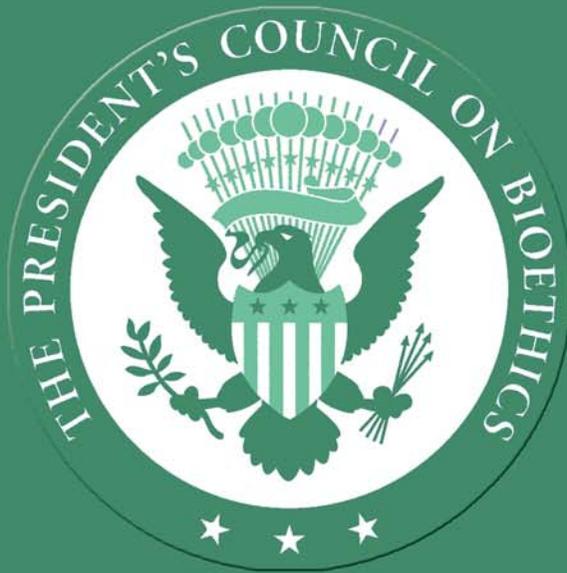


# The Changing Moral Focus of Newborn Screening:

An Ethical Analysis by  
the President's Council on Bioethics



December 2008

THE CHANGING  
MORAL FOCUS OF  
NEWBORN SCREENING



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[www.bioethics.gov](http://www.bioethics.gov)



# CONTENTS

LETTER OF TRANSMITTAL TO THE PRESIDENT.....	ix
MEMBERS OF THE PRESIDENT’S COUNCIL ON BIOETHICS .....	xi
COUNCIL STAFF .....	xv
PREFACE .....	xvii
INTRODUCTION .....	1
CHAPTER ONE: NEWBORN SCREENING TODAY .....	5
I. The Practice of Newborn Screening .....	5
A. Education .....	7
B. Screening .....	8
C. Follow-up and Diagnosis .....	12
D. Treatment and Evaluation .....	15
II. Public Policy and Newborn Screening .....	17
CHAPTER TWO: THE CHANGING PRINCIPLES AND PRACTICE OF NEWBORN SCREENING .....	21
I. The Classical Principle: Screen Only If You Can Effectively Treat .....	21
II. Newborn Screening and the ACMG’s Expanded Uniform Panel .....	27
A. Reactions to the ACMG Report.....	30
B. The Core or Primary Conditions .....	35
C. The Secondary Conditions .....	37

D. The Role of Multiplex Screening Platforms.....	41
E. A Broadened Conception of Benefit .....	44
F. Impact of a Broadened Conception of Benefit on the ACMG Recommendations.....	45
III. The Significance of the ACMG’s Recommended Screening Panel.....	48
CHAPTER THREE: THE FUTURE OF NEWBORN SCREENING.....	51
I. Newborn Screening at the Dawn of the Genomic Era....	52
II. The Case for Newborn Profiling .....	56
A. The Logic of Personalized Medicine and Technological Progress .....	56
B. The Benefits of Biobanking .....	58
C. The Psychosocial Consequences of Testing Positive: A Silver Lining? .....	61
D. The Support of Parents and Advocacy Groups.....	62
III. The Case for Caution.....	65
A. “Personalized Medicine” in the Traditional and Increasingly Rare Sense .....	65
B. Doubts About the Power of Genomic Medicine .....	67
C. Newborn Profiling and the Problem of Risks And Benefits .....	70
D. Ownership of Genetic Information and the Challenge of Informed Consent .....	74
E. Genetic Disease and Human Difference.....	77
F. Newborn Screening, Genomic Medicine, and Eugenics.....	77
G. Genetic Information and the Problem of Self-Knowledge .....	82
IV. On the Necessity and the Limits of Speculation .....	83

CHAPTER FOUR: NEWBORN SCREENING: MANDATORY,  
ELECTIVE, OR BOTH?..... 85

    I. Mandatory Screening Versus Informed Parental  
    Consent..... 86

    II. A Two-Tiered Approach to Newborn Screening..... 93

        A. The Massachusetts Model..... 94

        B. The Future of Screening in Massachusetts ..... 97

    III. Combining the ACMG’s Recommended Panel and  
    a Two-Tiered Approach..... 100

    IV. An Ethical Framework for the Ongoing Expansion of  
    Newborn Screening: A Recommendation by the  
    President’s Council on Bioethics ..... 105

PERSONAL STATEMENTS ..... 109

    Floyd E. Bloom, M.D., and  
    Michael S. Gazzaniga, Ph.D. .... 111

    Jean B. Elshtain, Ph.D. .... 115

    Gilbert C. Meilaender, Ph.D. .... 119

    Carl E. Schneider, J.D. .... 123

BIBLIOGRAPHY..... 127





# LETTER OF TRANSMITTAL TO THE PRESIDENT OF THE UNITED STATES

The President's Council on Bioethics  
1425 New York Avenue, NW, Suite C100  
Washington, DC 20005  
December 2008

The President  
The White House  
Washington, DC

Dear Mr. President:

With this letter, I am transmitting a white paper entitled *The Changing Moral Focus of Newborn Screening: An Ethical Inquiry by the President's Council on Bioethics*.

Nearly four million newborns undergo genetic screening every year in the United States. Yet, the process of genetic screening and its ethical implications are not well understood by their parents. Public discussion and education about recent changes in public policy and screening techniques is insufficient for parents to make informed choices. One aim of this white paper is to provide the background information every parent needs in order to understand the issues and to make informed choices.

Most states have mandatory genetic screening programs for newborn babies. Until recently such screening was limited to diseases that were well understood and for which effective treatments were available. Now, however, most mandatory screening programs also test for diseases that are not well understood and for which there is no available treatment. Some believe this change is ethically justifiable because much knowledge of little understood diseases could be gained and lead eventually to treatment and cure.

This white paper describes how the change in policy to include screening for untreatable as well as treatable diseases came about. To this end, it provides basic information about the techniques of screening, the practical and ethical choices parents must face, and the public policies behind those choices.

The Council concludes that the potential benefits of mandatory, population-wide newborn screening for diseases for which there is no current treatment are outweighed by the potential harms. These harms will be accentuated once new DNA technologies make it possible to expand screening to target additional diseases and to detect disease susceptibility as well. But the Council also acknowledges that the gains in biomedical knowledge from expanded screening programs should not be ignored.

Therefore, the Council recommends that the states mandate newborn screening only for diseases that meet traditional criteria, including the availability of an effective treatment. But the states are encouraged to implement pilot studies for newborn screening of conditions that do not meet the traditional criteria. Participation in these pilot studies should require the voluntary, informed consent of the infant's parents.

In this way, the present benefits of newborn screening can be optimized in an ethical way, and the future benefits of new techniques to expand our knowledge of untreatable diseases will be facilitated in an ethically sensitive way.

Sincerely yours,

A handwritten signature in black ink, appearing to read "E. D. Pellegrino".

Edmund D. Pellegrino, M.D.  
Chairman

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## PREFACE

*The Changing Moral Focus of Newborn Screening* is a white paper of the President's Council on Bioethics. The Council was established on November 28, 2001, to advise the President on bioethical issues related to advances in biomedical science and technology. In connection with its advisory role, the Council undertakes fundamental inquiry into the human and moral significance of developments in biomedical and behavioral science and technology, with the aim of fostering greater understanding and public discussion of bioethical issues.

The subject of this white paper is a type of genetic screening that is widely practiced in the United States—and yet little understood, especially by the parents of the nearly four million newborns who are screened every year. In the last few years, both the practice and the moral focus of newborn screening have begun to change, also in ways that are little understood or publicly discussed. With the hope of promoting discussion and understanding of these changes, among policymakers and the public at large, the Council undertook the inquiry that now culminates in the publication of this white paper.

The origins of this inquiry date back to December 2005, when the Council began to consider the topic of children and bioethics; in September 2006, the Council also took up the topic of ethical issues in genetic research and technology. This white paper began to take shape at the confluence of these two broader streams of inquiry. It reflects a careful study of the published literature on the ethics, policy dimensions, and technologies of newborn screening. The ideas and arguments presented herein were initially developed in working papers authored by the Council staff and in discussions among the Council members themselves.

The ideas and arguments in this white paper have been shaped in significant ways by presentations at Council meetings by some of the leading experts and scholars in the field: Duane Alexander, director of the National Institute of Child Health and Human Development; Jeffrey R. Botkin of the University of Utah School of Medicine; Francis Collins, former director of the National Human Genome Research Institute; Norman Fost of the University of Wisconsin School of Medicine and Public Health; Kathy Hudson, director of the Genetics and Public Policy Center; Michael S. Watson, executive director of the American College of Medical Genetics; and Nancy Wexler, president of the Hereditary Disease Foundation. (Transcripts of their remarks are available online at [www.bioethics.gov](http://www.bioethics.gov).) The Council extends its thanks to these individuals and to Michele A. Lloyd-Puryear, chief of the Genetic Services Branch of the Maternal and Child Health Bureau at the Health Services and Resources Administration, U.S. Department of Health and Human Services, and Kevin Fitzgerald, the David Lauler Professor of Catholic Health Care Ethics at Georgetown University, who met with the Council staff to discuss ethical issues confronting the practice of newborn screening today.

Finally, the Council is grateful to the following experts for their willingness to read and offer criticism of earlier drafts of portions of this white paper: Duane Alexander, Jeffrey R. Botkin, Wylie Burke of the University of Washington, Ellen Wright Clayton of Vanderbilt University Law School, Thomas Murray of The Hastings Center, Lainie Friedman Ross of the University of Chicago, and Benjamin S. Wilfond of the University of Washington School of Medicine.



## INTRODUCTION

*What ethical principles should guide the practice of newborn screening in the United States?* That question is the starting point for this white paper by the President's Council on Bioethics. It has been a serious question since newborn screening began over four decades ago; in recent years, however, it has taken on new urgency in light of significant and ongoing changes in the practice of newborn screening. In this white paper, the Council analyzes these changes and their ethical implications.

The great majority of babies born in the United States each year<sup>1</sup> undergo screening soon after birth to identify genetic defects that could cause serious illness if left undetected and untreated. The goal is to detect diseases as early as possible so that timely, effective treatment can be initiated even before the onset of symptoms. In most states, newborn screening is now mandated by law. The number of conditions screened for by state health departments has expanded considerably since the 1960s, when microbiologist Robert Guthrie invented the heel-stick blood test for phenylketonuria (PKU). In the United States today, almost all infants are screened at birth for between thirty and fifty genetic disorders, depending on the screening program of the state in which they are born. Of the approximately four million babies screened each year, about 5,000 are identified as having serious heritable disorders, most of which are, in varying degrees, amenable to treatment.<sup>2</sup>

Newborn screening has produced undeniable benefits: for example, PKU—which causes severe, irreversible mental retardation if left untreated—is one of the few genetic diseases whose symptoms can

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<sup>1</sup> More than ninety-eight percent in 2008, according to the Centers for Disease Control and Prevention's Division of Laboratory Sciences. See [www.cdc.gov/nceh/dls/newborn.htm](http://www.cdc.gov/nceh/dls/newborn.htm).

<sup>2</sup> *Ibid.*

be controlled by a restricted diet, and newborn screening identifies about 200 infants with PKU in the United States every year. Another notable success story has been the early detection of congenital hypothyroidism (CH), whose symptoms—including abnormal growth and mental retardation—can easily be controlled with a daily dose of thyroid hormone; newborn screening for CH, initiated in the 1970s, now detects over 1,000 cases of CH in the United States each year. In the wake of these and other achievements, more and more disorders have been added to state-mandated newborn screening programs. Today, we routinely screen infants for dozens of rare genetic disorders, including some whose medical implications are not clearly understood and for which effective treatments are not yet available.

Traditionally, a population screening program (whether for children or for adults) has been considered justifiable only if the targeted condition is an important health problem, whose natural history is well-understood, and whose symptoms are amenable to early intervention and effective treatment. On this view, the object of screening is to discover those among the apparently well who are in fact suffering from disease, in order to initiate timely and effective treatment. Accordingly, the mere availability of a reliable test would not justify routine screening for a condition, unless such screening could be shown to provide *direct medical benefit* to those who test positive for the condition. In short, for more than forty years the moral focus of newborn screening has been *what is good for the infant*.

As more and more disorders have been added to state newborn screening programs, however, the traditional ethical principles of screening have been called into question. Some have argued that the central criterion of direct medical benefit to the infant need not be strictly satisfied in order to justify routine screening for a condition; according to this view, a *broader conception of benefit*—including benefits to the family and to society at large as well as indirect benefits to the child—justifies screening even for conditions that are poorly understood or that do not, as yet, have an effective treatment. Others have argued that all (or almost all) conditions that can be detected should be screened for at birth—reasoning that such screening is the most effective way to gain knowledge of and

find treatments for diseases that are rare, poorly understood, and at present untreatable. According to both of these positions, newborn screening should be considered an appropriate tool of *biomedical research*, which benefits society as a whole by increasing our knowledge of rare diseases and, ultimately, our ability to treat them.

The aim of the present white paper is to foster public awareness of the practice of newborn screening, the ethical principles that have guided it until now, and the ethical problems posed by its current and future expansion. The white paper consists of four chapters. In the *first chapter*, we describe the current practice of newborn screening in the United States: how a blood sample is taken from each infant at birth, how the blood is tested for heritable disorders, and what is done with the information gleaned from those tests. We also identify some of the ethical challenges that confront us as we try to reap the benefits of newborn screening while minimizing the harms. Finally, we explain the public policies that shape the practice of newborn screening in the United States. In the *second chapter*, we explain the ethical principles that have guided the practice of newborn screening for the past forty years, and we consider whether those ethical principles have been altered or abandoned by the new regime of expanded newborn screening that is currently being adopted by most states. In the *third chapter*, we attempt to envision the future of newborn screening, examining the ethical implications of the vast expansion of newborn screening that can be anticipated as the age of personalized genomic medicine advances. Finally, in the *fourth chapter*, we take up the urgent question of whether the states should have mandatory screening programs (as most currently do), elective programs, or some combination of the two. We close this chapter and the white paper as a whole by recommending an ethical framework for a sound newborn screening policy in the United States—a framework that we believe to be not only appropriate for the present phase of newborn screening but also valuable for addressing future medical and technological advances in newborn screening.





# CHAPTER ONE

## NEWBORN SCREENING TODAY

Newborn screening in the United States today is a complex public health endeavor that touches the lives of nearly every one of the four million babies born in the country each year. In this chapter we offer an account of the basic features of newborn screening as it is practiced in the United States. We first trace the origins and describe the current practice of newborn screening, noting some of the challenging aspects of it that raise ethical questions. Then, we briefly describe the state and federal policies pertaining to the practice of newborn screening.

### **I. The Practice of Newborn Screening**

Screening is a public health initiative that surveys an entire population (or sub-population) for evidence of an illness before it exhibits symptoms. The purpose of screening is to identify those among the apparently well who are suffering from (or who will likely develop) a disease and who are likely to benefit from early detection and intervention.<sup>1</sup> Because screening is applied to the healthy and the sick alike, the screening assay must be both sensitive—it should identify all or almost all cases of disease—and specific—it should minimize the number of false positives, i.e., of healthy individuals who are incorrectly identified as having the disease. When screening for rare disorders in large populations, it is all but inevitable that some healthy individuals will initially test positive for the disease. Because of this problem of false positives,

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<sup>1</sup> Screening of populations is different from testing of individuals; an individual patient who exhibits certain symptoms of illness will typically undergo diagnostic testing to ascertain the cause and the severity of the illness.

screening programs typically require follow-up testing to confirm or deny the initial result.

As practiced in the United States, newborn screening is almost entirely *genetic* screening.<sup>2</sup> That is, the illnesses targeted are heritable disorders that are caused by abnormalities in the individual's genes and chromosomes.<sup>3</sup> Newborn screening is applied to the entire population shortly after birth. Genetic screening at other stages of life is also possible, but is generally practiced more selectively when there is a perceived need. For example, preimplantation genetic diagnosis (PGD) involves screening human embryos before transfer to a woman's uterus after in vitro fertilization; prenatal screening (e.g., by amniocentesis) looks for genetic defects in the fetus prior to birth; post-infancy screening is applied to children in the years after birth; carrier screening (at any stage of life, but especially in prospective parents) is used to identify healthy people who carry one copy of a defective gene that, if present in two copies, would cause an illness.<sup>4</sup>

Newborn screening began in the United States in the early 1960s after American microbiologist Robert Guthrie developed a test for phenylketonuria (PKU), an inborn error of metabolism that, if left untreated, causes severe mental retardation. Guthrie's simple, sensitive test for PKU required absorbing a drop of the infant's blood on a piece of filter paper. During the 1960s most states

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<sup>2</sup> On similarities and differences between genetic and non-genetic testing, see Michael J. Green and Jeffrey R. Botkin, "'Genetic Exceptionalism' in Medicine: Clarifying the Differences between Genetic and Nongenetic Tests," *Annals of Internal Medicine* 138 (2003): 571-575.

<sup>3</sup> A few states also screen newborns for infectious diseases: Massachusetts and New Hampshire screen infants for toxoplasmosis. Connecticut, Illinois, and New York screen for HIV; Connecticut and Illinois do so only if the mother was not tested for HIV during pregnancy. See the National Newborn Screening and Genetic Resources Center's "National Newborn Screening Status Report," (November 10, 2008, version), available online at <http://genes-r-us.uthscsa.edu/nbsdisorders.pdf>.

<sup>4</sup> For example, couples of Eastern European Jewish descent who are contemplating marriage and childbearing may prospectively undergo carrier screening for Tay-Sachs disease, an invariably fatal genetic disorder that will affect about a quarter of their children if both parents are carriers of the defective gene.

passed laws requiring that a drop of blood be drawn after pricking the heel of each infant at birth, so that the blood could be analyzed for evidence of PKU. The rationale for mandatory PKU screening was that affected infants could suffer devastating neurological damage if there were even a few weeks of delay in starting them on a low-phenylalanine diet. Afterwards, other diseases that also could be detected in that blood spot were added to the state screening programs: galactosemia (GALT), maple syrup urine disease (MSUD), and homocystinuria (HCY) in the late 1960s, congenital hypothyroidism (CH) in the 1970s, and sickle cell disease (SCD) in the 1980s. Over the years, newborn screening has steadily expanded so that today, depending on the state, an infant born in the United States is likely to be screened for somewhere between twenty-nine and fifty-four conditions.

The practice of newborn screening varies from state to state; there is no unified systematic approach at the national level. However, since 1985, the Council of Regional Networks for Genetic Services (CORN) has endeavored to provide public health services with an overall framework for a systems approach to newborn screening.<sup>5</sup> Ideally, an effective newborn screening program includes the following elements: education, screening, follow-up and diagnosis, treatment, and evaluation.

### ***A. Education***

An effective newborn screening program must ensure that medical professionals, parents, and the general public are adequately informed about newborn screening and the heritable disorders that it targets. Educating parents about newborn screening is a challenge that will only grow with the increasing number and complexity of

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<sup>5</sup> See Bradford L. Therrell, et al., “U.S. Newborn Screening System Guidelines: Statement of the Council of Regional Networks for Genetic Services (CORN),” *Screening* 1 (1992): 135-147; Kenneth A. Pass, et al., “US Newborn Screening System Guidelines II: Follow-Up of Children, Diagnosis, Management, and Evaluation. Statement of the Council of Regional Networks for Genetic Services (CORN),” *Journal of Pediatrics* 137 (2000): S1-S46; and American Academy of Pediatrics, “Serving the Family From Birth to the Medical Home. Newborn Screening: A Blueprint for the Future,” *Pediatrics* 106 (2000): 389-422.

the disorders for which babies in the future will be screened. Typically, for prospective parents a state publishes an informative brochure that attempts to educate them about what newborn screening is and what consequences it may have for their child.<sup>6</sup> The obstetrician may discuss newborn screening with the parents sometime late in the third trimester, in the course of preparing them for what will happen at the hospital when their baby is born.<sup>7</sup> Yet, as studies have shown, most parents are only vaguely aware that their newborns are being screened, even after the drawing of blood; they are even less aware of the particular conditions for which screening is carried out:

Very rarely did parents say they sought or received information about newborn screening before their infant was born. Many recalled receiving a newborn screening brochure in a packet of information given to them during the hospital stay after delivery; very few, however, reported reading it or remembering the information in the brochure. Even fewer actually recalled being told anything about newborn screening while in the hospital. If they were told anything, it was that their infant had a “blood test.” “The hospital visit was a fog; the only thing I wanted to know was ‘is the baby OK?’”<sup>8</sup>

### ***B. Screening***

The fact that parents of newborns are generally ignorant about newborn screening is hardly surprising. The birth of a child is a momentous and exhausting experience for parents; so much is

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<sup>6</sup> See Bradford L. Therrell, et al., “Status of Newborn Screening Programs in the United States,” *Pediatrics* 117 (2006): S212-S252, Table 3, “Responses to Survey of Processes Related to State/Territorial Newborn Screening Information Brochures,” pp. S218-S219; and Kathryn E. Fant, et al., “Completeness and Complexity of Information Available to Parents from Newborn-Screening Programs,” *Pediatrics* 115 (2005): 1268-1272.

<sup>7</sup> See Ellen W. Clayton, “Talking With Parents Before Newborn Screening,” *Journal of Pediatrics* 147 (2005): S26-S29.

<sup>8</sup> Terry C. Davis, et al., “Recommendations for Effective Newborn Screening Communication: Results of Focus Groups With Parents, Providers, and Experts,” *Pediatrics* 117 (2006): S326-S334.

going on in the first minutes and hours after birth that the drawing of a drop of blood from the infant's heel is not likely to loom large in the parents' minds as a significant event. From the moment of birth the newborn baby is constantly being evaluated, beginning with the Apgar scores (recorded at one minute and five minutes after birth) that assess the baby's skin color, heart rate, reflexes, muscle tone, and breathing. The baby is also being measured, washed, and given eye drops to prevent infection, a vaccine against hepatitis B, and a vitamin K shot to improve clotting. Sometime before the baby leaves the hospital (usually between twenty-four and ninety-six hours after birth), the heel is pricked and a few droplets of blood are squeezed out and absorbed onto a piece of filter paper, and that is the last that most parents will hear about genetic screening of their infant, unless a positive result is reported for one of the assays.<sup>9</sup>

The specimen of the baby's blood is sent to a laboratory, where concentrations of specific chemical compounds are measured and compared with the normal ranges expected for healthy babies. Within the last five years, most screening laboratories in the United States have begun to use a technology called tandem mass spectrometry (MS/MS) as the principal tool for analyzing newborn blood samples. MS/MS has made the screening process easier because it is a "multiplex testing platform," i.e., it can be used to screen at once for over forty of the "inborn errors of metabolism" that comprise a large majority of the conditions targeted by newborn screening. These metabolic disorders detected by MS/MS can be separated into three categories: fatty acid disorders, amino acid disorders, and organic acid disorders.

Fatty acid disorders are caused by deficiencies in the enzymes that help the body derive energy from fat. Fat must be used as a source of energy when the body runs out of glucose, the principal source of energy production. If blood glucose levels are depleted and the

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<sup>9</sup> Some states require that infants be screened a second time, some days or weeks after birth, though most states require repeat screening only if the initial screening was performed less than twenty-four hours after birth. The purpose of such repeat screening is to catch disorders that for a variety of reasons might not show up in blood samples taken so soon after birth.

body is unable to metabolize fat, the cells of the body suffer an energy crisis, which can lead to lethargy, coma, or death. Fatty acid disorders may also result in excessive fat buildup in the liver, heart, and kidneys, causing a variety of symptoms, including liver failure, encephalopathy (diseases of the brain), heart and eye complications, and problems with muscle development. Two examples of fatty acid disorders are medium-chain acyl-CoA dehydrogenase deficiency (MCAD) and very long-chain acyl-CoA dehydrogenase deficiency (VLCAD).

Amino acid disorders are caused by one of two sorts of enzyme deficiencies: either a failure of the enzymes needed to break down certain amino acids, or a failure of the enzymes needed to rid the body of ammonia (a by-product of amino acid metabolism) by way of the urea cycle. The buildup of amino acids or ammonia in the blood can cause severe medical complications, including mental retardation, developmental delays, failure to thrive, and death. Two examples of amino acid disorders are PKU and MSUD.

Organic acid disorders involve deficiencies in the enzymes that normally help in the breakdown of amino acids (as well as, in some cases, lipids and sugars). When these substances are not broken down, toxins accumulate in the body. The enzyme deficiencies are farther down the pathways of amino acid metabolism, so there is not a buildup of amino acids but of certain organic acid intermediates. Infants with these disorders are usually well at birth, but may soon develop poor feeding, irritability, lethargy, vomiting, and other symptoms, including coma or death. Some of these disorders have later onset or milder symptoms. Two examples of organic acid disorders are isovaleric acidemia (IVA) and glutaric acidemia type 1 (GA1).<sup>10</sup>

Before MS/MS was introduced for newborn screening, a separate assay was needed for each condition. Now only endocrine disorders

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<sup>10</sup> See the National Newborn Screening and Genetics Resource Center at <http://genes-r-us.uthscsa.edu/> for more information on these conditions.

(e.g., CH), hemoglobin disorders (e.g., SCD), and a few others require different screening platforms.<sup>11</sup>

MS/MS employs two mass spectrometers, which are analytical instruments that weigh the molecules present in a minute sample. A mass spectrometer can determine exactly what kinds of molecules are present in the sample and in exactly what concentrations. In MS/MS, the two mass spectrometers are connected together by a chamber called a collision cell. The collision cell's job is to break up the molecules after one of the mass spectrometers has weighed and sorted them. The other mass spectrometer then sorts and weighs the pieces of the molecules that are of interest to those conducting the screening.

In newborn screening, the molecules whose concentrations are measured by MS/MS include amino acids (abnormal levels of which indicate an amino acid disorder) and acylcarnitines (abnormal levels of which indicate a fatty acid or organic acid disorder). Tandem mass spectrometry is the most reliable, widely available method for measuring these compounds in a child's blood.<sup>12</sup>

Recent studies have shown that MS/MS also can be used to detect a class of genetic conditions known as lysosomal storage disorders, including the rare Fabry, Gaucher, Krabbe, Niemann-Pick, and Pompe diseases. Because clearly efficacious treatments are not yet available for the lysosomal storage disorders, assays for these conditions have not been included in most MS/MS newborn

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<sup>11</sup> The hemoglobinopathies are detected by one of two other multiplex testing platforms: either high pressure liquid chromatography (HPLC) or isoelectric focusing (IEF). Besides CH and congenital adrenal hyperplasia (CAH), the disorders that require separate assay platforms ("singletons") include congenital hearing loss, biotinidase deficiency (BIOT), cystic fibrosis (CF), and GALT.

<sup>12</sup> American College of Medical Genetics/American Society of Human Genetics Test and Technology Transfer Committee Working Group, "Tandem Mass Spectrometry in Newborn Screening," *Genetics in Medicine* 2 (2000): 267-269; Sandra Banta-Wright and Robert Steiner, "Tandem Mass Spectrometry in Newborn Screening, A Primer of Neonatal and Perinatal Nurses," *Journal of Perinatal and Neonatal Nursing* 1 (2004): 41-58; and Donald Chace, "A Layperson's Guide to Tandem Mass Spectrometry and Newborn Screening," online at [www.savebabies.org](http://www.savebabies.org).

screening panels. New York is one exception; children born there are routinely screened for Krabbe disease.<sup>13</sup>

### *C. Follow-up and Diagnosis*

Abnormal screening results are reported to the newborn's primary care physician or pediatrician, who communicates them to the parents. How the results of newborn screening are reported varies from state to state. Most states report abnormal results to the birth hospital by letter, fax, phone call, or lab report. Normal results are also usually reported to the birth hospital, though sometimes also to the pediatrician or the parents.<sup>14</sup> Most of the time, abnormal results are reported within a week after the screening.

It is, however, important to recognize that *an initial positive screening result is not the same as a diagnosis of disease*. If for any reason the reliability of the initial screening result is questionable, a repeat test may be ordered. Even if the screening result is considered reliable, the possibility of false positives means that more detailed confirmatory testing (sometimes involving DNA analysis or other quantitative methods) will be required before a definitive diagnosis is reached. With rare exceptions, when treatment for a detected disorder is available, it is not started until after the diagnosis is confirmed. In the meantime, the parents will receive counseling about the possible implications of the positive result, while the newborn is referred to the appropriate health care providers for proper medical evaluation, confirmatory testing, diagnosis, and treatment.

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<sup>13</sup> See Michael Gelb, et al., "Direct Multiplex Assay of Enzymes in Dried Blood Spots by Tandem Mass Spectrometry for the Newborn Screening of Lysosomal Storage Disorders," *Journal of Inheritable Metabolic Disease* 29 (2006): 397-404; Yijun Li, et al., "Direct Multiplex Assay of Lysosomal Enzymes in Dried Blood Spots for Newborn Screening," *Clinical Chemistry* 50 (2004): 1785-1796; and David Millington, "Newborn Screening for Lysosomal Storage Disorders," *Clinical Chemistry* 51 (2008): 808-809.

<sup>14</sup> See Franklin Desposito, et al., "Survey of Pediatrician Practices in Retrieving Statewide Authorized Newborn Screening Results," *Pediatrics* 108 (2001): E22; and Kenneth D. Mandl, et al., "Newborn Screening Program Practices in the United States: Notification, Research, and Consent," *Pediatrics* 109 (2002): 269-273.

