The Changing Moral Focus of Newborn Screening: An Ethical Analysis by the President's Council on Bioethics

Appendix
Newborn Screening: An International Survey

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In addition to explicating the changing moral focus of newborn screening in the United States, the President's Council and its staff have explored this topic in an international context, i.e., by gathering and analyzing information on newborn screening in other countries. The aim has been to provide a context of useful and illuminating comparisons between the relevant policies and practices in the United States and those in other parts of the world. This appendix summarizes the results of this process, providing highlights that are especially significant from the perspective of ethics and public health.

Since the inception of newborn screening in the United States in the 1960s, newborn screening has gradually been introduced throughout the world. Screening programs in other nations tend to focus on the detection of phenylketonuria (PKU) and congenital hypothyroidism (CH). In addition to these two conditions, other disorders may be targets for screening in different countries, based on disease prevalence, newborn screening infrastructure, and cost. As a preview of this international survey, the following observations may be made:

- Screening for PKU is nearly universal in Europe, although the national panels for other disorders are less uniform.
- By contrast, CH is the most widely targeted disorder in Latin America and the Asia-Pacific region.
- Countries in the Middle East and North Africa exhibit wide variation in their screening panels, with three countries screening for more than ten disorders, whereas other countries provide routine screening for as few as one.
- In many parts of the world there has been a recent push toward implementing population-wide screening for an expanded list of disorders via tandem mass spectrometry (MS/MS). Newborn screening by this technology is available nationwide in several European countries (Austria, Belgium, Denmark, Germany, the Netherlands, Poland, Portugal, Spain, Switzerland, and the United Kingdom), as well as in a few countries in the Middle East and North Africa (Israel, Qatar, and Saudi Arabia), the Americas (Canada and Costa Rica), and the Asia-Pacific region (Australia and New Zealand).

Unless specifically noted and identified as *pilot* programs, all screening programs described in the following are population-wide. Moreover, information about newborn

screening programs and practices is, for the most part, relevant to understanding three variables:

1. coverage, which refers to the portion of the population screened for a particular genetic disorder or panel of disorders, and "universal" screening, either as a goal or as an achievement, refers to screening targeted at 100 percent of the given—in this case, newborn—population;
2. the genetic conditions that are targets for screening, which are often grouped in panels; and
3. the technologies deployed for the purposes of screening, e.g., tandem mass spectrometry.

In the following, information about these three variables is provided on a region-by-region, as well as country-by-country basis. In addition, pages 16 and 17 provide, in table format, information on the genetic disorders and deficiencies that are the targets of newborn screening in the U.S.A. and abroad: table 1 lists the 29 conditions on the core panel recommended by the American College of Medical Genetics; table 2 identifies other conditions for which some countries, but not all, screen; and table 3 lists the secondary conditions that are targets for screening in countries that utilize tandem mass spectrometry.

I. The Americas

This section includes information on the newborn screening programs in Canada as well as Latin America. Canada has a newborn screening program in many ways comparable to that of the United States, with newborn screening programs governed provincially. Latin America is comprised of twenty countries[1] with varying levels of newborn screening coverage. Some countries—for example, Chile, Costa Rica, Cuba, and Uruguay—have almost 100 percent coverage, whereas in countries such as El Salvador, Honduras, and Haiti, there is no routine screening.[2] Although countries may exhibit high levels of newborn screening coverage, there is wide variation in the number of disorders screened. Uruguay and Costa Rica, for example, both have close to universal coverage, but Uruguay only screens for CH, whereas Costa Rica screens for a panel of up to twenty-four disorders.[3] Overall, programs in the Latin American region—which started screening newborns in the 1970s—primarily target CH (with mandated screening in ten countries). PKU is screened systematically only in Argentina, Brazil, Chile, Costa Rica, Cuba, Guatemala, Paraguay, and Venezuela.[4] Screening for cystic fibrosis (CF) is

[1] These countries are Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, Guatemala, Haiti, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Uruguay, and Venezuela.

[2] Gustavo Juan Carlos Borrajo, "Newborn screening in Latin America at the beginning of the 21st century," *Journal of Inherited Metabolic Disease* 30 (2007): 466-481. Other countries, such as Brazil, Mexico, and Argentina, are rapidly expanding their programs.

[3] Ibid., p. 476.

[4] Ibid. Screening for PKU is mandatory in five countries: Argentina, Brazil, Chile, Costa Rica, and Paraguay.

mandatory in Argentina and Brazil[5] and galactosemia (GAL) is mandatory only in Argentina and Costa Rica.[6] Some countries, such as Brazil and Chile, target a few disorders with routine screening, although parents may request testing for additional disorders.[7]

A. Brazil

Brazil is the largest of all Latin American countries,[8] comprising twenty-seven states. Newborn screening began for PKU in 1973—the first program of its kind for inborn errors of metabolism in Latin America—and by 1976 included CH.[9] Federal law in July of 1990 made newborn screening mandatory (Law No. 8069) and by 1992 specified two disorders, PKU and CH.[10]

A Newborn Screening National Programme (NSNP) was created in 2001 by federal law (GM No. 822 2001).[11] Currently, all twenty-seven states screen for at least PKU and CH, making newborn screening coverage available to 80.2 percent of the population.[12] Ten states screen additionally for the haemoglobinopathies and sickle cell disease (SCD), while another three states also include screening for CF.[13] Although there are no data available for the screening performed in private laboratories, some include up to thirty disorders.[14]

