and for the receiving hospital or institution to verify that screen was sent and subsequently to repeat the screen if appropriate.

8. *Not collecting an adequate newborn screening sample.*

In each state, a variable percentage of healthy babies are never screened. Reasons for failing to screen a healthy baby vary. A sample may have been collected but failed to reach the laboratory, or the newborn screening laboratory may receive a sample that is inadequate for testing because of insufficient

sample, unacceptable collection, or sample contamination. Despite the fact that records will show a sample was collected, that baby was never screened. In other cases, no sample is ever collected. This may be a result of human or system error, and is one reason that the primary care provider must ascertain that each baby has been screened. Home births present special issues, as the lay midwife or delivering family member who would be responsible to collect and send the screening sample may be uninformed about the purpose and process of newborn screening.

9. *Assuming that an abnormal newborn screen is a false positive because the baby is well and/or because one or more factors known to be associated with false positive results are present.*

The screening process is successful when affected babies are identified before onset of symptoms. The corollary is that the appearance of good health is not evidence against the presence of the disorder. Even in the presence of special clinical circumstances known to be associated with an increased frequency of physiologic false positive screening tests, a baby who tests positive may be truly affected. For example, the baby who is premature or tested very early, and who has a positive test for thyroid disease, may have real disease and needs prompt confirmatory testing.

10. *Referring to the newborn screening test as a "PKU test."*

This is a very common practice among hospital staff and practicing physicians. It is misleading to refer to the newborn screen as a "PKU test," because tests for other diseases are included. Parent confusion about the full scope of testing may impact compliance with follow-up should the newborn screen be abnormal. It is good practice to use the term "newborn screen" and to inform the family of the breadth of the newborn screen.

Contributed by Carol Greene, MD (CO)

Announcements

The following useful documents are available on the Internet at MSRGSNet at URL http://ahsc.arizona.edu/msrgsn/publicat.htm

1996 Newborn Screening Practitioners Manual

MSRGSN Service Provider Directory

A number of previous issues of Genetic Drift

Much more!

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