The problem of false positives deserves further comment. In detecting rare genetic disorders by analyzing metabolites in the blood a serious dilemma is encountered. If the presence of a disorder is signaled by an abnormally high level of a certain metabolite in the infant's blood, exactly how high does the level have to be in order to judge that the infant has tested positive for the disorder? Set the threshold level too high, and a certain number of infants who actually have the disorder will go undetected; these are called false negatives. Set the level too low, and most or all infants with the disorder will be detected, but many additional infants will test positive without actually having the disorder. The rate of such false positives has been considerably reduced with the introduction of MS/MS and other precise testing platforms. Such screening protocols are extremely sensitive (i.e., they successfully identify the vast majority of infants actually suffering the disorder) while being at the same time extremely specific (i.e., the vast majority of positive results are true positives, not false positives). Unfortunately when a population is screened for extremely rare disorders, even a highly specific and sensitive assay can yield very large numbers of false positives.<sup>15</sup>

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<sup>15</sup> To understand the problem of false positives, one has to consider not only the sensitivity and specificity of a screening protocol but also its positive predictive value, which is defined as the proportion of patients with positive test results who are correctly diagnosed. Even if sensitivity and specificity are high, positive predictive value can be quite low when the disease is very rare (i.e., when the prevalence of the disease is very low.) If  $PPV$  = positive predictive value,  $Se$  = sensitivity,  $Sp$  = specificity, and  $P$  = prevalence, it can be shown that

$$PPV = \frac{Se \cdot P}{Se \cdot P + (1 - Sp)(1 - P)} = \frac{1}{1 + \frac{(1 - Sp)}{Se} \cdot \left(\frac{1}{P} - 1\right)}$$

Even more simply, if  $TP$  = true positives and  $FP$  = false positives, since  $PPV = \frac{TP}{TP + FP}$ , it follows that the ratio of false positives to true positives is

$$\frac{FP}{TP} = \frac{(1 - Sp)}{Se} \cdot \left(\frac{1}{P} - 1\right)$$

These formulae mean that, no matter how high the test specificity (as long as it is not 100 percent), a sufficiently rare disease (i.e., low prevalence  $P$ ) can make the positive predictive value of a test extremely low and the ratio of false positive results to true positive results correspondingly high.

As a result, for many of the conditions that most states screen for, a large majority of the initially positive screening results will turn out to be incorrect. For instance, in 2007, 3,364,612 infants were tested for MSUD in the United States. Of those tested, 1,249 were initially reported back as testing positive, but only eighteen newborns were eventually confirmed, after further testing, as having the disease.<sup>16</sup> The other 1,231 out of 1,249 positive results turned out to be false.<sup>17</sup> Pediatrician Beth Tarini and colleagues have calculated that the screening of all American newborns for metabolic disorders by MS/MS is likely to yield some tens of thousands of false positive results per year.<sup>18</sup>

Such high rates of false positives may be an unfortunate but unavoidable side effect of trying to identify every infant with a rare genetic disorder. Concerns have been raised, however, about the potential impact of false positive screening results on parental anxiety and stress, parent-child relationships, and perceptions of the child's health,<sup>19</sup> and there is always the risk that a child incorrectly identified as suffering from a genetic disorder will be given inappropriate treatment before further testing establishes that the

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<sup>16</sup> Data downloaded from the National Newborn Screening Information System, available online at [www2.uthscsa.edu/nnsis](http://www2.uthscsa.edu/nnsis).

<sup>17</sup> With sixty-eight false positives for every true positive detected, and an estimated prevalence of one in 180,000, newborn screening for MSUD in 2007 had a positive predictive value of about 1.4 percent, which would be consistent with a sensitivity approaching 100 percent and a specificity as high as 99.96 percent. This shows vividly how an extraordinarily sensitive and specific test can nonetheless yield high numbers of false positives if the targeted condition is exceedingly rare. See Andreas Schulze, et al., "Expanded Newborn Screening for Inborn Errors of Metabolism by Electrospray Ionization-Tandem Mass Spectrometry: Results, Outcome, and Implications," *Pediatrics* 111 (2003): 1399-1406.

<sup>18</sup> Beth Tarini, et al., "State Newborn Screening in the Tandem Mass Spectrometry Era: More Tests, More False-Positive Results," *Pediatrics* 118 (2006): 448-456. They calculated a best-case scenario of 2,575 false positives per year, and a worst-case scenario of 51,059 false positives per year, but this was for the year 2005, before most states had implemented the ACMG's expanded screening panel.

<sup>19</sup> See, for example, Elizabeth Gurian, et al., "Expanded Newborn Screening for Biochemical Disorders: The Effect of a False-Positive Result," *Pediatrics* 118 (2006): 1915-1921. The psychosocial impact of false positive screening results will be explored further in Chapter Three.

initial screening result was false. In Chapter Three, we shall return to the problem of false positives in our discussion of ethical issues raised by the expansion of newborn screening. For our present purposes, it is sufficient to note that the great majority of initially positive results are, on further testing, shown to be inaccurate. And the rarer the disease targeted by newborn screening, the more likely it is for screening to produce a multitude of false positives for every true positive result.

#### ***D. Treatment and Evaluation***

Newborns confirmed to have a genetic disease need to be referred to metabolic specialists, endocrinologists, hematologists, or pulmonologists who will be responsible for developing a specific plan for the care and treatment of the child. In many cases, disease management will continue throughout the affected child's life. For a few serious genetic diseases, the treatment is simple, inexpensive, effective, and relatively unobtrusive. Thus, for the one in 4,000 children suffering from congenital hypothyroidism, a daily thyroxin tablet makes possible a normal life instead of a grim future of growth failure and permanent mental retardation. For other disorders, the treatment is difficult but manageable. Thus children diagnosed with PKU can grow up free of its devastating neurological symptoms by maintaining a diet low in phenylalanine for the rest of their lives. This course of treatment is effective but quite burdensome, as it entails severely restricting (or eliminating) the eating of high-phenylalanine foods such as breast milk, meat, chicken, fish, nuts, cheese, and legumes.

For certain other detectable genetic disorders, as we shall see, the prognosis is much less clear, and the appropriate course of treatment is not known with certainty. Moreover, even when a treatment is "available," many other steps have to be taken to realize the treatment's benefits for the affected children. Not only must the diagnosis be confirmed, but resources must be effectively and consistently delivered to the child and family over a long period of time. In some cases, state newborn screening programs may adequately fund the *detection* of genetic disorders without ensuring

that affected infants receive adequate long-term *care*.<sup>20</sup> For example, children found to have SCD are supposed to take a daily prophylactic dose of the antibiotic penicillin, through at least the age of five, in order to prevent life-threatening bouts of pneumonia and other infections. Most states have been screening newborns for SCD since the 1980s, and each year about 2,000 new cases are detected, chiefly among African-American infants; but a 2003 study revealed that children affected with SCD received, on average, only forty percent of the recommended medication (i.e., the mean number of days of the year that an affected child received the antibiotic was only 148).<sup>21</sup> Clearly, success at identifying infants with the disease does not guarantee that children are truly benefiting from newborn screening for SCD; yet SCD screening is a well-established program and is widely considered one of the more successful examples of mandatory newborn screening.<sup>22</sup>

Finally, to establish that a certain newborn screening program is truly effective, rigorous evidence-based studies are needed to find out whether early detection and intervention produce a truly positive outcome for the affected infants. Yet, all too often, diseases are added to mandatory screening panels without adequate pilot studies establishing the efficacy of detection and intervention, and then without adequate follow-up studies evaluating all the long-term consequences, both good and bad, for the children identified by the program. In 1992, Norman Fost examined the unintended

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<sup>20</sup> See Celia I. Kaye, et al., “Assuring Clinical Genetic Services for Newborns Identified Through U.S. Newborn Screening Programs,” *Genetics in Medicine* 9 (2007): 518-527.

<sup>21</sup> Colin M. Sox, et al., “Provision of Pneumococcal Prophylaxis for Publicly Insured Children with Sickle Cell Disease,” *Journal of the American Medical Association* 290 (2003): 1057-1061. As for why the children do not receive proper medication, Sox and his colleagues wrote the following: “Reasons for such poor provision of prophylactic medication are unknown, but may include physicians not writing prescriptions for prophylactic antibiotics or patients not taking written prescriptions to the pharmacy. Notably, children frequently interacted with the health care system, with a mean of 13 outpatient encounters per year, suggesting ample missed opportunities to emphasize and assess compliance with prophylaxis.” (Ibid., p. 1060.)

<sup>22</sup> Richard S. Olney, “Preventing Morbidity and Mortality from Sickle Cell Disease: A Public Health Perspective,” *American Journal of Preventive Medicine* 16 (1999): 116-121.

consequences of the screening programs for PKU and sickle cell anemia, among other illnesses, and drew an important general lesson: that screening asymptomatic individuals for genetic abnormalities is not simply a neutral gathering of information with no effect on the lives of those screened; instead, every screening program must be considered an *experiment* until the benefits and risks have been clarified by well-designed empirical studies.<sup>23</sup> In Chapter Two of this white paper, we return to this question of the efficacy of newborn screening as we examine the expansion in state-mandated newborn screening programs that is occurring today.

## II. Public Policy and Newborn Screening

Both federal and state governments make policy governing newborn screening, but the federal government has so far played a comparatively limited role in shaping screening programs. It offers grants to help states pay for screening costs and research.<sup>24</sup> It has working committees designed to explore the ethical, social, clinical, and political implications of newborn screening.<sup>25</sup> It ensures that laboratories processing the screening tests meet strict standards.<sup>26</sup> It

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<sup>23</sup> Norman Fost, “Ethical Implications of Screening Asymptomatic Individuals,” *FASEB (Federation of American Societies for Experimental Biology) Journal* 6 (1992): 2813-2817, p. 2814.

<sup>24</sup> Section 300b-8 of Title 42 of the United States Code states that the Secretary of the Department of Health and Human Services (HHS) must award grants to entities to improve state and local health agencies’ ability to provide screening, counseling, or health care services to newborns and children who have or are at risk for heritable disorders. See also Sections 300b-1, 300b-6, and 300b-9 for more details on the federal government’s role.

<sup>25</sup> Section 300b-10 of Title 42 states that the Secretary must establish the “Advisory Committee on Heritable Disorders in Newborns and Children.” The Committee is to offer advice to the Secretary on grants awarded under Sec. 300b-8.

<sup>26</sup> The Clinical Laboratory Improvement Amendments of 1988 (CLIA-88), which improved upon the Clinical Laboratory Improvement Act of 1967 (CLIA-67), is the law that permits the Secretary of HHS to create quality standards for laboratory testing. Laboratories can choose to receive CLIA certification either by an appropriate state agency or by an approved private organization, such as the Joint Commission on Accreditation of Healthcare Organizations, the College of American Pathologists, or the American Society for Histocompatibility and

approves screening platforms for public use,<sup>27</sup> as well as the labeling and advertising of screening platforms.<sup>28</sup>

The state governments play a much larger role in shaping screening programs. Each state chooses the screening platforms that will be

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Immunogenetics. HHS, through the Centers for Medicare and Medicaid (CMS), published most of the regulations pertaining to CLIA in 1992.

At the time CLIA-88 was enacted and its regulations formulated, MS/MS was just becoming available and the Human Genome Project was just beginning. Much in genetics and genetic testing has changed since then. So while genetic testing laboratories are still subject to CLIA-88, some have argued that the law offers very little guidance regarding genetic testing. As far back as 1997, the National Institutes of Health-Department of Energy Task Force on Genetic Testing issued a report (*Promoting Safe and Effective Genetic Testing in the United States*) calling for the HHS Clinical Laboratory Improvement Advisory Committee (CLIAC) to recommend the creation of a subspecialty on genetics in order to address this shortcoming of CLIA-88. CLIAC then proposed some changes to the regulation in 1998. In 2000, the Secretary's Advisory Committee on Genetic Testing (SACGT), the predecessor to the Secretary's Advisory Committee of Genetics, Health, and Society (SACGHS), also acknowledged this shortcoming of the law and supported CLIAC's recommendations. In 2003, HHS revised the CLIA regulations and included some of CLIAC's proposals. Nevertheless, some continued to maintain that a separate subspecialty for genetic screening should be created. But in November 2006, CMS told SACGHS that there is no need for a subspecialty for genetic testing, and that in fact CLIA-88 regulations already fully cover genetic testing. For more information see the CMS website, [www.cms.hhs.gov](http://www.cms.hhs.gov).

In addition to the role of CMS, the Centers for Disease Control and Prevention's Environmental Health Laboratory evaluates the performance of laboratories involved in the analysis of newborn screening tests and provides technical assistance to resolve diagnostic problems. For more information see the CDC website, [www.cdc.gov](http://www.cdc.gov).

<sup>27</sup> The Food and Drug Administration (FDA) is responsible for ensuring the safety and efficacy of medical devices. Included within this category are genetic test kits, including newborn screening test kits. Recently, the FDA has been considering the safety and efficacy of MS/MS. In fact, in 2004 the Center for Devices and Radiological Health of the FDA published detailed guidance for industry and FDA staff on the use of MS/MS. See the following for more information: Center for Devices and Radiological Health, Food and Drug Administration, "Class II Special Controls Guidance Document: Newborn Screening Test Systems for Amino Acids, Free Carnitine, and Acylcarnitines Using Tandem Mass Spectrometry," November 24, 2004. For more information see the FDA website, [www.fda.gov](http://www.fda.gov).

<sup>28</sup> The Federal Trade Commission (FTC) regulates these aspects of the tests. See the FTC website, [www.ftc.gov](http://www.ftc.gov), for more information.

used within its jurisdiction. Each state chooses the panel of conditions for which newborns will be screened. Each state is responsible for ensuring that every newborn within its borders at least has the opportunity to be screened. Finally, each state pays most of the costs of the screening process (in most cases by collecting fees to cover the expense).<sup>29</sup>

Although the states have virtually unlimited freedom to determine how to organize and conduct their own screening programs, many states have at least a few similar policies. For example, many states have privacy and confidentiality policies to protect personal information, including genetic information. Many states allow the parents to opt out of the screening. And many states have education programs that provide parents with information on the screening process, such as the conditions being screened for, a description of the conditions, the manner of the collection procedure, and an explanation of why the health care professionals might need to retest.<sup>30</sup>

Just as there are important similarities among the programs, there are also some differences. One of the main differences is in the quality of parental education. Many states do not provide parents with information on the accuracy of screening, the possibility of false positives, when the results of the screening tests will be available, the privacy and confidentiality laws governing the information obtained, or how the parents might decline the offer for screening. The states also differ in the fees charged for newborn screening. Some states charge no fee at all, while other states charge as much as \$140.<sup>31</sup> Still another difference is in the number of initial

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<sup>29</sup> See Kay Johnson, et al., “Financing State Newborn Screening Programs: Sources and Uses of Funds,” *Pediatrics* 117 (2006): s270-s279; and Bradford L. Therrell, et al., “Status of Newborn Screening Programs,” s212-s252.

<sup>30</sup> *Ibid.*

<sup>31</sup> Where no fee is charged, the cost of screening is covered by a combination of state and federal revenues. If a fee is charged, it may be paid by Medicaid, SCHIP, private insurers, health providers, laboratories, hospitals, or the parents themselves. (Kay Johnson, et al., “Financing State Newborn Screening Programs: Sources and Uses of Funds,” pp. S271, S276.)

screening tests required, with some states requiring only one test to be conducted and other states requiring two initial tests.<sup>32</sup>

Of particular significance—especially for the purposes of this white paper—is the fact that almost all the states have substantially increased the number of conditions targeted by their newborn screening programs. Until the advent of MS/MS, most states screened newborns for only a handful of conditions. Yet today, every state screens for or will soon be screening for at least thirty conditions, and some states screen for as many as fifty-seven.<sup>33</sup> Many of these conditions were added to state screening panels in the past few years, in response to recommendations issued in 2005 by the American College of Medical Genetics (ACMG). In the next chapter we turn to a detailed analysis of the ACMG’s newborn screening recommendations and the ethical issues they raise.



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<sup>32</sup> Bradford L. Therrell, et al., “Status of Newborn Screening Programs.”

<sup>33</sup> See the National Newborn Screening and Genetics Resource Center’s “National Newborn Screening Status Report” at <http://genes-r-us.uthscsa.edu/nbsdisorders.pdf>.

## CHAPTER TWO

### THE CHANGING PRINCIPLES AND PRACTICE OF NEWBORN SCREENING

We now turn to the ethical principles that have guided newborn screening in this country since the 1960s, principles that are today being challenged as the states rapidly expand their newborn screening programs. A new regime of expanded newborn screening is being implemented in most states, in large measure as a response to recommendations advanced by the ACMG in a report published in 2005. That report has spurred controversy, with some critics arguing that the expansion of newborn screening is proceeding too rapidly and without sufficient deliberation and care. We explore these developments in the present chapter, first by introducing and explaining the classical principles of newborn screening, and then by assessing the ACMG's recommended expansion and the controversy it has provoked. We are especially interested in the following question: Is the expansion recommended by the ACMG consistent with the classical ethical principles of screening, or does it represent a radical departure?

#### **I. The Classical Principle: Screen Only If You Can Effectively Treat**

From the late 1960s until recently, there was a durable consensus on the ethical principles that ought to guide the practice of newborn screening. The most in-depth and influential presentation of those principles was the 1968 World Health Organization monograph by James Wilson and Gunnar Jungner, *Principles and Practice of Screening*

*for Disease*.<sup>1</sup> The ten Wilson-Jungner criteria for including a condition in a screening program are as follows:

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding<sup>2</sup> (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a “once and for all” project.<sup>3</sup>

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<sup>1</sup> James M. G. Wilson and Gunnar Jungner, *Principles and Practice of Screening for Disease* (Geneva: World Health Organization, 1968), available online at [whqlibdoc.who.int/php/WHO\\_PHP\\_34.pdf](http://whqlibdoc.who.int/php/WHO_PHP_34.pdf).

<sup>2</sup> By case-finding, Wilson and Jungner mean “that form of screening of which the main object is to detect disease and bring patients to treatment, in contrast to epidemiological surveys.” In contrast, the main purpose of surveys is “not to bring patients to treatment but to elucidate the prevalence, incidence, and natural history” of the disease or symptom under study. (Ibid., p. 12.)

<sup>3</sup> Ibid., pp. 26-27.

Wilson and Jungner emphasize the crucial importance of their second criterion: “of all the criteria that a screening test should fulfill, *the ability to treat the condition adequately, when discovered, is perhaps the most important.*”<sup>4</sup> They offer an exceptionally cogent explanation of this principle:

In adhering to the principle of avoiding harm to the patient at all costs (the *primum non nocere* of Hippocrates), treatment must be the first aim. For declared disease there is, of course, the ethical obligation to provide an accepted treatment whether or not this is of scientifically proved value; *but, when new territory is being explored by the early detection of disease, it is clearly vital to determine by experimental surveys whether a better prognosis is given by treating the conditions found at an earlier stage than was previously the practice.* Unless this is so, there can be no advantage to the patient and, in fact, *in alerting him or her to a condition that has not been shown to benefit by treatment at an earlier stage actual harm may be done.*<sup>5</sup>

The third Wilson-Jungner criterion—the availability of facilities for diagnosis and treatment—means that a large-scale screening program cannot be justified unless resources will be available both to confirm the diagnosis and to treat effectively those who are identified as having the disease. As we shall see, this can be an issue in state-mandated newborn screening if states have the resources to screen newborns for a condition but not necessarily to follow-up and manage the care of all those who test positive.

The seventh Wilson-Jungner criterion—that *there must be an adequate understanding of the natural history of the disease*—is also highly pertinent to the subject of this white paper. Wilson and Jungner suggest certain questions that need to be answered about a medical condition before screening can be justified:

- What changes should be regarded as pathological and what should be considered physiological variations?

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<sup>4</sup> *Ibid.*, p. 27; emphasis added.

<sup>5</sup> *Ibid.*, pp. 27-28; emphasis added.

- Are early pathological changes progressive?
- Is there an effective treatment that can be shown either to halt or to reverse the early pathological condition?<sup>6</sup>

Wilson and Jungner point out the risks of embracing population-wide screening and treatment before a disease is well-understood and before controlled clinical trials have established the effectiveness and benefits of intervention:

Without well-planned surveys, carried out in advance of the main body of medical opinion, the view that early diagnosis and treatment successfully improves the outlook for the condition in question is likely to become generally accepted. This in turn automatically renders unethical planned randomized trials of intervention by treatment, following early diagnosis; with the result that ideas about the effect of treatment pass into the realm of folklore rather than of scientific knowledge.<sup>7</sup>

Although not specifically formulated for pediatric screening, the Wilson-Jungner criteria have largely guided the practice of newborn screening over the past four decades. Thus, in an important 1974 paper on the principles that should govern pediatric screening,<sup>8</sup> pediatrician William K. Frankenburg presented those principles in a way that clearly echoed the work of Wilson and Jungner:

The availability of a suitable screening test does not justify screening for a disease unless the disease is important, relatively prevalent, and amenable to early treatment. Screening for a disease which has the necessary characteristics cannot be justified unless there is an acceptable, reliable and valid test which can be carried out at reasonable cost.

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<sup>6</sup> Ibid., p. 32.

<sup>7</sup> Ibid., p. 28.

<sup>8</sup> William K. Frankenburg, "Selection of Diseases and Tests in Pediatric Screening," *Pediatrics* 54 (1974): 612-616.

Screening which is carried out without knowledge and consideration of these criteria is likely to be wasteful of scarce medical resources and may actually do more harm than good.<sup>9</sup>

Similarly, a 1994 report of the Institute of Medicine (IOM, one of the four U.S. National Academies) on assessing genetic risks recommended that “newborn screening only take place 1) for conditions for which there are indications of clear benefit to the newborn, 2) when a system is in place for confirmatory diagnosis, and 3) when treatment and follow-up are available for affected newborns.”<sup>10</sup> In 1995, the American Society of Human Genetics (ASHG) and the ACMG issued a joint report affirming that “timely medical benefit to the child should be the primary justification for genetic testing in children and adolescents,”<sup>11</sup> and this judgment was reaffirmed by a 1997 report by the NIH Task Force on Genetic Testing.<sup>12</sup> In 2000, a report by the American Academy of Pediatrics stated that a condition is a good candidate for newborn screening only if “the treatment for the condition is effective when initiated early, accepted among health care professionals, and available to all screened newborns.”<sup>13</sup> In all these statements of principle, *direct benefit to the newborn child* was identified as the paramount and indispensable criterion for inclusion of a disease in a uniform screening panel. To justify such inclusion, the natural history of the disease must be well understood, the diagnostic test for its presence

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<sup>9</sup> Ibid., p. 616.

<sup>10</sup> Committee on Assessing Genetic Risks, Institute of Medicine, *Assessing Genetic Risks: Implications for Health and Social Policy*, Lori B. Andrews, Jane E. Fullarton, Neil A. Holtzman, and Arno G. Motulsky, eds. (Washington, D.C.: National Academies Press, 1994).

<sup>11</sup> American Society of Human Genetics and American College of Medical Genetics, “Points to Consider: Ethical, Legal, and Psychosocial Implications of Genetic Testing in Children and Adolescents,” *American Journal of Human Genetics* 57 (1995): 1233-1241, p. 1233.

<sup>12</sup> Neil A. Holtzman and Michael S. Watson, *Promoting Safe and Effective Genetic Testing in the United States: Final Report of the Task Force on Genetic Testing* (Bethesda, Maryland: National Institutes of Health, 1997), available online at <http://biotech.law.lsu.edu/research/fed/tfgt/>.

<sup>13</sup> American Academy of Pediatrics Newborn Screening Task Force, “Serving the Family from Birth to the Medical Home. Newborn Screening: A Blueprint for the Future,” p. 394.

must be clear and precise, and an effective treatment must be available.

Despite this enduring consensus, the principle “screen only if you can effectively treat” has not gone unchallenged. A 1975 report by a committee of the National Research Council (NRC, another of the four National Academies) began by stating that newborn screening is appropriate when there is evidence that it provides “substantial *public* benefit,” i.e., benefit not limited to the timely and effective treatment of the infant’s condition. The report went on to describe three forms of such benefit other than direct treatment: 1) to the infant (to provide management and support even when direct treatment is unavailable), 2) to the family (to inform subsequent reproductive decisions), and 3) to society (to provide knowledge of the true range and incidence of the condition).<sup>14</sup>

Meanwhile, in recent years some prominent figures in the world of newborn screening—including the director of the National Institute of Child Health and Human Development (NICHD)—have forcefully criticized the principle that “it is appropriate to screen only for conditions for which effective treatment already exists” as a “dogma” that ought to be discarded. They favor a significantly more expansive approach to newborn screening, in which all conditions—no matter how rare, poorly understood, or currently untreatable—are presumed to be eligible for screening unless specifically excluded on a case-by-case basis.<sup>15</sup> At the same time, the NICHD is funding efforts to move beyond today’s limited, phenotypic methods of newborn screening toward DNA-based platforms that can “offer enormous opportunities to identify staggering numbers of potentially pathogenic mutations in a very large number of disease-associated genes.”<sup>16</sup> Clearly, proponents of

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<sup>14</sup> National Research Council Committee for the Study of Inborn Errors of Metabolism, *Genetic Screening Programs, Principles, and Research* (Washington, D.C.: National Academy of Sciences, 1975), p. 1.

<sup>15</sup> Duane Alexander and Peter C. van Dyck, “A Vision of the Future of Newborn Screening,” *Pediatrics* 117 Supplement (2006): S350-S354.

<sup>16</sup> Duane Alexander and James W. Hanson, “NICHD Research Initiative in Newborn Screening,” *Mental Retardation and Developmental Disabilities Research Reviews* 12 (2006): 301-304, p. 302.

this change understand that, if the principle “screen only if you can effectively treat” is set aside and if the technology of newborn screening shifts to primarily DNA-based multiplex platforms, such as gene chips or even whole genome sequencing, the stage will be set for a vast expansion in newborn screening. The new principle guiding newborn screening would then be “screen unless there is a compelling reason not to screen.”

## II. Newborn Screening and the ACMG’s Expanded Uniform Panel

This scenario is no longer entirely hypothetical; change has already come to the practice of newborn screening in this country. In the past few years, newborn screening has undergone rapid expansion throughout the United States in accordance with recommendations made by the ACMG in its 2005 report, *Newborn Screening: Toward a Uniform Screening Panel and System*.<sup>17</sup> That document is the final report of an ACMG working group commissioned and funded in 2002 by the federal Maternal and Child Health Bureau (MCHB) of the Health Resources and Services Administration, a division of HHS. The ACMG’s task was to gather evidence on the effectiveness of newborn screening, to recommend a uniform panel of conditions that ought to be screened for in every state, and to consider other critical components of the newborn screening system.<sup>18</sup> In its report, the ACMG recommended that all state-based newborn screening programs adopt a uniform panel of twenty-nine *core* conditions as well as twenty-five *secondary* conditions.<sup>19</sup> Their

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<sup>17</sup> American College of Medical Genetics, *Newborn Screening: Toward a Uniform Screening Panel and System* (Washington, D.C.: 2005), hereafter cited as ACMG, *Newborn Screening*. The full report is available online at <http://mchb.hrsa.gov/screening> (the version cited here) and (in a version published as a supplement to *Genetics in Medicine* 8 (2006): pp. 1S-252S) at [www.acmg.net/resources/policies/NBS/NBS-sections.htm](http://www.acmg.net/resources/policies/NBS/NBS-sections.htm).

<sup>18</sup> ACMG, *Newborn Screening*, p. 7.

<sup>19</sup> The crucial distinction between core and secondary conditions is explained later in the chapter. For the present, let the primary or core conditions be understood as those that fully meet the criteria for inclusion in the uniform screening panel, while the secondary conditions are those that fall short of that standard but—according to the ACMG—merit inclusion in the panel on other grounds.

recommendation was promptly endorsed by the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children in a June 2005 letter to Michael O. Levitt, Secretary of HHS.<sup>20</sup> By November 2008, almost all of the states had adopted the ACMG's panel of twenty-nine core conditions,<sup>21</sup> and most had initiated screening for a majority of the twenty-five secondary conditions.<sup>22</sup> As these numbers indicate, the states have moved with unprecedented speed to implement a newborn screening system that is both considerably more uniform and considerably expanded compared to even a few years ago. For comparison, as recently as 2005 (the year the ACMG report was released), the states varied widely in their use of newborn screening tests, "with some mandating screening for as few as three conditions and others mandating as many as forty-three conditions."<sup>23</sup>

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<sup>20</sup> In its letter, the Advisory Committee "strongly and unanimously recommends that the Secretary initiate appropriate action to facilitate adoption of the ACMG recommended screening panel by every State newborn screening program." The letter may be found online at [www.hrsa.gov/heritabledisorderscommittee/reports/letterstoSecretaryofHHS.htm](http://www.hrsa.gov/heritabledisorderscommittee/reports/letterstoSecretaryofHHS.htm).

