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NEWBORN SCREENING

Newborn screening in North America

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Summary Newborn screening in North America dates to the early work of Bob Guthrie in the USA. Screening programmes in both the USA and Canada began in the early 1960s, with documented programmes in both countries as early as 1962. Throughout the 1960s and 1970s, many of the screening tests that later became part of routine screening around the world were developed in US and Canadian laboratories, including tests for phenylketonuria, other inborn errors of metabolism, congenital hypothyroidism, congenital adrenal hyperplasia, and haemoglobinopathies. An automated punching machine developed in the USA facilitated screening expansion by significantly reducing sample preparation time and effort. US and Canadian programmes were leaders in applying computerized data management to newborn screening in the 1980s. In the 1990s, DNA and tandem mass spectrometry testing protocols were developed in the USA and applied to newborn screening. US programmes have continually expanded over time, while most Canadian programmes have not. With impetus from private laboratories and professional and consumer groups, many US programmes now screen for more than 50 conditions and there is increased expansion activity in Canada. NBS research in the USA is focused on improving system efficiency and translating other genetic testing to NBS, particularly where new technologies and treatment therapies exist. Although national newborn screening policies do not exist in either Canada or the USA, there are intense efforts to provide uniform access to screening nationwide in both countries. New partnerships between health professionals, consumers and politicians are benefiting the overall screening systems in both countries.

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Abbreviations

AAP	American Academy of Pediatrics
ACMG	American College of Medical Genetics
APHL	Association of Public Health Laboratory Directors
ASTPHLD	Association of State and Territorial Public Health Laboratory Directors
BIO	biotinidase deficiency

CAH	21-hydroxylase-deficient congenital adrenal hyperplasia
CDC	Centers for Disease Control and Prevention
CF	cystic fibrosis
CH	congenital hypothyroidism
CORN	Council of Regional Networks for Genetic Services
DNA	deoxyribonucleic acid
DBS	dried blood spot
GAL	galactosaemia
HCY	homocystinuria
HIV	human immunodeficiency virus
HRSA	Health Resources and Services Administration
IEM	inborn error of metabolism
LIMS	laboratory information system
LSD	lysosomal storage disease
MS/MS	tandem mass spectrometry
MSUD	maple syrup urine disease
NBS	bloodspot newborn screening
NNSGRC	National Newborn Screening and Genetics Resource Center
NNSIS	National Newborn Screening Information System
PKU	phenylketonuria
PT	proficiency testing
RNA	ribonucleic acid
SCD	sickle cell diseases
S,S-disease	sickle cell anaemia
T_4	thyroxine
TSH	thyrotropin (thyroid-stimulating hormone)
TOXO	toxoplasmosis
TYR	tyrosinaemia

Introduction

Blood spot newborn screening (NBS) in North America dates to the work of Bob Guthrie in Buffalo, New York, USA in the late 1950s (Guthrie 1992; Koch 1997). His first publications and the first true newborn population screening began in the early 1960s (Guthrie 1962; Guthrie and Susi 1963). This report discusses the development and current status of NBS in North America. For purposes of this report, we will define North America as including only the United States of America (USA) and Canada, although Mexico and other Caribbean countries are considered by most to be a part of North America. The Spanish language in the Caribbean and Mexico creates closer ties with other Spanish-speaking countries in South America, and these jurisdictions typically identify themselves collectively as Latin America. Mexico and the Caribbean countries (with the exception of Puerto Rico and the Virgin Islands) take an active part in the Latin American Society for Inborn Errors of Metabolism and Congenital Hypothyroidism and we will leave their details to discussions of Latin America.

Guthrie was the first to reliably demonstrate that blood could be taken from a newborn, absorbed and dried onto standardized filter paper, transported to a testing laboratory and then analysed for biochemical indicators indicative of congenital disorders. His work on testing for phenylketonuria (PKU) in this way marked the beginning of NBS, not only for the USA and North America but for the world. In the ensuing four decades, NBS has become a vital public health programme preventing debilitating health consequences and providing exceptional health benefits to families and society. Throughout North America, it has evolved from a laboratory test for a single disorder, PKU, to a six-part integrated public health system that includes education, screening, follow-up/tracking, confirmatory testing/diagnosis, appropriate disease management, and system evaluation/quality improvement (Therrell 2001). Because neither the USA nor Canada has a national NBS policy, the evolution of NBS in North America has varied markedly between states, provinces and territories, similarly in many ways to the variations from country to country in other parts of the world.

