

NEWBORN GENETIC SCREENING: EVOLVING TECHNOLOGIES AND PUBLIC HEALTH POLICY

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Abstract:

Newborn screening programs historically sought to identify infants born with inborn errors of metabolism as early as possible so that timely intervention could mitigate the harm and improve the overall outcome. One of the earliest victories in newborn screening was testing for phenylketonuria (PKU), a genetic disorder that makes it impossible for the individual to break down phenylalanine, an amino acid found in many foodstuffs. PKU testing originated as a medical practice modality and eventually evolved into the standard of care, ultimately becoming public health law as a result of legislative advocacy on the part of parent and patient support groups. The newborn screening and testing movement has increased in volume and vitality over the last three decades providing testing for a growing number of genetic and congenital disorders. Multiplex technology such as tandem mass spectrometry (MS/MS) allows testing for a substantial number of genetic and metabolic disorders at once. However, many of these diseases are extraordinarily rare and do not have known treatments or preventive options.

As science delivers an increasing number of tests for the newborn, questions of clinical utility and resources allocation are rapidly emerging. How can new genetic and other newborn screening tests be assessed in terms of their usefulness and positive effect on health outcomes? Which disorders should be included in a uniform or model screening program and how should clinical utility be used to determine disorders to be included in the screening programs? When should screening be advocated for all newborns and when should a screening test be limited only to those in a defined risk group? What are the possible harms of using MS/MS and other multiplex technologies in newborn screening programs and identifying an ever increasing number of genetic mutations, many of which have limited clinical utility and no defined, easily administered "treatment"? This paper and presentation will consider these questions in the context of public health policy.

Keywords: Genetics; Public Health; Law

Introduction

In the United States, as well as in most other industrialized countries of the world, there is a longstanding commitment to government funded and sanctioned programs to improve public health. Many of these programs focus on improving and securing the health and well-being of the next generation. These include child protection services, laws and programs to ease access to health care, including mandatory vaccination and disease screening programs for children. Advances in genetic knowledge and technologies have generated a raft of new testing and screening opportunities for children and newborns.

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Public health programs and parents have begun to grapple with these new opportunities, despite the fact that understanding of the clinical implications and utilities of many of these tests are undetermined. This paper will review the history of newborn screening programs and consider the challenges genetics presents for their future.

History of Public Health Newborn Screening Programs in the United States

The history of public health newborn screening programs tracks back to the middle of the last century. In 1960, Dr. Richard Guthrie developed a screening test that could determine whether an individual was afflicted with phenylketonuria (PKU), a genetic inability to process the amino acid phenylalanine, that results in irreversible mental retardation. Guthrie found that PKU disease metabolites could be detected in a very small sample of blood. Once so determined, the patient could adopt dietary restrictions to prevent the harms caused by the disorder. The key, however, was that the test needed to be done in the newborn before the harmful metabolites could accrue. This discovery ushered in the concept of newborn testing to detect the illness before it could manifest. The disease is rare and sporadic, so the detection requires mass screening.

This testing originated as a medical practice modality and eventually evolved into the standard of care, ultimately becoming public health law as a result of legislative advocacy on the part of parent and patient support groups. By 1973, 43 states had mandatory testing and public health authorities became the prime movers for newborn screening programs.

Although Massachusetts initiated a voluntary PKU newborn screening program in 1962, the testing technology did not enjoy immediate widespread adoption. It was unclear who should bear responsibility for implementing such programs. Many public health authorities believed that this should be a medical practice standard and that pediatricians should prescribe the screening. Pediatricians were concerned about the accuracy of the test, its sensitivity and specificity, and validity. Moreover, in these early years, it was unclear whether an individual, even with stringent restrictions, could sufficiently excise phenylalanine from their diet. These questions led to federally funded research to determine the feasibility and effectiveness of PKU screening and treatment.