<sup>21</sup> More precisely, as of November 2008, all of the states screen for at least twenty-six of the twenty-nine core conditions, and forty-four states screen for all of them. See the screening statistics compiled by the National Newborn Screening and Genetics Resource Center (NNSGRC) at <http://genes-r-us.uthscsa.edu/nbsdisorders.pdf>. Note that the NNSGRC status report may not accurately reflect the mandatory or voluntary status of newborn screening in each state. For example, Massachusetts currently offers two screening panels, a mandatory panel of ten conditions and an optional panel of twenty others.

<sup>22</sup> More precisely, as of November 2008, thirty states are now or soon will be screening for more than twenty of the twenty-five secondary conditions; at the other end of the spectrum, three states (Arkansas, Kansas, and Louisiana) screen for only two of the secondary conditions.

<sup>23</sup> ACMG, *Newborn Screening*, p. 7. According to a November 2008 report by the CDC, "After 2006, most states began to expand their panels to include all 29 disorders; currently, 21 states and the District of Columbia have fully implemented the ACMG panel." The CDC also analyzed newborn screening data from 2001 to 2006 from states with well-established MS/MS screening programs to "estimate the number of children in the United States who would have been identified with disorders in 2006 if all 50 states and the District of Columbia had been using the ACMG panel." This analysis led the CDC to conclude that such an expansion would have increased the number of children identified in 2006 by only thirty-two percent (from 4,370 to 6,439). But the additional children identified would have had "many rare disorders that require local or regional

In light of these extraordinarily rapid developments, the question now before us is, what, if any, alterations in the ethical principles of newborn screening have occurred in the course of the expansion recommended by the ACMG and implemented by most of the fifty states? In particular, is that expansion consistent with the classical principles that have governed newborn screening for the past forty years? Or has there been a break with those principles, and, if so, how significant a break? Answering these questions requires a close look at some features of the ACMG's complex and lengthy report.<sup>24</sup>

In carrying out its mandate, the ACMG working group evaluated eighty-four heritable disorders for possible inclusion in a uniform newborn screening program that all fifty states would be encouraged to adopt. After conducting a broad survey of expert opinion, the working group assigned a numerical score to each condition, with a high score indicating that the condition was a plausible candidate for mandatory screening. The eighty-four conditions were initially divided into three groups, composed of high-, middle-, and low-scoring conditions. In a second tier of analysis, each condition's initial ranking was re-evaluated by a small number of experts, after which the conditions were assigned to one of three final categories: a core panel of conditions meriting mandatory screening (twenty-nine conditions); a secondary panel of conditions not meeting the standards of the core panel but deemed appropriate for screening anyway (twenty-five conditions); and the remaining conditions, deemed not appropriate for screening at this time.<sup>25</sup>

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capacity to deliver expertise in screening, diagnosis, and management.” According to the CDC's analysis, nine of the disorders detectable by MS/MS each accounted for an estimated fifteen cases or fewer; in contrast, SCD and CH (both already targeted by population-wide screening in the United States) together accounted for sixty-one percent of the total estimated number of cases. See Centers for Disease Control and Prevention, “Impact of Expanded Newborn Screening—United States, 2006,” *Journal of the American Medical Association* 300 (2008): 2242-2244.

<sup>24</sup> The report itself is 108 pages long, with an additional 221 pages of figures and appendices.

<sup>25</sup> ACMG, *Newborn Screening*, pp. 9-10. The working group deferred a decision regarding screening for three infectious diseases included among the eighty-four

### ***A. Reactions to the ACMG Report***

As we have seen, the ACMG report and its recommendations received strong support from the HHS Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children. It also was endorsed by the American Academy of Pediatrics,<sup>26</sup> by the March of Dimes,<sup>27</sup> and by other advocacy groups and professional organizations. At the same time, the methods by which the ACMG working group arrived at its recommended screening panels have been faulted on a number of grounds, leading some critics to conclude that the expansion of newborn screening is proceeding too rapidly and without sufficient deliberation and caution. Others have defended the proposed expansion against these criticisms. Before giving our own assessment of the ACMG's report, let us briefly summarize the objections that have been raised by others.

Commenting on the ACMG's recommendations, pediatrician-ethicist Jeffrey Botkin and colleagues urge a cautious approach to expansion.<sup>28</sup> They note that, even in its most celebrated and paradigmatic successes (e.g., PKU), newborn screening has proved to be a mixed blessing, with adverse consequences as well as benefits. That is, although they consider PKU screening to be a clear success, they point to avoidable missteps in its implementation and to some continuing adverse consequences, largely from false positive screening results. They also caution that each genetic illness is unique; that population-wide screening of asymptomatic individuals for uncommon diseases has rarely proved effective; that the benefits and risks must be carefully weighed on a condition-by-

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conditions evaluated: human HIV infection, congenital toxoplasmosis, and congenital cytomegalovirus infection. See p. 66.

<sup>26</sup> "AAP Endorses Newborn Screening Report from the American College of Medical Genetics," press release of May 12, 2005, available online at [www.aap.org/advocacy/releases/mayscreening.htm](http://www.aap.org/advocacy/releases/mayscreening.htm).

<sup>27</sup> "March of Dimes Statement on Newborn Screening Report," September 22, 2004, available online at [www.marchofdimes.com/aboutus/10651\\_13507.asp](http://www.marchofdimes.com/aboutus/10651_13507.asp).

<sup>28</sup> Jeffrey R. Botkin, et al., "Newborn Screening Technology: Proceed With Caution," *Pediatrics* 117 (2006): 1793-1799.

condition basis; and that rapid expansion of the uniform screening panel without adequate empirical studies would be unwise.

Responding to the ACMG working group's expanded panel of fifty-four conditions and to the prospect of further expansions as new test modalities become available, Botkin and colleagues strongly urged the merits of implementing newborn screening within a circumscribed research paradigm, involving thorough empirical studies to determine for each disorder whether it is suitable for routine screening. The questions that would need study include: Do the benefits of screening for this disorder outweigh the harms, if any? What are the actual medical, psychological, and social outcomes for infants testing positive for the disorder? How common are false-positive results, and what are their consequences? What are the secondary benefits of screening to the family and to the public, and are they substantial enough to justify screening when the traditional standard of direct medical benefit to the child cannot be met? Such research would be conducted in carefully controlled pilot studies, with the aim of gathering vital information about the risks and benefits involved, well before the implementation of population-wide newborn screening.<sup>29</sup>

Pediatrician Virginia Moyer and colleagues (including Jeffrey Botkin, among others), writing on behalf of the United States Preventive Services Task Force (USPSTF), have criticized the ACMG working group for failing to “conform to contemporary standards of evidence-based decision-making.”<sup>30</sup> They complain that a “technological imperative”<sup>31</sup> has driven the ACMG to include in the recommended panel diseases that are poorly understood, untreatable, or both, merely because the technology exists to detect

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<sup>29</sup> Of course, for the rarer conditions, affecting fewer than one in 10,000 newborns, it will prove quite difficult to conduct statistically valid research on smaller subpopulations prior to full-scale screening. For a proposal for a structured sequence of research protocols to evaluate potential applications for newborn screening before their formal implementation in public health programs, see Jeffrey R. Botkin, “Research for Newborn Screening: Developing a National Framework,” *Pediatrics* 116 (2005): 862–871.

<sup>30</sup> Virginia A. Moyer, et al., “Expanding Newborn Screening: Process, Policy, and Priorities,” *Hastings Center Report* 38 (2008): 32–39, p. 33.

<sup>31</sup> *Ibid.*, p. 33.

them. Believing that the goal of screening should be to improve the health of affected newborns, they find it ethically questionable to mandate screening “in order to recruit research subjects.”<sup>32</sup> They invoke the “time-honored tenet of medicine that clinicians should not order a test if the results will not change clinical management,”<sup>33</sup> and they find that many of the conditions the ACMG urges states to screen infants for should be excluded on this basis. They argue that the process by which the ACMG working group evaluated conditions for inclusion was flawed, insofar as it relied on unsystematic reviews and colloquial evidence and made use of dubious or obscure criteria. Applying USPSTF decision-making standards, Moyers and colleagues find that for only a handful of the twenty-nine recommended conditions is there adequate evidence that the benefits of screening would outweigh the harms. They suggest that “state and federal policymakers should further evaluate each condition proposed for screening before recommending that it be included in a mandated screening panel.”<sup>34</sup> Finally, Moyers and colleagues urge states that implement the expanded panels to “commit to collecting longitudinal data on infants who test positive,”<sup>35</sup> to help us implement in the future truly effective evidence-based screening programs.

Mary Ann Baily and Thomas Murray of the Hastings Center have offered a somewhat different critique of the ACMG’s recommended expansion of newborn screening.<sup>36</sup> They emphasize that a responsible newborn screening policy must take into account the opportunity costs of expanded screening, which will inevitably draw scarce resources away from other worthy public health programs and needs. They point out that the true costs of a newborn screening program include not only the price of the test itself (which might seem quite small) but also the cost of “parental education, follow-up of all positives to a definitive diagnosis, treatment of affected children, and ongoing data collection and

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<sup>32</sup> Ibid., p. 34.

<sup>33</sup> Ibid., p. 35.

<sup>34</sup> Ibid., p. 33.

<sup>35</sup> Ibid., p. 39.

<sup>36</sup> Mary Ann Baily and Thomas H. Murray, “Ethics, Evidence, and Cost in Newborn Screening,” *Hastings Center Report* 38 (2008): 23-31.

evaluation.”<sup>37</sup> In light of these concerns about allocation of health care resources, Baily and Murray criticize the ACMG for including in their panel “conditions that do not urgently need treatment in the newborn period, or for which no proven treatment is available, or for which the benefit of treatment is much less significant and certain than the benefit of treatment for a condition like PKU.”<sup>38</sup> In response to the argument that expanded screening and early diagnosis of obscure conditions will help families of affected infants to “avoid a diagnostic odyssey,” they urge that these benefits be weighed against “the burdens of different kinds of odysseys.” First, there is “the period of anxious searching and wandering” that many families of healthy children will experience between an initial false positive result and the confirmatory testing that eventually reassures them that their children are well. Second, there will be families whose children are diagnosed with a serious genetic disorder and yet never become symptomatic:

Perhaps the child has a mild or subclinical form that was unknown before newborns were routinely screened for the disorder... Meanwhile, the family reorganizes its life around medical monitoring and planning for something terrible that never happens.<sup>39</sup>

Third, there will be children who are accurately diagnosed with disorders for which there are as yet no proven treatments. Their families may begin a “treatment odyssey, searching the Internet, visiting specialists, running up debt, medicalizing the child’s life—only to have that life end in early death anyway.”<sup>40</sup> Baily and Murray fear that, with expanded screening, such unhappy medical odysseys will become more widespread.

Rebutting such criticisms, R. Rodney Howell, pediatrician and member of the ACMG’s Newborn Screening Steering Committee that supervised the preparation of the 2005 report, observed that controversy over the current expansion is reminiscent of early

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<sup>37</sup> *Ibid.*, p. 27.

<sup>38</sup> *Ibid.*, p. 28.

<sup>39</sup> *Ibid.*, p. 29.

<sup>40</sup> *Ibid.*, p. 29.

opposition to PKU screening when it was introduced over forty years ago; but that thanks to that program we now have “a whole generation of young adults with treated PKU who have normal intelligence and are productive members of society.”<sup>41</sup> He also pointed to the enormous benefits we have reaped from screening for CH and BIOT. Responding to the criticisms of Botkin and colleagues, Howell acknowledged that an expansion of screening will require a complex infrastructure (to support testing, counseling, education, treatment, and follow-up) that is not yet in place. He defended the efficacy of newborn screening in general, however, and pointed out that “there is little advantage at this time to discuss whether there should be expansion of newborn screening; it is occurring briskly at this very moment.”<sup>42</sup> Indeed, it is notable that both those urging caution and those enthusiastically embracing the expansion of newborn screening are more or less in agreement that rapid expansion is already taking place, and even more accelerated expansion in the future is all but inevitable.

Howell acknowledged the lack of controlled trials for the treatment of some of the serious metabolic disorders included in the recommended panel, but he insisted that, when the evidence is clear that untreated infants face grave illness or death and that treatment has some efficacy, “no prudent physician would fail to provide treatment information to such families if the condition had been identified.”<sup>43</sup> Addressing the issue of false positives, Howell acknowledged that they are problematic and called for more research to keep their numbers to a minimum. Regarding informed parental consent, Howell considered it desirable in the case of poorly understood conditions, but he noted that it is a daunting challenge to try to explain to parents the array of tests to be performed and the various potential outcomes of accepting or rejecting them. Finally, Howell predicted that, with new technologies and new treatments, the number of genetic disorders for which newborns will be screened in the future will expand far beyond the currently recommended panel, and he urged the nation

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<sup>41</sup> R. Rodney Howell, “We Need Expanded Newborn Screening,” *Pediatrics* 117 (2006): 1800-1805, p. 1802.

<sup>42</sup> *Ibid.*, p. 1802.

<sup>43</sup> *Ibid.*, p. 1802.

to get to work building the infrastructure that will support such programs, which will have enormous potential benefits for infants in the future.

The issues involved in this debate are complex, and there are numerous cogent arguments on both sides of the controversy. Here, however, we shall focus our attention on two distinctive features of the ACMG's approach: their use of a *broadened conception of benefit* to justify newborn screening, and their readiness to allow progress in *multiplex screening technology* to dictate the pace and scope of the expansion of newborn screening. Before turning to these issues, let us first examine the principles that guided the composition of the ACMG's core and secondary screening panels.

### ***B. The Core or Primary Conditions***

On a first reading, the ACMG report conveys a strong impression of having followed accepted screening principles in recommending its expanded uniform panel. Consider the following clear statement of a “basic principle developed at the onset of the project”:

To be included as a primary target condition in a newborn screening program, a condition should meet the following minimum criteria:

- It can be identified at a period of time (24 to 48 hours after birth) at which it would not ordinarily be clinically detected.
- A test with appropriate sensitivity and specificity is available.
- There are demonstrated benefits of early detection, timely intervention, and efficacious treatment.<sup>44</sup>

Elsewhere the report affirms that, when evaluating a disorder for inclusion in the screening panel, “benefit to the child being screened is the overriding consideration.”<sup>45</sup> Ultimately, the twenty-

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<sup>44</sup> ACMG, *Newborn Screening*, p. 28.

<sup>45</sup> *Ibid.*, p. 42.

nine conditions included in the core panel were those that, in the judgment of the ACMG, met three final criteria. All of them have

1. Specific and sensitive screening tests;
2. A sufficiently well understood natural history; and
3. Available and efficacious treatments.<sup>46</sup>

And indeed, a review of the twenty-nine conditions designated “core” or “primary” reveals that, in every case, the ACMG working group concluded that effective treatment was available that could prevent all (for four conditions), most (ten), or, at any rate, some (fifteen) of the disease’s symptoms; they also determined that there was clear (fourteen) or some (fifteen) evidence that treatment would benefit the affected newborn. Finally, for twenty-five of the twenty-nine core conditions, the ACMG concluded that the available treatment was efficacious at preventing mortality, independent of any reduction in morbidity.<sup>47</sup>

Whether all twenty-nine of the core conditions do actually meet the chief criterion—the availability of an effective treatment that will clearly benefit those newborns who test positive for the condition—is open to debate.<sup>48</sup> In this context, it is significant that a comprehensive study of the effectiveness and cost-effectiveness of newborn screening for metabolic disorders in the United Kingdom concluded in 2004 that the evidence supports screening for only two of the conditions detectable by MS/MS: PKU and MCAD. As for the other conditions identifiable by MS/MS, the authors concluded the following:

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<sup>46</sup> Ibid., p. 62. Note that these three benchmarks correspond roughly to the fifth, seventh, and second Wilson-Jungner criteria, respectively.

<sup>47</sup> These numbers are collected in a helpful review of the ACMG report by Donald Bailey and colleagues; Donald B. Bailey, Jr., et al., “Changing Perspectives on the Benefits of Newborn Screening,” *Mental Retardation and Developmental Disabilities Research Reviews* 12 (2006): 270-279, p. 273, Table 1.

<sup>48</sup> In addition to the article by Moyer, et al., “Expanding Newborn Screening: Process, Policy, and Priorities,” see Marvin Natowicz, “Newborn Screening—Setting Evidence-Based Policy for Protection,” *New England Journal of Medicine* 353 (2005): 867-870.

Robust evidence on the underlying incidence and outcomes for many of the disorders was lacking, particularly differences in long-term outcomes that could be attributed to therapies initiated as a consequence of presymptomatic detection using tandem MS.<sup>49</sup>

The British recommendation to screen only for two metabolic disorders was based on a systematic analysis of the same evidence that led the ACMG working group, a year later, to include *twenty* conditions detectable by MS/MS in its core panel of twenty-nine, and *twenty-two* more in its secondary panel of twenty-five conditions—to which we now turn our attention.

### ***C. The Secondary Conditions***

Besides the twenty-nine core or primary conditions, the ACMG report also recommended mandatory screening for twenty-five “secondary” conditions that did not meet the three criteria (listed in the preceding section) for inclusion among the core conditions. More precisely, these are conditions that, despite the availability of a specific and sensitive screening test, lacked a well understood natural history, an efficacious treatment, or both. Why, then, were they recommended for mandatory screening?

When first introduced in the ACMG report, the secondary conditions are described as “conditions that are part of the differential diagnosis of a core panel condition.”<sup>50</sup> In other words, some core conditions, in order to be diagnosed with precision, require the gathering of data that also would reveal the presence in the newborn of one or more other conditions—conditions whose natural history is poorly understood or for which effective treatment is not currently available. The necessity of screening for these secondary conditions would therefore seem to be a mere accident of the testing protocol, an unintended and even regrettable consequence of the determination to screen for the core conditions.

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<sup>49</sup>Abdullah Pandor, et al., “Clinical Effectiveness and Cost-Effectiveness of Neonatal Screening for Inborn Errors of Metabolism Using Tandem Mass Spectrometry: A Systematic Review,” *Health Technology Assessment* 8 (2004): 1–121.

<sup>50</sup> ACMG, *Newborn Screening*, p. 8.

The ACMG working group concluded that positive results for these secondary conditions ought to be reported by the laboratory to the health care provider and to the family of the infant, presumably on the grounds that clinically significant results, once obtained, could not ethically be withheld from the newborn's physician and parents.<sup>51</sup>

It may indeed be ethically problematic to withhold clinically significant test results for the secondary conditions, even if they were included in the screening panel only because they show up as part of the differential diagnosis of core conditions. For most of these conditions, however, the clinical significance of a positive screening result is very much in doubt. And it is necessary to consider the consequences of informing physicians and parents that a child has been identified as having a serious genetic disorder, when the natural history of that disorder is poorly understood and the appropriate treatment—or even the need for treatment—is highly uncertain.

An instructive case is Wisconsin's experience with the organic acid disorder 2-methylbutyryl-coenzyme A dehydrogenase deficiency (2-MBG), now included in the ACMG's secondary panel because it is part of the differential diagnosis (by MS/MS) of the core condition IVA.<sup>52</sup> As of November 2008, forty-three states were screening

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<sup>51</sup> Ibid., pp. 11, 20, 62, 75. Rodney Howell ("We Need Expanded Newborn Screening," p. 1801) says that the ACMG's experts felt strongly that any serious abnormality revealed by the secondary screening panel "should not be kept secret" from the child's physician and parents. He contrasted this approach with that of the German screening program, "in which information about conditions not listed on their panel would not only be withheld but that the information should be destroyed." According to Rodney J. Pollitt, in 2004 the German Federal Ministry for Health and Social Security approved screening newborns for fourteen disorders, but the government also forbade screening for any other condition and "decreed that accidentally obtained results arising from the allowed screens must be ignored and not communicated to anyone. All blood-spot samples are to be destroyed within three months." Rodney J. Pollitt, "International Perspectives on Newborn Screening," *Journal of Inherited Metabolic Disease* 29 (2006): 390–396, p. 392.

<sup>52</sup> Sandra C. van Calcar, et al., "2-Methylbutyryl-CoA Dehydrogenase Deficiency in Hmong Infants Identified by Expanded Newborn Screen," *Wisconsin Medical*

newborns for 2-MBG. Outside of the United States, only a handful of infants have been diagnosed with 2-MBG, some of whom have suffered severe developmental delay, failure to thrive, seizures, muscle atrophy, and/or cerebral palsy, while others have remained entirely asymptomatic. Some of those infants have been treated with a restricted diet, with inconclusive results. Only five cases of 2-MBG had been described worldwide when the state of Wisconsin, in 2000, added 2-MBG to its mandatory newborn screening panel. Surprisingly, over the next six years, twenty-seven Wisconsin infants were identified with 2-MBG, all but one of whom were offspring of Hmong parents.<sup>53</sup> Most of these infants were put on a diet low in protein and supplemented with carnitine, although parental compliance with this diet was quite variable. In any event, as of 2007, *all of the Wisconsin children who had been diagnosed at birth with 2-MBG were normal, healthy, and asymptomatic*. It is at this point uncertain whether the restrictive diet was effective, whether the genotypic variant of 2-MBG shared by Hmong infants is essentially benign, and whether infants identified at birth with 2-MBG ought to be treated presymptomatically at all. What is clear is that nationwide screening for 2-MBG, as recommended by the ACMG, will result in a significant number of children (mostly of Hmong descent) being labeled with a serious illness, despite the fact that the majority of them might remain asymptomatic even without any treatment.

We cannot say how typical the case of 2-MBG is of the conditions on the ACMG's secondary screening panel. However, with twenty-five of these rare and poorly understood disorders being proposed to the states for mandatory screening, and with more presumably on the way as the panel of primary conditions expands further, the number of American children in this doubtful situation seems

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*Journal* 106 (2007): 12-15. We are grateful to Norman Fost for bringing this case to our attention.

<sup>53</sup> Van Calcar, et al., estimate that, in Wisconsin, 2-MBG has a prevalence of 1:223 among Hmong infants, but only 1:325,593 among white newborns. See van Calcar, et al., "2-Methylbutyryl-CoA Dehydrogenase Deficiency in Hmong Infants Identified by Expanded Newborn Screen." As of 2008, eighty-one cases of 2-MBG had been identified in the United States, seventy-two of them in Wisconsin and Minnesota, where large Hmong populations have settled. (Data downloaded from the National Newborn Screening Information System, available online at [www2.uthscsa.edu/nnsis](http://www2.uthscsa.edu/nnsis).)

destined to grow considerably. In addition to the possibility of overtreating (and possibly harming) children who are healthy, there also is concern about contributing to “vulnerable child syndrome” and parental overprotectiveness.<sup>54</sup> Thus, the call for a mandatory secondary screening panel—however necessary it may be for differential diagnosis of the core conditions—is a proposal fraught with unintended but possibly serious consequences.

So far, at least, it would appear that the recommendation to screen for a panel of secondary conditions—poorly understood, not clearly treatable, or both—is merely an artifact of the way some primary conditions are detected, an unfortunate necessity that could be avoided altogether if there were a way to screen only for the primary condition. Only twenty of the twenty-five secondary conditions, however, were included in the panel on this basis. When spelled out fully, the ACMG’s standard for including a condition in the secondary panel is that the condition must be either “part of the differential diagnosis of a primary target condition” or merely “apparent in the result of the multiplex assay.”<sup>55</sup> In fact, five conditions were evidently added to the secondary panel on this less stringent basis.<sup>56</sup> Each of these five conditions is very far from

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<sup>54</sup> On parental attitudes toward the “vulnerable child,” see Morris Green and Albert J. Solnit, “Reactions to the Threatened Loss of a Child: A Vulnerable Child Syndrome,” *Pediatrics* 34 (1964): 58-66; Morris Green, “Vulnerable Child Syndrome and Its Variants,” *Pediatrics in Review* 8 (1986): 75-80; and Michael Thomasgard and W. Peter Metz, “Parental Overprotection and Its Relation to Perceived Child Vulnerability,” *American Journal of Orthopsychiatry* 67 (1997): 330-335. According to Thomasgard and Metz, families of children who recovered from a potentially fatal medical condition were found “to share a number of characteristics that centered on the marked discrepancy between the child’s normal health, growth, and development, and the parent’s unfounded belief that the child continued to be at risk for serious illness and was destined to die prematurely.”

<sup>55</sup> ACMG, *Newborn Screening*, p. 9.

<sup>56</sup> *Ibid.*, p. 64. The report indicates that only four rare conditions were moved into the secondary target panel for this reason (*viz.*, that they are detectable in a multiplex assay, although detecting them is not required for the differential diagnosis of any primary condition): the fatty acid oxidation disorders Short-chain acyl-CoA dehydrogenase deficiency (SCAD) and Dienoyl-CoA reductase deficiency (DE-RED), the organic acid disorder Isobutyryl-CoA dehydrogenase deficiency (IBG), and the amino acid disorder Argininemia (ARG). But it appears

meeting the classical standards for inclusion in a newborn screening program.

For example, one of the five is the fatty acid oxidation defect, dienoyl-CoA reductase deficiency (DE-RED). The incidence of this disorder is unknown, but it must be extremely rare, as *only one case of it has ever been reported*. It therefore is impossible to be certain whether the symptoms exhibited by that one infant were coincidental or in fact were caused by the genetic defect. The ACMG report comments that “the sensitivity and specificity of the primary marker are also unknown,”<sup>57</sup> as are the availability, cost, and potential efficacy of any treatment. DE-RED is not detected as part of the differential diagnosis of any other condition; nonetheless, simply because it is possible to detect DE-RED using MS/MS, the ACMG report recommends that DE-RED screening be included in the mandatory (secondary) screening panel in all fifty states. As of November 2008, newborn screening for DE-RED was mandated by law in sixteen states and offered in three others.

#### ***D. The Role of Multiplex Screening Platforms***

To understand why these five rare, poorly understood conditions were included in the ACMG’s secondary target category, it is necessary to delve more deeply into the technology of present-day newborn screening. Some conditions that are candidates for newborn screening are identified by way of unique testing methodologies, but many can be detected using multiplex platforms that screen simultaneously for several conditions. Of the twenty-nine core conditions, twenty-three are identified using multiplex platforms: MS/MS for the six amino acid disorders, the nine organic acid disorders, and the five fatty acid oxidation disorders; and either high pressure liquid chromatography (HPLC) or isoelectric focusing (IEF) for the three hemoglobinopathies. Only six of the core conditions require unique “singleton” tests.<sup>58</sup> Of the

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that the organic acid disorder Malonic acidemia (MAL) also was included in the secondary panel on this basis.

<sup>57</sup> Ibid., p. 233.

<sup>58</sup> Ibid., p. 10. The six exceptions are CH, BIOT, CAH, GALT, hearing loss, and CF.

twenty-five secondary conditions, all but two are detectable using multiplex platforms.<sup>59</sup>

The ACMG report emphasizes the advantages of multiplex screening technology:

Particularly notable is the implementation of multiplex platforms that allow a single type of specimen preparation and simultaneous (or nearly simultaneous) screening for multiple different disorders. Going from one test for one disorder to one test for multiple disorders has the potential to reduce costs per condition tested and can lead to test expansion if these new technologies can be integrated safely and effectively into newborn screening programs.<sup>60</sup>

The report notes that, with some multiplex platforms, the screener must select specific targets for inclusion in the test (this is known as “selective reaction monitoring” or SRM), while for others the test automatically screens for multiple targets without the need for specific target selection (this is known as “full profile testing”).<sup>61</sup> MS/MS in particular can be used in either selective or full profile mode.<sup>62</sup> Selective monitoring means using the multiplex platform *to target only those conditions deemed appropriate for screening*. In contrast, the full profile approach means making maximum use of the technology’s information-gathering powers, *without regard to the distinction between appropriate and inappropriate target conditions*.

Remarkably, the ACMG report makes a forceful case that, whenever possible, MS/MS screening should be carried out in full

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<sup>59</sup> Those two are the carbohydrate disorders galactokinase deficiency (GALK) and galactose epimerase deficiency (GALE), conditions included in the secondary panel because they are a part of the differential diagnosis of GALT.

<sup>60</sup> *Ibid.*, pp. 18-19.

<sup>61</sup> *Ibid.*, p. 19. An example of selective multiplex screening is the use of “gene chips” to test for the presence of a specific set of single nucleotide polymorphisms (SNPs) in the human genome; an example of full profile testing is DNA-sequencing of the entire genome.

<sup>62</sup> *Ibid.*, pp. 19, 60-61.

profile mode. The report gives several reasons for this judgment, one of which is simply that “the use of MS/MS profiles allows for the maximal use of the technology for the identification of clinically significant conditions.”<sup>63</sup> Elsewhere the report extols “the inherent value of multiplex technologies to public health.”<sup>64</sup> But why should “maximal use of the technology for the identification of clinically significant conditions” be considered inherently good, when some of the conditions that will be detected are considered inappropriate for screening? Here is the report’s answer to that question:

Although information about conditions for which treatment options are scarce or not yet reported can lead to increased stresses on families and the health care system, early information can also lead to knowledge of the condition for the family, thus avoiding a potential diagnostic odyssey or inappropriate therapies. In addition, *early information provides opportunity for better understanding of disease history and characteristics, and for earlier medical interventions that might be systematically studied to determine the risks and benefits. Multiplex testing and the identification of conditions falling outside of the uniform screening panel provides the opportunity for such conditions to be included in research protocols.*<sup>65</sup>

In other words, screening for a condition that fails to meet the classical criteria can be justified under a *broadened conception of benefit* that includes not only helping the *family* avoid “the diagnostic odyssey” but also helping *society* by providing opportunities for *biomedical research* aimed at understanding the natural history of the disorder and finding an effective treatment for it.

