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Since the early 1960s, newborn screening programs for inborn errors of metabolism have served as a standard component in routine neonatal health care in the United States and have played an important role in fostering child health.[1–3] Currently, roughly 4 million newborns are screened each year in the United States. From the beginning, these programs have evolved within and been conducted under the jurisdiction of the individual states.[4] Since these programs have been developed on a state-by-state basis, screening policies vary widely, both with regard to diseases screened for (anywhere from three to eleven conditions, including biotinidase deficiency, branched chain ketoacidemia, congenital adrenal hyperplasia, congenital hypothyroidism, cystic fibrosis, galactosemia, homocystinuria, phenylketonuria, hemoglobinopathies, toxoplasmosis, and tyrosinemia) and with regard to regulatory policies.[5–6]

The Iowa Neonatal Metabolic Screening Program (INMSP) is located with the agency of the University of Iowa Hygienic Laboratory (the Hygienic Lab), the state of Iowa's primary agency of public health analysis and information. The INMSP obtains blood samples in the form of blood-spotted filter-paper cards from each of the 37,000–40,000 babies born in Iowa each year and uses these to screen for five metabolic disorders: hypothyroidism, phenylketonuria (PKU), galactosemia, congenital adrenal hyperplasia (CAH), and hemoglobinopathies. Until recently, a sixth disorder, branched chain ketoacidemia, also known as "maple syrup urine disease" (MSUD), was also assayed, but MSUD screening was discontinued due to lack of cost effectiveness. Using different microbiological, biochemical, and radio-immuno assays, the INMSP detects roughly three dozen total cases of these disorders per year. In these cases, early detection and diagnosis leads to dietary and other interventions which, if followed carefully, can reduce or forestall the often catastrophic effects of these diseases, such as severe mental retardation or early death.

We obtained newborn screening filter cards from the INMSP for a pilot project using DNA-based analysis. The purpose of this study was twofold.

First, we wanted to determine the suitability of using DNA-based techniques on these samples on a large scale as alternatives to the INMSP's microbiological, biochemical, and radio-immuno assays. The above disorders can be detected through various types of metabolic assays, since the immediate and severe effects of the disease are directly related to abnormally high levels of specific metabolic products. The etiologic cause of four of the five conditions, excepting hypothyroidism, are, however, genetic. Because of mutations in relevant genes, these individuals fail to produce a protein necessary for normal metabolism or produce a defective form of a protein. Consequently, these conditions seem likely candidates for detection and diagnosis through DNA-based analysis. Moreover, other disorders stemming from genetic mutations do not result in the types of metabolic changes that can be assayed through these techniques, but recent advances in human genetics have made direct detection of disease-causing DNA mutations possible.[7] In some instances, again, early detection and treatment may improve outcome. However, one consideration for any newborn screening program or comprehensive population screening study is the ability efficiently and accurately to process large numbers of samples in a reasonably short period (quickly enough to initiate an efficacious therapeutic intervention). To move from metabolic assays to strictly DNA-based techniques would require that DNA-based assays could be performed under these constraints.

As a second purpose of this study, we wished to ascertain the efficacy of using these samples and DNA-based techniques for measuring various types of genetic variation in the Iowa population, where "genetic variation" encompasses both carrier frequencies for disease-related mutations and normal trait variation. As mentioned, the specimens for the INMSP are collected, transported, and analyzed via "Guthrie" or filter-paper cards. These Guthrie cards in general, when not discarded by states after the newborn screening assays are complete, have been described as "inchoate 'DNA banks.'"[8–9] Along these lines, it was recognized that these samples could provide a sort of genetic databank for the Iowa population, which, after the development of an efficient technique for extracting DNA from the filter cards, could serve as a useful reference or control database for comparison in other genetic research or could provide important public health information.

As with most developments in biomedicine and genetics, these projects — though technical and data-oriented on their face — cannot be separated from the ethical issues that surround them. In particular, two sets of issues are raised. First, how would the introduction of DNA-based techniques alter the practice of newborn screening? What additional concerns or issues might these techniques introduce? What lacunae in current newborn screening prac-

tices does the specter of these techniques illuminate? A second issue is that of "DNA databanking." Specifically, for our purposes, what issues arise when samples obtained from patients for one purpose (e.g., newborn screening) are then used for secondary purposes unrelated to the original intent (e.g., research, forensic, diagnostic, or commercial purposes)? What different issues are presented by the uses of "anonymized" samples versus samples that retain identity linkages to the original patient? These questions are addressed in our discussion.

First we describe our pilot test of DNA-based analysis using anonymized newborn screening cards in Iowa. After testing several methods for extracting DNA samples from the blood spots on the filter-paper cards, we carried out an analysis for three different disease-producing mutations: the cystic fibrosis (CF) ΔF508 mutation, variations in exon 12 of the phenylalanine hydroxylase gene (mutations in which contribute to PKU), and variations in the gene responsible for MCADD (Medium Chain Acyl-CoA Dehydrogenase Deficiency). These genes represent three different classes of conditions relative to newborn screening programs: (1) PKU screening is currently conducted in all fifty states using traditional methods; (2) CF is screened for in two states using metabolic assays, with pilot programs for the addition of a DNA-based confirmation assay being tested in Wisconsin and internationally[5, 10–14]; and (3) MCADD is not currently screened for in any state in the United States.

Methods

In 1989 the Hygienic Lab began participating in a study sponsored by the Centers for Disease Control (CDC) which sought to determine the prevalence of human immunodeficiency virus (HIV) infection in newborns.[15–16] For this study, the Hygienic Lab utilized the newborn screening filter cards from the INMSP to determine HIV seroprevalence for the state of Iowa. Prior to being entered into the HIV study, the filter cards were rendered anonymous: name identifiers were removed, and each card was assigned a random number. Although random, this number remained correlated with the INMSP database of demographic and clinical information created from the original sample. (For each sample tested, the INMSP enters into its database the sample number, the test results, and a set of demographic characteristics of the newborn.) Consequently, for each anonymous sample, important information has been preserved, but it is impossible to trace a particular sample back to a particular newborn.

While in a number of states newborns' screening cards are retained for

different lengths of time and policies regarding their testing and subsequent usage vary,[4, 8] in Iowa, once these samples were analyzed by both the INMSP and the Hygienic Lab/CDC HIV study, they would be destroyed. Prior to our study, this was done. Following review by both the Iowa State Board of Health and the Birth Defects Institute, we were able to obtain these samples for the purpose of this study. From July 1994 through May 1995, 31,249 newborn screening filter cards were obtained from the INMSP via the Hygienic Lab.