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[5] Ibid.
[6] Ibid.
[7] Ibid., p. 475. For Brazil, in addition to the routine screening of CH, PKU, CF, and the hemoglobinopathies, tests are also available for GAL, congenital adrenal hyperplasia (CAH), biotinidase deficiency (BD), maple syrup urine disease (MSUD), glucose 6 phosphate dehydrogenase (G6PD), the aminoacidopathies, medium-chain acyl-CoA dehydrogenase (MCAD), as well as the infectious diseases toxoplasmosis (TOXO), Chagas disease, rubella, HIV, and cytomegalovirus. In Chile, in addition to legislation that mandates screening for PKU and CH, parents may request additional screening for MSUD, tryosinemia type 1 (TYR-I), propionic acidemia (PA), methylmalonic aciduria (MMA), isovaleric aciduria (IVA), glutaric aciduria type 1 (GA-I), MCAD, and short-chain-acyl-CoA dehydrogenase deficiency (SCAD).
[8] See Borrajo, p. 470: Geographically, Brazil accounts for 42.6 percent of the total land in the region and 34 percent of the total population. When combined with the population of Mexico, these two countries contribute 53.3 percent of the total Latin American population and 47.9 percent of the total births.
[9] T. Marini de Carvalho, et al., "Newborn screening: A national public health programme in Brazil," *Journal of Inherited Metabolic Disease* Short Report #068 online (2007); 1-7; p. 2. http://www.springerlink.com/content/0442828h11366v26/fulltext.pdf (accessed January 26, 2009).
[10] Ibid., p. 3.
[11] Ibid., p. 4. Objectives of the NSNP include: increasing the number of disorders; providing 100% coverage; and determining the process of newborn screening activity among the states.
[12] Ibid., p. 4.
[13] Ibid.
[14] Ibid., p. 6.

B. Canada

Canada is a federation comprising ten provinces and three territories.[15] Newborn screening started in the maritime province of Prince Edward Island in 1963—around the same time that it was being developed in the United States—and almost all provinces had screening services by 1970.[16] Even though newborn screening is now offered (with the option to refuse) in all ten provinces and three territories, no nationwide policy currently exists. Only PKU and CH are screened for universally throughout Canada. The province programs differ significantly in the number of disorders for which screening is conducted, ranging from five to thirty-eight.[17] There is a strong push, however, to provide uniform access throughout the country.[18] Although Canada has recently considerably expanded its screening programs, only six of eight provincial laboratories have implemented MS/MS.[19]

The American College of Medical Genetics (ACMG) report seems to have been influential in Canada. For example, Ontario screens for all twenty-nine of the ACMG report's core conditions, while Saskatchewan offers (but does not require) screening to all newborns for twenty of the ACMG's core conditions[20] and fourteen of the secondary targets.[21] Screening for six other secondary disorders is offered to select populations or by request.[22]

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[15] The ten provinces are Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Nova Scotia, Ontario, Prince Edward Island, Quebec, and Saskatchewan; the three territories are the Northwest Territories, Nunavut (consists of Eastern, Western, and Central sections), and Yukon.

[16] Bradford L. Therrell and John Adams, "Newborn screening in North America," *Journal of Inherited Metabolic Disease* 30 (2007): 447-465; p. 453.

[17] Ibid., p. 460. For a breakdown of the targeted core and secondary disorders, see the Canada Status Report (updated July 9, 2008), available at http://genes-r-us.uthscsa.edu/CA_nbsdisorders.pdf (accessed February 3, 2009).

[18] Therrell and Adams, p. 447.

[19] Ibid., p. 460.

[20] These disorders are CH, long-chain hydroxyacyl-CoA dehydrogenase (LCHAD); MCAD; trifunctional protein (TFP); very long-chain acyl-CoA dehydrogenase (VLCAD); GA-I; 3-hydroxy 3-methylglutaric aciduria (HMG); IVA; 3-methylcrotonyl-CoA carboxylase (3-MCC); methylmalonic academia (vitamin B12 disorders) (Cbl-A,B); beta ketothiolase (BKT); methylmalonyl-CoA mutase (MUT); PA; multiple carboxylase (MCD); argininosuccinate acidemia (ASA); citrullinemia type I (CIT I); homocystinuria (HCY); MSUD; PKU; and TYR-I. Screening for CH and PKU are required by law. Several other core conditions are offered universally but not yet implemented: CAH, BD, and CF. Hearing screening (HEAR), transferase deficient galactosemia (GALT), and carnitine uptake defect (CUD) are offered to select populations or by request.

[21] These disorders are carnitine acylcarnitine translocase (CACT); carnitine palmitoyltransferase I (CPT-Ia); carnitine palmitoyltransferase II (CPT-II); glutaric acidemia type II (GA-II); SCAD; 2-methylbutyrly-CoA dehydrogenase (2MBG); 3-methylglutaconic aciduria (3MGA); methylmalonic acidemia (Cbl-C,D); malonic acidemia (MAL); arginemia (ARG); citrullinemia type II (CIT-II); benign hyperphenylalaninemia (H-PHE); hypermethioninemia (MET); and tyrosinemia type II (TYR-II).

[22] These disorders are dienoly-CoA reductase (DE-RED), defects of biopterin cofactor biosynthesis (BIOPT-BS), defects of biopterin cofactor regeneration (BIOPT-REG), galactose epimerase (GALE), galactokinase (GALK), and variant hemoglobins.