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<sup>63</sup> Ibid., p. 61. The other reasons are the following: 1) Most of the other conditions identifiable by MS/MS are already required for the differential diagnosis of the high-scoring core conditions; thus full profile screening ensures that the core conditions are diagnosed with the maximum specificity and sensitivity. 2) “Allowing all information to be assessed can reveal the presence of spurious signals and/or contaminants.” 3) Full profile testing can “enhance clinical interpretation of results by revealing anomalies in associated compounds or in compounds that provide internal standards against which excesses or deficiencies can be better interpreted.”

<sup>64</sup> Ibid., p. 51.

<sup>65</sup> Ibid., p. 20, emphasis added.

### *E. A Broadened Conception of Benefit*

The ACMG’s emphatic preference for the use of multiplex platforms in “full profile” mode is thus indicative of a broadened conception of benefit that could justify screening for nearly any condition. Traditionally, as we have seen, the only relevant benefit was the benefit to the infant of a timely and effective treatment for a serious illness. The ACMG report, on the other hand, is quite explicit in embracing a broader notion of public benefit, not limited to direct treatment of the child. In assessing each testable condition for inclusion in the uniform panel, the authors of the ACMG report gave “overriding consideration” to benefits of early intervention for the individual screened (chiefly when there is a known and effective treatment), but they also gave weight to “benefits of early intervention for family and society”:

Families could benefit from establishing that there may be a genetic risk to others in the family. Society could benefit by a reduction in medical diagnostic odysseys that are costly to the healthcare system.<sup>66</sup>

Elsewhere, the report makes clear that the *societal benefits* of newborn screening include the opportunity for progress in *biomedical research*.<sup>67</sup> Thus, it seems clear that, in extolling the advantages of multiplex platforms and in calling for their use in “full profile” mode—even when some of the conditions detected are rare, poorly understood, and as yet untreatable—the ACMG working group was thinking more broadly about benefits to family and to society, and especially about *the value of studying rare and obscure disorders in order to understand them and to find an effective treatment*.

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<sup>66</sup> Ibid., p. 43. On expansive notions of benefit in the ACMG’s report, see also Donald B. Bailey, Jr., et al., “Changing Perspectives on the Benefits of Newborn Screening.”

<sup>67</sup> Note the phrase “understanding prevalence and natural history” in Table 2 on page 44 of the ACMG’s report, as well as the earlier reference, on page 20, to the “opportunity for better understanding of disease history and characteristics, and for earlier medical interventions that might be systematically studied to determine the risks and benefits.”

### ***F. Impact of a Broadened Conception of Benefit on the ACMG Recommendations***

The impact of this broadened conception of benefit on the ACMG working group's final recommendations can be seen in two different places: in the initial scoring of the conditions that assigned them to one of three categories (low-, middle-, and high-scoring), and in the way certain conditions found their way into the secondary panel.

When surveying expert opinion for the initial ranking of the eighty-four conditions that were candidates for screening, the ACMG asked a series of questions and assigned points to each condition based on the answers of hundreds of experts. With extremely favorable answers from the experts, a condition could score a maximum of 2,100 points. Of these, up to 700 points were awarded to a condition based on some of the main attributes of the condition (incidence, burden if untreated, benefits of intervention, etc.), up to 700 points for attributes of the screening test (sensitivity, specificity, multiplex versus singleton, etc.), and up to 700 points for aspects of treatment and management (availability, cost, efficacy, etc.). Among many other criteria, up to 200 points were awarded to a condition for evidence of “individual benefits of early intervention.” But up to 100 points were awarded to a condition for evidence of “family and societal benefits of early intervention.” Moreover, another 200 points were awarded to a condition *just for being detectable using a multiplex platform*, and fifty additional points were awarded to a condition if, in the course of detecting it, other conditions were also identified. In other words, a condition might well be bumped up to the middle- or even to the high-scoring division despite showing scant evidence of benefit to the newborn child.

After the initial scoring, the eighty-four conditions were re-evaluated using a decision tree that is depicted in Figure 9 of the ACMG report (reproduced below). High-scoring (>1,200) conditions were added to the core panel if, on further review, experts determined that a treatment was available and necessary and that the natural history of the disease was well understood. But

high-scoring conditions for which there was no treatment still ended up in the secondary panel if they were part of the differential diagnosis of a core condition, or *even if they were merely detectable as part of a multiplex assay in full profile mode*. If a treatment was available but the natural history of the disease was poorly understood, the high-scoring condition still ended up in the secondary panel. And indeed, the report notes that three conditions that initially scored high on the survey “were moved to the secondary target category on the basis of scientific evidence indicating that the natural history was not sufficiently well understood.”<sup>68</sup> In other words, the lack of an effective treatment or of an adequate understanding of the natural history of a disease (or both) was not sufficient to remove it from the mandatory screening panel; it merely led to the disease being re-classified as a secondary rather than a primary target.

Meanwhile, middle-scoring conditions (1,000-1,200) were added to the secondary panel as long as they were part of a differential diagnosis or were detectable by multiplex assay. And even low-scoring conditions (<1,000) were to be bumped up to the secondary panel if they were detectable in a multiplex assay.<sup>69</sup> In this regard, it is worth noting that the ACMG working group considered for inclusion but ultimately rejected the rare lysosomal storage disorders Fabry, Krabbe, Pompe, and Hurler-Scheie, scores of which ranged from 447 to 707. These extremely low scores reflect not only the absence, at present, of a sensitive and specific screening test, but also the unavailability of any effective treatments. Nevertheless, researchers are well on their way to developing MS/MS assays for these conditions,<sup>70</sup> and the ACMG report’s

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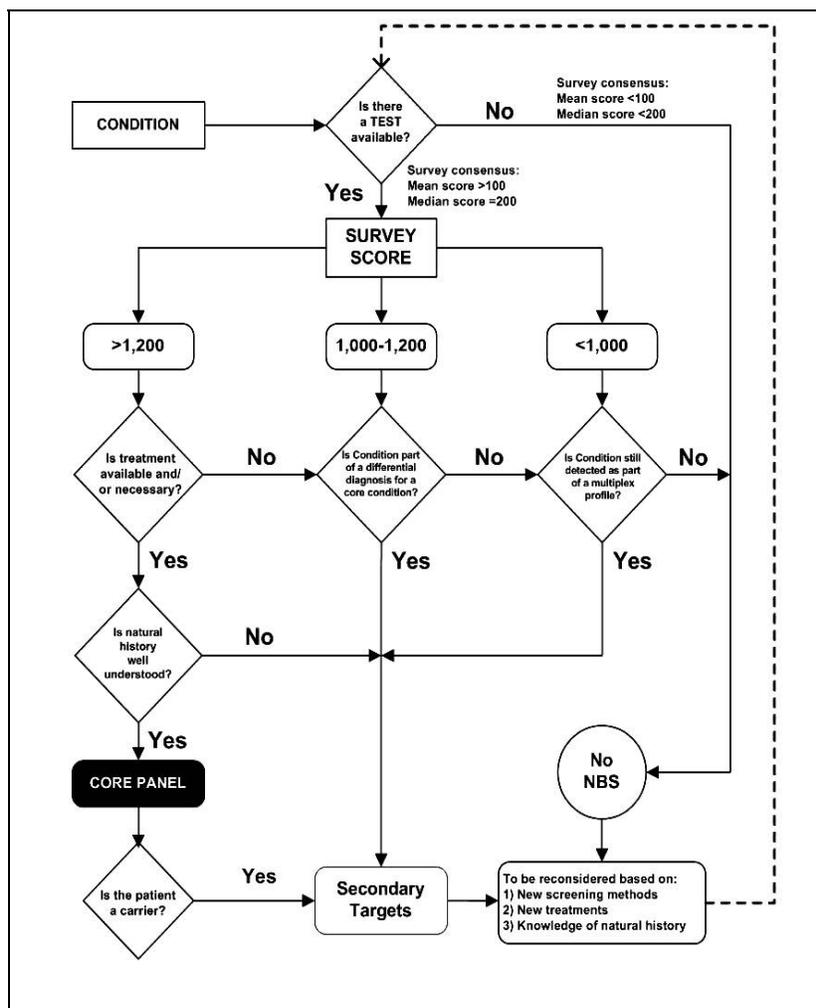
<sup>68</sup> Ibid., p. 64. In fact, all three of these conditions are identified as part of the differential diagnosis of one of the core conditions, so they would have been included in the secondary panel regardless of their survey score.

<sup>69</sup> In fact, no condition scoring <1,000 was moved to the secondary panel on this basis; the lowest-scoring condition in the secondary panel is Citrullinemia type II (CIT-II, score 1,001), included because it is in the differential diagnosis of Citrullinemia type I (CIT-I). However, it is to be noted that, of the thirty disorders specifically excluded from screening, fully twenty-three of them were rejected simply because *no reliable test is currently available*. Many of these conditions would presumably be moved into the secondary panel (and some even to the core panel) if a test became available, especially if it were part of a multiplex assay.

<sup>70</sup> See the references in Chapter One, Footnote Thirteen.

decision tree would seem to dictate the automatic inclusion of all these untreatable and poorly understood disorders (and related disorders such as Gaucher, Hunter, Niemann-Pick, and Tay-Sachs) in the secondary panel as soon as it becomes feasible to detect them using a multiplex platform such as MS/MS.

Figure 9 from the ACMG's *Newborn Screening Report*<sup>71</sup>



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<sup>71</sup> Ibid., p. 121.

### III. The Significance of the ACMG's Recommended Screening Panel

In considering this decision-making process, it is important to bear in mind that *whether a state program mandates screening for a condition as part of the core panel or part of the secondary panel makes no practical difference as far as the infant and family are concerned*. If a state screening program embraces the ACMG's recommendation of *mandatory* screening for both primary and secondary conditions (and most states seem to be on their way to doing so), a positive screening result is reported to the physician and the family regardless of the target category in which the condition happened to be included. With this in mind, the ACMG report's decision tree seems to depart much more radically from classical screening principles than it first appeared to do.

As noted above, the twenty-nine core conditions were each judged by the ACMG working group to meet the traditional standard of having 1) a specific and sensitive screening test, 2) a sufficiently well understood natural history, and 3) an available and efficacious treatment. Moreover, for twenty of the twenty-five secondary conditions, screening could be considered justified on the grounds that it was necessary for the differential diagnosis of one of the core conditions. Only five exceedingly rare conditions were added to the secondary panel without that compelling justification. Seen in this light, the expansion in newborn screening recommended by the ACMG would appear to be rather moderate and fairly consonant with accepted screening principles.

But a careful examination of the ACMG working group's decision tree—and, above all, of its procedures for adding conditions to the secondary panel—makes it clear that the foundations have been laid for a much more radical expansion of newborn screening in the future, and for a significant loosening of the traditional screening standards. Under the ACMG's procedures, a rare and poorly understood genetic condition, even one with no available treatment, will routinely be added to the secondary target panel (recommended for mandatory screening in all fifty states) as soon as it becomes possible to detect that disorder using a multiplex assay in full profile

mode. Even if only a handful of conditions have so far qualified for the secondary panel under that rubric, it is clear that many more conditions could be added to the panel in the future, especially if rapid progress is made in the exploitation of DNA-based multiplex screening platforms, with their potential to detect hundreds of thousands of genetic abnormalities at one stroke.

In brief, it seems fair to conclude from a careful reading of the report that the ACMG working group has effectively recommended mandatory newborn screening for two categories of conditions: the relatively small number of treatable and well understood disorders that satisfy the classical Wilson-Jungner criteria, and the potentially much larger set of untreatable and poorly understood disorders that fall short of those criteria but are detectable by multiplex screening. If the chief purpose of screening conditions in the former category is to benefit the affected newborn with timely and effective treatment, the chief purpose of screening conditions in the latter category would seem to be to advance the scientific study of the disorder, with the ultimate goal of finding an effective treatment. That is certainly a laudable goal, but as a basis for including conditions in a *mandatory* newborn screening panel it represents a sharp departure from the principles expressed in the Wilson-Jungner criteria. Hitherto, for diseases that were poorly understood or for which no effective treatment was available, we as a nation have not been in the habit of subjecting individuals to compulsory screening merely for research purposes. In the wake of the ACMG report and its enthusiastic reception by the states, our approach to newborn screening seems to be heading into uncharted territory.





# CHAPTER THREE

## THE FUTURE OF NEWBORN SCREENING

In the previous chapter, we considered certain urgent ethical dilemmas that confront us today as the states proceed to expand their mandatory newborn screening programs. In this chapter, we lift our eyes from the present scene and contemplate how newborn screening may continue to evolve as the age of genomic medicine advances. Over the next years and decades, anticipated developments in the technology and the practice of medicine are likely to alter the landscape of newborn screening entirely, ushering in a potentially vast increase in the kinds and amounts of genetic data that can be routinely collected upon the birth of a child.<sup>1</sup> It is quite possible that today's debates over whether to add this or that rare disorder to a uniform screening panel will be swamped, in the context of genomic medicine, by a radically more expansive approach to genetic screening. It is the burden of this chapter to sketch some of the possible consequences for newborn screening and to outline the serious ethical dilemmas that we are likely to face in the future.

This chapter has three parts, addressing the following topics: first, newborn screening in the age of genomic medicine; second, the case for newborn profiling; and third, the case for caution.

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<sup>1</sup> And not only genetic data: the medically relevant information that will be collected is likely to embrace both “epigenetics,” the systematic study of heritable but non-genetic factors that influence an organism's development, and “proteomics,” the systematic study of the full complement of an organism's proteins (“proteome” being a word formed by analogy with “genome”).

## I. Newborn Screening at the Dawn of the Genomic Era

The completion of the Human Genome Project in 2003 signaled the beginning of the age of genomic medicine. With the full mapping of the human genome, researchers are increasingly able to pinpoint errors in genes that cause or contribute to a multitude of conditions, from rare genetic disorders to common illnesses. On the basis of comprehensive genomic knowledge, it is believed that physicians of the future will be able to tailor diagnosis and treatment to the unique genetic profile of the individual patient, thereby eliminating much of the guesswork of traditional “one size fits all” medical practice.

To achieve its full potential, personalized medicine will require physicians to gather large amounts of genetic information from their patients. The National Human Genome Research Institute (NHGRI) has announced the goal of reducing the cost of sequencing an individual human genome first to \$100,000 and then to \$1,000. At this last price point, thought to be reachable by 2014, an individual’s full genome could be added to his or her medical file as part of routine medical care—to supplement and in some ways to supersede the patient’s family medical history. The \$1,000 genome may arrive sooner than even this optimistic projection would suggest. In 2007, the complete genome of geneticist and co-discoverer of the double helix James D. Watson was sequenced at a cost of about \$2 million;<sup>2</sup> in the fall of 2008, a company in California announced plans to begin offering complete human genome sequences for \$5,000, starting in the spring of 2009.<sup>3</sup>

In the meantime, it is already feasible, using “gene chips,” microbeads, and other state-of-the-art multiplex technologies, to test an individual’s DNA for the presence of hundreds of thousands

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<sup>2</sup> The company that sequenced Watson’s DNA is called “454.” See Emily Singer, “The \$2 Million Genome,” *Technology Review*, June 1, 2007.

<sup>3</sup> The company is called Complete Genomics, and its website is [www.completegenomicsinc.com/](http://www.completegenomicsinc.com/). See Emily Singer, “Five Thousand Bucks for Your Genome: A New Sequencing Service Could Change the Face of Human Genomics,” *Technology Review*, October 6, 2008; and Erica Check Hayden, “\$5,000 Genome Next Year, Company Promises,” *Nature News*, October 6, 2008.

of distinct single nucleotide polymorphisms (SNPs), which are minute variations in the DNA sequence that can affect how (or correlate with other DNA variations that affect how) the individual develops diseases and responds to pathogens, drugs, vaccines, and so forth.<sup>4</sup> Already, a handful of private companies are offering, for as little as \$399, to check your genome for known variations believed to correlate with particular traits, conditions, and susceptibilities.<sup>5</sup> Clearly, the genomic era is already upon us.

Rapid medical and technological progress aided by the Human Genome Project is challenging both the practice and the principles of newborn screening. As mentioned, most babies born today in the United States are screened at birth for between thirty and fifty genetic disorders, primarily by using MS/MS to detect abnormal levels of metabolites in the infant's blood. At the same time, the National Institute of Child Health and Human Development (NICHD) is spearheading efforts to move beyond such limited, phenotypic methods of newborn screening toward DNA-based platforms that can "offer enormous opportunities to identify staggering numbers of potentially pathogenic mutations in a very

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<sup>4</sup> Gene chips are glass or silicon chips to which are bonded thousands of microscopic spots containing short DNA sequences called oligonucleotides. Each spot serves as a probe to detect the presence of a particular SNP in the target DNA sample. The leading developer of gene chips is a company called Affymetrix. Another approach is to bond the oligonucleotide probes to thousands of microscopic silica beads, which are then randomly deposited onto a glass substrate. The resulting array is then used to check the target DNA sample for particular SNPs. A company called Illumina has pioneered the use of microbeads.

<sup>5</sup> See, for example, the websites [www.23andme.com](http://www.23andme.com) and [www.decodeme.com](http://www.decodeme.com), each of which offers to test a client's DNA for several hundred thousand known SNPs. See Robert F. Service, "Gene Sequencing: The Race for the \$1000 Genome," *Science* 311 (2006): 1544–1546; and Sarah E. Gollust, et al., "Direct-to-Consumer Sales of Genetic Services on the Internet," *Genetics in Medicine* 5 (2006): 332–337. For a thoughtful discussion of some ethical and legal implications of the \$1,000 genome, see John A. Robertson, "The \$1000 Genome: Ethical and Legal Issues in Whole Genome Sequencing of Individuals," *American Journal of Bioethics* 3 (2003): W35–W43.

large number of disease-associated genes.”<sup>6</sup> Many competent observers expect that, in the not too distant future, simple and inexpensive DNA-based multiplex platforms will be the standard instruments of newborn screening in most states (supplemented with phenotypic testing for conditions that require it).<sup>7</sup>

In 2006, Duane Alexander, Director of the NICHD for more than two decades and thus one of the nation’s leading voices in pediatric medicine, coauthored an article with his colleague Peter van Dyck offering their “vision of the future of newborn screening.”<sup>8</sup> In that article, Alexander and van Dyck refer to the principle that “it is appropriate to screen only for conditions for which effective treatment already exists” as a *dogma* that “dooms us to continued ignorance and unavailability of treatment because affected individuals are not identified until they exhibit symptoms, too late for effective preventive interventions to be tested or applied.”<sup>9</sup> They call for the development and implementation of DNA-based multiplex platforms that can be used to screen newborns for “virtually all target conditions with one test system.”<sup>10</sup> More fundamentally, in their view every medically significant genetic

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<sup>6</sup> Duane Alexander and James W. Hanson, “NICHD Research Initiative in Newborn Screening,” *Mental Retardation and Developmental Disabilities Research Reviews* 12 (2006): 301-304, p. 302.

<sup>7</sup> Nancy S. Green and Kenneth A. Pass, “Neonatal Screening by DNA Microarray: Spots and Chips,” *Nature Reviews. Genetics* 6 (2005): 147-151.

<sup>8</sup> Duane Alexander and Peter C. van Dyck, “A Vision of the Future of Newborn Screening,” *Pediatrics* 117 Supplement (2006): S350-S354.

<sup>9</sup> *Ibid.*, pp. S351, S352.

<sup>10</sup> *Ibid.*, p. S351. In his presentation before this Council on June 23, 2006, Dr. Alexander elaborated: “[Tandem mass spectrometry] still doesn’t go as far as we need it to go. And so we’re looking at potential DNA-based systems. If we could have this, we could screen for basically anything we have the gene for... The numbers go into the hundreds. And each time we discover a new gene or a new abnormality of a gene the number of conditions would go up.

“...[T]hese are things that are coming along and that we are investing in, trying to develop an enhanced capability to screen, and to have a test that is so attractive, so simple, and not too expensive, so that every state will want to use this in their screening program, and no longer will there be this state-to-state variability, so that what you get screened for depends on the state in which you’re born.” (For an online transcript of Dr. Alexander’s remarks, see [www.bioethics.gov/transcripts/june06/session5.html](http://www.bioethics.gov/transcripts/june06/session5.html).)

marker should be assumed to be screenable *except those specifically excluded on a case-by-case basis*.<sup>11</sup> Assuming that in a matter of years or at most decades the Human Genome Project will bear fruit in the form of affordable whole-genome sequencing or at least affordable multiplex SNP genotyping, this vision seems a plausible picture of a not-too-distant future in which infants are routinely screened at birth for almost all medically significant genetic markers (with a few conditions deliberately excluded), to be treated immediately when possible, and otherwise to be enrolled in registries to await trials of experimental therapies. Personalized genomic medicine will then start from the moment of birth, as the pediatrician will be in possession of a complete map of each young patient's known genetic defects, vulnerabilities, and susceptibilities. In what follows, we shall denote this vision of a vastly expanded screening program by the phrase "newborn profiling."<sup>12</sup>

Thus, in contemplating the future of newborn screening, Alexander and van Dyck are calling for the old "dogma"—"screen only if you can effectively treat"—to be superseded by a new principle—"screen unless there is a compelling reason not to screen." Such a radical change in the ethical framework of newborn screening might seem far-fetched today, but in some ways the ground for it has already been prepared by the ACMG in its 2005 report. As described in the preceding chapter, the ACMG report's recommended expansion in newborn screening quietly incorporates

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<sup>11</sup> In their article, Alexander and van Dyck mention only Huntington's disease (an invariably fatal, as yet untreatable, adult-onset, Mendelian dominant, neurological disorder) as a *possible* candidate for exclusion. ("A Vision of the Future of Newborn Screening," p. S353.) It is not clear what other disorders they would put in the same category. At Duane Alexander's June 23, 2006, appearance before the Council, Council Member Floyd Bloom pointed out that Huntington's would seem to fulfill "all of the criteria by which you listed the tests that you want to include, even though we can't treat them." (See [www.bioethics.gov/transcripts/june06/session5.html](http://www.bioethics.gov/transcripts/june06/session5.html).) If a new treatment were developed that, when started early in life, produced even a modest decrease in the morbidity or mortality of Huntington's disease, it is reasonable to suppose that Alexander and van Dyck would move Huntington's into the "screen" column.

<sup>12</sup> We borrow this informative phrase from the 2005 report, *Profiling the Newborn: A Prospective Gene Technology?*, published by the Human Genetics Commission of the United Kingdom, available online at [www.hgc.gov.uk/](http://www.hgc.gov.uk/).

the principle that *all conditions that can be detected by multiplex assay should be included in the mandatory screening panel, regardless of whether or not they meet the traditional Wilson-Jungner criteria*. The fact that, in the ACMG report, this principle led to the inclusion of only a handful of rare disorders detectable by MS/MS should not obscure the fact that the stage has been set for a truly vast expansion in multiplex newborn screening, once DNA-based assays become widely available and affordable. Therefore, in the face of a possible future where full-scale newborn *profiling* is routine, it is essential that we consider both the promise and the peril of that prospect. In the remainder of this chapter we look at each in turn.

## II. The Case for Newborn Profiling

Given that the current debate is mostly about whether to add this or that disorder to the limited panel of conditions for which newborns are routinely screened, why should we believe that in the future the default practice could be to screen *all* newborns for *every* known genetic abnormality? The short answer is this: *because the logic of personalized medicine and of technological progress will inexorably demand it*.

### *A. The Logic of Personalized Medicine and Technological Progress*

In 2001, Francis Collins, who led the Human Genome Project from 1993 to 2008, described what genomic medicine would look like in its earliest stage:

By the year 2010, it is expected that predictive genetic tests will be available for as many as a dozen common conditions, allowing individuals who wish to know this information to learn their individual susceptibilities and to take steps to reduce those risks for which interventions are or will be available. Such interventions could take the form of medical surveillance, lifestyle modifications, diet, or drug therapy. Identification of persons at highest risk for colon cancer, for example, could lead to targeted efforts to

provide colonoscopic screening to those individuals, with the likelihood of preventing many premature deaths.<sup>13</sup>

Collins' example illustrates the powerful intuitive appeal of personalized genomic medicine. Colonoscopy is normally recommended to begin at age fifty, but with a family history of colon cancer it is recommended to begin at forty years or earlier. But as geneticists discover correlations between particular combinations of SNPs and elevated risk of colon cancer, it will increasingly be possible to adjust the time at which colonoscopy should commence to the specific genome of the patient, thereby catching many cancers at an earlier, treatable stage. In principle, the same sort of adjustment of routine screening schedules will be possible when screening for other cancers, tremendously improving the odds of detecting and eliminating those cancers before they turn deadly. As renowned obstetrician-gynecologist Alan Guttmacher and colleagues put it, “genomics-based knowledge and tools promise the ability to approach each patient as the biological individual he or she is, thereby radically changing our paradigms and improving efficacy.”<sup>14</sup>

The drive toward unlimited expansion of newborn screening will also be fueled by technological progress, which has given us—in MS/MS—a method of screening for dozens of metabolic disorders at once, and which will soon deliver—in the form of DNA-based multi-array platforms—the ability to screen whole genomes for tens or hundreds of thousands of medically significant markers. Some observers believe that a “technological imperative” in modern society (combining a desire for commercial profit with a belief that “knowledge is power” and that “if we can do it, we should”) makes it inevitable that maximal use of genomic information will become part of the medical practice of the future.<sup>15</sup>

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<sup>13</sup> Francis S. Collins, “Implications of the Human Genome Project for Medical Science,” *Journal of the American Medical Association* 285 (2001): 540-544, pp. 543-544.

<sup>14</sup> Alan E. Guttmacher, et al., “Educating Health-Care Professionals about Genetics and Genomics,” *Nature Reviews. Genetics* 8 (2007): 151-157.

<sup>15</sup> On the “technological imperative” in modern medicine, see Evan Willis, “The ‘New’ Genetics and the Sociology of Medical Technology,” *Journal of Sociology* 34

Once personalized genomic medicine becomes standard medical practice for adults, the logic of providing physicians with this powerful tool earlier and earlier in the patient's life may prove inescapable. Even if cancers, for example, are relatively rare in children and adolescents, why wait until adulthood to uncover susceptibilities and vulnerabilities that could well be countered by changes in diet and life habits (to say nothing of prophylactic therapies) at an early age?<sup>16</sup> As Collins suggests, "with increasing genetic information about common illnesses, this kind of risk assessment will become more generally available, and many primary care clinicians will become practitioners of genomic medicine..."<sup>17</sup> Because so many of our habits are formed in childhood, there will be compelling reasons for pediatricians to become genomic practitioners as well. To fulfill its promise of predictive and preventive as well as personalized care, genomic medicine will push the point of data collection to the moment of birth—if not earlier.

### ***B. The Benefits of Biobanking***

Biobanks, which are huge repositories of tissue samples or health information that interlink human genotypes with lifelong medical histories, could help us make use of the large quantities of genetic data collected from newborns.<sup>18</sup> Biobanks at present are typically

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(1998): 170-183; Daniel Callahan, *What Price Better Health Care? Hazards of the Research Imperative* (Berkeley: University of California Press, 2003); and Arnold Pacey, *The Culture of Technology* (Cambridge, Massachusetts: MIT Press, 1985).

<sup>16</sup> On the other hand, there is some evidence that DNA risk information may be less likely to achieve behavior change than other types of health risk information. See Theresa M. Marteau and John Weinman, "Self-Regulation and the Behavioural Response to DNA Risk Information: A Theoretical Analysis and Framework for Future Research," *Social Science and Medicine* 62 (2006): 1360-1368.

<sup>17</sup> Francis S. Collins, "Implications of the Human Genome Project for Medical Science," p. 544.

<sup>18</sup> See Dan M. Roden, et al., "Development of a Large-Scale De-Identified DNA Biobank to Enable Personalized Medicine," *Clinical Pharmacology and Therapeutics* 84 (2008): 362-369. Some countries are or will soon experiment with large-scale biobanks. One example is the UK Biobank, whose database will cover 500,000 volunteers and will interlink their health, lifestyle, and environmental histories with gene maps of DNA extracted from their blood. See their website at [www.ukbiobank.ac.uk](http://www.ukbiobank.ac.uk). An even more ambitious genomic biobank, intended to include the entire population of Iceland, was inaugurated by an act of the

considered to be research enterprises, but, under the rubric of genomic medicine, it seems likely that in the future they will more and more become a tool for the clinician, a sort of “family history” writ large. It will be crucial not only to collect genotypic data from a large number of patients, but to correlate these data with exact medical histories recorded over many years.<sup>19</sup> Most genetic determinants of disease are likely to be complex and polygenic, and the more these cross-linked databases are mined for significant correlations, the more we will learn about each patient’s differential risks and susceptibilities.<sup>20</sup>

Here, too, the logic of personalized medicine dictates that the collection of genotypic data and its correlation with individual medical, environmental, and lifestyle histories should cover the whole human lifespan, not excluding adolescence, childhood, birth, and even gestation in the womb.<sup>21</sup> Moreover, the day of their birth

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Icelandic parliament in 1998, but has subsequently been scaled back considerably in the face of legal and ethical controversy. See Henry T. Greely, “Iceland’s Plan for Genomics Research: Facts and Implications,” *Jurimetrics* 40 (2000): 153-191.