DNA was extracted from 8,920 samples in 96-well microtiter plates. Using a ⅛" punch, a ⅛" blood-spot sample was punched from each newborn screening card directly into one well of the plate. (Spaces were left for positive and negative controls.) After autoclaving, extraction solution was added to the sample, the sample was processed, and the resulting supernatant was transferred, using a multichannel micropipet, to a fresh 96-well microtiter plate in which the samples were frozen and stored. These plates also then served as templates for PCR analysis. We are in the process of developing an optimal method for long-term storage of the blood-spot filter-paper cards.[8]

A PCR-based protocol was developed, and we assayed 7,194 samples for the presence of the ΔF508 mutation in the cystic fibrosis transmembrane conductance regulator gene (CFTR), the common mutation accounting for approximately 70 percent of the incidence of cystic fibrosis. Cystic fibrosis is the most common severe autosomal recessive disorder affecting Caucasians of European descent, with an incidence of approximately 1 in 2,500 births. The CFTR ΔF508 mutation is a three base-pair deletion which is easily detected on 6 percent polyacrylamide gels. Control DNA was provided by Coriell.

In addition, we developed a polymerase chain reaction (PCR)–based assay to detect mutations in exon 12 of the phenylalanine hydroxylase (PAH) gene and tested 1,070 samples. Different mutations in this gene when present in recessive fashion contribute to the disease phenylketonuria (PKU), which occurs in approximately 1 in 12,000 births. Individuals with PKU lack the enzyme which metabolizes the amino acid phenylalanine; the resulting elevated phenylalanine levels can result in severe brain damage. Early intervention and a diet low in phenylalanine can prevent mental impairment.

This assay detected three known mutations, R408W, Y414C, and IVS12nt1, as well as two other variants. These variants all resulted from nucleotide substitutions rather than deletions or insertions and were therefore not detectable by polyacrylamide sequencing gels. Instead, these samples were analyzed using mutation detection electrophoresis (MDE) gel solution in a single strand conformational polymorphism (SSCP) protocol. To determine which signals corresponded with which variants, anonymous specimens from individuals known to have PKU were extracted, amplified through PCR, and analyzed on

MDE gels. The samples showing variations under the gel conditions were excised and sequenced. The sequence data enabled identification of the particular mutation. These samples then served as controls.

We are now in the initial phases of testing for a mutation in the gene responsible for MCADD, an autosomal recessive disorder that has been associated with Sudden Infant Death Syndrome in a small percentage of SIDS cases. MCADD can also cause a disorder associated with mental retardation. Again, since presymptomatic diagnosis and dietary intervention can minimize symptoms and forestall life-threatening episodes, and there appears to be one common point mutation in Caucasian populations, MCADD is a natural candidate for this approach. A single mutation, T1067C, comprises about 85 percent of known cases of MCADD, and we designed primers to amplify a 188-bp segment of DNA that includes this region. Fortuitously, it also flanks a A985G change that causes MCADD in a small group of cases.

Results

As noted above, DNA samples were prepared from 8,920 blood-spot filter-paper cards. Of the 7,194 samples assayed for the CFTR ΔF508 mutation, 6,659 individuals did not carry the mutation, 177 individuals were heterozygous for the mutation, and 1 individual was homozygous; 357 samples did not produce an interpretable result (through failure to amplify or defects in the gels).

The CF screening on neonatal cards from August 1994 to August 1995 yielded the following results:

No. tested	7,194
No. failures	375 (5.6%)
Carrier rate	1/38
Allele frequency	0.013
Heterozygotes (carriers) detected	177
Homozygotes detected	1

The MCADD pilot DNA screening on neonatal cards (May 20, 1996) had the following results:

No. tested successfully	857
No. of mutations	13
A985G	11
T1067C	2
Carrier rate	1/67
Predicted homozygotes in Iowa per year (40,000 births)	2

The results of the PKU screening on neonatal cards (July 9, 1995) were as follows:

No. tested	1,070
No. of failures	252 (23.5%)
No. of variants	73 (6.8%)

This results in a carrier frequency of 1:38 for the CFTR ΔF508 mutation in the Iowa population, which is similar to that reported in a study of the Wisconsin population [10,11] as well as in other Caucasian populations. Although the overall sample failure rate for the CF portion of the pilot study was 5 percent, the rate improved over the course of the study as the protocol was optimized; for the last 2,460 samples, the rate dropped considerably, to 1.4 percent (35 out of 2,460). We hope that, with additional modifications of our current protocols, the current sample failure rate will fall even further.

Of the 1,070 samples assayed for the variants in exon 12 of the phenylalanine hydroxylase gene, 997 did not show evidence of a detectable mutation and 73 individuals with variants were found. While these 73 variants comprise a large number of PKU mutations, the variability of our SSCP results makes it likely that most of these will be sequence polymorphisms and not etiologic mutations.

An SSCP assay was used to screen 857 newborn screening samples for the MCADD mutations. Eleven individuals were heterozygous for T1067C and two for A985G. Thus, 1.5 percent of Iowa newborns are heterozygotes for MCADD, and we would predict 1 in 17,000 newborns (about 2 per year) to be homozygous affected. This assay could readily be carried out by a screening facility.

While the first aim of this study was to develop and conduct DNA-based analyses on dried blood spots on a large scale, a second aim was to develop a databank of anonymous samples for control purposes and other genetic research. As mentioned above, at the conclusion of this study, a sample bank of 31,249 blood-spot filter-paper cards had been obtained; 8,920 of these were prepared as DNA samples with a volume of approximately 150 microliters. These DNA samples are frozen and stored in capped 96-well microtiter plates, providing for relatively easy storage, maintenance, and utilization. At the same time, the original source of each sample is maintained on the filter-paper cards, making verification or re-extraction relatively easy and ensuring that samples will remain available for subsequent research. This pool will provide an important resource for conducting comprehensive surveys of genetic variation in the Iowa population.

Discussion

DNA-BASED ANALYSIS FOR NEWBORN SCREENING: TECHNICAL CONSIDERATIONS

Through this study, we have developed a relatively efficient procedure for extracting DNA from large numbers of samples. As the protocol was optimized, we were consistently able to extract DNA from over 98 percent of the samples. With all steps of the protocol — extraction, PCR, storage — conducted in 96-well microtiter plates, we were able to process large numbers of samples relatively efficiently. Much of this process could be automated, increasing efficiency.

But even under manual conditions the efficiency of the DNA-based assay is comparable to that required for a newborn screening program. For example, with a birth rate for the state of Iowa of approximately 37,000–40,000 annually and 20 percent repeat specimen (see below), the INMSP processes an average of 900 samples per week, conducting six different metabolic assays on each specimen with a staff of six. In the DNA-based protocol we developed, it was relatively easy for one person to extract and PCR 1,600 samples per week. For the cystic fibrosis protocol, using the 6 percent polyacrylamide gels made the analysis relatively straightforward; because each gel could be loaded five or six times, it is feasible for one person to analyze the same 1,600 samples within the same time frame. The SSCP/MDE protocol for the PKU assay presented more challenges. Since it was not amenable to double-loading and the results of the SSCP procedure seemed more variable, it was not as efficient. Moreover, our results demonstrate that, to date, we have been able to assess accurately the frequency of the cystic fibrosis mutation in the state of Iowa, and we find that the frequency is similar to that identified in other predominantly Caucasian populations. Finally, although the results are preliminary, we did not observe evidence of contamination from filter-card to filter-card or evidence of cross-contamination between extracted and stored samples within the plates when handled carefully, even though the samples were processed in close proximity.