C. Costa Rica

A National Neonatal and High Risk Screening Program has been operating in Costa Rica since March of 1990 to include CH, PKU, and MSUD.[23] In January of 2002, the program was expanded to include screening for CAH, and the galactosemias, GALT and galactokinase (GALK).[24] A couple of years later, the Japanese Agency of International Cooperation (JICA) donated a tandem mass spectrometer, which allowed the program to expand considerably by June of 2004, i.e., to screen for an additional thirteen organic acidemias and fatty acid oxidation disorders.[25] Currently, Costa Rica has legislation covering twenty-four diseases and the following disorders have been added since 2004: α-thalassemia, β-thalassemia, Hb S, Hb C, Hb D, Hb E, and CPT-II, with pilot screening for CF and BD.[26]

II. The Asia-Pacific Region

The Asia-Pacific region comprises twenty-four countries[27] and roughly half the births in the world.[28] In many of these countries, newborn screening programs have been introduced relatively recently. In general, CH is the most frequently targeted condition, followed by PKU, GAL, MSUD, and CAH. Some countries—for example, Australia, Japan, New Zealand, the Philippines, and Taiwan—have quite robust panels, while for others—for example, Cambodia, Laos, Nepal, and North Korea—no data is available.[29] Other countries, such as Singapore, are moving in the direction of adding disorders to its panel; beyond screening for PKU and CH, screening by MS/MS is available by parental request in government hospitals and the country intends to expand screening to include over twenty-five metabolic conditions.[30] For implementing newborn screening programs throughout the region, current challenges include differences in language and culture, extremes in geography, depressed economies, unstable governments, and—for developing countries—the number of births outside of the hospital setting, approaching eighty percent in some areas.[31]

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[23] Carlos de Céspedes, et al., "Evolution and Innovations of the National Neonatal and High Risk Screening Program in Costa Rica," *Revista de Biología Tropica* 52 (2004): 451-466.
[24] Ibid.
[25] Ibid. These disorders are MCAD, VLCAD, LCAD, SCAD, CPT-II, GA-II, PA, GA-I, MMA, IVA, 3-MCC, BKT, and HMG.
[26] Borrajo, p. 475.
[27] These countries are Australia, Bangladesh, Cambodia, China, Hong Kong, India, Indonesia, Japan, Laos, Malaysia, Mongolia, Myanmar, Nepal, New Zealand, North Korea, Palau, Pakistan, the Philippines, Singapore, South Korea, Sri Lanka, Taiwan, Thailand, and Vietnam.
[28] Carmencita D. Padilla and Bradford L. Therrell, "Newborn Screening in the Asia Pacific Region," *Journal of Inherited Metabolic Disease* 30 (2007): 490-506.
[29] Ibid.
[30] Ibid., p. 502.
[31] Ibid., p. 492.

Currently, CH screening is offered population-wide in eleven countries;[32] PKU screening in nine countries;[33] and GAL screening in seven countries.[34] Screening for other conditions is less common. For example, MSUD is screened population-wide only in Australia, Japan, New Zealand, and Palau;[35] CAH only in Japan, New Zealand, the Philippines, and Taiwan;[36] HCY only in Australia, New Zealand, and Taiwan;[37] CF only in Australia and New Zealand;[38] and G6PD only in Malaysia, the Philippines, and Taiwan.[39] In contrast to other countries in the region, newborn screening is mandated by law in the Philippines and China.[40] And in the two countries with the largest disease panels routinely screened by MS/MS—Australia and New Zealand—consensus is still lacking on which disorders to include in the panels.[41]

A. Australia

Australia is divided into six states—Western Australia, South Australia, Victoria, New South Wales, Queensland, and Tasmania—and newborn screening services are coordinated from five centralized laboratories.[42] Each state health department determines its own newborn screening policy. Although there are some differences in policy (e.g., there are variations in the card retention period), there are few differences with respect to the disorders screened, with all states including at least twenty-five conditions.[43]

Australia instituted blood spot screening in 1967 and newborn screening policy for the country—as well as for New Zealand (see next section)—is developed by the Joint Subcommittee of the Human Genetics Society of Australasia[44] and the Division of Paediatrics of the Royal Australasian College of Physicians.[45] Their screening programs are based on professional guidelines that are described in a work entitled "Newborn Blood Spot Screening."[46] These guidelines recommend voluntary participation, adequate

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[32] Ibid., p. 503. These countries are Australia, Bangladesh, China, Japan, South Korea, Malaysia, New Zealand, Palau (contracted with the Philippines to begin screening panel), Philippines, Taiwan, and Thailand.
[33] Ibid. These countries are Australia, China, Japan, South Korea, New Zealand, Palau (contracted with the Philippines to being screening panel), Philippines, Taiwan, and Thailand.
[34] Ibid. These countries are Australia, Japan, South Korea, New Zealand, Palau (contracted with the Philippines to begin same screening panel), Philippines, and Taiwan.
[35] Ibid. Palau has contracted with the Philippines to screen for this disorder.
[36] Ibid.
[37] Ibid.
[38] Ibid.
[39] Ibid.
[40] Ibid., p. 502.
[41] Ibid.
[42] Ibid., pp. 495-496. Newborn screening services for Tasmania are coordinated from the laboratory in South Australia.
[43] Sylvia A. Metcalfe, et al., "Australia: Public Health Genomics," *Public Health Genomics* 12 (2009): 121-128; p. 126.
[44] See the Society's website: http://www.hgsa.com.au/ (accessed February 3, 2009).
[45] See the College's website: http://www.racp.edu.au/ (accessed February 3, 2009).
[46] The guidelines, which are currently under review, are available at: http://www.hgsa.com.au/images/UserFiles/Attachments/NEWBORNBLOODSPOTSCREENING.pdf (accessed February 3, 2009).

written information for parents, and a policy for sample card retention, storage, and use. The policy statement *highly recommends* screening for PKU, CH, and CF (which can be diagnosed early and treated, leading to demonstrated benefit to affected newborns), while it simply *recommends* the screening for some other disorders (e.g., BD, CAH, GAL, and the hemoglobinopathies) because there are likely benefits from early detection. Several disorders are *not recommended*, either because tests are unavailable, the benefits from early diagnosis are uncertain, or the test is unsuitable. These disorders include ADA deficiency, duchenne muscular dystrophy (DMD), familial hypercholesterolemia II, G6PD, hemochromatosis, lysosomal storage disorders, neuroblastoma, and TOXO.