Despite the fact that Guthrie lived only a few miles from the Canadian border, the history and evolution of NBS in the two countries is quite different. Although some of the early screening activities were similar, the evolutionary differences over time have been significant. While all newborns in both countries have access to some form of NBS, the degree of access covers a broad spectrum. All states in the USA have a law that either mandates or allows for screening (or the offering of screening) as a public health responsibility. On the other hand, only one province in Canada has a newborn screening law that mandates screening for two conditions; the other provinces and territories rely on standards of good medical practice to encourage appropriate NBS. In both countries, the extent of government financial and political support for NBS varies across state, provincial and territorial jurisdictions. Some jurisdictions encourage/mandate screening for a few conditions, while others encourage/mandate screening for dozens of conditions. In each country, NBS laboratory services occur in public health laboratories, commercial or not-for-profit laboratories, or

combinations of the two. Follow-up and educational activities also occur in different ways involving public and private service providers. Fee-based private NBS laboratory services exist in both countries, providing screening tests to supplement local screening activities.

The health care systems of the two countries, in which NBS must be sustained, also differ. The US system is a complex multi-payer system that relies on the individual to obtain and pay for medical services. Most employers provide medical insurance as an employee benefit, although benefits vary. Government-subsidized programmes exist for the poor and elderly. The federal government provides funding for certain health care activities to the states, with wide discretion as to their use. In some cases, federal and state funding streams significantly impact NBS (Therrell et al 2007). In Canada, on the other hand, the federal government makes substantial payments for health care services to the individual provinces and territories, with limited guidelines or conditions on the use of funds. All citizens and, with few exceptions, landed immigrants and refugees qualify for government health insurance regardless of medical history, personal income, or standard of living. Government health insurance pays for basic but not all hospital services and most but not all doctors' services. It does not cover out-of-hospital prescription drugs or dental services. Private insurance and clinics also exist. Fifty-five per cent of health care in the USA and 33% in Canada is paid privately (Yeates 2007).

Because NBS policy is left to each state, province or territory, there are uneven numbers of screened conditions, follow-up services and family benefits across both the USA and Canada. Treatment and other follow-up services in both countries occur through programmes that are either government sponsored, private or public-private collaborations. Benefits for children with special health care needs resulting from a condition detected through NBS are included (at least partially) in the government-funded health care programmes in both countries. Some US states have laws requiring insurance coverage of metabolic formulas and foods, but corresponding laws do not currently exist in Canada. Families of children diagnosed with conditions through NBS in both countries are financially challenged in obtaining metabolic foods and formulas. Other medical interventions (drugs, surgeries, etc.) may also create financial challenges for children diagnosed through NBS in both countries.

Both the USA and Canada have rich histories and have played leadership roles in shaping NBS worldwide. The history of NBS in both countries is summarized here as background not only for the current NBS practices in each country, but also to trace the evolution of many of the NBS practices that have shaped newborn screening around the globe.

The United States of America

In 1962, the Erie County (New York) Department of Health, in Dr Guthrie's home county, began offering NBS for PKU, detecting the first case of PKU after screening only 800 newborns (Guthrie 1992). About the same time, the Maternal and Child Health Division of the US Children's Bureau (now the Health Resources and Services Administration (HRSA)) provided support funding for a national trial of Guthrie's PKU procedure. Because urine screening for PKU had been ongoing in some parts of the country, the screening trial included comparisons between blood and urine screening case detection. These data eventually provided evidence that screening a newborn's blood was a more effective screening process for inborn errors of metabolism (IEM).

Notwithstanding the fact that research to learn and validate the Guthrie testing process was occurring during the latter part of 1961, 1962 is considered the beginning of NBS in the USA. In mid-1962, the Massachusetts Department of Health began pilot NBS, and became the first state to mandate screening in early 1963 (Guthrie 1992). Throughout that year, Guthrie trained technicians in testing procedures from 29 different state NBS programmes. Guthrie's active involvement with the Association for Retarded Citizens and other non-physician groups was a major impetus for the public health mandates that occurred during the 1960s. By the end of the decade, 45 states had passed NBS legislation or regulations (see Table 1) (National Research Council 1975). Guthrie became an active international NBS advocate and travelled extensively, encouraging others to begin screening (Koch 1997).