However, even before research into the effectiveness of PKU screening could be undertaken, state and federal legislators began to feel the pressure of parent and advocacy groups. Notably the National Association of Retarded Citizens and the March of Dimes engaged in drafting and lobbying for model legislation to create mandatory newborn screening for PKU. At the federal level, the President's Advisory Commission on Mental Retardation launched a public education campaign to alert parents to the risks of PKU and the availability of a screening test.

Because of parent and special interest group lobbying and federal interest, states began legislate mandated PKU newborn screening programs. By 1973, forty three states had created screening programs. Although state health departments often implemented the programs, funding for the testing was not necessarily fully authorized by the statutes. In 1976, federal legislation was passed to support state genetic service programs that would develop screening programs for genetic disease. As a result of this and follow-on federal legislation, newborn screening programs have expanded and become increasingly

comprehensive. Additional disorders, that like PKU, can be both detected in infancy and have treatment options have been added to the newborn screening packages mandated by state law.

By 2005, all 50 states had substantial newborn screening programs. All 50 states require newborns to be screened for PKU, congenital thyroid disease, and benign hyperphenylalanemia. All but one state requires all newborns to be tested for sickle cell trait, sickle cell disease and thalassemia (hemoglobinopathies). Virtually all of the states have a list of newborn screening tests in addition to these that are required, offered but not yet required, offered to select populations, or in the pipeline for the immediate future. See National Newborn Screening Status Report, available at <http://genes-r-us.uthscsa.edu/nbsdisorders.pdf>.

Expanding Newborn Genetic Screening: The Clinical Utility Question

Newborn screening historically sought to identify infants born with inborn errors of metabolism as early as possible so that timely intervention could mitigate the harm and improve the overall outcome. As detailed above, one of the earliest victories in newborn screening was PKU testing and successful treatment of infants and children with the disorder. Science and medical practice has developed tests for a growing number of metabolic conditions, hemoglobinopathies (blood cell disorders), endocrine disorders, and other congenital medical problems. Moreover, there has been substantial improvement in the testing technologies, notably through multiplex technology (laboratory techniques that for several disorders on one test “platform”) and the positive predictive values of the tests themselves. There is increasing capacity to detect genetic anomalies and other inborn errors of metabolism.

The sheer number of detectable anomalous genetic "disorders" has provided parents, physicians and policy-makers with a new set of questions and concerns. With respect to medical science, one of the first issues of import is the status of the test in terms of analytic validity, clinical validity and clinical utility. Analytic validity refers to how well the genetic assessment performs in measuring the property or characteristic it is intended to measure. In the context of a genetic mutation, analytic validity refers to the accuracy of the test in testing for the specific mutation. Once analytic validity is established, it is necessary to assess clinical validity. Clinical validity refers to the predictive value of a test for a given clinical outcome -- that is the likelihood that a disease will develop in someone with a positive test for the gene related to that disease. Clinical validity is primarily determined by the sensitivity and specificity with which a test identifies people with a defined clinical condition. Sensitivity of a test refers to the proportion of persons who test positive from among those with a clinical condition; specificity refers to the proportion of persons who test negative from among those without the clinical condition. The clinical validity of a genetic test is the likelihood that the disease associated with that genetic mutation will develop in someone with a positive test result. This likelihood is affected not only by the presence of the gene itself, but also by any modifying factors that affect the penetrance of the mutation, such the environment, nutrition, and other genes. Finally, and perhaps most important, is the clinical utility of a genetic test. Will the test and the interventions that flow from it effect an improved health outcome? Once known, can the disease be prevented or ameliorated by therapy or lifestyle modification? The question of

clinical utility is the ultimate determinant of whether a genetic test has merit for clinical application.

Thus, in the case of testing for a disorder that cannot be prevented, ameliorated or cured, the clinical utility of the test is questionable. Such would be the case with genetic tests that test for incurable diseases that cannot be prevented. It may be, as in the case of hemochromatosis or Factor V Leiden, that the genetic mutation is but one of many factors disposing an individual to the disease and clinical utility is questionable at best. Only if identification of the mutation results in a change in medical management and an improved qualitative and/or quantitative outcome is the aim of clinical utility realized. Analysis of analytic validity, clinical validity and clinical utility are critical to the risk/benefit analysis of each genetic test. It is essential that this analysis be performed before the test is adopted in practice or by a legislatively sanctioned screening program.