DNA-BASED ANALYSIS FOR NEWBORN SCREENING: ETHICAL CONSIDERATIONS

If DNA-based techniques came to be used in place of traditional microbiological or biochemical assays, would it be a zero-sum exchange? Would it simply mean the substitution of one technical approach for another? Decidedly not. Because of the nature of genetic information and the current social

and cultural context into which DNA-based newborn screening would be introduced, additional issues must be considered carefully to determine whether DNA-based techniques are appropriate for programs such as newborn screening, and, if so, under what conditions or parameters. These issues include advantages, cost, precision or diagnostic efficacy, scope of application, collateral information, and informed consent.

Advantages: Solution to Problem of Early Discharge and Mutation Identification

DNA-based techniques would provide one primary advantage over current traditional methods. If technically feasible, DNA-based assays would offer a solution to what has become a significant problem for many state newborn screening programs, namely, the current practice of early discharge of infants. In an effort to reduce health care costs, many insurance providers and HMOs either encourage or require that healthy infants be discharged twenty-four hours after birth; some infants are being discharged as early as twelve hours. This has presented a problem for newborn screening programs insofar as many newborn screening tests rely on time-dependent changes in the concentration of an analyte in the blood for diagnosis.[5] If a sample is taken too early, the true concentration of these compounds in the infant's blood may be masked by maternal analytes, rendering false negative results. Until technological advances enable age-independent analyses, the INMSP will continue to request a second specimen on roughly 17 percent (or 7,800) of all babies tested annually. This results not only in increased costs; clearly, some of these babies will be missed.

A second possible advantage of DNA-based techniques is that, in making the diagnosis, they not only would indicate that an infant suffered from a particular disease, but would often be able to specifically identify the mutation or mutations responsible for the disease-state. As genetic medicine becomes more sophisticated, this may render information relevant to diagnosis and treatment (e.g., some mutations may cause more severe symptoms than others). However, it may be more efficient to reserve DNA-based assays for confirmatory tests on the small subsample of newborns who are determined to be "presumptive positives" through metabolic assays. This approach is being tested in Wisconsin and elsewhere for cystic fibrosis.[10–14]

Cost and Diagnostic Efficacy

While DNA-based techniques could resolve the problem of false negatives due to early discharge and offer enhanced diagnostic precision in some cases, they would not necessarily result in reduced costs or reduced numbers of false

negatives. Currently, the metabolic screening assays used to detect PKU, galactosemia, MSUD, CAH, hypothyroidism, and hemoglobinopathies are relatively inexpensive and efficient.[5] The INMSP currently charges $25.00 for the battery of five tests. The costs of a genetic assay are comparable, in the range of approximately $2.00 per assay, when one takes into consideration the costs of supplies and labor.

But while the direct costs of the genetic assays are comparable to those for the metabolic assays, a difficulty arises in the area of precision or diagnostic accuracy due to the genetic nature of these diseases. Each condition can be caused by any number of mutations, each of which may require a different DNA-based assay. For example, over 100 disease-related mutations have been reported in the PAH gene. Our protocol assayed for a number of mutations in exon 12, a region of the gene which seems to be particularly susceptible to mutations and which is the location of some of the more frequent mutations. And while we detected variants in seventy-three individuals, the individual listed in the INMSP database as a "presumptive positive" for PKU based on the metabolic assay performed by the INMSP appeared as "normal" in our assay. Thus, to design an efficient protocol which would not give false-negative results would be quite difficult under the current technological conditions. A condition such as CF would be more amenable, since such a large proportion of the mutations occur at one locus; but again, although the ΔF508 mutation accounts for approximately 70 percent of the cases of cystic fibrosis, approximately 400 other disease-causing mutations in the CFTR gene have also been identified. Likewise, while in MCADD 85 percent have a single mutation, other mutations can contribute to disease.

But while a particular gene may be susceptible to a large number of mutations (the PAH gene, for example) the metabolic disease-producing effects of different mutations are, in general, similar (elevated levels of the amino acid phenylalanine, which can be measured through a single assay which measures gene expression). Consequently, the current consensus holds that DNA-based assays are not yet sufficiently "cost-effective" and are susceptible to false negative results. The American Society of Human Genetics and others[17–18] have argued on this basis that CF screening on a population-wide basis is premature at this time. Likewise, although a large number of PKU mutations have been identified through this protocol, at the present time we conclude that current methodologies are more appropriate and cost-effective for carrying out this analysis.

Scope of Application and Collateral Information

The possibility of large-scale genetic screening next raises the question of the scope of conditions to which it could be applied. At issue in this question

is whether genetic information, obtained through DNA-based techniques, is different in kind from the sort of medical information obtained through traditional metabolic assays.[19] Current metabolic techniques assay for single, well-defined conditions that result in active disease states. DNA-based assays would yield not only this information but what we could call "collateral information" as well.

Two types of collateral information can become available through genetic assays. A first type is information predictive of the infant's possible medical future. DNA-based assays could detect conditions of late onset presymptomatically, possible predispositions to certain conditions, "behavioral" traits, or diseases for which no therapy exists. A second kind of collateral information is heterozygosity or carrier status. These types of information are materially relevant not only to the individual newborn; both categories divulge information about parents, siblings, and other relatives as well: that they may also be carriers or bearers of latent illness. Thus, not only is the information detected through DNA-based assays different in kind; it is different in scope as well.