While many US programmes began pilot screening for PKU shortly after Guthrie's reports in 1961, the various state NBS histories are not well documented. The dates in Table 1 refer to documented dates for the official (statutory) mandate that required either universal NBS or the universal offering of NBS. Required screening is often referred to as 'informed dissent' since all newborns must be screened and the only mechanism for not being screened is to actively dissent from it (a process not allowed in a limited number of states). In programmes where the mandate is to offer screening, the process is sometimes called 'informed consent', although in actual practice it differs little

Table 1 Date screening mandated in US newborn screening programmes (screening may have begun before the date listed as mandate)

Jurisdiction	Date of statutory provision for newborn screening	Jurisdiction	Date of statutory provision for newborn screening	Jurisdiction	Date of statutory provision for newborn screening
Alabama	1965[a]	Kentucky	1966[a]	North Dakota	1967[a]
Alaska	1965[a]	Louisiana	1964[a]	Ohio	1965[a]
Arizona	1979[b]	Maine	1965[a]	Oklahoma	1965[a]
Arkansas	1967[a]	Maryland	1965[a]	Oregon	1963[a]
California	1965[a]	Massachusetts	1963[a]	Pennsylvania	1965[a]
Colorado	1965[a]	Michigan	1965[a]	Rhode Island	1965[a]
Connecticut	1965[a]	Minnesota	1965[a]	South Carolina	1965[a]
Delaware	1962[c]	Mississippi	1985[b]	South Dakota	1973[a]
District of Columbia	1980[d]	Missouri	1965[a]	Tennessee	1968[a]
Florida	1965[a]	Montana	1965[a]	Texas	1965[a]
Georgia	1966[a]	Nebraska	1967[a]	Utah	1965[a]
Hawaii	1965[a]	Nevada	1967[a]	Vermont	1962[e]
Idaho	1965[a]	New Hampshire	1965[a]	Virginia	1966[a]
Illinois	1965[a]	New Jersey	1964[a]	Washington	1967[a]
Indiana	1965[a]	New Mexico	1966[a]	West Virginia	1965[a]
Iowa	1965[a]	New York	1964[a]	Wisconsin	1965[a]
Kansas	1965[a]	North Carolina	1983[b]	Wyoming	1983[b]

[a] Reference: National Academy of Sciences (1975), Table 3.1.
[b] Reference: Andrews (1985).
[c] Regulations established under Title 16 Delaware Code Sec. 122 (1) and Sec. 122 (3)(h) and Title 29 Delaware Code Section 7904. A separate screening law does not exist.
[d] Reference: Department of Health and Human Services (1980).
[e] Regulations established under Title 18 Vermont Statues Annotated Sec. 115 and Sec. 102. A separate screening law does not exist. Formal rules first adopted in 1989.

from the dissent process. That is, consent is usually a part of hospital admission forms and most report not being aware of specifically consenting to newborn screening. While most states have legislation specifically identifying the NBS activity(ies), in some cases rules or regulations govern the programme as a part of other statutory health authority. In such cases, the date of the governing rule or regulation establishing universal screening or its offering is indicated.

During the 1960s, much of the NBS research that occurred was centred in Guthrie's laboratory and was concentrated on tests for IEMs (Guthrie 1964; Murphey et al 1972). Automated procedures for preparing blood spots for analysis also evolved during this period through collaborations with St Joseph's Hospital in Los Angeles, California and inventor Robert Phillips (Guthrie 1992). The eventual development of the Phillips Punch Index Machine was a major contributor to expanding NBS in many countries. This machine allowed four small samples to be simultaneously punched from a single blood spot and distributed mechanically into four separate reaction vessels (Houston and Veale 1971). Automating the punching process significantly reduced the time and labour required for multiple sample preparation. It also accentuated the need for improved analytical sensitivity so that smaller samples could be obtained from a single blood spot specimen.

In the 1970s, interest in expanded NBS increased. Dussault developed a sensitive DBS thyroxine (T_4) screening test for congenital hypothyroidism (CH) (Dussault and Laberge 1973). The combination of automated punching and a dried blood spot (DBS) procedure for detecting CH significantly impacted the NBS world. Since CH was known to be of higher incidence than PKU, its detection from the 'PKU specimen' vastly improved the cost-effectiveness of the screening process. During the 1970s, DBS procedures were also developed to screen newborns for haemoglobinopathies (Garrick et al 1973), thyrotropin (TSH) (Dussault et al 1976) and 21-hydroxylase-deficient congenital adrenal hyperplasia (CAH) (Pang et al. 1977) in addition to many other metabolic conditions (Murphey et al 1972; Naylor et al 1977; Naylor and Guthrie 1978; Orfanos et al 1978). The fact that automated punching could simultaneously initiate four

testing processes, with little or no increase in personnel, led many programmes to consider expansion. By the end of the decade, a large number of US NBS programmes had expanded their screening panels to include CH. Some were taking advantage of the quadratic (4 samples) Phillips Punch Index Machine by adding other conditions. Most popular screening additions included galactosaemia (GAL), homocystinuria (HCY), maple syrup urine diseases (MSUD), and sickle cell anaemia (S,S-disease), or more broadly, sickle cell diseases (SCD). Some programmes took double advantage of the punch index machine and added up to 8 screening conditions, including CAH, biotinidase deficiency (BIO) and others.