B. New Zealand

In 1966, New Zealand became one of the first countries in the world to initiate a program for newborn screening for metabolic disorders. Its program is coordinated by the National Screening Unit, a separate unit of the Ministry of Health that provides program oversight of funding, monitoring, and strategic direction. Although parents are permitted to opt-out of screening services, the program boasts roughly ninety-nine percent participation. The current program has expanded recently in December 2006 to include twenty-eight disorders: BD, CAH, CF, GAL, CH, MSUD, PKU, ASA, CIT, GA-I, HCY, HMG, IVA, BKT, 3-MCC, MUT, MCD, PA, TYR-I, CACT, CUD, CPT-I, CPT-II, LCHAD, TFP, MAD, MCAD, and VLCAD.[47]

C. Republic of the Philippines

Newborn screening in the Republic of the Philippines has developed relatively recently, beginning with a 1996 pilot project to map and quantify the incidence of CH, CAH, GAL, PKU, and HCY.[48] After the program was evaluated for cost-effectiveness and policy changes, newborn screening became a national, comprehensive policy, with the promulgation of the "Newborn Screening Act of 2004,"[49] and today targets the following disorders: PKU, CH, CAH, GAL, and G6PD.[50]

The Act mandates the offering of newborn screening services (Article 1, Section 3) and makes clear an "obligation to inform" (Article 3, Section 5) parents of the availability, nature, and benefits of newborn screening. The parents may refuse screening for religious reasons (Article 3, Section 7), but this refusal must be stated in writing, and the risks involved must be explained. Finally, an Advisory Committee on Newborn Screening was created (Article 4, Section 11) to annually review the program, as well as recommend new conditions for inclusion. Newborn screening services are not free, although subsidies are provided based on the financial situation of the parents. Current challenges include

[47] A breakdown of these disorders can be found at http://www.nsu.govt.nz/Current-NSU-Programmes/914.asp (accessed February 3, 2009).
[48] Padilla and Therrell, p. 501
[49] The Act is available at http://www.ops.gov.ph/records/ra_no9288.htm (accessed February 3, 2009).
[50] Padilla and Therrell, p. 503.

financing issues and a high percentage of home births (around seventy-five percent), which leaves coverage for screening at sixteen percent.[51]

III. Europe

One of the world's first national newborn screening programs for PKU was introduced in Ireland in February 1966.[52] Since that time, newborn screening has been recognized as an important component of public health in Europe,[53] although the expansion of disease panels beyond PKU and CH did not occur until fairly recently. Screening for these two disorders is a requirement of all member states of the European Union (with accession prior to May 2004)[54] as well as those countries seeking candidate status—Turkey, for example.[55] By January 2007, several countries—Austria, Belgium, Denmark, Germany, the Netherlands, Poland, Portugal, Spain, Switzerland, and the United Kingdom—were using MS/MS to detect a larger number of disorders.[56] In those countries in which MS/MS is not yet nationwide, the technology has been under review, and some countries are considering its implementation.[57] In the countries that use MS/MS, the panels are quite diverse, possibly reflecting different assessments of risks and benefits, although each program claims to be based on the original screening criteria of Wilson and Jungner.[58] Whereas some countries—for example Austria, Belgium, and Denmark—screen for up to twenty disorders, the panel in Spain includes eleven and Switzerland's

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[51] Ibid., p. 501.
[52] See the website of the National Newborn Screening Programme: http://www.nnsp.ie/master.html (accessed February 3, 2009).
[53] For the purposes of this discussion, Europe encompasses the forty-five member countries of the Council of Europe, as well as Scotland and Wales. These forty-five member countries are Albania, Armenia, Austria, Azerbaijan, Belarus, Belgium, Bosnia-Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Macedonia, Malta, Moldova, Montenegro, Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, Ukraine, and the United Kingdom.
[54] Walter W. Holland, et al., *Policy Brief: Screening in Europe*, European Observatory on Health Systems and Policies. (Geneva: World Health Organization, 2006), p. 21. http://www.euro.who.int/Document/E88698.pdf (accessed February 3, 2009).
[55] Correspondence with Turgay Coskun, Professor of Pediatrics, Hacettepe University Faculty of Medicine, Hacettepe, Ankara, January 18, 2007.
[56] Olaf A. Bodamer, et al., "Expanded newborn screening in Europe 2007," *Journal of Inherited Metabolic Disease* 30 (2007): 439-444.
[57] For example, three out of twenty regions of Italy are screening for an expanded panel of disorders by MS/MS (the mandatory program in Tuscany covers forty-four disorders and the pilot programs in Liguria and Lazio target around thirty disorders). Two other regions—Campania and Veneto—started pilot programs for expanded screening in 2007, and the region of Emilia Romagna will begin a regional program in the next year. (Correspondence with Antonella Olivieri, Department of Cell Biology and Neuroscience, Istituto Superiore di Sanità, November 16, 2008). For a discussion of the most expansive program in the country, see Giancarlo la Marca, et al., "Progress in expanded newborn screening for metabolic conditions by LC-MS/MS in Tuscany: Update on methods to reduce false tests," *Journal of Inherited Metabolic Disease* Short Report #127 online (2008). http://www.springerlink.com/content/c148110814371300/fulltext.pdf (accessed November 18, 2008).
[58] Bodamer, et al., p. 442.