Clearly, in the context of newborn screening programs, testing for these sorts of conditions differs little from the genetic testing of children in other contexts. Although far from resolved, the contentious debate surrounding the propriety of the genetic testing of children has recently begun moving toward a tentative resolution. The particulars of this debate as well as the outlines of the emerging consensus can be found in the joint statement of the American Society of Human Genetics/American College of Medical Genetics[20] and an analysis by D. C. Wertz et al.[21]

Genetic tests for children can be separated into two basic categories: (1) tests that provide an immediate or timely medical benefit and (2) those that do not but might prove medically useful at a later time or might provide some sort of psychosocial benefit. Agreement is unanimous regarding the first category: testing that may detect conditions for which treatment or preventive measures are available is similar to other medical diagnostic evaluations and is not only ethically sound but mandated.[20–21]

With regard to the second category of genetic tests on children — those that offer no immediate medical benefit — there is less unanimity, precisely because of the collateral information that is divulged by these tests and the risks of harm that it presents to both individual children and their families. Certainly, these sorts of tests provide certain benefits, as noted by the ASHG/ACMG: either increased or reduced medical surveillance (as appropriate); early intervention; preventive measures, including lifestyle changes; clarification of diagnosis; reduction of anxiety and uncertainty; opportunity for psy-

chological adjustment; ability to make realistic plans for education, employment, insurance, and personal relationships; alerting other relatives to genetic risk; and avoiding or preparing for the birth of a child with genetic disease.[20]

However, the current consensus holds that these sorts of benefits, when calculated in the context of individual testing, are greatly outweighed by the risks of harm presented by collateral information. These risks include alteration of self-image (latent feelings of unworthiness, "survivor guilt," pessimism about the future, blaming oneself for the illness and the burdens it places on the family); distortion of parents' perception of the child (manifested possibly in the overindulging "vulnerable child syndrome," stigmatization, or scapegoating and rejecting); lowered expectations by self, parents, and others for education, employment, and personal relationships; and alerting relatives to reproductive or health risks.[22–23] In addition, this sort of information may generate rather than reduce anxiety. N. A. Holtzman notes that anxiety generated by false positive results from neonatal assays is, at times, difficult to dispel, even with follow-up testing.[24] Finally, as has been discussed at length elsewhere,[25–30] this sort of information presents the additional risk of illegitimate access, in this era of increasing computerized and electronic datakeeping, by third parties (i.e., insurers, employers, educational institutions) with the attendant possibilities for discrimination. These types of discrimination can exacerbate and reinforce the social stigmatization and marginalization that often accompany chronic illness and "difference."

Based on the scope of these risks, many persons find it difficult to justify subjecting children to genetic tests that provide no immediate medical benefit. The ASHG/ACMG recommends that "if the medical or psychosocial benefits of a genetic test will not accrue until adulthood, as in the case of carrier status or adult-onset diseases, genetic testing should generally be deferred."[20] Exceptions are made to take into account the emerging identity, cognitive ability, and self-determination of children, especially as they move through adolescence. Consequently, the recommendations almost categorically oppose testing children under the age of seven (understood as the age where children are beginning to be capable of "assent"); they allow for more flexibility and contextual decisionmaking as the age, maturity, and ability of the child to participate in the decision to be tested increase.

Thus, when located in the context of the genetic testing of children, the issues of the scope of application of DNA-based assays in newborn screening and the management of collateral information seem relatively straightforward. Current newborn screening programs exemplify the first category mentioned above. Newborn screening programs have been developed within a framework of preventive therapeutic medicine guided by the two ethical principles of

preventing harm and providing benefit: the goal of these programs has been to identify affected infants prior to imminent development of symptoms where treatment is available in order to prevent serious morbidity or death.[22] Harvey Levy has identified four traditional criteria that have governed newborn screening programs: (1) that there be a disease, not simply a laboratory variation; (2) that the disease should cause significant problems; (3) that the problems caused by the disease be amenable to treatment directed at preventing symptoms; and (4) that a marker for the disease be identifiable in the newborn prior to the appearance of symptoms and irreversible damage.[23] The use of well-defined DNA-based assays in newborn screening, guided by these criteria, would likely meet with widespread support.

Likewise, it would probably be difficult to justify the implementation of DNA-based assays in a newborn screening context for diseases for which the benefit of early intervention is uncertain or no therapy exists, for presymptomatic or susceptibility testing, or for carrier testing. While one could conceivably extrapolate the benefits listed earlier to a public health context (e.g., presymptomatic testing could identify, far in advance of their symptoms, individuals who will develop specific disorders; this information could direct prevention, surveillance, and early-intervention efforts toward those who need them most), the risks would likewise be extrapolated and, in a public health context, would be magnified exponentially.

Current newborn screening programs have, of course, already wandered into some of this territory. For some conditions, DNA-based or traditional assays are relatively straightforward, but early medical or psychosocial intervention is not known to affect outcome. Consensus has not been reached on this issue, for example, with regard to neonatal testing for cystic fibrosis, using either metabolic assays or a two-tiered (metabolic/DNA-based) approach.[23–24, 31] Moreover, carrier status information already emerges from newborn screening technologies: identification of an affected child identifies both parents as carriers. The move toward DNA-based assays, however, would exacerbate this already difficult problem by introducing a new variable into the outcome of newborn screening tests: DNA-based tests would, like current tests for hemoglobinopathies, detect not just disease incidence but heterozygosity as well. If the stated and enacted purpose of newborn screening programs is the diagnosis and treatment of early-onset disease, how might information on heterozygosity be handled? If heterozygosity for a recessive condition is detected in an infant, it might seem prudent — and guided by the same preventive therapeutic goals as newborn screening — to counsel the parents for both to be tested, to determine the disease risk for future offspring. This has, in fact, come to be understood by some as a secondary goal of new-

born screening programs.[22–23] Is there an obligation to make carrier status for a particular disease (e.g., PKU) available to identified infants, either as part of their medical record or when they reach reproductive age?

The Committee on Assessing Genetic Risks of the Institute of Medicine, in its 1994 report *Assessing Genetic Risks*, addressed both of these issues. First, with regard to the scope of application, it articulated three principles that should guide the development of newborn screening programs, namely, that there is: (1) clear benefit to the newborn; (2) a system in place to confirm the diagnosis; and (3) treatment and follow-up available for affected newborns regardless of families' ability to pay.[32] This would disqualify presymptomatic or susceptibility screening; the Council of Regional Networks of Genetic Services (CORN) concurs.[33] The committee further recommends that the development of new population-based newborn screening programs be viewed as research protocols and be conducted under established guidelines for human subjects research, requiring informed consent and well-designed and peer-reviewed pilot studies that demonstrate safety, effectiveness, and clear benefit to the newborn prior to implementation. Finally, they counsel that carrier status information (and by analogy, other sorts of collateral information) on newborns should be withheld from either or both parents in the absence of a specific request for the information. This accords with the findings of the ASHG/ACMG and others. We affirm these guidelines and recommend that the development of newborn screening programs be limited to those with demonstrable clinical outcomes. This conclusion derives both from a sense of the purpose and practice of medicine, of which genetics is a part, and from a sense of stewardship of community resources.