<sup>19</sup>In the United States, the “Genomics and Personalized Medicine Act of 2007,” sponsored in the 110<sup>th</sup> Congress by then Senator (and now President-Elect) Barack Obama in order “to secure the promise of personalized medicine for all Americans by expanding and accelerating genomics research and initiatives to improve the accuracy of disease diagnosis, increase the safety of drugs, and identify novel treatments,” calls for the establishment of “a national biobanking distributed database for the collection and integration of genomic data, and associated environmental and clinical health information, which shall facilitate synthesis and pooled analysis of such data.” The text of the proposed legislation may be found online at [www.govtrack.us/congress/billtext.xpd?bill=s110-976](http://www.govtrack.us/congress/billtext.xpd?bill=s110-976).

On the prospects for a large-scale U. S. biobank, see also the March 2007 report of the Secretary’s Advisory Committee on Genetics, Health, and Society, *Policy Issues Associated with Undertaking a New Large U. S. Population Cohort Study of Genes, Environment, and Disease* (Bethesda, Maryland: U. S. Department of Health and Human Services, 2007), available online at [www4.od.nih.gov/oba/sacghs/reports/SACGHS\\_LPS\\_report.pdf](http://www4.od.nih.gov/oba/sacghs/reports/SACGHS_LPS_report.pdf).

<sup>20</sup> See Kaare Christensen and Jeffrey C. Murray, “What Genome-Wide Association Studies Can Do for Medicine,” *New England Journal of Medicine* 356 (2007): 1094-1097.

<sup>21</sup> However, for a study of the legal and ethical problems posed by the establishment of genotypic databases, see Henry T. Greely, “The Uneasy Ethical and Legal Underpinnings of Large-Scale Genomic Biobanks,” *Annual Review of Genomics and Human Genetics* 8 (2007): 343-364.

is arguably the most convenient opportunity to enroll children, with the cooperation of their parents, in the comprehensive data-gathering system on which their personalized medical care will be predicated. In fact, pediatric biobanks are already being established in this country, and it stands to reason that the most powerful and useful form of such databases would include comprehensive genotypic data and medical histories collected from infants starting at birth or even *in utero*.<sup>22</sup>

The hope of finding a cure for rare and as yet untreatable genetic disorders will provide a powerful incentive for comprehensive newborn profiling. Disorders that afflict only a handful of persons each year are more difficult to study than more common diseases whose victims are easy to locate and study. An obscure illness for which there is as yet no treatment is more likely to be elucidated and ameliorated or cured if newborn screening gives the medical community an accurate picture of the prevalence of the disorder as well as early access to as many of its sufferers as possible. Genomic medicine offers a compellingly systematic approach to the search for treatment of such illnesses, including the following methodical steps: comprehensive genetic profiling at birth, followed by enrollment of all afflicted patients in a biobank of genotypic data; careful study of the course of the illness in each patient, with all significant medical histories entered in the biobank; and finally, when innovative therapies become available, easy access to pools of potential research subjects, to be contacted and enrolled in experimental trials if they are willing. Surely it will be seen to be in the patients' interests, broadly understood, to push their incurable genetic ailments into the column of treatable illnesses, even if no actual treatment is available at the time of their diagnosis.

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<sup>22</sup> See Jocelyn Kaiser, "U.S. Hospital Launches Large Biobank of Children's DNA" (News of the Week: Genetics), *Science* 312 (2006): 1584-1585. According to Kaiser, Children's Hospital of Philadelphia plans "to analyze DNA from 100,000 children and begin searching for links to childhood diseases such as asthma, diabetes, and obesity." See also Alon B. Neidich, et al., "Empirical Data About Women's Attitudes Towards a Hypothetical Pediatric Biobank," *American Journal of Medical Genetics Part A* 146A (2008): 297-304; and David Kaufman, et al., "Ethical Implications of Including Children in a Large Biobank for Genetic-Epidemiologic Research: A Qualitative Study of Public Opinion," *American Journal of Medical Genetics Part C: Seminars in Medical Genetics* 148C (2008): 31-39.

***C. The Psychosocial Consequences of Testing Positive: A Silver Lining?***

With comprehensive screening, there is hope that the psychosocial consequences of testing positive for a genetic ailment will be less severe. When knowledge of genetic abnormalities is rare, the news that one carries a dangerous and defective gene is potentially devastating. It can entail debilitating anxiety, depression, and despair, not to mention stigmatization and discrimination by others. This is one of the strongest reasons for protecting the individual's right of informed consent with respect to genetic testing, a right that is admittedly compromised when parents (or state governments) make the decision to have children genetically screened.<sup>23</sup>

But a case can be made that, with the full flourishing of genomic medicine and the routine gathering of thousands of data points from every human genome, the stigma attached to most genetic defects will largely dissipate, and along with it some of the most severe psychological sequelae. It will be better understood then that every one of us, without exception, carries a multitude of minute genetic variations, some of them favorable to health and happiness, others less auspicious. The sense that we are all in the genetic lottery together, and no one is simply a winner or a loser, may well provide the best foundation for a healthy and realistic attitude toward the vicissitudes of inheritance. This is not to say that the discovery that one carries a fatal or incapacitating gene defect, like the trinucleotide repeats that cause Huntington's, will be easy to bear, but it does suggest that a comprehensive transformation of American medicine in the genomic direction will render genetic disease as a whole less horrifying and isolating.<sup>24</sup>

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<sup>23</sup> See Rony E. Duncan, et al., "You're One of Us Now": Young People Describe Their Experiences of Predictive Genetic Testing for Huntington Disease (HD) and Familial Adenomatous Polyposis (FAP)," *American Journal of Medical Genetics Part C: Seminars in Medical Genetics* 148 (2008): 47-55.

<sup>24</sup> On psychosocial risks and of comprehensive genomic testing of children compared to genetic testing, see Benjamin Wilfond and Lainie Friedman Ross, "From Genetics to Genomics: Ethics, Policy, and Parental Decision-making," *Journal of Pediatric Psychology*, July 22, 2008 (epublication ahead of print), pp. 1-9;

#### *D. The Support of Parents and Advocacy Groups*

Finally, one can anticipate growing pressure from parents and advocacy groups to embrace rapid expansion of newborn screening.<sup>25</sup> As Alexander and van Dyck noted in their response to a critical colleague, there is an “almost unanimous preference of parents for knowing the diagnosis in the newborn period.”<sup>26</sup> And indeed, studies have consistently shown strong (and growing) public support for genetic screening, especially among parents of children with genetic disorders.<sup>27</sup> Parents in the latter group seem to believe

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and Morris W. Foster and Richard R. Sharp, “Ethical Issues in Medical-Sequencing Research: Implications of Genotype–Phenotype Studies for Individuals and Populations,” *Human Molecular Genetics* 15 (2006): R45-R49.

<sup>25</sup> Some of the same social pressures are at work in driving the states to offer the maximal panel of conditions for newborn screening. As Jeffrey Botkin put it in remarks to the Council on February 3, 2006, “I think there’s a strong social attitude that screening is a good thing, and I see it in the paper every morning with the body scanners. You know, spend 600 bucks. Detect disease early and save your life. Well, there’s no data to support any of that, but it’s part of the social consciousness now, and I think how that’s translated into newborn screening is the strong sense that if you’ve got five tests, that’s good. If you’ve got 20 tests, that’s really terrific, and any self-respecting state, you know, should not have less than 40 tests on its panel.” (Remarks available online at [www.bioethics.gov/transcripts/feb06/session6.html](http://www.bioethics.gov/transcripts/feb06/session6.html).)

<sup>26</sup> Duane Alexander and Peter C. van Dyck, “Neonatal Screening: Old Dogma or Sound Principle?” (in reply), *Pediatrics* 119 (2007): 407.

<sup>27</sup> For example, Fragile X syndrome, the most common inherited form of mental retardation, does not meet the criteria for routine newborn screening, as there is currently no cure or medical treatment. But in a recent survey of parents of children with Fragile X, large majorities (over ninety percent) favored screening newborns both for the genetic disorder and for carrier status. See Debra Skinner, et al., “Screening for Fragile X Syndrome: Parent Attitudes and Perspectives,” *Genetics in Medicine* 5 (2003): 378-384.

Another example: Although professional guidelines recommend against testing minors for adult-onset genetic conditions, medical oncologist and family risk assessment expert Angela Bradbury and colleagues found that, among parents who are carriers of the BRCA mutations (which correlate with increased risk for breast cancer) and their adult children, as many as forty percent supported genetic testing of minors for the mutations. In fact, the adult children viewed such testing even more favorably than their parents, suggesting that succeeding generations are growing more and more comfortable with the idea of routine genetic screening. See Angela R. Bradbury, et al., “Should Genetic Testing for BRCA1/2 Be Permitted for Minors? Opinions of BRCA Mutation Carriers

that they have a *right to know* whether their child has a genetic disorder, even if it is untreatable, and they believe that such knowledge is good.<sup>28</sup> Notwithstanding the traditional principle that we should screen only for conditions that can be effectively treated, many American parents seem increasingly willing, if not eager, to learn whatever they can about their children's health, including any genetic abnormalities that can be detected at birth.<sup>29</sup>

Such parents may be exhibiting a tendency that the French writer Alexis de Tocqueville noticed in Americans as long ago as 1831: He found that Americans are unwitting followers of the French rationalist philosopher, Descartes, in that they tend "to take tradition only as information, and current facts only as a useful study for doing otherwise and better; to seek the reason for things by themselves, and in themselves alone, [and] to strive for a result

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and Their Adult Offspring," *American Journal of Medical Genetics Part C: Seminars in Medical Genetics* 148C (2008): 70-77.

<sup>28</sup> In a 1998 survey, North American parents (mostly mothers) of children with diagnosed or unconfirmed genetic conditions were asked, "Some conditions can be found at birth through a simple blood test. Sometimes there is no treatment for the child. In these cases, the main purposes of testing the newborn child are to find out if this child has a genetic condition and to let the parents know that they could have another child with the same condition. If you were a parent, would you want your newborn child tested right away so that you could find out if your next child would have a genetic condition?" Seventy-one percent said "yes," eleven percent said "no," and eighteen percent said "I don't know." See Dorothy C. Wertz and John C. Fletcher, *Genetics and Ethics in Global Perspective* (Dordrecht: Kluwer Academic Publishers, 2004), p. 72, and Dorothy C. Wertz, "Ethical Issues in Pediatric Genetics: Views of Geneticists, Parents and Primary Care Physicians," *Health Law Journal* 6 (1998): 3-42. The conductors of the survey report that, "in write-in comments, parents said they had a right to know, that the information would help them relate to their child, and that they wanted the information so they could decide about having another child." (Wertz and Fletcher, *Genetics and Ethics in Global Perspective*, p. 72)

<sup>29</sup> Surveying the general public on these questions, a 2007 report released by the University of Michigan C. S. Mott Children's Hospital National Poll on Children's Health found that fifty-four percent of adults endorsed genetic testing of children even if no effective treatment is available, and thirty-eight percent of parents were willing to have their children's DNA stored in a government DNA biobank. (Report available online at [www.med.umich.edu/opm/newspage/2007/NPCH\\_4.pdf](http://www.med.umich.edu/opm/newspage/2007/NPCH_4.pdf).)

without letting themselves to be chained to the means.”<sup>30</sup> In short, if their child has a problem, American parents simply want to know everything they can about it. That tendency may help to explain why the American public today, when surveyed, often shows more enthusiasm for expanded newborn screening than pediatricians do.<sup>31</sup> Whether it is indeed the parents’ right to decide on behalf of their young child that every genetic abnormality should be brought to light, is another question.

It would be difficult to exaggerate the role of patient advocacy groups in pressing for the expansion of newborn screening.<sup>32</sup> As March of Dimes Foundation president Jennifer Howse and colleagues put it, “Expansion of [newborn screening] has been driven primarily by a combination of advances in technology and medical treatment, and the sustained advocacy efforts of consumers and voluntary health organizations.”<sup>33</sup> University of North Carolina pediatrician Donald Bailey and colleagues noted that, during public commentary on the ACMG’s report, *every* advocacy group that commented endorsed the uniform screening panel and noted a range of benefits that would result from expanded screening. Moreover, “there was no mention of any risks or burdens of screening other than to discount arguments that conditions for which there is no proven medical treatment for the child should not be included in newborn screening.”<sup>34</sup> Parents who discover that their newborn child suffers from a rare genetic illness are quite

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<sup>30</sup> Alexis de Tocqueville, *Democracy in America*, trans. Harvey C. Mansfield and Delba Winthrop (Chicago: University of Chicago Press, 2000), Volume 2 (1840), Part 1, Chapter 1, “On the Philosophic Method of the Americans,” p. 403.

<sup>31</sup> Pediatrician Kruti Acharya and colleagues found that “most physicians support diagnostic genetic testing of high-risk children but are less supportive of expanding newborn screening, particularly for conditions that do not meet the Wilson and Jungner criteria.” See Kruti Acharya, et al., “Pediatricians’ Attitudes Toward Expanding Newborn Screening,” *Pediatrics* 116 (2005): e476-e484, p. e476.

<sup>32</sup> Diane B. Paul, “Patient Advocacy in Newborn Screening: Continuities and Discontinuities,” *American Journal of Medical Genetics Part C (Seminars in Medical Genetics)* 148C (2008): 8-14.

<sup>33</sup> Jennifer L. Howse, et al., “Critical Role of the March of Dimes in the Expansion of Newborn Screening,” *Mental Retardation and Developmental Disabilities Research Reviews* 12 (2006): 280-287.

<sup>34</sup> Donald B. Bailey, Jr., et al., “Changing Perspectives,” p. 275.

likely to add their support to groups calling both for universal screening and for increased funding of research to find a cure. Undoubtedly, such vigorous advocacy of newborn profiling makes a good deal of sense under the paradigm of genomic medicine. But it also means that those promoting the agenda of personalized genomic medicine and newborn profiling have a strong and energetic natural ally in the parents of genetically afflicted children and the groups that represent them.

### **III. The Case for Caution**

We have seen that there are powerful arguments—and potent technological and social forces—favoring the eventual realization of the vision of universal DNA-based profiling of newborns, with all genetic markers of medical interest included by default, and perhaps only a handful of disorders excluded on a case-by-case basis. We now turn to some of the reasons for doubting whether this vision is likely to be realized, and whether—even if it is attainable—the benefits would outweigh the costs. In the long run, it may, in fact, prove impossible to hinder the logic of genomic medicine from assimilating the currently limited practice of newborn screening to its all-embracing paradigm. Nonetheless, even if these future developments turn out to be unstoppable, it would be prudent to remind ourselves of some of the reasons for doubting whether the new regime of maximal screening will be altogether benign. We can at least approach the future with our eyes open, alert for signs of peril amidst the progress.

#### ***A. “Personalized Medicine” in the Traditional and Increasingly Rare Sense***

As we have seen, there is some plausibility to the view that “the logic of personalized medicine” will inevitably push us in the direction of sequencing everyone’s genome as early as possible, and that lifetime clinical care will eventually consist of personalized prevention and treatment strategies based on a detailed analysis of the patient’s genetic predispositions and susceptibilities. And yet, there is an older and perhaps deeper notion of personalized medicine that is likely to push back against the assumption that

genome-based health care will necessarily be better and more personal. In this sense, the personalized medicine that is most meaningful to patients is based on the physician's knowledge of the patient's medical and life circumstances and on the trusting relationship between patient and physician.<sup>35</sup> Only a crude genetic determinism could lead us to expect that an individual's decoded genome would ever be an adequate substitute for the physician's understanding of the whole person entrusted to his or her care. Adding a complete sequence of the genome to everyone's medical file from birth onward is not likely to replace a significant portion of medical care with algorithmic diagnosis and treatment.

Of course, this is not to say that genomic information will not play a valuable part in future medical care. In some cases, genomic analysis will certainly alert the physician to health risks that might not otherwise be evident from an examination of the patient and from knowledge of the family history. A realistic expectation might be that, for any given health condition, a small minority of patients will benefit from knowledge about genomic risk—and that, with the breadth of information likely to be available, everyone will likely benefit from genomic risk information at some point—but that much of health care will continue to proceed independently of genomic risk profiling.<sup>36</sup> On the whole, then, the goal of providing

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<sup>35</sup> See Edmund D. Pellegrino and David C. Thomasma, *For the Patient's Good: The Restoration of Beneficence in Health Care* (New York: Oxford, 1988); and David C. Thomasma and Judith Lee Kissell, eds., *The Health Care Professional As Friend and Healer: Building on the Work of Edmund D. Pellegrino* (Washington, D.C.: Georgetown University Press, 2000).

<sup>36</sup> On the other hand, the reality of medical practice in the current era is one in which the physician's time with patients is seriously compromised by various demands, including the intrusive burdens of documentation and paperwork and the financial imperative to "process" as many patients as possible in increasingly abbreviated periods of time. Some argue that genomic medicine and information technology will combine forces to alleviate this often distressing reality: information technologies will simplify and speed the acquisition and processing of clinically relevant information, including genetic information, while the application of genomic medicine itself will involve the use of genetic counselors as aids to the physician and will thereby ease the challenges of today's one-on-one patient-physician encounters. See Kenneth M. Ludmerer, *Time to Heal: American Medical Education from the Turn of the Century to the Era of Managed Care* (New York: Oxford University Press, 1999); and Ralph Snyderman and R. Sanders Williams,

personalized medical care in the older and perhaps more fundamental sense of the term will continue to depend on the character, commitment, and skill of the physician in developing an understanding of the patient as a whole person. In the words of Wylie Burke and Bruce M. Psaty,

[G]enuinely personal health care, as practiced by physicians for centuries, is based on the relationship between patient and physician rather than on any particular technology. Even in the genomic era, the focus on individual patient needs and concerns will remain at the core of health care; and if genetic testing diverts physicians' attentions away from the specific concerns of the patient, it may interfere with the practice of personalized medicine.<sup>37</sup>

### ***B. Doubts About the Power of Genomic Medicine***

Although many scientists and policymakers are confident that studies of the human genome will provide a wealth of valuable information about health status and health risk in the near future, not all competent observers agree. In particular, doubts have been expressed about the potential of genomic studies to find markers for susceptibility to the most common diseases afflicting mankind, as opposed to the rare metabolic disorders that are the primary target of newborn screening today.

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“Prospective Medicine: The Next Health Care Transformation,” *Academic Medicine* 78 (2003): 1079-1084.

<sup>37</sup> Wylie Burke and Bruce M. Psaty, “Personalized Medicine in the Genomic Era,” *Journal of the American Medical Association* 298 (2007): 1682-1684, p. 1684. Burke and Psaty continue, “Personalized medicine has always been a component of good medical practice. Genetic tests may provide new tools, but they do not change the fundamental goal of clinicians to adapt available medical tests and technologies to the individual circumstance of their patients. As genetic tests become widely available, personalized medicine will include assisting patients to make wise use of genetic risk assessment, taking into account the cautions discussed in this article. When genetic testing is used, the personalized nature of the care will extend well beyond the patient’s base pair sequences.” (Ibid.)

For example, the population geneticist David B. Goldstein has publicly dissented from the idea that unlocking the human genome will lead to the discovery of common variants that predispose people to various forms of cancer, heart disease, Alzheimer's, and other common major illnesses. This idea, known as the Common Disease/Common Variant hypothesis, suggests that genome-wide association studies will contribute powerfully to the development of personalized medicine and to the precise tailoring of medical treatment to the patient's individual susceptibilities to serious illness.<sup>38</sup> According to Goldstein, the enormous labor of cataloging all the common genetic variations in the human population as part of the HapMap project has led to the discovery of only a handful of genes that account for a disappointingly small portion of the genetic risk for disease. Goldstein said recently:

There is absolutely no question, that for the whole hope of personalized medicine, the news has been just about as bleak as it could be... For schizophrenia and bipolar disorder, we get almost nothing; for Type 2 diabetes, 20 variants, but they explain only 2 to 3 percent of familial clustering, and so on... It's an astounding thing that we have cracked open the human genome and can look at the entire complement of common genetic variants, and what do we find? Almost nothing. That is absolutely beyond belief.<sup>39</sup>

In a review of the recent achievements of genome-wide association studies, Goldstein and colleagues wrote the following:

Despite understandable celebration of these achievements, sober reflection reveals many challenges ahead... [F]or most of the traits studied, known variants explain only a

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<sup>38</sup> On the Common Disease/Common Variant hypothesis, see David E. Reich and Eric S. Lander, "On the Allelic Spectrum of Human Disease," *Trends in Genetics* 17 (2001): 502-510; and Neil Risch and Kathleen R. Merikangas, "The Future of Genetic Studies of Complex Human Diseases," *Science* 273 (1996): 1516-1517.

<sup>39</sup> See Nicholas Wade, "A Dissenting Voice as the Genome Is Sifted to Fight Disease," *The New York Times*, September 15, 2008.

fraction of observed familial aggregation, limiting the potential for early application to determine individual disease risk... The ultimate objectives—full descriptions of the susceptibility architecture of major biomedical traits and translation of the findings into clinical practice—remain distant.<sup>40</sup>

Neil Holtzmann and Theresa Marteau, prominent experts on genetic testing, agree:

It would be revolutionary if we could determine the genotypes of the majority of people who will get common diseases. The complexity of the genetics of common diseases casts doubt on whether accurate prediction will ever be possible... Although we do not contend that the genetic mantle is as imperceptible as the emperor's new clothes were, it is not made of the silks and ermines that some claim it to be. Those who make medical and science policies in the next decade would do well to see beyond the hype.<sup>41</sup>

Other experts remain optimistic, while acknowledging that the full benefit of the human genome project will take time to realize.<sup>42</sup> Yet it may well be that, for quite some time, detailed knowledge of the human genome will remain primarily useful for the diagnosing of rare genetic disorders rather than for ascertaining a given individual's susceptibilities to a large number of serious common illnesses.

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<sup>40</sup> Mark I. McCarthy, et al., "Genome-Wide Association Studies for Complex Traits: Consensus, Uncertainty and Challenges," *Nature Reviews. Genetics* 9 (2008): 356-369. See also James H. Ware, "The Limitations of Risk Factors as Prognostic Tools," *New England Journal of Medicine* 355 (2006): 2615-2617.

<sup>41</sup> Neil A. Holtzman and Theresa M. Marteau, "Will Genetics Revolutionize Medicine?" *New England Journal of Medicine* 343 (2000): 141-144.

<sup>42</sup> See Alan E. Guttmacher and Francis S. Collins, "Welcome to the Genomic Era," *New England Journal of Medicine* 349 (2003): 996-998.

### ***C. Newborn Profiling and the Problem of Risks and Benefits***

Many of the same concerns that have been expressed in regard to limited expansion of the newborn screening panel would *a fortiori* be applicable in the case of newborn profiling. Norman Fost's judgment<sup>43</sup> that every genetic disorder is different, and that every screening is an experiment with potentially bad as well as good consequences, would be all the more pertinent in the event of a greatly expanded screening panel. At the very least, we would need to plan for an immensely expanded infrastructure for testing and confirming, sorting out false-positives, counseling families, and assessing the outcomes for the affected children.

In clarifying the possible harms of gathering genetic information pre-symptomatically, it is important to distinguish the different components of the problem:

- First, such information may be clinically valid but not practically useful. Detected genetic variations in the genome may suggest an elevated risk for a condition that never actually develops, and to initiate treatment pre-symptomatically may do the patient more harm than good.<sup>44</sup>
- Second, genomic risk information that is assumed to be valid may sometimes turn out to be unreliable—if, for example, it is based on population studies that were too small or that failed to take into account critical non-genetic variables.<sup>45</sup>
- Third, there are the psychosocial effects of false positive results and, in the case of true positive results,

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<sup>43</sup> Norman Fost, "Ethical Implications of Screening Asymptomatic Individuals," p. 2814.

<sup>44</sup> Mary Ann Baily and Thomas H. Murray, "Ethics, Evidence, and Cost in Newborn Screening."

<sup>45</sup> Neil A. Holtzman and Theresa M. Marteau, "Will Genetics Revolutionize Medicine?"

of adversely labeling the individual as suffering from disease from the moment of birth.<sup>46</sup>

- Fourth, there is the danger that screening will lead to a cascade effect—in which genetic risk information of perhaps uncertain validity leads to additional tests and interventions, causing anxiety, extra costs, and even some risk of medical harm.<sup>47</sup>

If genomic data come to play a large role in the health care of the future, health care systems will have to learn how to manage such data prudently, so as to reveal the information that can potentially benefit the patient while suppressing the information that is likely to lead to net harm.

One example will suffice to show just how complex and elusive are the benefits and harms involved in each component of genetic screening. The case of Duchenne muscular dystrophy (DMD) has been examined with great sensitivity by pediatrician-ethicist Lainie Friedman Ross, whose review of the case we draw on here.<sup>48</sup> Newborn screening for DMD is currently being offered to parents at certain hospitals in Ohio as part of a pilot project funded by the CDC.<sup>49</sup> DMD is an X-linked degenerative disease of the muscles that affects about one in 3,500 boys. Symptoms usually begin before the age of six and lead to braces, wheelchair dependence, and death before the age of thirty. There is considerable support for newborn screening of DMD even though it does not meet the Wilson-Jungner criteria of having an accepted treatment and an

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<sup>46</sup> Robert T. Croyle, *Psychosocial Effects of Screening for Disease Prevention and Detection* (New York: Oxford, 1995).

<sup>47</sup> James W. Mold and Howard F. Stein, “The Cascade Effect in the Clinical Care of Patients,” *New England Journal of Medicine* 314 (1986): 512-514; and Richard A. Deyo, “Cascade Effects of Medical Technology,” *Annual Review of Public Health* 23 (2002): 23-44.

<sup>48</sup> Lainie Friedman Ross, “Screening for Conditions that Do Not Meet the Wilson and Jungner Criteria: The Case of Duchenne Muscular Dystrophy,” *American Journal of Medical Genetics Part A* 140A (2006): 914-922.

<sup>49</sup> See [www.cdc.gov/ncbddd/duchenne/screening.htm](http://www.cdc.gov/ncbddd/duchenne/screening.htm). CDC is also funding a pilot DMD screening program in Georgia for boys ages six through fifteen months.

agreed policy on whom to treat. DMD is more common than PKU and its natural history is well understood. But, as Ross writes, “the main concern is whether early diagnosis improves prognosis.”<sup>50</sup>

One problem is that the standard treatment for DMD with corticosteroids has deleterious side effects and may be inappropriate for younger boys. If treatment is to be delayed until later in childhood, screening at birth may not be justified; some would argue, however, that “avoiding the diagnostic odyssey” is reason enough to screen at birth. Perhaps it would be better to improve pediatricians’ abilities to recognize early symptoms of DMD, for early identification of a genetic disease might subject the child to stigmatization, discrimination, and unnecessary psychological harm. On the other hand, there are data indicating that early screening is the only effective way to diagnose DMD without considerable delay.

Some experts argue for DMD screening as a way to assist “reproductive decision-making” and “life planning”; but these alleged benefits to the family must be weighed against the potential harms of diagnosing the child months or years before he or she becomes symptomatic, harms that include needless anxiety, disruption of the parent-child bond,<sup>51</sup> and the possibility that parents will misuse the information<sup>52</sup> or seek out dangerous

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<sup>50</sup> Lainie Friedman Ross, “Screening for Conditions that Do Not Meet the Wilson and Jungner Criteria: The Case of Duchenne Muscular Dystrophy,” p. 915.

<sup>51</sup> If the diagnosis is made later in life, then a strong bond is allowed to form early, and the parents’ love for the child will lead them to do what is in the child’s best interest. If the diagnosis is made too early, there is a risk that a parent will see the child from the beginning as a “defective” being and not simply as “my” child.

<sup>52</sup> When a child has been identified early as genetically “abnormal,” the parents may be inclined to treat him or her as a second-class member of the family. Nancy Wexler tells of a woman whose two young children were at risk for Huntington’s disease and who wanted to have them tested early because “she only had enough money to send one to Harvard.” See Nancy S. Wexler, “Clairvoyance and Caution: Repercussions from the Human Genome Project,” in *The Code of Codes: Scientific and Social Issues in the Human Genome Project*, eds. Daniel J. Kevles and Leroy Hood (Cambridge, Massachusetts: Harvard University Press, 1992), pp. 211-243.

alternative treatments,<sup>53</sup> not to mention the ill effects of false-positives.<sup>54</sup> To further complicate the issue, a study by nursing investigator Evelyn Parsons and colleagues found that early diagnosis of DMD caused transient increases in parental distress but *no long-term disruption of the parent-child bond*.<sup>55</sup>

Despite the uncertain benefits of screening for DMD at birth, voluntary screening is offered in some countries, usually requiring explicit consent from the parents. In Wales, where informed consent is required, as many as ninety-four percent of parents agree to the screening at birth. In Germany, on the other hand, where voluntary screening is offered between one and twelve months of age, only five percent of parents elect to participate; these differences in parental acceptance of voluntary DMD screening may simply reflect the different circumstances in which the screening is offered.

All in all, it is difficult to judge whether the benefits of newborn screening for DMD outweigh the risks. All we can safely say is that

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<sup>53</sup> Elizabeth Campbell and Lainie Friedman Ross, "Parental Attitudes Regarding Newborn Screening of PKU and DMD," *American Journal of Medical Genetics* 120A (2003): 209-214.