The recently published report, "Newborn Screening: Toward a Uniform Screening Panel" has attempted to catalogue what is covered by state newborn screening programs and provide a platform upon which to develop a Uniform Screening Panel. What would be the advantages of such a Uniform Screening Panel? What would be the disadvantages? The conclusion of the American College of Medical Genetics/Health Resources Services Agency (ACMG/HRSA) panel that authored the report was that 29 conditions might be included in a uniform panel based on their analysis of the validity and utility of the tests. However, only three of the conditions fully met the criteria. These included PKU, congenital hypothyroidism, and MCAD.

In the case of PKU and congenital hypothyroidism, both conditions can be treated, and indeed must be treated in infancy, to prevent permanent harm to the infant. In these cases, the clinical utility is clear. MCAD is a genetic enzyme deficiency that renders the infant highly susceptible to severe physiologic response when ill, dehydrated or fasting. Infants with MCAD may go into cardiovascular collapse and die when confronted with otherwise minor infections or illnesses. As a result 60% die within the first two years of death of what appears to be sudden infant death syndrome. There is no treatment for MCAD, but once informed, parents and providers are alerted to be vigilant and aggressive in treating even the most minor of illnesses in the child. Improvement in outcome is dependent upon continued, unremitting surveillance and rapid medical intervention.

MCAD is one of many diseases that can be detected using a multiplex technology, tandem mass spectrometry (MS/MS). MS/MS detects abnormal levels of amino acids and acylcarnitines. Abnormal elevations of these amino acids may indicate the newborn is at risk for variety of disorders of amino acid metabolism. MS/MS technology allows testing for a substantial number of genetic and metabolic disorders at once. However, many of these diseases are extraordinarily rare and do not have known treatments or preventive options. This raises significant questions for parents, patients and public health.

Parents, Patients, and Public Health: The Promises and Peril of Newborn Screening

The growing number of newborn screening tests, especially for genetic disorders that are not fully understood with respect to disease manifestation and outcome, presents parents, patients and public health with new challenges.

What are the possible harms of using MS/MS other advanced technologies to identify an ever increasing number of genetic mutations? What is the downside of testing for more and more disorders, many of which, like MCAD, do not have a defined, easily

administered "treatment"? Which disorders should be included in a uniform or model screening program is just one of the questions bedeviling health policy. Among the others are: How will parents be able to understand and assimilate the meaning of these tests? How will physicians and providers be able to provide parents fully informed consent when the meaning of the tests may still be nebulous? What effect will a "positive" test have on the parent-child attachment? Should all newborns be screened or only those in defined risk groups? Who has access to test results? What are the potential risks of screening? And who pays for the screening program, and how? What role should government-funded public health programs play

From the perspective of parents, the plethora of tests presents an additional quantum of knowledge that must be understood. Particularly in the United States where the concept of patient autonomy is highly developed, many parents will be presented with testing opportunities and decisions shortly after the birth of their child -- a time that is highly emotional and stressful. Complicating the scenario is the fact that much of the information is highly technical and complex. Moreover, because the test may not be dispositive with respect to a disease entity, merely one of several indicators, parents may be in a quandary with respect to how to best protect their child. Many more may be simply confused and unable to grasp the purpose and meaning of the tests. Physicians and other health care providers will likely find that the burden of explaining these tests and their ramifications onerous and difficult as they attempt to engage in the informed consent process. This burden will be increased manifold in the case of a positive or ambiguous test results.