Informed Consent in Newborn Screening

The ability of parents to request possible carrier status findings requires that they be informed in advance that such information will be available; this requires that they know that a sample has been obtained from their child and that such a test is going to be performed, which is not often the case. This brings us to the role of informed consent in newborn screening. Like many other facets of newborn screening, the role of informed consent has evolved in an ad hoc manner, and policies vary widely from state to state. Currently, forty-eight states and the District of Columbia have statutes regulating newborn screening. Delaware and Vermont conduct screening on a voluntary basis but have not regulated these programs by statute. In three jurisdictions (District of Columbia, Maryland, and North Carolina) screening is entirely voluntary, while in five (Arkansas, Iowa, Michigan, Montana, and West Virginia) it is mandatory; the rest legally permit parents to "opt-out."[4]

The extent to which parents are informed of this option, however, is unclear. Lori Andrews' 1985 study of state newborn screening programs found that only thirteen states require or specify that parents be informed that neonatal screening tests are even going to be performed; only four of these states require that parents be given an opportunity to object. In thirty-two additional states, Andrews found there to be no requirement for informing parents that the tests are to be conducted, for obtaining their consent, or for apprising them of their right to refuse (although most states permit parents this right, specifically on religious grounds).[4] A recent statement of CORN, however, maintains that "most state screening programs use informed refusal."[34]

In Iowa the statutes governing newborn screening provide for what could be called "informed screening" but not for informed consent. The statute states: "Parents or guardians shall be informed of the type of specimen, how it is obtained, the nature of the diseases being screened, and the consequences of treatment and nontreatment. Should a parent refuse the test, said refusal shall be documented in writing and will become a part of the medical record."[34] The main strength of the Iowa statute is that the parents are to be informed that a sample is to be taken and that the tests are to be conducted. But while the statute requires written documentation of parental refusal (the grounds for which are not specified), it does not specifically require consent or written documentation of consent. Furthermore, while the content of the information provided to parents is relatively comprehensive (including the consequences of treatment and nontreatment), the language of the statute addresses issues related to metabolic screens. The law clearly does not understand this information according to the paradigm of "genetic" information; it does not apprise the parents of the types of collateral information that might be obtained from a genetic test or therefore of the risks and benefits of the test itself.

Although controversy still exists, consensus is shifting toward agreement that newborn screening ought to be understood under a model of genetic information and that, at the least, it ought to be governed by standard canons of informed consent. The Committee on Assessing Genetic Risks of the Institute of Medicine recommended that "informed consent should also be an integral part of newborn screening, including disclosure of the benefits and risks of the tests and treatments."[32] Likewise, the proposed Genetic Privacy Act (see below) would require written parental authorization before obtaining a sample for testing.[35] Some persons believe, however, that the costs of obtaining (in terms of the time of the practitioner) and of documenting such consent would be prohibitive.[36] Additionally, such information, even if properly communicated to parents, might discourage them from consenting. States

would have to weigh the value of the practice of parental consent against the low risk that the child will suffer from one of the diseases tested for. Nevertheless, given the changing nature of the information being obtained through newborn screening and the evolution in current understandings of informed consent in medicine, it will be increasingly difficult to justify conducting newborn screening in the absence of informed consent. The content of such consent is a separate matter and is addressed below.

NEWBORN SCREENING FILTER CARDS AS DNA DATABANKS: ETHICAL CONCERNS SURROUNDING SECONDARY USES

Until technological advances are made, many of the issues surrounding the use of DNA-based assays in newborn screening programs will remain hypothetical; it is prudent, however, to think them through carefully and shape provisional policies in advance of exigency. A second set of issues is, however, upon us: issues related to DNA databanking and secondary use of newborn screening samples. Recently, the general issue of DNA databanking and secondary use of biological samples has received significant attention. A review of this discussion is necessary to set the context for consideration of the ethical issues surrounding newborn screening filter cards as DNA databanks.

DNA Databanking: An Overview

The American Society of Human Genetics (ASHG) outlined points to consider regarding DNA banking and analysis as early as 1987.[37] Philip Reilly initiated discussion of newborn screening filter cards as a form of DNA databanking in 1992.[9, 8] In 1995 DNA databanking was addressed in four separate settings: the American College of Medical Genetics (ACMG),[38] a workshop held under the aegis of the National Center for Human Genome Research (NCHGR),[39] a working group under the aegis of the National Institutes of Health/ethical, legal, and social implications (of genome research) (NIH/ELSI) program that drafted the Genetic Privacy and Nondiscrimination Act,[19] and a study of informed consent in genetic research conducted by Robert Weir and Jay Horton at the University of Iowa.[40]

DNA databanks can be comprised of samples gathered in different contexts. Reilly identifies at least six: (1) academically based repositories of scientists who are studying one or more genetic disorders; (2) commercially based repositories that offer DNA banking as a service to researchers and individuals who may have some reason to store their DNA; (3) state-based DNA forensic banks; (4) DNA banking by the military to assist in the identification of human remains; (5) specimens obtained for clinical diagnosis and then retained; and (6) newborn screening cards.[9, 8, 28]

The extent to which newborn screening programs have become de facto or "inchoate" DNA databanks is unclear. McEwen and Reilly, in a study published in 1994, noted that currently forty (or 75 percent) of the newborn screening programs in the United States retain the blood-spot filter cards from one year to indefinitely.[8] CORN, however, maintains that only eighteen states retain their cards for more than one year, stating that "most newborn screening programs destroy all residual DBS samples within a year after the newborn screening analytical process has been completed."[33] McEwen and Reilly further note that most who retain these cards have begun doing so recently and that there is a trend nationally toward retaining them and toward retaining them for longer periods as their value as a databank is increasingly recognized. CORN concurs with this latter point.

Samples collected in newborn screening labs, as well in other repositories, can be used for four types of secondary purposes: forensics, diagnostics, research, or the development of commercial products. They can be used for these secondary purposes in two forms, either retaining identifying linkages to the original source or in an "anonymized" fashion. Finally, a distinction is generally made between biologic samples that have already been collected (i.e., existing repositories) and the collection of samples in the future.

Consideration of issues surrounding secondary uses of newborn screening samples returns us to the issue of informed consent raised earlier. The recommendations of the ACMG mentioned earlier, the NCHGR Workshop on Genetic Research on Stored Tissue Samples, the Genetic Privacy Act, and the Weir/Horton study pertain almost exclusively to issues of informed consent. While a detailed account of these recommendations is beyond the scope of this essay, a brief summary will provide a context for thinking through issues of consent for newborn screening.

In specifying the content of the information that ideally ought to be communicated to patients/research participants who become the source of the genetic material collected in these databanks, the four sets of guidelines and recommendations recognize the importance of the traditional, central element of informed consent: in order to protect the research participant's autonomy and to minimize harm, participants must be apprised of the nature of the project and the possible risks and benefits that might accrue to them through participation; they can authentically choose to undertake certain courses of action if they value the end sufficiently to deem the risks worth taking. In addition, these four proposals expand on this traditional understanding to encompass a more substantive understanding of the relationship between the patient/participant and the investigator. They attend seriously to

the participants' contribution to the research endeavor, almost locating participants as equal partners with investigators.