<sup>54</sup> Even false-positive newborn screening results (quickly corrected) have been found, in some cases, to cause lasting harm to the early bonding of parent and child. See Elizabeth A. Gurian, et al., "Expanded Newborn Screening for Biochemical Disorders: The Effect of a False-Positive Result," *Pediatrics* 117 (2006): 1915-1921; and Josephine M. Green, et al., "Psychosocial Aspects of Genetic Screening of Pregnant Women and Newborns: A Systematic Review," *Health Technology Assessment* 8 (2004): 1-109. For the impact of false positives in screening for particular diseases, see Michael B. Rothenberg and Edward M. Sills, "Iatrogenesis: The PKU Anxiety Syndrome," *Journal of the American Academy of Child Psychiatry* 7 (1968): 689-692; Audrey Tluczek, et al., "Psychological Impact of False-Positive Results When Screening for Cystic Fibrosis," *Pediatric Pulmonology Supplement* 7 (1991): 29-37; and Göran Bodegård, et al., "Psychological Reactions in 102 Families With a Newborn Who Has a Falsely Positive Screening Test for Congenital Hypothyroidism," *Acta Paediatrica Scandinavica Supplement* 304 (1983): 2-21.

<sup>55</sup> The authors conclude that, "Concerns about the negative effect of newborn screening on the early mother-baby relationship have not been substantiated." Evelyn P. Parsons, et al., "Newborn Screening for Duchenne Muscular Dystrophy: A Psychosocial Study," *Archives of Disease in Childhood Fetal and Neonatal Edition* 86 (2002): F91-F95.

a thorough informed consent process may help parents understand the advantages and disadvantages and make a more thoughtful choice for their infant. Yet multiply this example a hundred or a thousand fold and it is easy to see just how difficult it would be to ask parents to weigh the benefits and harms of a greatly expanded newborn screening panel. Already, when states are screening newborns for at most dozens of heritable disorders, it is impracticable to explain to parents the peculiar risks and benefits of screening for each condition. This task would be all the more daunting if newborn screening for thousands of genetic markers were to become widely available.

#### ***D. Ownership of Genetic Information and the Challenge of Informed Consent***

Another problem concerns the ownership of the information gathered by newborn screening and, perhaps in the future, by genomic profiling. To whom does this information properly belong?<sup>56</sup> Does it belong to the child alone, to use or to disregard as he or she sees fit once he or she becomes an adult? Or do parents (as some of them seem to believe) have an unlimited right to know the genetic abnormalities of their children? Do physicians have a claim on such information once it exists? Should the state in which the child is born, in the interest of building ever more useful genomic databases, have a presumptive right to “biobank” the child’s genotypic data? If newborn screening detected a range of unfavorable predispositions in the child’s genome, would they amount to “pre-existing conditions” that insurers or even potential

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<sup>56</sup> The question of what should be done with the dried blood specimens left over from newborn screening is resolved differently in different states. Some states store the samples indefinitely; others discard them after a few months. Some states have policies permitting the use of residual blood spots outside of the newborn screening context, for forensic, clinical, evaluative, or epidemiological investigations. Very few states inform the parents that their child’s blood might be retained. When used for such research purposes, the blood samples are “anonymized,” but some observers are concerned that they could be re-identified through database linkage or genomic fingerprinting. See Richard S. Olney, et al., “Storage and Use of Residual Dried Blood Spots from State Newborn Screening Programs,” *Journal of Pediatrics* 148 (2006): 618-622.

employers would be entitled to consult before offering the patient health insurance or employment?<sup>57</sup>

These questions point to the inevitable tension between newborn screening and the principle of informed consent. Ideally, we would want a momentous decision such as whether to be tested for a serious genetic disorder to be made by the patient, with full understanding of the implications of a positive result. With newborn screening (or with testing later in childhood) we allow the parent (or the state, if the screening is mandatory) to make that decision on the infant's behalf, but such a transfer of responsibility raises serious ethical questions. The case of Huntington's disease is instructive here. As noted above, Huntington's is a late-onset neurological disorder, always fatal, and at present untreatable. It is a dominant and fully penetrant Mendelian disorder, which means that children of a parent who has been diagnosed with Huntington's have a fifty percent chance of having the gene and the disease themselves. The defective gene has been identified, and there is a definitive DNA-based test for its presence. Nancy Wexler has written with passion and eloquence on the tremendous complexity of the question of whether or not someone at risk for Huntington's should choose to be tested.<sup>58</sup> In the end she concludes that there is no right decision for everyone, and that each person at risk must be allowed to make that decision for him or herself after reaching

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<sup>57</sup> The fear that genetic information, once gathered, might subject the individual to insurance or employment discrimination led Congress to pass (and President Bush to sign into law) the Genetic Information Nondiscrimination Act (GINA) of 2008. The Act "prohibits group health plans and health insurers from denying coverage to a healthy individual or charging that person higher premiums based solely on a genetic predisposition to developing a disease in the future. The legislation also would bar employers from using individuals' genetic information when making hiring, firing, job placement, or promotion decisions." See Statement of Administration Policy, April 25, 2007, online at [www.genome.gov/Pages/PolicyEthics/GeneticDiscrimination/SAPonHR493.pdf](http://www.genome.gov/Pages/PolicyEthics/GeneticDiscrimination/SAPonHR493.pdf). Only time will tell whether GINA will prove successful in preventing insurance and employment discrimination based on the results of genetic screening and testing.

<sup>58</sup> Nancy S. Wexler, "The Tiresias Complex: Huntington's Disease As a Paradigm of Testing for Late-Onset Disorders," *FASEB (Federation of American Societies for Experimental Biology) Journal* 6 (1992): 2820-2825. See also Wexler's presentation before this Council on September 8, 2006, available online at [www.bioethics.gov/transcripts/sept06/session6.html](http://www.bioethics.gov/transcripts/sept06/session6.html).

young adulthood. Although Huntington's is far from typical of most genetic disorders, Wexler draws some general conclusions: above all, that truly informed consent, including a full psychological appreciation of the ramifications of the information, must be the principle upon which testing programs are designed. Information should not be foisted on someone without permission.<sup>59</sup>

As there is currently no treatment and no medical benefit from early detection, and a positive diagnosis is so potentially devastating, there has been widespread agreement that Huntington's is one of the genetic disorders least suitable for routine screening, especially at birth or in early childhood. Alexander and van Dyck, for example, mention it as a prime candidate for exclusion from a greatly expanded newborn screening panel. It is reasonable, in fact, to try to range genetic disorders on a continuum, with those like PKU that unquestionably merit newborn screening (and where the patient's right of informed consent is properly waived) at one end, and those like Huntington's that should be left up to the individual at the other end. Yet it is quite likely that the psychological complexity of the personal decision whether to be tested for Huntington's would also be present in the case of other genetic disorders, even if they are not fully penetrant and invariably fatal. Deciding to screen for a multitude of conditions means taking from children the right to decide these questions for themselves when they have reached an age of sufficient maturity and thoughtfulness. Although nominally exercised for the benefit of the child, routine newborn screening is inevitably in some measure a violation of the child's right "not to know," if that were his or her choice. This may be a price worth paying, but it ought to be paid in full awareness of its meaning.<sup>60</sup>

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<sup>59</sup> Nancy S. Wexler, "The Tiresias Complex: Huntington's Disease As a Paradigm of Testing for Late-Onset Disorders," p. 2824.

<sup>60</sup> See Dena S. Davis, "Genetic Dilemmas and the Child's Right to an Open Future," *The Hastings Center Report* 27 (1997): 7-15. We shall return to the issue of informed consent in our discussion of state-mandated newborn screening in Chapter Four.

### *E. Genetic Disease and Human Difference*

There is also a danger that, with genomic medicine and universal genetic profiling, there will be a blurring of the distinction between genuine disease and mere difference. Only a small proportion of the abnormal gene variants uncovered by newborn profiling will lead directly and inexorably to serious illness. Typically, medically important SNPs will merely correlate (often in combination with other SNPs) with elevated susceptibilities for various medical conditions, and even these correlations will be unpredictable and highly variable, depending on a host of unknown factors. The important discipline of epigenetics teaches that an individual's actual health will be a complex result of genetic and environmental factors and will not be determined simply by his or her genes.

Yet some people, ignorant of these subtleties, may have an exaggerated idea of the degree to which “bad” genes doom us to dreadful outcomes. Thus, with expanded newborn screening, significant decisions may often be made by parents in light of the identification of genetic “abnormalities” in their children that might end up having no clinical expression at all. Accordingly, it remains an open question whether all this information about the children's possible medical future will be used for their benefit and will not shape in adverse ways the parents' view of their children, their worth, and their prospects for happiness. Furthermore, what will it be like for children to grow up in possession of this vast storehouse of genetic information? Will they see it as an entirely beneficial resource, to be used throughout life to improve their health, adjust their habits and lifestyle, and assist their physicians when diagnosis proves elusive? Or will it instead be a burden, weighing them down with a fatalistic sense of limitations and lost possibilities?

### *F. Newborn Screening, Genomic Medicine, and Eugenics*

Advocates of a broadened notion of “benefit” often extol the utility of newborn screening for helping parents make future reproductive decisions (e.g., adoption, egg or sperm donation, IVF and PGD,

amniocentesis and abortion, etc.).<sup>61</sup> But this notion of “benefit to the family” is not unproblematic. First, if the putative benefit to the family is to be realized by preventing the birth of siblings with the detected genetic defect, then it would make more sense to screen for the defect prenatally, so that the family is not burdened with even one defective child.<sup>62</sup> Putting it so callously highlights the morally problematic character of screening for family planning. If we test an infant, not in the hope of providing treatment for his or her condition, but with a view to making sure that no further children come into the family with the same defect, are we not in effect telling the child that he or she was, in some ways, a regrettable mistake—that, had we known his or her genetic makeup in advance, we would have tried to prevent his or her birth? To the affected child, family planning in this sense means not “limiting the incidence of a defective gene” but “preventing the birth of any more kids like me.” Here the laudable goal of reducing the incidence of genetic disease comes into collision with the wish and the obligation to treat every family member as a being with inherent and equal worth. Moreover, should the uniform panel of conditions be greatly expanded, the propriety of its use for family planning purposes would become even more questionable. Suppose that expanded screening of an infant reveals not a fatal and incurable disease but instead a host of genetic variants, each of which merely confers elevated risk for some condition or other? Who is to say at what point an uncovered defect becomes serious enough to warrant preventing the birth of other children who might carry it? At what point have we crossed the line from legitimate family planning to capricious and morally dubious eugenics?

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<sup>61</sup> See, for example, Alexander and van Dyck, “A Vision of the Future of Newborn Screening,” p. S352.

<sup>62</sup> In a response to Alexander and van Dyck, the noted British epidemiologist Nicholas Wald made the following argument: “Neonatal screening is, in general, a poor method of alerting couples to a disorder before the birth of an affected child, because it cannot detect the first affected pregnancy in any family. Prenatal screening would often be more effective, identifying most affected pregnancies, including the first one in any family. The argument that neonatal screening is useful in influencing “prenatal diagnosis and family planning” is more an argument in favor of prenatal screening than a reason for neonatal screening.” See Nicholas Wald, “Neonatal Screening: Old Dogma or Sound Principle?” (letter to the editor), *Pediatrics* 119 (2007): 406-407, p. 406.

Indeed, the expansion of newborn screening, however reasonable it may be in itself, seems symptomatic of a broader phenomenon, a sort of Faustian imperative driving the search for genetic knowledge back to earlier and earlier points along life's path. Neither PGD nor amniocentesis is new, but it seems likely that as time goes on these procedures will come to seem more and more like routine options for prospective parents. Should the information gleaned from these tests seem sufficiently "negative," some parents will be tempted to discard the "defective" embryo or abort the "defective" fetus, and that choice will no doubt be justified as "good" for someone: for the unborn child, for the unimplanted embryo, for the parents themselves, for the future siblings, or for society at large. In this way, the blameless intention to diagnose and treat our children's illnesses will have drifted into the rather more sinister project of purifying future generations of their undesirable members. The specter of "eugenicide" hovers over the eagerly anticipated marriage of newborn screening with genomic medicine.

Of course, prenatal genetic testing has been underway for several decades and preimplantation genetic diagnosis for the last decade or more. The development and spread of these techniques can hardly be attributed to the emergence and proliferation of newborn screening.<sup>63</sup> Nor can we say that expanded newborn screening (or even full newborn profiling) will necessarily lead to more prenatal or preimplantation testing or that, with the growing acceptance of genomic medicine, parents will be more likely to resort to IVF and PGD (or to amniocentesis and selective abortion) to prevent the birth of genetically inferior offspring—although there are, in this regard, relevant lessons to be learned from the declining incidence of Down syndrome due to selective abortion.<sup>64</sup> Genomics *could* teach us to accept that all of us are born with an assortment of

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<sup>63</sup> Moreover, limiting the expansion of newborn screening would not affect the existing cases in which parents seek prenatal testing based on their desire to avoid the birth of another child with a genetic disorder.

<sup>64</sup> See Ralph L. Kramer, et al., "Determinants of Parental Decisions After the Prenatal Diagnosis of Down Syndrome," *American Journal of Medical Genetics Part A* 79 (1998): 172-174; and Darrin P. Dixon, "Informed Consent or Institutionalized Eugenics? How the Medical Profession Encourages Abortion of Fetuses with Down Syndrome," *Issues in Law & Medicine* 24 (2008): 3-59.

disease susceptibilities, that genetic perfection is therefore unattainable, and hence that prenatal “weeding out” of undesirable genomes is impractical and therefore unnecessary, at least in many instances. Certainly there are today many advocates of expanded newborn screening whose chief concern is with the health and well-being of our born children and who are not advocates of expanded prenatal screening and selective abortion.<sup>65</sup> Nonetheless, it is prudent to consider now the possibility that, if genomic profiling of infants at birth were to become standard practice, people might begin to wonder: why wait until birth to make use of such a powerful tool?<sup>66</sup>

Indeed, the use of multiplex platforms to screen for genetic abnormalities *prenatally* is not merely a distant promise, it is a reality. Already, a private company and an academic medical center are offering to the public a cutting-edge DNA-based procedure for prenatal identification of dozens or even hundreds of genetic

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<sup>65</sup> For example, the Cystic Fibrosis Foundation ([www.cff.org](http://www.cff.org)) places all its emphasis on newborn screening rather than on prenatal diagnosis. On the other hand, their website does explain that carrier testing is available to expectant parents (or to those who are considering having a child) to “determine if a person might have a child that may have certain diseases or health care needs, such as cystic fibrosis (CF).” The website continues, “Your decision to be genetically tested to learn if you carry a mutation or mutations of the CF gene may be difficult and is a personal choice. You may wish to talk with your medical or religious advisors to help you decide. The American College of Obstetricians and Gynecologists (ACOG) suggests that all couples who are considering having a child—or those who are already pregnant—should have genetic carrier testing for CF.”

For its part, the ACOG website explains, “The purpose of having this information about your developing baby is so you can prepare yourself to care for a child with special health care needs or so you can terminate the pregnancy.” (See [www.acog.org/from\\_home/wellness/cf001.htm](http://www.acog.org/from_home/wellness/cf001.htm).)

<sup>66</sup> Again, this is not to suggest that the expansion of newborn screening should be held responsible for any future increase in the use of prenatal and preimplantation testing. The availability of less invasive testing methods, such as blood tests for pregnant women, will be a more likely cause of significant growth in the practice of prenatal testing. See Ainsley J. Newson, “Ethical Aspects Arising from Non-Invasive Fetal Diagnosis,” *Seminars in Fetal and Neonatal Medicine* 13 (2008): 103-108.

abnormalities while the fetus is gestating.<sup>67</sup> The technique, called “microarray-based comparative genomic hybridization,” or “array CGH” for short, examines the DNA of the fetus for minute deletions and insertions that have been linked to disease or deformities.<sup>68</sup> The private company, Signature Genomic Laboratories of Spokane, Washington, charges \$1,850 for the use of its “Signature PrenatalChip,” and already (as of November 2008) 380 mothers have had their physicians send in DNA samples from their fetuses so that they could be analyzed for the presence of more than seventy genetic syndromes associated with mental retardation, physical malformation, and health and behavioral problems.<sup>69</sup> The medical center, Baylor College of Medicine in Houston, offers a similar service at a cost of \$1,600 and has already analyzed more than 300 samples of fetal DNA collected from mothers undergoing amniocentesis or chorionic villus sampling. In addition, a federally-funded study is currently evaluating prenatal genetic screening by array CGH in 4,000 pregnancies.<sup>70</sup> Should that study be deemed a success, multiplex prenatal screening might soon become a commonplace practice.

It is not at all clear what parents are supposed to do with the information gleaned from such prenatal testing, especially if the identified abnormalities are of questionable or variable clinical significance, as many of them certainly will be. Some couples will presumably consider terminating the pregnancy if the results of

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<sup>67</sup> See Bridget M. Kuehn, “Prenatal Genome Testing Sparks Debate,” *Journal of the American Medical Association* 300 (2008): 1637-1639.

<sup>68</sup> See Trilochan Satoo, et al., “Prenatal Diagnosis of Chromosomal Abnormalities Using Array-Based Comparative Genomic Hybridization,” *Genetics in Medicine* 8 (2006): 719-727; Lisa G. Shaffer, et al., “Comparison of Microarray-Based Detection Rates for Cytogenetic Abnormalities in Prenatal and Neonatal Specimens,” *Prenatal Diagnosis* 28 (2008): 789-795; and Catherine D. Kashork, et al., “Prenatal Diagnosis Using Array CGH,” *Methods in Molecular Biology* 444 (2008): 59-70.

<sup>69</sup> Kuehn, “Prenatal Genome Testing Sparks Debate,” p. 1637; Rob Stein, “Fresh Hopes and Concerns as Fetal DNA Tests Advance,” *The Washington Post*, October 26, 2008. Signature Genomics Laboratories ([www.signaturegenomics.com/prenatalchip.html](http://www.signaturegenomics.com/prenatalchip.html)) assures potential users of its PrenatalChip that, when scanning the fetus’ DNA, “specific loci have been excluded which are associated with adult-onset conditions.”

<sup>70</sup> Rob Stein, “Fresh Hopes and Concerns as Fetal DNA Tests Advance.”

DNA testing are sufficiently “bad” (otherwise why pay for such an expensive procedure?). But how bad does the news have to be to tempt the parents to prevent the birth of a “defective” child? Substantial numbers of parents are prepared to terminate a pregnancy if the chromosomal abnormality that causes Down syndrome is revealed by amniocentesis. But what will they do when platforms like the Signature PrenatalChip reveal that their baby might suffer from such varied conditions as Marfan syndrome (a disorder of the connective tissue believed by some physicians to have afflicted Abraham Lincoln), brachydactyly (causing shortness of the fingers and toes), nail-patella syndrome (which may cause poorly developed nails and other deformities), or X-linked short stature (affecting only boys)? What are parents to do when told—as the Signature chip can tell them—that their unborn child has certain DNA deletions believed to confer a slightly elevated risk of schizophrenia? How such information will be used, and whether gathering it can truly be said to benefit the child who undergoes testing, are questions very much worth pondering as genomic medicine progresses. It is hard to judge how widespread prenatal testing for multiple genetic abnormalities will become as these techniques become cheaper, more powerful, and more widely available. But, as the genomic age advances, it would be foolhardy to assume that multiplex DNA screening will modestly confine itself to the period after the baby’s birth.

### ***G. Genetic Information and the Problem of Self-Knowledge***

We presented in the preceding part of this chapter the argument that, with newborn profiling, a sense that everyone has his or her own share of genetic imperfections and that “we are all in this together” might soften the impact of any bad news. The psychosocial burdens, to children as well as to parents, of living with an identified genetic abnormality, would certainly be more widely felt if every couple were to go home from the hospital with a virtual avalanche of information about the genetic defects and susceptibilities of their newborn child. But we then would be in uncharted territory, and it is not at all clear how human beings would adapt to such a massive increase in genetic self-knowledge.

More precisely, we are speaking here of a massive increase of self-*information*, which does not automatically translate into wisdom or genuine self-knowledge.

Such reflections lead, finally, to the deeper and more troubling question of the value of knowledge itself for human happiness. As Nancy Wexler wrote,

The blind seer Tiresias confronted Oedipus with the quintessential dilemma of modern genetics: “It is but sorrow to be wise when wisdom profits not.”<sup>71</sup>

The presumption of modern science, including medical genetics, has always been that knowledge is fundamentally good for human beings, and that the more we know about ourselves the better we will be able to live the kind of lives we want to live. Yet the truth of this supposition remains in doubt as we lift the lid of the Pandora’s box of our genomic inheritance. Surely there is much information there that, used wisely, will improve our lives and help free us from illness, infirmity, and uncertainty. Yet there is also the possibility that such knowledge will be misused or misinterpreted, that it will tempt us to stigmatize and to discriminate against the genetically unfortunate, and that under its weight some of us will incline toward fatalism and despair.

#### **IV. On the Necessity and the Limits of Speculation**

In the preceding two sections, we have sought to describe the essential elements of the cases for and against newborn profiling. We have marshaled arguments suggesting that the logic of personalized medicine and of technological progress will, in time, yield unequivocal benefits for infants and their parents, for pediatricians and biomedical scientists, and for society at large. But we have also assembled reasons to doubt whether the convergence of genomic medicine and newborn screening will be either as

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<sup>71</sup> Nancy S. Wexler, “The Tiresias Complex: Huntington’s Disease As a Paradigm of Testing for Late-Onset Disorders,” p. 2820, quoting Sophocles, *Oedipus Tyrannos*, lines 316-317.

impressive or ultimately as desirable as some of its proponents may believe. We have sought to tether these prognoses to certain known facts about the present: for example, to the plummeting cost of whole-genome sequencing; to the growing number of companies offering affordable gene chips and other DNA-based screening platforms; to surveys that have revealed keen parental interest in genetic information about offspring; and to the impact of amniocentesis on the declining incidence of children born with Down syndrome. Nonetheless, our analysis of the case for and the case against newborn profiling has been an exercise in speculation—one that is both necessary to attempt but also limited in its usefulness for purposes of ethical analysis and policymaking. It is limited insofar as the only definitive test of our prognoses—about both the benefits and the harms of newborn profiling—will be the day to day unfolding of this imagined future. But such speculation is also necessary if our ethical analysis and policymaking are to be well informed and anticipatory. Just as patients need to consider prospectively the possible risks and benefits of a course of treatment or of participation in a clinical trial—risks and benefits that may or may not materialize for any given patient—society at large must consider the long-term potential, for good and for ill, of an expansionist vision of newborn screening. Speculation is always doubtful, but if we do not try to think imaginatively about what the convergence of newborn screening and genomic medicine will bring, we may find ourselves overtaken by a future for which we are ill-prepared. Rather than approach the future blindly, we should—bearing in mind the limited range and sharpness of our prospective vision—opt for awareness and transparency.

Our concern for awareness and transparency has only been heightened by the ACMG report and its aftermath, for it appears that the implications of the report's recommendations—amounting to a fundamental change in the moral focus of newborn screening—were certainly not brought out in transparent ways for the purposes of public discussion and optimally informed policymaking. Thus, at both the federal and the state levels, we are confronted with the question: What should we do now?

## CHAPTER FOUR

### NEWBORN SCREENING: MANDATORY, ELECTIVE, OR BOTH?

Having explored, in Chapter Three, some of the ethical issues that are likely to emerge more fully in future decades as newborn screening evolves under the aegis of genomic medicine, we return, in this final chapter, to the present state of newborn screening, and specifically to an ethical dilemma that now confronts us with some urgency as the states continue to expand their newborn screening programs. We have sought to clarify—and to imagine—both the potential benefits and the potential harms of newborn screening, which are so intertwined that it will be difficult, in newborn screening policymaking, to avoid the latter while realizing the former. The prudent course, in our opinion, is to reaffirm that the primary goal of newborn screening is to provide direct medical benefit to children affected by serious disease, and that mandatory newborn screening can be justified only when there is convincing evidence that the benefits for the infant of screening and treatment outweigh the risks and burdens. For conditions that do not meet this standard of evidence, screening may proceed, but it should not be mandatory; instead, it should be offered to parents as a pilot program within a research paradigm, and it should require their voluntary, informed consent.

Our challenge in this chapter is to defend this recommendation. With this aim in mind, we begin, in the first part, with a discussion of two opposing approaches to newborn screening. One champions mandatory screening for both conditions that are treatable and those that are untreatable. This is the approach advocated by the ACMG in its 2005 report. The other approach insists that all newborn screening should be elective, requiring informed parental

consent. In the second part, we turn to an alternative approach, one that integrates mandatory screening for treatable conditions with elective or optional screening for as yet untreatable conditions that are appropriate targets for biomedical research. In the third part, we explore this alternative approach in relation to the ACMG report. In the fourth part, we conclude with a detailed recommendation that provides an ethically sound framework for public policy in newborn screening.

## I. Mandatory Screening Versus Informed Parental Consent

The question of whether or to what degree newborn screening should be mandatory has excited controversy ever since PKU screening began in the 1960s.<sup>1</sup> The paradigmatic justification for mandatory screening for a health condition is that the condition, if undetected and uncontrolled, would pose a threat to the health of others in the community (as is especially the case with certain highly contagious diseases). In the absence of such a threat, government coercion seems harder to justify, and screening of children is usually taken to require the parent's voluntary, informed consent.<sup>2</sup> No such

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<sup>1</sup> See Beth A. Tarini, et al., "Waiving Informed Consent in Newborn Screening Research: Balancing Social Value and Respect," *American Journal of Medical Genetics Part C (Seminars in Medical Genetics)* 148C (2008): 23-30.

<sup>2</sup> The report that Wilson and Jungner prepared for the World Health Organization in 1968 says little on the question of mandatory versus voluntary screening. But in their 2003 *Review of Ethical Issues in Medical Genetics*, also commissioned by the World Health Organization, Dorothy C. Wertz, John C. Fletcher, and Kåre Berg argue that genetic screening in general ought to be voluntary and to require informed consent, *except screening of newborns*, which ought to be mandatory "if and only if early diagnosis and treatment would benefit the newborn." Here are excerpts from their argument (on pp. 39-40 of the *Review*), which will prove quite pertinent to our analysis of the ACMG report's recommendations:

Societies have an ethical obligation to protect their most vulnerable members, especially if these people cannot protect themselves. Newborns deserve the special protection afforded by mandatory screening for disorders where early diagnosis and treatment favourably affect outcome. In arguing for inclusion of a disorder on the list of mandatory screens, public health authorities should be able to prove that early diagnosis and medical treatment make a difference for the population of newborns with the disorder. The psychosocial benefits

threat is posed by the heritable conditions for which newborns are routinely screened. Why is it, then, that state laws make newborn genetic screening mandatory throughout most of the United States?

Historically, the answer to this question dates to the years after Robert Guthrie invented the heel-stick blood test for PKU. The rationale for making PKU screening compulsory was chiefly that, in the face of reluctance by the medical establishment to embrace screening and dietary treatment for PKU, legal mandates were the only practical way to ensure that most children would be tested. Failure to identify affected children and start them promptly on a restricted diet could lead to irreversible neurological damage within a few weeks of birth. The momentum to enact state laws mandating PKU screening was reinforced by the lobbying efforts of state chapters of the National Association for Retarded Children (NARC), by the powerful support of President Kennedy, and by the tireless advocacy of Robert Guthrie himself, described here in his own words:

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of simply having a diagnosis, in the absence of treatment, are not sufficient to justify mandatory screening...

The primary purpose of mandatory newborn screening is to benefit the newborn through early treatment. Some treatments (e.g., for PKU) must be instituted immediately in order to be effective. It makes no sense to provide screening if timely treatment is not available...

The introduction of multiplex screens such as tandem mass spectroscopy raises new ethical issues, because it may lead to the identification of diseases that are not treatable at the present time. There are both benefits and risks associated with knowing that an apparently healthy newborn will develop one of these diseases early in life. For some parents, the knowledge may lessen self-blame and prevent weeks or months of searching for a diagnosis. Parental knowledge may also confer a benefit to the child, because parents could be prepared to take advantage of new and rapidly-evolving treatment. So, on the other hand, some parents may not wish to know, preferring to enjoy the months or years before symptoms appear. On balance, it appears that the benefits of parental knowledge outweigh the risks. However, parents who do not wish to know about currently untreatable disorders should have the opportunity to “opt-out” from receiving this information...

My father had been a traveling salesman and I must have inherited his genes, because I have always felt challenged by what he would have called the “hard sell.” I accepted every opportunity to travel and speak about the need for the screening test to detect and treat newborn infants with PKU. I spoke before many audiences in the United States, including lay groups such as the National Association for Retarded Children and physicians. The most positive responses came from non-physicians.<sup>3</sup>

Massachusetts became the first state to make PKU screening compulsory in 1963; by 1975, forty-three states had enacted such laws, and ninety percent of all newborns were being tested.<sup>4</sup> Today newborn screening is mandated in forty-eight states.<sup>5</sup> However, all but four of the states (Michigan, Montana, Nebraska, and South Dakota) permit parents to opt out of newborn screening for religious reasons, and some states allow parents to opt out for any reason.<sup>6</sup> The number of parents opting out of mandatory newborn

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<sup>3</sup> Robert Guthrie, “The Origin of Newborn Screening,” *Screening* 1 (1992): 5-15, p. 11. Of this period, historian of medical genetics Diane Paul writes, “Mandated screening was opposed by the American Medical Association and many state medical societies. More surprisingly, compulsory screening was also opposed rather quietly by many researchers in the field of human metabolism. For a variety of reasons, these researchers believed it premature to mandate that every infant be tested for PKU and their reservations intensified during the first few years of the screening programs.” Diane B. Paul, “The History of Newborn Phenylketonuria Screening in the U.S.,” Appendix 5 of Neil A. Holtzman and Michael S. Watson, *Promoting Safe and Effective Genetic Testing in the United States: Final Report of the Task Force on Genetic Testing* (Bethesda, Maryland: National Institutes of Health, 1997), available online at [biotech.law.lsu.edu/research/fed/tfegt/appendix5.htm](http://biotech.law.lsu.edu/research/fed/tfegt/appendix5.htm).