panel includes six. Overall, there is little consensus either on which disorders should be included[59] or on how to handle the incidental detection of other conditions.[60]

A. Germany

The Federal Republic of Germany is comprised of sixteen states and the coordination of screening services takes place in thirteen laboratories. The recent development of newborn screening in Germany provides an interesting comparison with other countries. Germany's program expanded in 2000 when it began to use MS/MS. Ten disorders were initially recommended by the Interdisciplinary Screening Commission of the German Society of Pediatrics in 2002, as well as six others for further evaluation.[61] These original ten disorders were eventually approved in late 2004 by the Federal Ministry for Health and Social Security, along with CH, CAH, BD, and GAL.[62] A number of disorders were found to require further evaluation and were not included to the panel; some of these were regarded as non-diseases or as biochemical abnormalities with doubtful pathological meaning.[63] For example, 3-MCC was excluded from the panel because only a small proportion of affected children developed a life-threatening hypoglycemia.[64]

The current screening panel includes the following fifteen disorders: PKU, CH, CAH, GAL, BD, MCAD, MSUD, MCAD, LCHAD, VLCAD, CPT-Ia, CPT II/CACT, IVA, and GA-I.[65] In addition to this screening panel, there are pilot programs for CF and G6PD.[66] One of the German states, Hessen, has officially added disorders beyond these recommended conditions, producing a panel that more closely resembles the core panel recommended by the ACMG.[67]

The German program includes the following notable features: First, the screening program is not mandatory, but recommended.[68] Second, written consent is required by at least one parent.[69] Third, any incidental findings—i.e., of disorders that are necessarily

[59] Rodney J. Pollitt, "Introducing new screens: Why are we all doing different things?" *Journal of Inherited Metabolic Disease* 30 (2007): 423-429; p. 426.
[60] Ibid., p. 425.
[61] Rodney J. Pollitt, "International perspectives on newborn screening," *Journal of Inherited Metabolic Disease* 29 (2006): 390-396; p. 392. Recommended disorders included PKU (and HPA), MSUD, IVA, GA-I, CPT-I, CPT-II, CACT, VLCAD, LCHAD, and MCAD. Disorders recommended for further evaluation included TYR-I, ASA, PA, MUT, Cbl deficiencies, and 3-MCC.
[62] Ibid.
[63] Bodamer, et al., p. 442.
[64] Pollitt, "Introducing new screens," p. 427.
[65] Loeber, p. 432; Bodamer, et al., p. 441.
[66] Loeber, p. 432.
[67] Correspondence with Martin Lindner, December 2, 2008.
[68] The German guidelines "Bekanntmachung des Bundesministerium für Gesundheit und Soziale Sicherung" (March 2005) are available at http://www.screening-dgns.de/screening-2a.htm (accessed February 3, 2009).
[69] The Heidelberg newborn screening program, for example, provides a pamphlet entitled, "Parent information for Heidelberg newborn infant screening," accessible at: http://www.klinikum.uni-heidelberg.de/fileadmin/kinderklinik/Abteilung_I/elterninfo_englisch.pdf (accessed February 3, 2009).

detected while trying to detect the primary targets—are to be discarded and not shared with the infant's physician or parents.[70]

B. The Netherlands

There is a national program for newborn screening in the Netherlands in which participation is voluntary with informed parental consent.[71] This program originally targeted three conditions—PKU, CH, and CAH.

Newborn screening policy is based on recommendations of the Health Council of the Netherlands to the Minister of Health who decides whether to include or exclude a condition.[72] On August 12, 2003, the Health Council of the Netherlands was asked by the State Secretary of Health, Welfare and Sport to report on the current state of knowledge of newborn screening, especially concerning whether the criteria for screening were still adequate in light of new developments in technology and whether new disorders should be considered for program expansion. On August 22, 2005, the Health Council responded with a report entitled, "Newborn Screening," which reaffirmed the original criteria for screening[73] and recommended the addition of fifteen disorders.

A significant feature of this report is its insistence that screening should only be performed when there is a tangible health benefit to the newborn.[74] More than thirty disorders in total were considered based on international literature that suggested their merit for inclusion. The Committee assigned disorders to the following three categories: (1) disorders that can prevent considerable irreparable damage (should be included); (2) disorders for which this applies to a lesser degree or for which the evidence is

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[70] Pollitt, "Introducing new screens," p. 426. According to Pollitt, other countries in Europe approach the question of incidental findings differently: "The ACMG report included almost all possible incidental findings in its definition of a secondary target. In the Danish pilot project, full use was made of all available MS/MS data, resulting in the diagnosis of three babies with diseases not formally covered in the project. In the Netherlands, incidental data are retained for possible use should clinical problems develop. In Switzerland, only phenylalanine and octanoylcarnitine are allowed to be seen during routine screening, with the ability to call up tyrosine, hexanoylcarnitine and decenoylcarnitine in the case of a possible positive result. Other raw data are stored separately but can be viewed for a single baby in response to a formal request. In the UK, MS/MS screening is to be limited to selective-reaction monitoring for octanoylcarnitine (for MCAD deficiency) and phenylalanine only, thus greatly limiting the possibility of incidental diagnoses" (Ibid.).

[71] Health Council of the Netherlands. Neonatal Screening. (The Hague: Health Council of the Netherlands, 2005); http://www.gr.nl/pdf.php?ID=1258&p=1 (accessed February 3, 2009).

[72] Correspondence with J. Gerard Loeber, December 4, 2008.