Newborn screening leads to the question of the ethical, legal and psychosocial implication of genetic testing in children. The newborn is the most affected by and the most unrepresented in medical decision-making with respect to screening for genetic diseases. This is particularly true with respect to testing that belies a future illness that may not manifest until adulthood. Both the Institute of Medicine and the American Academy of Pediatrics recommend that childhood testing not be done unless diagnosis of a genetic condition can provide a clear benefit to the child, the diagnosis is confirmable, and treatment is available for the diagnosed condition. These conditions are not met with respect to many of the conditions included in the proposed Uniform Screening Panel. Although one assumes that the parent is the best arbiter of the child's best interests, it is possible that the newborn's interests may diverge from those of the parent. In fact, one recent study of parental attitudes indicates that parents believe that their decisional authority should trump professional policy statements. The chances that parents can justifiably speak for the adult their child will be in the future seem slim at best.

Genetic testing may not only fail to benefit the newborn, it may lead to an altered self-image for the child and impair the psychosocial relationships in the family. If one child is perceived to be imperfect by virtue of a genetic screening test result, that child might be stigmatized within the family and also be labeled with respect to educational and other opportunities of childhood. Beyond that, knowledge of an adult-onset disease conferred upon a child may significantly alter their life and perspective with respect to life choices. Even taking into account the difficulty in living with uncertainty about the health status of the child, the child has an inherent right to make an independent decision with respect to testing after they are adult, unless there is some treatment that needs to be undertaken before then. This is sometimes termed the child's right to an "open future." As more and more tests become available, the questions with respect to the benefits for the child will become even more pressing.

From a public health and policy standpoint, the plethora of available tests presents questions as to how whether potential screening should be undertaken. If indeed a Uniform Screening Panel is adopted by state authorities, what implications does this have with respect to impairing autonomy of the parent and child? Even assuming that parents may opt out, how many parents will fully realize this option and how many will tacitly agree to the testing without fully understanding and realizing the implications and limitations of each and every one of the many screening tests. How will the public health system, chronically under-funded and understaffed, absorb the additional work and responsibility of implementing ever more complex newborn genetic screening programs?

As testing panels become more complex, the direct and indirect costs will increase. At the present time, newborn screening programs are financed primarily by patient fees. In fact, 45 states fund their programs by fees, while only 5 (plus the District of Columbia) do not collect fees. However, the fees for newborn testing typically cover only the laboratory testing costs. With more tests and expensive testing technologies, states will and indeed have increased the fees. In Minnesota, for instance, the newborn screening fee increased from \$13 in 1997 to \$61 in 2004, a 369% increase. These fees are usually not covered by Medicaid or third-party payors, thus as the fee level increases beyond nominal, the expectation would be that they will be unaffordable to a significant subset of the population and become an unfunded mandate. Mandated screening does not necessary provide for genetic counseling and parent education in the case of a positive result. Equally and perhaps of even greater concern, the treatment and long-term care of children identified through newborn screening is not likely to be covered by Medicaid and third party payers. For example, many of the disorders identified require special diets or even prescription food, which may not be covered by payors and may be extraordinarily expensive. For example, this has played out dramatically in the case of PKU. Most states do not require coverage of specialized food created for those with PKU. Absent compliance with diet restrictions, the patient will suffer the effects of the disease, including mental retardation. Thus as states decide which tests to include in the newborn screening panel, they must also struggle with financing the tests, the counseling and the treatment if the aim is indeed improved health outcomes.

Conclusion

It remains to be seen whether the ASCMG/HRSA recommendations for a Uniform Screening Panel will become the new standard for medical care of the newborn. The recommendations bring to the forefront questions of clinical utility with respect to an increasing array of newborn genetic tests. Advances in testing technologies and expanded test opportunities offer opportunities for earlier diagnosis and recognition of genetic disease. However, only a minority of the tests offer an opportunity for prevention or amelioration of disease. The complexities of testing present challenges to parents who are not necessarily attuned to the nuances of the test results and to health care providers who will struggle to educate parents. The newborn test subject may be subjected to a plethora of tests that may have significant psychosocial risks for the child and alter his standing within the family. Finally, the testing proposed in the Uniform Screening Panel has profound implications for state-funded testing programs in which newborn screening must compete with other pressing public health needs

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