<sup>4</sup> Diane B. Paul, “The History of Newborn Phenylketonuria Screening in the U.S.”

<sup>5</sup> One state (Massachusetts) mandates screening for certain conditions while offering optional screening (requiring informed parental consent) for other conditions. The Massachusetts model of newborn screening is discussed in detail in the next section.

<sup>6</sup> See Bradford L. Therrell, et al., “Status of Newborn Screening Programs,” S212-S252, Appendix 2, “Information From Statutes and Regulations on State Genetic Privacy and Newborn Screening,” pp. S226-S228; see also Elaine H. Hiller, et al., “Public Participation in Medical Policy Making and the Status of

screening tends to be quite low, with many states reporting a compliance rate of 99.9 percent or greater.<sup>7</sup> In states where opting out is permissible, it is not always made clear to parents that they have that option.<sup>8</sup> Nonetheless, it is important to bear in mind that, despite the prevalence of “legally mandated” newborn screening, parents who are determined to refuse such screening are able to do so almost everywhere in the United States.<sup>9</sup>

In Maryland, Wyoming, and the District of Columbia, newborn screening explicitly requires informed parental consent.<sup>10</sup> In general,

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Consumer Autonomy: The Example of Newborn Screening Programs in the United States,” *American Journal of Public Health* (1997): 1280-1288.

<sup>7</sup> Personal communication, November, 2008, from Susan R. Panny, MD, Director, Office for Genetics and Children with Special Health Care Needs (OGCSHCN), Maryland Department of Health and Human Hygiene. In view of these high compliance rates, the number of babies who are born with genetic diseases that go undetected because of parental refusal of newborn screening is likely to be very small. According to Dr. Panny, an informal survey of the states in 2007 turned up only nine known “missed cases” due to parental refusal, some of them dating to the early 1990s.

<sup>8</sup> For example, Kathryn Fant and colleagues found that, among forty-two states that grant parents the option to refuse newborn screening, only twenty-three (fifty-five percent) mention that option in the educational materials they give to parents prior to drawing the infant’s blood. See Kathryn Fant, et al., “Completeness and Complexity of Information Available to Parents from Newborn-Screening Programs,” p. 1270.

<sup>9</sup> Of the four states whose laws do not explicitly permit parents to opt out of newborn screening, only Nebraska has a legal enforcement provision, and it has chosen to exercise it only once: in 2007, a baby born to parents who objected to the drawing of blood on religious grounds was seized by sheriff’s deputies so that the heel-stick blood test could be administered. See Anna Jo Bratton, “Lawsuit Says Seizure of Baby for Test Violated Rights,” *The Associated Press*, October 25, 2007.

<sup>10</sup> In Maryland, parental informed consent for newborn screening is required by *regulation* (not by statute). Title 10, Department of Health and Mental Hygiene, Regulation No. 10.52.12.05, reads, in part: “Before administration of the test, the parent or guardian shall be informed fully of the reasons for the test and of his or her legal right to refuse to have the test performed on the child. An individual who has been provided and has signed a written explanation of the test approved and furnished by the Department shall be considered fully informed.” (available online at [www.dsd.state.md.us/comar/10/10.52.12.05.htm](http://www.dsd.state.md.us/comar/10/10.52.12.05.htm).) In Wyoming and the District of Columbia, parental consent is required by *statute*. Wyoming Statute §35-4-801, under Title 35, Public Health and Safety, reads, in part: “Informed consent of parents shall be obtained and if any parent or guardian of a child

the numbers of parents who withhold their consent for newborn screening in Maryland, Wyoming, and the District of Columbia are extremely low and are comparable to the numbers of parents who opt out of “mandatory” newborn screening in other states.<sup>11</sup> As a practical matter, therefore, it seems to make little difference whether the parents are given a newborn screening brochure to read and asked to sign a consent form, or given a brochure and asked if they would like to sign an “opt-out” form. Evidently, parents are very likely to accept newborn screening if they are assured by their doctors that it is a good idea. This is not surprising: in light of the number and the obscurity of the targeted conditions, and the complex balance of risks and benefits involved in each screening decision, it is unrealistic to expect parents to attain sufficient knowledge to make an informed decision about the conditions for which their children should be screened.<sup>12</sup>

As a matter of principle, however, it is notable that in 1975 the Committee for the Study of Inborn Errors of Metabolism of the

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objects to a mandatory examination the child is exempt from [newborn screening].” (available online at [legisweb.state.wy.us/statutes/dlstatutes.htm](http://legisweb.state.wy.us/statutes/dlstatutes.htm).) For the District of Columbia, D.C. Code Annotated §§ 7-834 reads, in part: “Participation of persons in metabolic disorder programs in the District of Columbia should be wholly voluntary, and...the Mayor shall further insure that: (A) No test be performed on any newborn over the objections of his or her parent and that no test be performed unless such parent is fully informed of the purpose of testing for metabolic disorders, and is given a reasonable opportunity to object to such testing; (B) No program requires mandatory participation...” (available online at [www.lawsources.com/also/usa.cgi?xdc](http://www.lawsources.com/also/usa.cgi?xdc)).

<sup>11</sup> For example: In Maryland, in recent years, five or fewer families have withheld their consent for newborn screening, out of approximately 75,000 babies born each year. These numbers are comparable to the numbers of parents who opt out of “mandatory” newborn screening in Indiana, Missouri, New York, and other states. (Susan R. Panny, personal communication.) In Wyoming, in 2007, two families refused newborn screening, out of approximately 6,800 babies born in the state. (Dena Freeman, “Informed Consent and Newborn Screening,” MPH Practicum, 2008, Institute for Public Health Genetics, University of Washington, available online at [sphcm.washington.edu/practicum/Dena%20Freeman.ppt](http://sphcm.washington.edu/practicum/Dena%20Freeman.ppt).)

<sup>12</sup> On doubts about the attainability of “genuine informed consent,” see Carl E. Schneider, “Some Realism About Informed Consent,” *Journal of Laboratory and Clinical Medicine* 145 (2005): 289-291; and C. H. Braddock, 3<sup>rd</sup>, et al., “Informed Decision Making in Outpatient Practice: Time to Get Back to Basics,” *Journal of the American Medical Association* 282 (1999): 2313-2320.

National Academy of Sciences issued a report recommending that “participation in a genetic screening program should not be made mandatory by law, but should be left to the discretion of the person tested or, if a minor, of the parents or legal guardian.”<sup>13</sup> In a 1994 report, the Committee on Assessing Genetic Risks of the Institute of Medicine (IOM) stated that “mandatory screening has not been shown to be essential to achieve maximum public health benefits; however, it is appropriate to mandate the *offering* of established tests (e.g., PKU and CH) where early diagnosis leads to improved treatable outcomes.”<sup>14</sup> In 2001, the Committee on Bioethics of the American Academy of Pediatrics (AAP) issued a report favoring the introduction of an informed consent process for newborn screening, in part because it would “promote more thorough understanding of the implications of the tests.”<sup>15</sup>

In support of the informed consent approach, some critics of mandatory newborn screening have raised doubts as to whether decision-making regarding screening should follow a *public health model* (e.g., for contagious diseases) as distinguished from a *medical model* (i.e., where only the good of the individual patient is in question). For example, in 1982, George Annas, an expert in health law and bioethics, wrote a brief on behalf of parental liberty and against governmental effectiveness, i.e., in favor of voluntary informed consent and against mandatory screening, even in the case of a highly successful newborn screening program such as PKU screening.<sup>16</sup> A study by bioethicist Ruth Faden and her colleagues had just shown that, in the state of Maryland, “requiring informed consent for PKU (phenylketonuria) screening is well-accepted by the public, improves the public knowledge about PKU screening,

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<sup>13</sup> National Research Council, *Genetic Screening Programs, Principles, and Research*.

<sup>14</sup> Committee on Assessing Genetic Risks, Institute of Medicine, *Assessing Genetic Risks: Implications for Health and Social Policy*, Lori B. Andrews, Jane E. Fullerton, Neil A. Holtzman, and Arno G. Motulsky, eds. (Washington, D.C.: National Academies Press, 1994); emphasis in original.

<sup>15</sup> Committee on Bioethics, American Academy of Pediatrics, “Ethical Issues With Genetic Testing in Pediatrics,” *Pediatrics* 107 (2001): 1451-1455.

<sup>16</sup> George J. Annas, “Mandatory PKU Screening: The Other Side of the Looking Glass,” *American Journal of Public Health* 72 (1982): 1401-1403.

and does not make the program any less cost-effective.”<sup>17</sup> But three of the study’s authors had concluded that compulsory PKU screening was still appropriate and that there could be no moral justification for allowing parents to deny their newborn children the benefit of such screening.<sup>18</sup> Against such arguments, Annas made the case that the few parents who refuse newborn screening are, in fact “morally justified in their refusal,” in part because the high rate of false positives poses health risks that may not be trivial.<sup>19</sup> Annas gave the following argument:

This may not strike one as an adequate reason for refusing PKU screening. But look into the future when we will be able to screen for 1,000 more diseases. Suppose, for example, a computerized screening test for 1,000 conditions. Suppose further that each of these tests has been so perfected that the false positive rate is only 1 percent. Each infant screened will then be diagnosed initially as suffering from 10 disorders, even though he/she suffers from none. If the false positive rate is 5 percent per test, he/she will appear to have 50 disorders, etc. The [more] tests that are performed for rare diseases, the more likely it is that pathology will be generated from the retesting procedures, and the more rational a decision not to screen initially becomes. This is independent of any stigma that may accompany a true positive diagnosis. The rare parent who refuses newborn screening, both today and in the future, is likely to be viewed as either a child

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<sup>17</sup> George J. Annas, “Mandatory PKU Screening: The Other Side of the Looking Glass,” p. 1401. The Maryland survey is, Ruth Faden, A. Judith Chwalow, Neil A. Holtzman, and Susan D. Horn, “A Survey to Evaluate Parental Consent as Public Policy for Neonatal Screening,” *American Journal of Public Health* 72 (1982): 1347-1352. Faden and colleagues found that, in Maryland, only five out every 10,000 mothers declined newborn screening. They also found that slightly more than half the mothers preferred to have their permission sought for newborn screening.

<sup>18</sup> The commentary is, Ruth Faden, Neil A. Holtzman, and A. Judith Chwalow, “Parental Rights, Child Welfare, and Public Health: The Case of PKU Screening,” *American Journal of Public Health* 72 (1982): 1396-1400.

<sup>19</sup> George J. Annas, “Mandatory PKU Screening: The Other Side of the Looking Glass,” p. 1401.

neglector or an irrational anti-science fanatic. Neither label seems accurate or helpful. Such labels seem to be the result of uncritically applying the public health model, with its emphasis on the good of the entire population, to family decisions where the medical model, with its emphasis on the good of the individual patient, is more appropriate.<sup>20</sup>

In their commentary, Faden and colleagues had emphasized that they were questioning informed consent *only* for PKU (and for any other condition where the benefits of newborn screening clearly outweigh the harms). When the benefits and risks of screening for a condition are less clear, they wrote,

[I]t may be necessary to inform parents that certain screening tests are optional while others are not. Before a policy of compulsory neonatal screening is adopted, each condition for which screening is contemplated must be considered individually against harm principle considerations, the role of parental expertise, the value of family privacy, and other factors.<sup>21</sup>

In this passage, Faden and her colleagues appear to be calling for an alternative approach to newborn screening that recognizes that, for some conditions, screening is appropriately mandatory; for others, screening should be elective and voluntary, at least until the condition is better understood and an effective treatment is developed.

## II. A Two-Tiered Approach to Newborn Screening

The approach that emerges from the ethical analysis of Faden and her colleagues is by no means merely hypothetical; it is what the state of Massachusetts has been practicing for almost a decade. In

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<sup>20</sup> Ibid., pp. 1402-1403.

<sup>21</sup> Ruth Faden, Neil A. Holtzman, and A. Judith Chwalow, "Parental Rights, Child Welfare, and Public Health: The Case of PKU Screening."

this section we present the “two-tiered” Massachusetts approach to newborn screening as a possible model for other states to follow.

### ***A. The Massachusetts Model***

Under Massachusetts law, all babies born in the state are screened for a “routine” panel of *ten* conditions, unless parents object on the basis of religious beliefs.<sup>22</sup> Parents are also offered “optional” newborn screening for an additional *twenty* disorders.<sup>23</sup> The optional screening is presented to the public in the form of two “pilot programs” (one for cystic fibrosis, the other for nineteen rare metabolic disorders), i.e., “research studies” whose purposes are the following:

1. To evaluate the benefit of newborn screening in bringing babies with possibly serious medical conditions to early medical attention.
2. To find out how often these disorders occur in Massachusetts.
3. To evaluate the laboratory tests used to screen for these disorders.<sup>24</sup>

In explaining the distinction between routine and optional screening, Kathleen Atkinson and colleagues at the Massachusetts

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<sup>22</sup> See the brochure “Answers to Common Questions About Newborn Screening” of the Massachusetts Newborn Screening Program, online at [www.umassmed.edu/uploadedfiles/nbs\\_eng.pdf](http://www.umassmed.edu/uploadedfiles/nbs_eng.pdf). The ten actually include eleven of the ACMG’s core conditions, plus the infectious disease congenital toxoplasmosis. (Three of the ACMG report’s hemoglobinopathies are counted by Massachusetts as one.)

<sup>23</sup> Kathleen Atkinson, et al., “A Public Health Response to Emerging Technology: Expansion of the Massachusetts Newborn Screening Program,” *Public Health Reports* 116 (2001): 122-131. The twenty include CF (an ACMG core condition) plus nineteen metabolic disorders detectable by MS/MS, some of them included in the ACMG core panel, others in the secondary panel.

<sup>24</sup> “Answers to Common Questions About Newborn Screening” of the Massachusetts Newborn Screening Program.

Newborn Screening Advisory Committee wrote about the rare metabolic disorders on the optional panel as follows:

The Committee recognized that each of these disorders was potentially life threatening and that early identification would allow better understanding of the illness and potential preventive action.

However, the Committee also determined the need for information, as yet unavailable, on the epidemiology, range of symptoms, natural history, and treatment of these disorders. Some children identified with biochemical abnormalities at birth might later have no clinical problems (overdiagnosis bias); nonetheless, these children might be considered ill by their parents throughout childhood, and they might also have difficulty obtaining health insurance.<sup>25</sup>

Although the pilot programs are primarily research-oriented,<sup>26</sup> Atkinson and colleagues reported that, by the fall of 2000, “approximately 97% of parents had participated in the investigational screening.”<sup>27</sup> Thus, their experience suggests that a voluntary, informed consent process, in a screening program offered to the public as an experimental “pilot study,” does not necessarily lead to low parental compliance with newborn screening.

It is important to emphasize that this high rate of parental compliance even with pilot screening does not mean that an informed consent process is effectively useless. We noted earlier that it is unrealistic to expect parents to attain a sophisticated knowledge of the multitude of obscure genetic conditions for which babies are now screened. The vast majority of parents seem to

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<sup>25</sup> K. Atkinson, et al., “A Public Health Response to Emerging Technology: Expansion of the Massachusetts Newborn Screening Program,” p. 126.

<sup>26</sup> Most Committee members agreed that “a population-based study of newborns for CF and metabolic disorders was indeed research on human subjects.” *Ibid.*, p. 126.

<sup>27</sup> *Ibid.*, pp. 127-128.

accept the medical establishment's judgment that such screening is beneficial for their children. But in the context of a two-tiered screening system, such as that of Massachusetts, an informed consent process is, potentially at least, of considerable value in educating the parents. They may not attain a precise understanding of the risks and benefits of screening for every obscure condition, but it is likely that they will acquire an awareness of the crucial distinction between conditions like PKU and CH, where the net benefits of screening and treatment are abundantly clear, and conditions that are not well-understood and clearly treatable and are, therefore, more properly the target of voluntary research studies. Moreover, however important this distinction may be in the present era of MS/MS, it will become all the more critical in the future, as we turn to multi-array DNA-based genetic screening, with its potential to reveal thousands or tens of thousands of genetic abnormalities of uncertain clinical significance. In a two-tiered approach to newborn screening, the great value of the informed consent requirement is that it encourages parents to keep firmly in mind the ethical difference between screening their children for well-understood, treatable diseases and enrolling them in medical research projects of uncertain risks and benefits. A clear public grasp of this distinction will prove to be vitally important as the line between therapeutic and research screening is increasingly blurred by the progress of genomic screening methods.

In addition to requiring explicit parental consent, the Massachusetts pilot screening programs were initiated only after winning approval from Institutional Review Boards (IRBs) at both the Massachusetts Department of Public Health and the University of Massachusetts.<sup>28</sup>

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<sup>28</sup> Atkinson and colleagues write that, "According to federal regulations, IRB approval is needed for all 'research involving human subjects,' with *research* defined as 'a systematic investigation (that is, the gathering and analysis of information) designed to develop or contribute to generalizable knowledge.'" (Ibid., p. 126.) However, federal regulations require IRB approval for research involving human subjects *only* if the research is "conducted, supported, or otherwise subject to regulation by [a] federal department or agency." See Office for Protection from Research Risks, *Institutional Review Board (IRB) Guidebook* (Washington, DC: National Institutes of Health, 1993), available online at [www.hhs.gov/ohrp/irb/irb\\_guidebook.htm](http://www.hhs.gov/ohrp/irb/irb_guidebook.htm).

The implementation of a two-tiered approach to newborn screening in Massachusetts occurred after many public hearings and was made possible by the broad charge given to the Newborn Screening Advisory Committee, which included representatives from all interested constituencies.<sup>29</sup> The Advisory Committee was also given the task of periodically re-examining the Massachusetts newborn screening system, to determine whether, based on additional information gathered since 1998, any additional disorders warranted inclusion in the mandatory screening panel, and whether any other disorders should be added to the pilot studies.

### ***B. The Future of Screening in Massachusetts***

As of November 2008, Massachusetts is considering amendments to its regulations governing newborn screening that will considerably expand the number of conditions on its mandatory screening panel. In recommending this expansion, the Massachusetts Newborn Screening Advisory Committee reaffirmed its commitment to a two-tiered approach to newborn screening and

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The idea that research involving human subjects requires external ethical oversight and approval has a distinguished history dating back to the late nineteenth century. As early as 1865, the great French physiologist Claude Bernard wrote, “The principle of medical and surgical morality...consists in never performing on man an experiment which might be harmful to him to any extent, even though the result might be highly advantageous to science, i.e., to the health of others.” (Claude Bernard, *Introduction to the Study of Experimental Medicine*, Henry C. Greene, trans. (New York: Dover, 1957), p. 101.) In this country, the need for IRB approval of federally-funded human subjects research was established by a memorandum issued by the Research Grants Division of the United States Public Health Service (USPHS) in 1966. Such research would thereafter require prior institutional review to “assure an independent determination: (1) of the rights and welfare of the individual or individuals involved, (2) of the appropriateness of the methods used to secure informed consent, and (3) of the risks and potential medical benefits of the investigation.” (U.S. Public Health Service, Division of Research Grants, Policy and Procedure Order #129, “Clinical Investigations Using Human Subjects,” February 8, 1966.) The USPHS memo was a direct response to an influential article by Harvard anesthesiologist Henry K. Beecher, exposing twenty-two examples of ethically questionable medical research with human subjects. (Henry K. Beecher, “Ethics and Clinical Research,” *New England Journal of Medicine* 274 [1966]: 1354-1360.)

<sup>29</sup> K. Atkinson, et al., “A Public Health Response to Emerging Technology: Expansion of the Massachusetts Newborn Screening Program,” p. 129.

its conviction that the original criteria for mandatory screening remain sound. On the basis of information gathered from the first decade of its pilot screening program, however, the Advisory Committee concluded in July 2008, that CF should be removed from pilot status and added to the mandatory screening panel, along with twelve of the nineteen rare metabolic disorders from the original pilot program. The Committee recommended that pilot screening be offered henceforth for six disorders, including two of the original nineteen pilot metabolic disorders, three other rare metabolic disorders, and Severe Combined Immunodeficiency (SCID), commonly known as Bubble Boy Syndrome. The Committee also recommended that, for the first time, the regulations should make explicit that some rare conditions that do not merit either mandatory or pilot screening will nonetheless be identified in the course of screening for mandated or pilot conditions. The Committee said that such “by-product conditions,” if found, will be “reported to the attending physician and infants would be followed (like the practice for pilot disorders).”<sup>30</sup>

If it amends its regulations as proposed, Massachusetts will, in February 2009, begin mandatory screening of all newborns for thirty conditions (plus twenty-three by-product conditions), while offering optional screening for six other conditions (and three by-product conditions). It should be emphasized that all twenty of the new candidate conditions for mandatory screening have been part of pilot screening studies in Massachusetts for close to a decade. Evidently, during that time, sufficient evidence was gathered from the pilot programs for the Advisory Committee to conclude that each of those twenty conditions was now well understood, that an

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<sup>30</sup> See Draft Regulations of July 18, 2008, Department of Public Health, 105 CMR 270.000: Blood Screening of Newborns for Treatable Diseases and Disorders, available online at [www.mass.gov/Eeohhs2/docs/dph/legal/newborn\\_screen\\_reg.doc](http://www.mass.gov/Eeohhs2/docs/dph/legal/newborn_screen_reg.doc). See also Memorandum of August 13, 2008, Re: Informational Briefing on Proposed Amendments to 105 CMR 270.000: Regulations Governing Testing of Newborns for Treatable Disease, available online at [www.mass.gov/Eeohhs2/docs/dph/legal/newborn\\_screen\\_reg.doc](http://www.mass.gov/Eeohhs2/docs/dph/legal/newborn_screen_reg.doc). We shall address, in the next section, the ethical question of whether and how states should report positive results for these “by-product” conditions.

effective treatment was available, and that the positive benefits of screening and treatment outweighed the risks and burdens.

Whether these twenty new candidate conditions truly meet the rigorous Massachusetts criteria for mandatory screening is perhaps open to question. For example, at the top of the list is the rare amino acid defect ARG, a “urea cycle” disorder that can cause muscular, neurological, and developmental problems, with onset of symptoms typically between two and four years of age.<sup>31</sup> Treatment for ARG consists of a “life-long ascetic regimen” of low protein intake and medication to reduce elevated levels of ammonia.<sup>32</sup> In 2005, the ACMG concluded that ARG did not meet its criteria for mandatory screening, chiefly because “natural history with treatment is poorly understood.”<sup>33</sup> In fact, ARG scored so low on the ACMG’s initial survey that it was judged “not appropriate for newborn screening” and was then added to their secondary panel only because it was detectable by MS/MS when used in “full profile mode.”<sup>34</sup> On the basis of a small number of case studies, at least some experts believe presymptomatic diagnosis and treatment is of sufficient benefit to justify newborn screening.<sup>35</sup> But with ARG it is not entirely clear (as it is with PKU, for example) that newborns who test positive for the disease should be started on a restricted diet before symptoms emerge later in childhood. All in all, because of our limited experience with and understanding of this disease, its natural history, and its treatment, it may be premature to claim that it is sufficiently well understood and treatable to warrant mandatory screening.<sup>36</sup>

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<sup>31</sup> Eric A. Crombez and Stephen D. Cederbaum, “Hyperargininemia Due to Liver Arginase Deficiency,” *Molecular Genetics and Metabolism* 84 (2005): 243-251. About thirty cases have been reported in the literature worldwide. (Ibid., p. 244.) The incidence of ARG is unknown, but is estimated at one in 360,000 births. (ACMG, *Newborn Screening*, p. 193.)

<sup>32</sup> Eric A. Crombez and Stephen D. Cederbaum, “Hyperargininemia Due to Liver Arginase Deficiency,” p. 250.

<sup>33</sup> ACMG, *Newborn Screening*, p. 193.

<sup>34</sup> Ibid., p. 64.

<sup>35</sup> Crombez and Cederbaum, “Hyperargininemia Due to Liver Arginase Deficiency,” p. 249.

<sup>36</sup> Similar questions could be raised about the Massachusetts Advisory Committee’s proposal to initiate mandatory screening for two related urea cycle

Thus, a cautious assessment of the available evidence might lead one to question whether all twenty of these conditions are truly ready to be moved from pilot status to mandatory screening. In any event, whether or not the expansion currently contemplated by Massachusetts is entirely justified by the evidence gathered for each candidate condition, the ethical framework for two-tiered screening has been preserved: conditions are to be moved into the mandatory screening panel only after studies have shown that their natural histories are sufficiently well understood and that efficacious treatments are available whose positive benefits clearly outweigh the risks and burdens of screening and treatment. The Massachusetts approach to newborn screening therefore remains a viable model for other states to follow as they expand their screening panels.

### III. Combining the ACMG’s Recommended Panel and a Two-Tiered Approach

If the two-tiered model of “routine plus optional newborn screening” were to be recommended for every state to follow, that would, of course, entail some revision of the ACMG report’s recommendations. It would have to be made clear that only those conditions that satisfy the classical Wilson-Jungner screening criteria—early-onset conditions that gravely threaten the health of the child, that are well understood in their natural histories, and that can be effectively treated by timely intervention—should be recommended to the states for inclusion in a *mandatory* screening panel. All other conditions—those illnesses whose health risks and natural histories are poorly understood and for which effective treatments are not yet clearly available—should be presented forthrightly as candidates for inclusion in pilot research studies,

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disorders: carbamylphosphate synthetase deficiency (CPS) and ornithine transcarbamylase deficiency (OTC). Both of these conditions were deemed by the ACMG to be unsuitable for newborn screening on the grounds that “natural history with treatment is poorly understood” and that the conditions cannot be consistently detected by MS/MS. (ACMG, *Newborn Screening*, pp. 201-202, 213-214.) For each of these conditions, the ACMG report concludes, “There is no objective evidence at this time in support of the availability of a screening test.” (Ibid., pp. 202, 214.) If Massachusetts adopts the amended regulations, it may be the only state in the nation that will screen newborns for OTC.

with optional participation by parents of newborns. Thus, in place of the ACMG's core and secondary panels, a revised recommendation would offer to the states a mandatory screening panel and a list of other conditions deemed suitable for optional pilot studies.

A Newborn Screening Advisory Committee in each state would then have to determine which of the ACMG's recommended conditions belong in the routine panel and which conditions should be included in pilot screening programs in that state. The Advisory Committee would also meet periodically to review and revise these decisions in light of continuing progress in the understanding and treatment of the disorders. IRB approval would be sought in each state for the pilot programs, as befits any research program involving human subjects.<sup>37</sup>

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<sup>37</sup> Statewide IRB oversight can be arranged in a variety of ways. In Massachusetts, for example, the pilot newborn screening programs require approval from review boards at both the state Department of Public Health and the University of Massachusetts Medical School. Kenneth Pass and colleagues have described how these two IRBs shaped the Massachusetts pilot screening programs:

Two independent human subjects review boards (one representing the MA Department of Health and one from UMassMed) determined that informed consent was necessary. The same two review boards recognized the presumed benefit and the operational impracticalities of conventional methods for requesting informed consent; they approved an alternative form of informed consent, i.e., verbal informed consent. Briefly, verbal informed consent requires

- that educational materials be provided to parents in the form of a brochure
- that parents be told (optimally in the prenatal period, at minimum after birth) of the optional research program
- that parents be asked whether or not they consent to the optional research testing
- that the only written documentation required would be that needed to indicate to the testing laboratory when a parent refuses consent.

See Kenneth Pass, et al., "Pilot Programs in Newborn Screening," *Mental Retardation and Developmental Disabilities Research Reviews* 12 (2006): 293-300, p. 296.

In the interest of *uniformity* and *equity*, it would be entirely appropriate to encourage all the states to adopt one and the same mandatory screening panel, assuming that all the conditions included in it are genuinely worthy of state-mandated newborn screening. The ACMG could help the states reach a consensus by recommending for mandatory screening only those conditions that rigorously meet the classical Wilson-Jungner criteria, while relegating other more doubtful conditions to the list of disorders that require further research and are, therefore, suitable for pilot study. In trying to bring uniformity to the mandatory screening panels, the states themselves could make use of a long-standing institution, the National Conference of Commissioners on Uniform State Laws (NCCUSL), whose purpose is “to strengthen the federal system by providing rules and procedures that are consistent from state to state but that also reflect the diverse experience of the states.”<sup>38</sup> As for the optional conditions, by encouraging the individual states to adopt their own diverse pilot screening programs under a research paradigm, the country can reap the benefits of *federalism*; i.e., the fifty states can serve as fifty laboratories in which to study the costs and benefits of screening for a multitude of conditions whose clinical significance and appropriate treatment are still in doubt. If all babies born in the United States are uniformly screened for exactly the same conditions, it becomes very difficult to study the overall efficacy of screening versus not screening for a particular disorder. It is a great advantage of our federal system that states can learn from each other what works best, adopting the successful models and discarding the failed ones.