[73] The criteria for newborn screening in the Netherlands have been developed from two important Health Council advisory reports: "Heredity: Science and Society" (1989) and "Genetic Screening" (1994). The 1989 report emphasized prevention, reliability, and informed consent, while the 1994 report stressed the importance of follow-up testing facilities, careful consideration of the burdens placed on the patient, and the potential psychological and social harms and benefits to all participants—the patient, the family, and community groups.

[74] On page 28, the report states: "The interests of family members, healthcare workers, and society as a whole are of secondary importance….The potential health gain must be substantial and clear, and not merely statistically significant or else lacking in factual support."

inconclusive (may be included); and (3) disorders for which newborn screening does not prevent damage to health (should not be included).[75]

The recommendations of the Health Council report formed the basis for an expanded panel of conditions to be screened in 2007.[76] The Minister of Health decided to add the following disorders in addition to PKU, CH, and CAH: BD, GA-I, HMG, MCD, HCY, IVA, LCHAD, MSUD, MCAD, 3-MCC, TYR-I, VLCAD, and SCD.[77] A pilot program additionally screens for CF with the aim of including it in the nationwide program by 2010.[78]

C. United Kingdom

The British newborn screening program is publicly funded and voluntary (requiring informed parental consent), and disorders are included in the program only after extensive review. Screening is overseen by the National Screening Committee (NSC), which was established in 1996 to advise the Ministers and the National Health Service (in all four U.K. countries) about screening policy and implementation.[79] In this role, the NSC evaluates whether a condition should be added based on research evidence, pilot programs, economic evaluation, as well as according to internationally recognized criteria.[80] The NSC's criteria for including a disorder are as follows: the condition should be an important health problem; the epidemiology and natural history of the condition should be adequately understood; effective treatment or intervention should be in place; and high-quality Randomized Controlled Trials must demonstrate the program's effectiveness in reducing mortality or morbidity. Standards to govern the newborn screening program were developed originally in April of 2005 and were updated in August of 2008. The recent document, entitled "Standards and Guidelines for Newborn Blood Spot Screening," aims to improve the quality of the blood spot sample and the timeliness of repeated screening.[81]

Additionally, the Newborn Screening Programme Centre was created in 2002 to provide uniform quality standards in each of the four countries, thus ensuring that every newborn has access to the same services regardless of place of birth. Currently three disorders are

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[75] *Neonatal Screening*, pp. 13-16. The Committee recommended the following disorders from the first category: BD, GAL, GA-I, HMG, MCD, HCY, IVA, LCHAD, MSUD, MCAD, 3-MCC, SCD, TYR-I, and VLCAD. Of the disorders in the second category, the Committee only recommended screening for CF (subject to a provision for better specificity). The Committee did not recommend screening for any third-catetgory disorder.

[76] Correspondence with J. Gerard Loeber, December 4, 2008.

[77] Ibid.

[78] Ibid. There is also discussion for including Pompe disease as well as other lysosomal storage diseases.

[79] These four countries are Britain, Northern Ireland, Scotland, and Wales.

[80] See the UK National Screening Committee's "Criteria for Appraising the Viability, Effectiveness and Appropriateness of a Screening Programme," (March 24, 2003), available at http://www.nsc.nhs.uk/uk_nsc/uk_nsc_ind.htm (accessed February 3, 2009).

[81] Available online at http://www.newbornbloodspot.screening.nhs.uk/download/UKNSPCstandards_guidelines_Aug2008.pdf (accessed February 3, 2009).

routinely screening in all four U.K. countries—PKU, CH, and CF.[82] A separate program targets SCD,[83] however at this time this disorder is screened population-wide only in England. Scotland plans to implement screening for SCD by March 2011.[84] Currently, a pilot program by MS/MS exists for MCAD that will be universal in England by March 2009, and Scotland will introduce screening for this disorder by March 2011.[85] No other disorders have been approved for screening by MS/MS.[86]

Parents are given a national pre-screening informational leaflet (usually in the third trimester),[87] and their consent is required for screening. At least 24 hours before screening, midwives are to discuss the newborn screening program with parents, specifically concerning the following: the conditions screened; how the sample is taken; why a second sample sometimes is necessary; when to expect testing results; the screening of sickle-cell disorders and CF; accuracy; and any questions that the parents might have. It is possible to decline testing either for a specific condition or for the entire program. In such cases, further information is offered to parents, including contact numbers should the parents change their minds. Blood spots are stored for a minimum of five years for quality management, and the cards are separated from personal information.

IV. The Middle East and Northern Africa

The region of the Middle East and Northern Africa (MENA) consists of twenty-one countries,[88] five of which have national programs for newborn screening,[89] while eight

[82] Screening for CF should be routine in Northern Ireland by April 2009. See the NSC's policy positions and estimated timeframe for future consideration of targeted disorders, available at http://www.nsc.nhs.uk/pdfs/policy-position-chart.pdf (accessed February 3, 2009). The website for the CF program is available at http://www.newbornbloodspot.screening.nhs.uk/cf/index.htm (accessed February 3, 2009).

[83] See the website for the SCD program, available at http://www.kcl-phs.org.uk/haemscreening/ (accessed February 3, 2009).

[84] Correspondence with Rodney Pollitt, December 5, 2008.

[85] Ibid.

[86] Pollitt, "Introducing new screens," p. 425. See also Bodamer, et al., p. 443. ("Organizational differences in the screening process can be part of the decision concerning inclusion of certain disorders: in the UK one argument against screening, for example, for the most common organic acidurias, methylmalonic aciduria and propionic aciduria, is that there is probably no direct benefit to the patient because first symptoms appear before the screening sample is taken or before the result will be available.")

