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THE CHANGING MORAL FOCUS OF NEWBORN SCREENING: AN ETHICAL ANALYSIS BY THE PRESIDENT'S COUNCIL ON BIOETHICS

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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.¹ 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.² No such 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:

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.³

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.⁴ Today newborn screening is mandated in forty-eight states.⁵ 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.⁶ The number of parents opting out of mandatory newborn screening tends to be quite low, with many states reporting a compliance rate of 99.9 percent or greater.⁷ In states where opting out is permissible, it is not always made clear to parents that they have that option.⁸ 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.⁹

In Maryland, Wyoming, and the District of Columbia, newborn screening explicitly requires informed parental consent.¹⁰ In general, 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.¹¹ 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.¹² As a matter of principle, however, it is notable that in 1975 the Committee for the Study of Inborn Errors of Metabolism of the 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.”¹³ 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.”¹⁴ 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.”¹⁵

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.¹⁶ 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, and does

not make the program any less cost-effective.¹⁷ 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.¹⁸ 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.¹⁹ 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 neglecter 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.²⁰

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.²¹

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 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.²² Parents are also offered "optional" newborn screening for an additional *twenty* disorders.²³ 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.²⁴

In explaining the distinction between routine and optional screening, Kathleen Atkinson and colleagues at the Massachusetts 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.²⁵

Although the pilot programs are primarily research-oriented,²⁶ Atkinson and colleagues reported that, by the fall of 2000, “approximately 97% of parents had participated in the investigational screening.”²⁷ 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 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.²⁸ 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.²⁹ 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 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).”³⁰

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 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.³¹ Treatment for ARG consists of a “life-long ascetic regimen” of low protein intake and medication to reduce elevated levels of ammonia.³² In 2005, the ACMG concluded that ARG did not meet its criteria for mandatory screening, chiefly because “natural history with treatment is poorly understood.”³³ 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.”³⁴ 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.³⁵ 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.³⁶

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, 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.³⁷

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."³⁸ 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 conditions.³⁹ 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.⁴⁰

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.⁴¹ 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.⁴² 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,
- 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.*⁴³

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.

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 sensible 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.”

1. 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.

2. 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 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...

3. 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/tfgrt/appendix5.htm.

4. Diane B. Paul, "The History of Newborn Phenylketonuria Screening in the U.S."

5. 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.

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

7. 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.

8. 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.

9. 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. On December 5, 2008, the Nebraska Supreme Court ruled that the state's mandatory newborn screening law does not violate the parents' right to religious freedom; however, the court also concluded that, in the 2007 case, the state had not proved parental neglect and should not have seized the baby. See *In re Interest of Joel Anaya, A Child Under 18 Years of Age*. No. S-07-1136, filed December 5, 2008. 276 Neb. 825; available online at www.supremecourt.ne.gov/opinions/2008/december/dec5/s07-1136.pdf.

10. 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.) 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 objects to a mandatory examination the child is exempt from [newborn screening]." (available online at 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).

11. 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.)

12. 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, III, et al., “Informed Decision Making in Outpatient Practice: Time to Get Back to Basics,” *Journal of the American Medical Association* 282 (1999): 2313-2320.

13. National Research Council, *Genetic Screening Programs, Principles, and Research*.

14. 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.

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

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

17. 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.

18. 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.

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

20. *Ibid.*, pp. 1402-1403.

21. Ruth Faden, Neil A. Holtzman, and A. Judith Chwalow, “Parental Rights, Child Welfare, and Public Health: The Case of PKU Screening.”

22. 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. 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.)

23. 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.

24. “Answers to Common Questions About Newborn Screening” of the

Massachusetts Newborn Screening Program.

25. K. Atkinson, et al., "A Public Health Response to Emerging Technology: Expansion of the Massachusetts Newborn Screening Program," p. 126.

26. 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.

27. *Ibid.*, pp. 127-128.

28. 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.

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.)

29. K. Atkinson, et al., "A Public Health Response to Emerging Technology: Expansion of the Massachusetts Newborn Screening Program," p. 129.

30. 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. 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. We shall address, in the next section, the ethical question of whether and how states should report positive results for these "by-product" conditions.

31. 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.)

32. Eric A. Crombez and Stephen D. Cederbaum, "Hyperargininemia Due to Liver Arginase Deficiency," p. 250.

33. ACMG, *Newborn Screening*, p. 193.

34. *Ibid.*, p. 64.

35. Crombez and Cederbaum, "Hyperargininemia Due to Liver Arginase Deficiency," p. 249.

36. Similar questions could be raised about the Massachusetts Advisory Committee's proposal to initiate mandatory screening for two related urea cycle 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.

37. 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

1. that educational materials be provided to parents in the form of a brochure
2. that parents be told (optimally in the prenatal period, at minimum after birth) of the optional research program
3. that parents be asked whether or not they consent to the optional research testing
4. 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.

38. See the NCCUSL website, www.nccusl.org, for more information.

39. 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.

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

41. 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.

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

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

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