One foreseeable problem with a two-tiered approach concerns those conditions that are necessarily identified as part of the differential diagnosis of the mandated conditions (referred to in this white paper as “incidental findings” or “by-product conditions”). Some would argue that any clinically significant results must be reported to the child’s physician and parents, even if those results were obtained inadvertently in the course of testing for other

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<sup>38</sup> See the NCCUSL website, [www.nccusl.org](http://www.nccusl.org), for more information.

conditions.<sup>39</sup> As we have seen, mandatory reporting of such results is recommended by the ACMG; elsewhere (e.g., Germany), such information is not routinely reported and may even be discarded.<sup>40</sup>

There exists, in fact, a rich literature on the ethics of disclosing or not disclosing clinically significant results to participants in medical (and especially genetic) research.<sup>41</sup> As regards the ACMG's secondary newborn screening disorders, the ethical question is whether it is obligatory to disclose to the patient inadvertent medical results that are *incidental* to the pursuit of *other* results that are intended to be disclosed.<sup>42</sup> Yet perhaps non-disclosure of such incidental results may be justified on the same principles that lead investigators to withhold clinical results from research subjects unless there is something that can be done to ameliorate the condition revealed. In 1999, the National Bioethics Advisory Commission (NBAC) issued the following guidance:

IRBs should develop general guidelines for the disclosure of the results of research to subjects and require investigators to address these issues explicitly in their research plans. In general, these guidelines should reflect the presumption that *the disclosure of research results to subjects represents an exceptional circumstance.*

Such disclosure should occur only when all of the following apply:

a) the findings are scientifically valid and confirmed,

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<sup>39</sup> See R. Rodney Howell, "We Need Expanded Newborn Screening," p. 1801; and Piero Rinaldo, et al., "Making the Case for Objective Performance Metrics in Newborn Screening by Tandem Mass Spectrometry," *Mental Retardation and Developmental Disabilities Research Reviews* 12 (2006): 255-261, p. 255.

<sup>40</sup> R. Rodney Howell, "We Need Expanded Newborn Screening," p. 1801; and Rodney J. Pollitt, "International Perspectives on Newborn Screening," p. 392.

<sup>41</sup> See, for example, Barbara P. Fuller, et al., "Privacy in Genetics Research," *Science* 285 (1999): 1359-1361; and Daryl Pullman and Kathy Hodgkinson, "Genetic Knowledge and Moral Responsibility: Ambiguity at the Interface of Genetic Research and Clinical Practice," *Clinical Genetics* 69 (2006): 199-203.

<sup>42</sup> See Ellen W. Clayton, "Incidental Findings in Genetics Research Using Archived DNA," *The Journal of Law, Medicine & Ethics* 36 (2008): 286-291.

- b) the findings have significant implications for the subject's health concerns, and
- c) *a course of action to ameliorate or treat these concerns is readily available.*<sup>43</sup>

Following this guidance, it would seem appropriate for state health departments to develop rules governing the disclosure or non-disclosure of “incidental” screening results, i.e., positive results for poorly understood or untreatable conditions obtained as part of the differential diagnosis of conditions included in the mandatory screening panel. One possible approach would be for the state to allow parents to decide, by a process of informed consent, whether they would want to be notified in the event of a positive “incidental” result. In other words, the question of whether they wish to be informed of such incidental findings could be decided by parents in connection with the decision about enrolling their children in pilot screening programs for other poorly understood disorders. Another possible approach would be for the state to inform parents that such incidental findings would be disclosed to them only if and when, as a result of future research, an improved understanding of the condition and how it can be effectively treated becomes sufficient to justify adding that condition to the mandatory screening panel. Obviously, the difficulty and costs of such arrangements would have to be weighed carefully before recommending them as a policy for states to follow. In any event, the rules for disclosure or non-disclosure of such incidental screening results should be formulated by each state, and there need be no blanket presumption that the states are ethically obligated to report incidental screening results to the infant's physician and parents.

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<sup>43</sup> National Bioethics Advisory Commission, *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance*, vol. 1 (Rockville, MD, 1999); emphasis added.

#### **IV. An Ethical Framework for the Ongoing Expansion of Newborn Screening: A Recommendation by the President's Council on Bioethics**

As we saw in Chapter Two of this white paper, the principles that have governed newborn screening for the past forty years are being challenged as the states rapidly expand the number of conditions for which newborns are routinely screened. It is cause for concern that this progress in the screening and treatment of newborns for serious heritable illnesses has been achieved only at the expense of undermining the prudent principles articulated by Wilson and Jungner. Yet it appears that reasonable compromises are possible that would permit uniform, mandatory newborn screening to expand at a reasonable pace in full accordance with classical screening principles, side by side with pilot screening programs throughout the states, in which disorders that are poorly understood, untreatable, or both could be studied in a research context, where infants are screened only after parental informed consent has been obtained.

Accordingly, this Council neither simply endorses the ACMG's recommended expansion nor rejects it outright, but instead proposes a modification of the ACMG's recommendations. With the Massachusetts approach as a model, an ethically sound approach to public policy in newborn screening would, in the Council's opinion, include the following elements. It would:

1. *Reaffirm the essential validity and continuing relevance of the classical Wilson-Jungner screening criteria.*
2. *Insist that mandatory newborn screening be recommended to the states only for those disorders that clearly meet the classical criteria.* Such a disorder must pose a serious threat to the health of the child, its natural history must be well understood, and timely and effective treatment must be available, so that the intervention as a whole is likely to provide a substantial benefit to the affected child.

3. *Endorse the view that screening for other conditions that fail to meet the classical criteria may be offered by the states to parents on a voluntary basis under a research paradigm.* Such screening programs should be presented forthrightly as pilot studies, whose benefits and risks to the infant are not certain, and for which IRB approval should be obtained in each state. A condition included in a pilot screening study should be moved to the mandatory screening panel only if the evidence clearly establishes that it now meets the classical criteria.
4. *Affirm that, when differential diagnosis of some targeted disorders entails detection of other poorly understood conditions that would not otherwise be suitable candidates for newborn screening, such results need not be transmitted to the child's physician and parents.* It should be left to the states to formulate rules governing whether and when to disclose those results.
5. *Encourage the states to reach a consensus on a uniform panel of conditions clearly meriting mandatory screening.* In contrast, diversity among the states in regard to the pilot conditions for which they offer optional screening is to be welcomed, as it permits the states to learn from each other's different experiences.
6. *Urge a thorough and continuing re-evaluation of the disorders now recommended for inclusion in the mandatory screening panel, to ascertain whether they genuinely meet the classical criteria that would justify mandatory screening of all newborns, or whether they instead are suitable candidates for pilot screening studies.* In support of such continuing re-evaluation, states should be encouraged to collect and share data on the short- and long-term outcomes for children who test positive for a genetic disorder, both those on the mandatory screening panel and those targeted by pilot programs.

7. *Reject any simple application of the “technological imperative,” i.e., the view that screening for a disorder is justified by the mere fact that it is detectable via multiplex assay, even if the disorder is poorly understood and has no established treatment. There should be no presumption that multiplex screening platforms are to be used in “full profile mode.”*





# PERSONAL STATEMENTS



PERSONAL STATEMENT OF  
FLOYD E. BLOOM, M.D., AND  
MICHAEL S. GAZZANIGA, PH.D.

Having read closely the final draft of the Council’s white paper on ethical issues in the current expansion of newborn screening, we feel obliged to add a statement of our own on the white paper’s tone and scope.

In our view, while the staff have conducted an admirable and comprehensive review of the current situation concerning the possible further consequences of continued expansion of mandatory genomic screening capacities, there is also frequent speculation about those future consequences of screening that goes too far. Worrying about logically possible but low probability outcomes down the road of the unknown has its limits. Furthermore, we think that the transition into speculating on the adverse consequences for medical practice and the “Doubts About the Power of Genomic Medicine” (Chapter Three) extends beyond both the needs of this white paper and the implications of the reality of how medicine is practiced today.

As the white paper notes early on, the expanded uniform screening panel proposed by the American College of Medical Genetics in 2005 was “promptly endorsed by the Advisory Committee [to the Secretary of Health and Human Services] on Heritable Disorders and Genetic Diseases in Newborns and Children,” and, “by November 2008, almost all of the states had adopted the ACMG’s panel of twenty-nine core conditions, and most had initiated screening for a majority of the twenty-five secondary conditions.” Given that state of adoption, any practical utility to be gained by having the Council speak out on the ethical issues that may be consequences of the transition from a “screen only if you can

intervene” to “screen unless there is some reason not to” must be reliant upon only the most scientifically based arguments. We are extremely skeptical that at this point in the national discussion we can expect to mount ethical arguments sufficiently persuasive to have 50 state legislatures reverse their prior commitments to the screening process.

When the white paper states (Chapter Three) that “doubts have been expressed about the potential of genomic studies to find markers for susceptibility to the most common diseases afflicting mankind, as opposed to the rare metabolic disorders that are the primary target of newborn screening today,” it moves well beyond the focus on newborn screening that we took to be the focus of the report. While we acknowledge that it is the potential benefit to societal health that drives the quest for identifying the heritable factors that can enhance or reduce vulnerabilities to disease pathways, raising the specter that such genomic information is irrelevant goes well beyond any existing science and prematurely casts doubt on that which will be knowable when more data have been gathered and analyzed. Forestalling knowledge strikes us as a blatantly anti-intellectual fear of knowledge. The NIH has, after all, already completed the major inventory of the human genome and extended it into inter-individual analysis, established the HapMap consortium, and facilitated the early stages of commercialization of complete individual genomes with their unique SNPs and HapMaps. How long it may take to convert those efforts into useful treatments or preventions may be unknowable now, but questioning that end seems to us to be well beyond the issues of newborn screening.

The ongoing difficulty of finding genomic markers for common diseases should not be misinterpreted as an indication that such markers do not exist. For instance, while some observers may be astounded that the analysis of the human genome to date reveals only minor inter-individual bases for identifying the “causes” of type 2 Diabetes Mellitus, the heritability of this and other genetically complex medical diseases is scarcely in doubt.

In addition and with specific regard to the example of Duchenne Muscular Dystrophy, it strikes us as illogical to question screening of newborns on the basis of the current treatment protocol, which would delay treatment with corticosteroids since it is not presently possible to institute such treatment until later in life. In our view, the inclusion of this genetic identifier in the newborn screening panel is already more than justified by the low cost to gain this potential diagnostic insight, and further, by the opportunity for future research to reveal better ways to treat earlier to reverse the disease.

The white paper poses the question, “Suppose that expanded screening of an infant reveals not a fatal and incurable disease but instead a host of genetic variants, each of which merely confers elevated risk for some condition or other? Who is to say at what point an uncovered defect becomes serious enough to warrant preventing the birth of other children who might carry it? At what point have we crossed the line from legitimate family planning to capricious and morally dubious eugenics?” In our view, it may be legitimate to pose the question, but it is not appropriate to narrowly focus the consequence of such discoveries to a sinister eugenics decision. Knowing the means by which a new discovery confers elevated risk may simply be the first step in knowing how to stem that and future individuals’ journey down an unhealthful pathway to disease, and may eventually lead to new methods of prevention or more effective treatments. In raising these questions in this anti-intellectual manner, the white paper seems to us to go much further down the road of unknown consequences than the facts offer and to un-heuristically constrain the grounds on which to imagine our future.

That overly constrained view of the future potential of genomic insights into disease prevention is further demonstrated in the white paper’s statement asserting—without any evidence to support it—the doubtfulness of the scientific perspective: “The presumption of modern science, including medical genetics, has always been that knowledge is fundamentally good for human beings, and that the more we know about ourselves the better we will be able to live the kind of lives we want to live.”

While we do agree that “there is...the possibility that such knowledge will be misused or misinterpreted,” that has historically always been the case when new knowledge becomes available, at least as far back as the invention of the printing press. Having informed the society of this potential danger, it is society’s responsibility to keep that danger, but not the potential benefit, from happening. To that end, this discourse should benefit the public discussion of future newborn screening.

However, when the white paper asserts that “we as a nation have not been in the habit of subjecting individuals to compulsory screening merely for research purposes,” we again see anti-scientific thinking at play. The phrase “subjecting individuals to compulsory screening” depicts a far more invasive procedure than the sampling of heel stick or cord blood that occurs, while “merely for research purposes” greatly diminishes the fundamental quest for self-knowledge. To the white paper’s assertion that, “In the wake of the ACMG report and its enthusiastic reception by the states, our approach to newborn screening seems to be heading into uncharted territory,” we ask: should Lewis and Clark have stayed home?



## PERSONAL STATEMENT OF JEAN B. ELSHTAIN, PH.D.

Congratulations to the staff for this white paper. It is lucid, clearly written, admiral in its judiciousness, a model of how to lay out complex and controversial issues in a way that opens up rather than shuts down essential debate.

The basic question is: What ethical principles should guide the practice of newborn screening in the United States?

Reading over the paper, I was reminded of the film *Gattaca*,<sup>1</sup> not a great film but an instructive one. *Gattaca* imagines a future world dominated by genetic screening. At birth, infants are screened and are either declared “valids” or “invalids.” The “invalids” are also known as “de-gene-erates.” As a result, they do the society’s “grunt work” and are denied access to what the society values most highly and rewards most generously. The film’s protagonist, by the way, is near-sighted—that is his most egregious genetic “sin.” But such a flaw is bound to happen, we learn, because he is a “faith birth”—a child born the old-fashioned way without the benefit of the pre-pregnancy rules and regulations of the eugenic society in which he lives. (Needless to say, these rules and regulations mandate abortion for all “imperfections,” however slight.)

Let’s turn to our own society at present. We learn that the “great majority of babies born in the United States each year undergo screening soon after birth to identify genetic defects that could cause serious illness if left undetected and untreated.” What is the goal? To detect diseases as early as possible in order that effective

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<sup>1</sup> Columbia Pictures (1997), dir. Andrew Niccol.

treatment can be initiated. This, at least, has been the dominant model and rationale.

Over the years there has been a nigh-exponential leap in the number of disorders for which infants are screened, and nearly all infants today are screened for between “thirty and fifty genetic disorders.” This includes screening for genetic disorders that are extremely rare and for which there is no known treatment. The natural history of such disorders is not well understood.

In the once prevailing model, the infant’s good was the moral focus: screening must be of direct medical benefit to the infant if screening itself is to be justified. In the emergent model, newborns are turned into research subjects and the emphasis is no longer the well-being of a singular child but the genetic profile of entire populations in a situation in which efficacious treatment is not available for a whole range of potential disorders. To “screen for” is not the same as to “diagnose” a disease.

With more promiscuous screening, dilemmas involving screening grow more pronounced and serious—for example, the problem of false positives. As we learn, the large majority of initially positive results for the conditions states now screen for “will turn out to be incorrect.” There are thousands of false positives each year, and extraordinary expense is involved in eliciting such erroneous, misleading, and potentially damaging information. Every screening program is an experiment and, as with any program—whether in the medical, social, or economic realm—there are always unintended consequences. (So much is this the case that social scientists actually speak of a *law* of unintended consequences.)

The white paper takes us through the changing ethical principles governing newborn screening practices. The consensus that once pertained—a medical model with the goal of treatment held as the overall *raison d'être*—has given way, or is giving way, to a research protocol model. Under the earlier consensus, large-scale programs were not justified unless resources existed to confirm diagnoses and to treat maladies. Screening when no established treatment was available was considered ethically dubious and rarely justified.

Otherwise, screening was a waste of scarce resources and likely to do more harm than good to both parents and their children. A “substantial benefit” to the infant and the family guided screening criteria.

Now, however, the older ethical norms are called “dogma”—in the language of critics. This is an interesting rhetorical move. When we hear “dogma” we think of those who criticize religion as something uncritically clung to when no “evidence” exists. We are told that dogma involves irrationality and stubborn immovability, especially from those who stand in the way of “progress.” The rhetoric of “dogma” is not deployed unthinkingly, one must assume, as those hoping to break down the earlier ethical and medical consensus strive to remove barriers to a vast research protocol involving tens of thousands of human infants.

Screening within a research paradigm holds forth vague future prospects of benefits to populations although there is no known improvement to be realized for any single individual at present. Justifications include a broadened concept of benefit and rationalizations for allowing technology to dictate the “pace and scope of the expansion of newborn screening.” Benefit remains at a hypothetical level. But the claim—held “dogmatically,” one might suggest—is that broad benefits will be derived at some future point. Critical consideration of knowledge in the absence of treatment is not foregrounded as a major concern.

My view is that one should not screen in the absence of any available treatment or when the benefits of treatment are insignificant; that families should not be overly burdened with anxiety, dread, “vulnerable child syndrome”—a sense that a genetic Sword of Damocles is hanging over their heads. The child’s life may be prematurely medicalized to no good or decent end. To this one must add the extraordinary, runaway costs of such screening in a society in which many are not receiving the immediate, necessary health care they require.

Babies should not be fodder for biomedical research if there is no available benefit to them as a result of that research. Although the

foundation has been laid for radical expansion of newborn testing, it is critical at this juncture to raise questions and to mount challenges. One should always take care when radical changes in “the ethical framework of newborn screening” are proposed. Should we not consider the possibility that earlier ethical guidelines contained some wisdom that we dare not lose or overthrow altogether in favor of a radical refashioning that undercuts the historic gravamen of infant care?

Above all, as thoughtful human beings, we cannot and must not permit what we do in medicine to be driven by the possession of technologies. We must keep technology in its proper place, which is a subordinate one to the overarching goal—if medicine is the focus—of the well-being of the individual patient. Here, surely, *do no harm* remains the surest guide.

I concur, therefore, with the recommendations proposed to the President’s Council on Bioethics, with this caveat: I would cast recommendation #3 in somewhat stronger language so that parents understand their baby is being tested as part of a research, not a medical, protocol.



## PERSONAL STATEMENT OF GILBERT C. MEILAENDER, PH.D.

In this white paper examining disputes about the proper focus and scope of newborn screening the Council offers a set of recommendations designed to keep a public health model (which focuses not on the health of individual patients but on the “health” of society) from swamping and eventually obliterating a medical model (which makes an individual patient’s good the central concern). The recommendations are judicious, and I am happy to endorse them. Nevertheless, insofar as the key recommendation is more procedural than substantive, I suspect that the recommendations constitute at best a temporary holding action and are likely to be overcome by a desire for knowledge that has no natural limit.

We recommend a two-tier approach: mandatory newborn screening for disorders that constitute a significant danger to health and for which medical treatment is available; voluntary screening of newborns, *done under the rubric of research and done only with informed consent of their parents*, for other disorders about which relatively little is known or for which no medical treatment is currently available.

Advocates of research might raise an obvious worry about this approach: What if few parents consent to have their newborns screened for disorders that cannot currently be treated? Would that not slow the progress of knowledge and limit the treatments available to future sufferers?

But, the white paper assures us, there is little need to fear such a result. In most states parents are currently permitted to opt out of otherwise mandatory newborn screening, but few do so. The number of parents who opt out is comparable to the number of parents who refuse to consent in those few states where newborn

screening is not mandatory but requires parental consent. Likewise, in pilot research programs requiring parental consent conducted in Massachusetts, approximately ninety-seven percent of parents chose to have their newborns screened.

Shall we therefore heave a sigh of relief, content in the belief that requiring informed parental consent will adequately protect newborn children without hindering at all the progress of research? Or shall we wonder whether the procedural requirement of informed consent, relatively inconsequential as it seems to be here, encourages us not to think about some of the deeper issues buried in a discussion of mandatory newborn screening?

Inclining as I do to the latter possibility, I offer here a very brief discussion aimed at calling such issues to mind. In some of its earlier work, especially in *Beyond Therapy*, the Council has already given attention to the way in which our desires for better (healthier and happier) children and longer life, having few limits, may undermine essential aspects of our humanity. Those concerns remain relevant here. We should not ignore the way in which an expanded program of newborn screening touches and transforms the relation between parents and children, nor should we overlook the questions it raises about the use of infants in the cause of medical research.

Expanded newborn screening is essentially *research* carried out for the public good, not the good of the infants being screened. It may be desirable to gain such knowledge, but it is not imperative. In “Philosophical Reflections on Experimenting With Human Subjects,” a classic essay in bioethics first published in 1969, Hans Jonas noted the difference. Sometimes it is imperative that a society avoid disaster; hence, for example, we conscript soldiers to fight. But we do not ordinarily conscript experimental subjects, because, however much we value the knowledge gained through research, we do not think ourselves obligated to acquire it. We seek volunteers, not conscripts, in the cause of medical progress.

For that reason, Jonas argued, rather than using those who might be most readily available as handy research subjects, we should be

especially reluctant to use them—governing ourselves in accord with “the inflexible principle that utter helplessness demands utter protection.” Were we really to take that principle seriously, we would be reluctant to ask parents to consent to screening for disorders for which no treatment is available, since such screening can only be aimed at the acquisition of generalizable knowledge and not at treatment of a patient.

Also at stake, though, is something deeper than a question of research ethics alone. The white paper notes that mandatory screening of disorders for which no treatment currently exists may foster a kind of parental overprotectiveness, distorting the relation between the generations. We might go farther and ask: How could it not foster such an attitude? To seek to protect one’s children from harm is part of what it means to be a good father or mother; yet, what will teach us or who will help us know when to stop? It is always possible to suppose that knowledge which cannot at the moment benefit one’s child may be useful in the future—and must therefore be sought. Hence, we press to know more and more, and we do so with a good conscience, secure in the knowledge that our concern is for our children. Indeed, rather than taking comfort in the fact that ninety-seven percent of parents are likely to consent to the use of their newborn children in research of no therapeutic value for those children, we might wonder whether in our culture they really feel free to refuse when the lure of increased knowledge is held before them.

Giving parents more choices does not necessarily give them greater freedom to carry out their parental duties. Sometimes, paradoxically, it constrains them in new ways. How many parents are truly prepared to say no to an offer of knowledge about their child’s health, even if that knowledge can have no impact at all on the medical care of the child? How many want to shoulder the burden of responsibility involved in declining to know whatever can be known about the health of their child? A request for informed consent suggests that we are free; the cultural force of our commitment to increased scientific knowledge belies that seeming freedom.

Ours is a culture that—having largely forgotten the stories of the Garden of Eden and Prometheus—has little appreciation for the ambiguity of increased knowledge. Ours is also a culture that all too readily confuses an increasing number of choices with freedom from constraint. When, therefore, we ask parents to consent before their newborn children are screened for disorders that cannot (now) be treated, no one should feel embarrassed to worry about the quality or adequacy of that consent. Drawn by our limitless desire for knowledge and constrained in unexpected ways by the very choices set before us, we may not be as free as we suppose to give genuinely parental care to our children—and the line between screening that is mandatory and screening that is voluntary may be more blurred than we are eager to acknowledge.

It is a sign of ill health—in a society, as in an individual—to attend too single-mindedly to health. I doubt that a requirement of consent is by itself sufficient to save us from the tyranny of our desire to know more, to be healthy and happy—indeed, to save ourselves and our children from the evils we fear. Therefore, this Council’s recommendations—judicious and cautious as they are—will need considerable cultural support if they are actually to achieve their aims.



## PERSONAL STATEMENT OF CARL E. SCHNEIDER, J.D.

The Council's white paper perceptively surveys and lucidly describes a complex problem. The white paper skillfully analyzes the problem by recruiting the approaches that have become standard in bioethical thought. Those approaches include a tight focus on the rights of the patient or research subject and a potent preference for using informed consent and the IRB system to protect those rights. These standard approaches provide one significant way to think about bioethics generally and newborn screening particularly. Standard approaches have dominated bioethics, not least because it is a movement more than a discipline, a regulatory regime more than a field of inquiry, and even a creed more than a question. But might a less conventional approach not only offer insights into newborn screening but also deepen and refresh a discourse in which dogmatism has always been a danger? Let us try the experiment.

Screening calls on scarce social and scarce personal resources. So what if we ask how good stewards of such resources should think about such calls? The white paper impressively canvasses the costs and benefits of newborn screening and rightly says that screening is wrong if its costs (economic, social, and personal) exceed its benefits. But even if its benefits exceed its costs, screening would still be a poor investment if other investments are more rewarding. For example, HHS reports that the United States "ranks 27th among industrialized countries" in infant mortality and that "disparities remain among racial and ethnic groups in many measures of maternal and child health." Dollars spent changing

these figures seem likelier to help children and families than dollars spent screening for rare illnesses.<sup>1</sup>

When the state makes screening policy, it not only allocates its own resources; it also shapes the way parents employ their resources (of time, energy, money, and medical services). Bioethical doctrine demands informed consent to screening, but to learn enough to make wise choices parents must devote resources—attention, energy, and medical-consultation opportunities—to that education. If newborn screening were all new parents had to think about, imposing that education on them could make sense. But of course new parents have more on their minds. And they should. When I asked a family-practice physician where newborn screening fell in his list of educational priorities for new parents, he tried to be tactful. He struggles to teach parents to bring babies in for attention when they have a fever, not to give babies water, to put babies to sleep on their back, and much else that is not obvious but saves lives.<sup>2</sup>

Telling parents to spend resources learning about newborn screening looks even less prudent given the sobering but ever-mounting evidence that informed consent cannot achieve the goal set for it—equipping people to reason their way to well-founded and well-considered medical decisions. Legions of able and earnest researchers have for decades labored nobly to make informed consent work, but even after the most arduous education patients regularly retain only a fraction of what they need to make a sound decision.<sup>3</sup> This should not be surprising. Teaching is hard. Learning is hard.

So once again we are brought back to stewardship: People can only learn so much; governments can only teach so much. Both need to

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<sup>1</sup> For helpful reflections on this likelihood, see Mary Ann Baily and Thomas H. Murray, “Ethics, Evidence, and Cost in Newborn Screening,” *Hastings Center Report* 38 (2008): 23-31.

<sup>2</sup> See Robert C. Langan, “Discharge Procedures for Healthy Newborns,” *American Family Physician* 73 (2006): 849-852.

<sup>3</sup> Carl E. Schneider, “After Autonomy,” *Wake Forest Law Review* 41 (2006): 411-444.

allocate their educational efforts wisely. (As Alfred North Whitehead put it, “Operations of thought are like cavalry charges in a battle—they are strictly limited in number, they require fresh horses, and must only be made at decisive moments.”) The Council’s white paper confirms that informed consent for screening is if anything less effective than informed consent generally.

If stewardship is our standard, we must also evaluate another feature of bioethical wisdom—IRB review. The IRB system is an experiment in censorship on a remarkable scale, but is the system justifiable? While the system’s proponents recite scandals, serious attempts to show systematically that the IRB system does more good than harm are hard to find. Yet a distressingly strong case can be made that the IRB system is an improvident steward of the resources it commands—that it is structured to make capricious and unwise decisions; that it delays, damages, and stops research that could save lives and relieve suffering; that it institutionalizes an impoverished ethics; that it imposes orthodoxy where there should be freedom; that it corrodes the values the First Amendment protects; that it flouts the most essential principles of due process; that it is a lawless enterprise that evades democratic accountability. These possibilities may seem startling, but more startling is that so potent an institution has never been held to the standards of justification we expect of any exercise of the state’s coercive power.

The stewardship approach leads us to one more question: If newborn screening is needed, how should it be instituted? The issue is not whether parents may exempt children from screening. It is whether the rule should be that children are screened unless their parents opt out or that children are not screened unless their parents opt in. This is a critical question because a large literature tells us that even when people care about a decision (like contributing to retirement accounts), they frequently leave themselves wherever default rules put them.

So which default rule should govern newborn screening? That depends on two things. First, which rule would best reflect parents’ preferences? That is, which rule is likeliest to leave parents where they want to be? The Council’s white paper persuasively answers

that question. Given a choice in surveys and in real life, parents almost all choose screening. So if conserving scarce social and personal resources is our goal, an opt-out system is plainly better. And if promoting parents' autonomy is our goal, an opt-out system is plainly better.

The second question about defaults is, which rule would best promote broader social interests? The arguments for screening are that it protects newborns and their families and that it promotes valuable research. Assuming that these arguments are reasonable, the opt-out rule again is preferable. One more social interest points in that direction: an opt-out rule attributes to parents a willingness to assist in medical research when they can do so at vanishingly small risk. An opt-out rule assumes that parents recognize that they and their children benefit from generations of participation in research and can repay their debt by participating in research that will help families yet to come. An opt-out rule thus stands in the long American tradition Tocqueville described: "The free institutions which the inhabitants of the United States possess, and the political rights of which they make so much use, remind every citizen, and in a thousand ways, that he lives in society. They every instant impress upon his mind the notion that it is the duty as well as the interest of men to make themselves useful to their fellow creatures; and as he sees no particular ground of animosity to them, since he is never either their master or their slave, his heart readily leans to the side of kindness."

The Council's mandate is to explore fundamental issues in bioethics. The Council's white paper does so by carefully and insightfully applying the principles of bioethics that have become canonical. This brief statement is a case study intended to ask—in the most allusive and possibly elusive way—whether the time has come to re-evaluate those principles, to identify their limits, and to supplement them with a richer range of ethical wisdom.



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