[87] This leaflet is available at http://www.newbornbloodspot.screening.nhs.uk/resources/delivery.htm#parents (accessed February 3, 2009).

[88] For the purposes of this discussion, these countries are Algeria, Bahrain, Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, UAE, and Yemen.

[89] Amal A. Saadallah and Mohamed S. Rashed, "Newborn screening: Experiences in the Middle East and North Africa," *Journal of Inherited Metabolic Disease* 30 (2007): 482-489. These countries are Egypt, Qatar, Saudi Arabia, and the United Arab Emirates (Note: this article does not include the national program in Israel).

have limited programs and pilot studies.[90] Because the population is characterized by high rates of consanguinity and first-cousin marriages,[91] genetic disorders are relatively common. Overall, newborn screening in this region is developing slowly and faces not only infrastructural challenges, but also political, ethical, and logistical difficulties.[92]

Population-wide screening occurs only in Egypt, Israel, Qatar, Saudi Arabia, and the United Arab Emirates. Screening in Egypt began in 2000, targeting only CH. In the United Arab Emirates, screening began for PKU in 1995 and expanded to include CH in 1998 and SCD in 2002; there is also pilot testing for CAH.[93] Tandem mass spectrometry was first performed by pilot study in Saudi Arabia from 1995 to 1998,[94] and selective screening by MS/MS has taken place in Oman and Lebanon.[95] Population-wide screening by MS/MS has been introduced only in Israel, Qatar, and Saudi Arabia.

A. Israel

Newborn screening in Israel is a national policy, conducted by the Department of Community Genetics, Ministry of Health, at the Sheba Medical Center.[96] Parents have an opt-out option. Initially, PKU and CH were the two disorders routinely screened, and, as of May 2008, Israel screens for an additional eight disorders by MS/MS: CAH, MSUD, HCY, TYR-I, GA-I, MMA, PA, and MCAD.[97] A pilot program is currently being conducted by the Metabolic Unit and the Ministry of Health to screen for an additional fifteen disorders by MS/MS.

B. Qatar

Newborn screening is coordinated in the capital city of Doha by the Hamad Medical Corporation (HMC), the largest medical center in the country.[98] In 2003, HMC decided

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[90] Ibid. These countries are Algeria (selective screening); Bahrain (private hospitals screen for hemoglobinopathies, G6PD and CHMS/MS-based selective screening sent to Saudi Arabia); Jordan (limited program for PKU and CH started in April 2006; covers 2 of the 14 governorates); Kuwait (selective screening); Lebanon (some hospital-based newborn and selective screening for PKU, CH, and GAL); Morocco (some hospital-based newborn and selective screening for PKU and CH); Tunisia (selective screening with help from France and collaboration with Algeria and Morocco); and Yemen (selected specimens are sent to Saudi Arabia for analysis).

[91] Ibid., p.482. Rates of consanguinity range from twenty-five to seventy percent.

[92] Ibid., p. 488.

[93] Ibid., p. 487.

[94] Ibid., p.486.

[95] Ibid., p.485. Selective screening by MS/MS in Lebanon targets MMA, MSUD, and PKU; ibid., p. 487. For a discussion of the program in Lebanon, see Issam Khneisser, et al., "International cooperation in the expansion of a newborn screening programme in Lebanon: a possibile model for other programmes," *Journal of Inherited Metablic Disease* Online Report #005 online (2008). http://www.springerlink.com/content/27764t758j713811/fulltext.pdf (accessed January 26, 2009).

[96] Correspondence with Shlomo Almashanu, Department of Community Genetics, Ministry of Health, December 11, 2008.

[97] Ibid., December 14, 2008.

[98] Martin Lindner, et al., "Implementation of extended neonatal screening and a metabolic unit in the State of Qatar: Developing and optimizing strategies in cooperation with the Neonatal Screening Center in Heidelberg," *Journal of Inherited Metabolic Disease* 30 (2007): 522-529.

to introduce screening by MS/MS, although it did not have the laboratory facilities to implement such expansion. As a result, HMC partnered with the University Children's Hospital of Heidelberg, Germany (roughly 6,000 km away from Doha) and, from December 2003 through July 2006, roughly 25,000 newborns were screened.[99] Population-wide newborn screening commenced within six months.[100]

Qatar's guidelines for newborn screening were based on the initial recommendations for the German program, although in total twenty-eight disorders were recommended—substantially more than in Germany.[101] This decision was based on several factors: although disease prevalences for the country were unknown, it was believed that, due to high rates of consanguinity and centuries-long genetic isolation, disorders that are quite rare in Germany might be more common in Qatar.[102] Neonatologists and nurses provided information to mothers verbally and also provided a written brochure prior to blood sampling.[103] The results were striking: a newborn in Qatar is twice as likely to suffer from one of the 28 diseases than a baby born in Germany.[104] This panel of disorders will be maintained; pending the outcome of a retrospective study, sickle cell disease may be added.[105]

C. Saudi Arabia

This country has screened newborns for CH since 1991; as of 2005, Saudi Arabia screens for GAL, BD, CH, and CAH, as well as targeting twelve metabolic conditions by MS/MS.[106] In terms of participation, however, expanded screening is in phase I, meaning that it only covers twenty-five percent of the newborn population.[107]

V. Conclusion

This brief survey summarizes the current state of newborn screening programs beyond the borders of the United States. Based on available data and information, this survey provides a useful perspective on the worldwide policy landscape and on the potential expansion of newborn screening in the coming years. If its findings were to be summarized in one generalization, it would be this: routine newborn screening of newborns is expanding considerably throughout all regions of the world.