Generally, these four sets of recommendations treat the use of identifiable or linkable samples and anonymized samples separately. Given their slightly different foci, not all of these four documents highlight the same concerns. However, broad areas of agreement can be identified. With regard to *identifiable or linkable samples* to be collected in the future, these findings recommend that fully informed consent, governed by well-established canons for both the practice of medicine and research involving human subjects, should be obtained. They recommend that patients/research participants should receive standard information regarding (1) the original purpose, risks, and benefits of the clinical test or research project; (2) retention of the sample, including location and conditions under which it will be retained; (3) possible secondary uses of the sample; and (4) possible ramifications for the individual of secondary uses. The patients/participants ought then be accorded the rights to consent and determination corresponding to these areas.

These recommendations also take up the issue of how to treat identifiable samples that have already been collected, already reposing in databanks, for which the sources may not have been thoroughly informed when they gave their original consent. How ought one then proceed? For research proposing to use these in an identifiable manner, three options have been presented. First, if possible, the source of the identifiable sample should simply be recontacted and give consent for the further use. Objections were raised, particularly in the NCHGR document, that this would be impracticable and would prove prohibitive to investigators.[39] Consequently, a second course of action proposed that the investigator and the IRB should revisit the consent document of the person who provided the sample to determine whether, in that context, he or she had agreed to the use of the sample for genetic research. The workshop concluded that, while it would probably be difficult to infer consent from most informed consent documents (given their general inadequacy), this would be a valid course of action; if it was successful, further consent would not be necessary. Finally, following federal regulations, if the research involves no more than minimal risk, and the investigator can *demonstrate* that reconsenting the participants would be prohibitively burdensome, members of the workshop agreed that consent might be limited or waived in some circumstances.[40]

Finally, in general, these four sets of recommendations say very little about the use of *anonymous or anonymized samples* (the NCHGR statement provides the most extensive discussion); for the most part, they simply presume the

propriety of the use of anonymized samples for secondary purposes. This accords with the recommendations of both the NIH Office of Protection from Research Risks (OPRR) and the Committee on Assessing Genetic Risks of the Institute of Medicine, who endorsed the use of anonymous stored samples for genetic research.[32, 41] This is also in keeping with the federal regulations which exempt from the requirements for protection of human participants the use of existing specimens "if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly, or through identifiers linked to the subjects."[42, 39]

This high degree of consensus, however, does not mean that the issue of the use of anonymized samples is settled. Some members of the NCHGR Workshop suggested, for example, that anonymizing an existing identifiable sample without seeking consent for the specific secondary research project or other use is problematic, insofar as the researchers had an opportunity to obtain consent but did not pursue it.[39] Others question whether biological samples can truly be anonymized, especially given the increasing power of computers to store data, network, and search multiple databases.[43] Members of the NCHGR Workshop defined a sample as anonymous "if and only if it is impossible under any circumstances to identify the original source." They concluded that this is more possible with data sets involving large population groups (even when certain demographic or clinical information is retained), but questioned whether this was truly possible for a small group of samples (e.g., from the laboratory of an individual researcher).[39] Ellen Wright Clayton further suggests that even the process outlined in the Genetic Privacy Act (GPA) for ensuring unlinkability is inadequate.[44]

But even if one could guarantee that the sample could not be linked back to its source, Clayton further argues that using anonymized samples is not simply nonproblematic.[44] Arguments for the use of anonymized samples are premised primarily on the concept of benefit versus harm. Through the use of anonymized samples, advocates argue, benefits can accrue to the public good through the acquisition of knowledge and the development of useful therapies. At the same time, since the samples are anonymous, no harm can come, via the research, to the individuals who donated the samples. Clayton maintains, however, that the use of anonymous samples without the participants' consents (which would pertain to the use of samples in existing repositories) or the open-ended blanket consent for the use of anonymized samples could harm participants in two ways. First, broadening the more traditional notion of informed consent (as mentioned above), Clayton suggests that samples that are anonymized could be used for research that could stigmatize or harm the particular demographic group to which the individual belongs

(e.g., women, African Americans); harm could thereby come to the individual. Second, taking a more substantive view of the participants' involvement in the research endeavor, Clayton argues that the use of anonymized samples could harm the participants' interests by potentially involving them in research that they would find objectionable (e.g., certain sorts of behavioral research) even if it did not harm them directly; such research would make them collaborators in a project that they would find offensive or antithetical to their values, commitments, and understanding of the common good.

To address this issue, Clayton recommends that research protocols using anonymized samples *not* be exempt from IRB review and that in their risk/benefit calculations IRBs consider not only harm to the individual participant but the larger possibility of harm to society or to particular groups within society. She also concurs with the recommendations outlined in these various documents that patients/participants be given the ability, as part of the consent process, to determine whether their samples will be retained in an identifiable or anonymized fashion and be apprised that their samples might possibly be used for research. Philip Reilly, on the contrary, strongly objects to the suggestion that individuals might be permitted to prohibit anonymous use of their samples. Arguing that this would alter a long-standing practice in medical research, he believes it would be unnecessary "and possibly socially harmful," by prohibitively increasing the expense of valuable research in order to "only abstractly protect individual autonomy."[36]

Council of Regional Networks for Genetic Services' "Guidelines"

In 1996 CORN issued a statement entitled "Guidelines for the Retention, Storage, and Use of Residual Dried Blood Spot Samples after Newborn Screening Analysis."[33] They report that currently most states have few or no procedures for retaining, storing, or retrieving and most programs have no laws or regulations governing the use of what they term "residual DBSs (dried blood spots)." CORN strongly recommends that each newborn screening program begin by developing a sound justification for either saving or discarding DBSs after analysis is complete; this justification ought to be based on anticipated secondary uses of DBSs, the public health goals of the newborn screening program, and sound scientific data about long-term storage and analyte stability. If a program decides to retain its DBSs, it should develop duration parameters, storage guidelines, and retrieval procedures (including extensive documentation systems) consistent with the uses articulated in its justification. Finally, they recommend that each organization establish a review process, a method for prioritizing and agreeing to requests, and a written policy to govern release of DBSs.

The guidelines articulate the importance of informed consent, noting that with current consent practices issues of ownership and secondary use remain unresolved and need to be clarified. In general, though, they say little about what information that consent ought to contain, with one exception: "The collection form and educational material for parents could indicate that the sample becomes the property of the state and that, unless the parents object in writing, the sample may be used without personal identifiers in studies related to preventing birth defects and disorders of the newborn or for protecting public health."[33] They are, however, explicit about the parameters which should govern release. First, as noted above, each request for release of DBSs should be subject to a review process within the agency. In addition, for all proposals (except for internal anonymous research uses), whether the samples are identifiable or anonymized, they recommend review and approval by "a Human Subjects Review process." They articulate one primary criterion that should guide the internal review, namely, that secondary uses of DBSs should contribute to the primary goals of newborn screening — public health or family health. CORN seems equally open to the use of anonymized and identifiable samples. The guidelines note that anonymized samples negate the need for parental consent, although they do recognize Clayton's concerns. The release of identifiable samples, however, or of identifying information, requires a signed parental consent, and they state that a protocol for obtaining parental consent needs to be developed. If implemented, these guidelines would result in elaborate documentation and retrieval systems aimed at ensuring privacy and confidentiality.

NEWBORN SCREENING BLOOD-SPOT FILTER CARDS AS DNA DATABANKS

Given these findings concerning DNA databanks in general and the retention, storage, and use of newborn screening samples, what factors ought to guide newborn screening programs as they consider whether or not their facilities will retain samples and indeed establish a DNA databank and as they evaluate individual requests for secondary release of these samples? Three factors are primary: informed consent, goal of the secondary use, and review process. A framework based on these factors should be helpful in addressing the different issues presented by research, legal/forensic, diagnostic, and commercial requests for these samples.

Before considering issues particular to different secondary uses, serious attention needs to be given to the process and content of informed consent in the current practice of newborn screening. This reflects in part the evolving understanding of informed consent within the scientific, legal, and ethical

community. But more importantly, the trend toward seeing newborn screening labs as DNA databanks which can provide samples for secondary purposes has fundamentally altered the nature or status of the blood-spot filter card. Previously, one could have argued that newborn screening was simply one of a series of diagnostic assays performed under the umbrella of general parental consent to actions promoting neonatal health. But now the blood-spot filter card has become a commodity, an item with "value," to be used for purposes unrelated to the health of the individual newborn. In this new context, it will be increasingly difficult to justify conducting newborn screening in the absence of informed consent.

What information ought to be included in this informed consent process? We find that most of the items specified by the ACMG, the NCHGR, the GPA, and Weir/Horton regarding informed consent for DNA banking in general are strongly supported with regard to newborn screening. Clearly, the information about the primary purpose, risks, and benefits of the tests themselves is required and should be explained thoroughly to parents. Furthermore, states would have to offer compelling justifications for not including information on retention, possible secondary uses, and access to subsequent information. Once state newborn screening programs develop protocols governing retention, storage, and use of residual DBSs, this information should be easy to convey to parents.

Until issues of ownership are clarified, some areas will remain contentious. As noted above, the CORN guidelines suggest, without discussion and contrary to others' recommendations,[19,40] that newborn screening samples should become the property of the state. If so, at what point would these ownership rights be established? How would this affect parents' abilities to make initial specifications about the disposition of their child's sample? Would parents be able to specify that the sample should be destroyed rather than retained? Would they be able to do so at a later date? Would they be able to specify which secondary uses they would permit and which they find objectionable? Would they be able to specify whether the sample ought to be anonymized or remain identifiable? Would they be able to specify which investigator or institution may have access to their child's sample? Are there analogies for such transfer of ownership to the state, in total, in the areas of public health and medicine, and, if so, what are the limits of these analogies with regard to newborn screening?

Much more work needs to be done with regard to these issues of ownership. In the meantime, restrictions of parental authority in these areas would make secondary uses of newborn screening samples much more difficult to justify. We suggest that, in thinking through this relationship between parent,

child, and state, it might be more fruitful to use a different model for understanding newborn screening cards (or samples retained in most DNA databanks), seeing them not as commodities to be "owned" but rather as material held in "trust" by the state and the newborn screening laboratory for purposes of public health and for the interests of the individual contributor. This suggests a fiduciary rather than a proprietary role for the state and the newborn screening laboratory. Insofar as the cards contain information about individuals which can affect them materially, individuals should be able to retain some interests in and rights *vis-à-vis* the samples. They should be able to decide whether their cards are to be retained or not, whether they can be used for secondary purposes, and, if so, what those purposes might be. At the same time, this model would suggest that newborn screening programs be understood as foundations or trusts, managing a finite public resource with implications for the common good. Examining the issues of ownership/stewardship as modeled by trusts and foundations in the United States context might provide a useful, although imperfect, analogy.

One distinctive characteristic of foundations or trusts is that they are generally circumscribed by specific goals which delimit the deployment of their resources. So likewise, we would like to suggest, are newborn screening programs. These programs, as mentioned above, have been established to promote two related goals: individual/family health and public health. Newborn screening programs exist, first, to protect and promote the health and well-being of the individual newborn; this original purpose ought never be contravened. Thus, uses that could bring risk to the individual newborns or their families, even if balanced by greater social goods, ought to be disallowed. The second goal, as noted by CORN, is the promotion of the goals of newborn screening and public health. Secondary uses that contribute to these goals, without compromising the well-being of the individual sources, ought to be permissible.

How is it to be determined whether a particular request falls within the parameters circumscribed by these goals? Especially at this early juncture, each request should be evaluated on a case-by-case basis through a thorough, goal-oriented review process. First, as CORN suggests, each newborn screening program should identify and articulate (in written form) what it understands to be its goals. Based on these, as CORN also recommends, each newborn screening program should develop a written protocol for the review of requests for secondary release. This process should include review and approval by both the newborn screening lab and/or state oversight body and the investigator's local IRB.

In conducting this review, the reviewers ought to look at three issues. The

first consideration would be whether proposed investigation directly fosters the purposes of newborn screening and public health, as discussed above. A second and related consideration would be the impact of the use of the samples and the research project's potential for harm to society as a whole or to a particular social group (the point raised early by Clayton). Insofar as newborn screening programs are guided by public health considerations, newborn screening programs must necessarily broaden the concept of "harm" from a narrowly individualized application; this broader vision makes consideration of the impact of research on certain social groups an integral part of the evaluation process. Third, this review process ought to evaluate requests based on scientific and allocation criteria. The NCHGR, for example, suggests that, for both previously anonymized samples and samples which are to be anonymized, IRB review is appropriate and ought to consider five factors: (1) can the information be obtained any other way; (2) is the proposed investigation scientifically sound; (3) how difficult would it be to recontact subjects and obtain consent; (4) if the samples are finite, what impact will this have on the clinical needs of the patient and family; and (5) will the pursuit of anonymous research preclude the sources from obtaining effective medical interventions?[39] Thus, newborn screening cards ought not be used simply because they are available and expedient. Two issues must be taken into account regarding the use of these cards as a public resource. First, is the proposed use scientifically sound and is it reasonable to presume that useful information will be forthcoming? In other words, some clear "benefit" should be justifiably anticipated. Second, since the newborn screening databank is a public resource, one request should not deplete a particular sample or sample set. The newborn screening laboratory should only release part of the original sample (which CORN recommends) or should require that the secondary user make samples available to others.