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[99] Ibid., pp. 526-27.
[100] Ibid., p. 526.
[101] Ibid., p. 525. The disorders are CH, CAH, PKU, H-PHE, BIOPT-BS, MSUD, HCY, TYR-I, Cit, ASA, MUT (Cbl-disorders), PA, GA-I, IVA, 3-MCC, multiple acyl-coenzyme A dehydrogenation disorders (MAD), isobutyryl-CoA dehydrogenase (IBG), MCAD, VLCAD, LCHAD/mTFP (trifunctional protein), SCAD, carnitine transporter deficiency (CUD), CPT-I, CPT-II, HMG, BKT, GAL, and BD.
[102] Correspondence with Martin Lindner, December 3, 2008.
[103] Lindner, et al., "Implementation of extended neonatal screening," p. 526.
[104] Ibid, p. 527.
[105] Ibid., p. 529.
[106] Saadallah and Rashed, p. 486.
[107] Ibid.

In several of these regions, genetic screening is already a routine part of the care of most newborns. Many countries screen all newborns for PKU and CH, although in some of the more developed countries, the routine screening panels include twenty or more conditions. In other parts of the world, newborn screening is only just getting started. Some countries have initiated population-wide screening only within the last several years. For countries in this category, the rate of participation in screening programs can be low, and external factors—such as births outside the hospital setting or financial issues—may hinder the further development of a nationwide program. Some international efforts are now under way to help developing countries gain the knowledge and skills to implement such a program.[108]

[108] See Masaru Fukushi, "An international training and support programme for the establishment of neonatal screening in developing countries," *Journal of Inherited Metabolic Disease* 30 (2007): 594-595. See also Kishor K. Solanki, "Training programmes for developing countries," *Journal of Inherited Metabolic Disease* 30 (2007): 596-599.

Table 1: ACMG Recommended Panel of 29 Genetic Disorders/Deficiencies					
BIO	Biotinidase	CBL A,B	Methylmalonic acidemia (Vitamin B12 Disorders)	3-MCC	3-Methylcrotonyl-CoA carboxylase
CAH	Congenital adrenal hyperplasia	CIT I	Citrullinemia type I (Argininosuccinate synthetase)	ASA	Argininosuccinate aciduria
CF	Cystic fibrosis	CUD	Carnitine uptake defect (Carnitine transport defect)	BKT	Beta ketothiolase (mitochondrial acetoacetyl-CoA thiolase ; short-chain ketoacyl thiolase; T2)
CH	Congenital hypothyroidism	GA-1	Glutaric acidemia type 1	MCD	Multiple carboxylase (Holocarboxylase synthetase)
GALT	Transferase deficient galactosemia (Classical)	HCY	Homocystinuria (cystathionine beta synthase)	MSUD	Maple syrup urine disease (branched-chain ketoacid dehydrogenase)
HB S/S	Sickle cell anemia	HMG	3-Hydroxy 3 - methylglutaric aciduria (3-Hydroxy 3-methylglutaryl-CoA lyase)	MUT	Methylmalonic Acidemia (methylmalonyl-CoA mutase)
HB S/C	Sickle – C disease	IVA	Isovaleric acidemia (Isovaleryl-CoA dehydrogenase)	PKU	Phenylketonuria/ hyperphenylalaninemia
HB S/A	S-βeta thalassemia	LCHAD	Long-chain L-3-hydroxyacyl-CoA dehydrogenase	PROP	Propionic acidemia (Propionyl-CoA carboxylase)
HEAR	Hearing screening	MCAD	Medium-chain acyl-CoA dehydrogenase	TFP	Trifunctional protein deficiency
VLCAD	Very long-chain acyl-CoA dehydrogenase			TYR-1	Tyrosinemia Type 1

Table 2: Other Disorders			
5-OXO	5-oxoprolinuria (pyroglutamic aciduria)	HHH	Hyperammonemia/ornithinemia/ citrullinemia (Ornithine transporter defect)
CPS	Carbamoylphosphate synthe tase	HIV	Human immunodeficiency virus
EMA	Ethylmalonic encephalopathy	NKH	Nonketotic hyperglycinemia
G6PD	Glucose 6 phosphate dehydrogenase	PRO	Prolinemia
		TOXO	Toxoplasmosis

Table 3: Secondary Conditions			
2M3HBA	2-Methyl-3-hydroxy butyric aciduria	GA-II	Glutaric acidemia Type II
2MBG	2-Methylbutyryl-CoA dehydrogenase	GALE	Galactose epimerase
3MGA	3-Methylglutaconic aciduria	GALK	Galactokinase
ARG	Argininemia (Arginase deficiency)	H-PHE	Benign hyperphenylalaninemia
BIOPT-BS	Defects of biopterin cofactor biosynthesis	IBG	Isobutyryl-CoA dehydrogenase
BIOPT-REG	Defects of biopterin cofactor regeneration	M/SCHAD	Medium/Short chain L-3-hydroxy acyl-CoA dehydrogenase
CACT	Carnitine acylcarnitine translocase	MAL	Malonic acidemia (Malonyl-CoA decarboxylase)
CBL-C,D	Methylmalonic acidemia (Cbl C,D)	MCKAT	Medium-chain ketoacyl-CoA thiolase
CIT-II	Citrullinemia type II	MET	Hypermethioninemia
CPT-Ia	Carnitine palmitoyltransferase I	SCAD	Short-chain acyl-CoA dehydrogenase
CPT-II	Carnitine palmitoyltransferase II	TYR-II	Tyrosinemia type II
De-Red	Dienoyl-CoA reductase	TYR-III	Tyrosinemia type III