Given the relative novelty of the use of newborn screening cards for secondary purposes, the concerns that surround them, the dubious consent conditions under which many currently retained samples were obtained, and the dearth of protocols within newborn screening laboratories concerning their use, it would be reasonable to recommend that for a certain defined period all proposals utilizing newborn screening cards (both identifiable and anonymized) be thoroughly reviewed by institutional IRBs as well as the appropriate state agencies responsible for newborn screening. At the end of this period, these protocols could be retrospectively reviewed, problems identified, concerns allayed, and guidelines established. We suggest that this would be a cautious yet constructive way to proceed.

This framework, then, should be able to provide guidance for the spectrum

of secondary uses for which newborn screening cards might be requested: research, legal (or forensic), diagnostic, or commercial. First, research conducted utilizing newborn screening cards could contribute to the goals of newborn screening and public health. At this juncture, it is difficult to imagine research scenarios which would *require* identifiable samples. Thus, we suggest that only anonymized samples be released for research, unless a compelling case can be made by the investigator and specific consent is obtained from the parents and/or source. This accords with the recommendations of the Committee on Assessing Genetic Risks.[32] Implementation of a review process, such as that outlined above, should ameliorate concerns about the use of previously obtained anonymized samples. Samples obtained in the future should carry with them permission to be enrolled in research in an anonymized fashion. If samples are to be released with identifying information attached, parents should be recontacted for consent. This step would also partially ameliorate concerns regarding the lack of original consent with previously stored samples. To reiterate CORN's recommendations, each agency needs to develop very carefully justified and written procedures for retention, storage, use, and processing of newborn screening cards and once armed with these procedures should still proceed very cautiously. In developing these procedures, great care will need to be taken with regard to the protections of confidentiality and privacy, given the public nature of the databank.

Second, release of newborn screening cards for legal or forensic purposes would be justifiable only on a more limited basis. Clearly, these samples would need to be released in an identifiable form; the use of large quantities of anonymized newborn screening samples to gather data on genetic variations within a population would not, for example, be justified given that this particular application does not fall under the aegis of the goals of newborn screening or public health. With regard to individual situations, the CORN guidelines maintain (although they do not discuss) that samples should be released in legal cases only "after careful consideration" and consultation with legal counsel. CORN does provide examples of compelling circumstances in which such use might be appropriate, primarily for determination of a previously unknown cause of death of the newborn from which the sample was obtained. Beyond issues of benefit to an individual or family of an individual source, or the determination of issues of negligence against a laboratory, it would be difficult to justify legal uses of newborn screening samples within a public health framework.

Ought newborn screening samples be used for secondary diagnostic purposes? Again, the range of justifiable situations in which this might be appro-

priate is more limited. For if, for example, the source of the individual sample is alive, diagnostic tests could be conducted on fresh samples taken within explicitly medical settings, where proper informed consent and counseling could be provided. This would be more appropriate. The use of these samples for diagnosis of later-onset conditions, should new diagnostic tests be developed, would not, per our discussion above, be appropriate within a newborn screening context. Again, in the case of a deceased child, retained newborn screening samples might be able to provide useful information to families regarding diagnosis of siblings, linkage studies, or subsequent decisions about pregnancies. Release for diagnostic use in these settings could be justified under a broad understanding of "benefit to the newborn," if one perceives a child and his or her interests as being intimately connected with those within the family network. Release in these circumstances would require parental consent, and issues of confidentiality and privacy would need to be well protected.

Finally, ought newborn screening cards be released to commercial entities for the purpose of developing proprietary products or services? This is an area which has received the least attention with regard to DNA databanking overall and newborn screening in particular. The CORN guidelines allude briefly to the possibility of commercial requests, noting only that "reimbursement should also be considered for provision of DBSs to commercial manufacturers for research applications." The premise of this position is that commercial ventures can help offset the costs associated with the storage and retrieval of the newborn screening cards. Within the framework that we have developed, release for commercial use could be justified only in the context of an investigation explicitly designed to benefit public health, particularly the goals of newborn screening (i.e., diagnosis of conditions for which treatment is available and for which immediate intervention will make a difference). Beyond this, it is difficult to imagine plausible scenarios. In addition, the possibility of commercial release again raises issues of ownership and profit-sharing. Clearly, it is not unreasonable to suggest that ownership rights in the samples ought not be transferred to commercial interests and that a percentage of the profits from a commercial venture should devolve to the newborn screening program for the benefit of public interests (cognitive of the issue of conflict-of-interest that this might raise).

If such release is approved, ought the samples be released in an identifiable or anonymized form? Straightforward anonymizing of the samples provides the strongest safeguards on privacy and confidentiality but eliminates the possibility of profit-sharing with the individual sources. An alternative might be to reobtain the consent of those whose samples are to be used and then to

release them in an anonymized fashion, a percentage of the profits then devolving equally to all who participated in the study. Clearly, this issue needs further study.

Conclusion

This study illustrates a relatively easy and efficient method for conducting DNA-based analyses on large numbers of samples derived from blood-spot filter cards. This method, when used on samples from the INMSP, could be used to determine allele- or carrier-frequencies within the Iowa population. This would provide a means of identifying additional types of genetic disorders that affect Iowa newborns and could thereby provide useful data to inform legislative or other public decisionmaking regarding public health policy and expenditures.

With further refinements, this approach could feasibly be used to develop DNA-based analyses for newborn screening programs. Such an application is not recommended at this time. Although technical issues concerning diagnostic efficacy could be resolved, and although DNA-based analyses would resolve certain problems like early discharge of newborns, DNA-based assays also introduce the issue of collateral information, and they pose real risks to newborns and their families. Until guidelines or legislation are implemented that will minimize those risks, current methodologies will remain more appropriate and cost-effective. We further hold that if DNA-based assays are introduced into newborn screening, the scope of application should be limited to the diagnosis of diseases in newborns for which treatment is available and for which immediate intervention makes a difference in morbidity or mortality. Testing for presymptomatic conditions, susceptibility, or carrier status is not appropriate within the parameters of newborn screening.

Finally, we recommend that well-established standards for obtaining informed consent from parents for newborn screening be implemented wherever newborn screening is conducted, especially in light of the developing trend toward seeing repositories of newborn screening samples stored in state facilities as DNA databanks amenable to secondary uses. With regard to secondary use of newborn screening samples, appropriate informed consent ought to be obtained for these uses. We recommend that prior to the release of newborn screening samples for secondary purposes state newborn screening labs, in conjunction with CORN, develop thorough written guidelines and procedures to govern retention, storage, and release, and institute substantive review processes to determine which instances of secondary use correspond

with the goals and responsibilities of newborn screening programs. In light of this, we suggest that both identifiable and anonymized samples can be used in the context of research, with appropriate protections. Further study needs to be done regarding legal and commercial applications. Overall, it remains a question of how to balance legitimate interests and goals of research that contributes to the common good while protecting the well-being and interests of those newborns who contribute to the research endeavor.

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