NBS expanded slowly in most US jurisdictions. Policy makers struggled to decide which disorders should be required in their screening mandates. Primary in their policy dilemmas was whether to screen all or a selected group of newborns who might be at increased risk (World Health Organization 1968), a struggle that continues today (American Academy of Pediatrics 2000; Therrell 2001). In general, state screening policies followed the recommendations of Wilson and Jungner (Wilson and Jungner 1968) concentrating on cost-beneficial outcomes resulting from treatable disorders of relatively high population prevalence. However, decisions in individual states were often influenced by local politics, economics and culture (as in most developing NBS programmes around the world). The single unifying principle was general agreement that NBS was best accomplished within, and with support of, state public health systems, a fact reiterated by the US National Academy of Science in 1975 (National Research Council 1975). While no national NBS policy existed, the US medical and medical/legal system was (and is) such that as more states mandated screening for additional conditions, others followed. That is, screening mandates expanded as screening for new conditions became the 'standard of practice.'

The National Academy of Science's 1975 report also recommended that "a single laboratory—within Centers for Disease Control for instance—should be responsible for sustaining the proficiency of the regional laboratories" (National Research Council 1975). In 1977, the Centers for Disease Control and Prevention (CDC), with financial assistance from its sister agency, HRSA (formerly the Children's Bureau), began a national external proficiency testing (PT) programme as part of a national quality assurance initiative. Initial emphasis was on harmonizing the testing results for CH (both T_4 and TSH), in response to request from the Association for State and Territorial Public Health Laboratory Directors, ASTPHLD (now the Association for Public Health Laboratories, APHL). A formal PT programme was established in 1978. The NBS Quality Assurance Program that began at the CDC in 1978 continues today, reaching over 325 laboratories in 53 countries in 2006 (Therrell and Hannon 2006).

In the early 1980s, advances in computer science led to the use of microcomputers in NBS (Therrell 1982; Wolfson and Wu 1988). The result was increasing use of computerized data management and facilitation of expansion of NBS. Laboratory information management systems (LIMS) emerged and NBS programmes attempted to incorporate case management/follow-up into the LIMS (Kling et al 1988; Meaney 1988). Because commercial LIMS were by definition laboratory-based, they were often inadequate for comprehensive follow-up management, and this led some programmes to develop 'in-house' information systems. Programmes restricted in growth because of data handling issues (i.e. personnel time and expense resulting from manual data manipulation and record keeping) were increasingly able to expand (Mordaunt et al 1988; Therrell and Brown 1988). The three larger population states, Texas and New York (both with over 250 000 births/year at the time) and California (with over 400 000 births/year at the time), were particularly progressive in developing computerized data management for NBS, although all three expanded differently and at different rates. New York, initially a decentralized laboratory screening system, became centralized. Texas, always centralized, began to require all newborns to be screened twice (before hospital discharge and again at 1–2 weeks of age), based on CH data from the Oregon programme (LaFranchi et al 1985) and pilot Texas data (Levine and Therrell 1986). California, responding to pressure to support private-sector screening, developed a multilaboratory public/private partnership in which the state purchased and controlled the equipment/procedures and private laboratories bid for their use. All three states currently continue the systems developed then. California now has seven contract laboratories and the Texas programme tests over 750 000 specimens annually on its 340 000 newborns.

A comprehensive review of screening practice errors in US NBS programmes in the mid-1980s found that most late diagnoses (missed cases) were the result of clerical and not analytical errors (Holtzman et al 1986). In order to improve the quality of screening, HRSA began funding expert assistance to state

programmes in 1987 (Therrell et al 1992a). Information gained from these reviews and an interest in programme harmonization led to published guidance for US NBS systems (Therrell et al 1992b) as an activity of the HRSA-funded Council of Regional Networks for Genetic Services (CORN). Programme reviews based on experience and the published guidance continue today as a responsibility of the National NBS and Genetics Resource Center (NNSGRC) (Therrell and Hannon 2006). In the late 1980s, CORN also developed a voluntary NBS data reporting system to assist with national quality assurance and programme evaluation efforts. Today this effort continues as an Online service of the NNSGRC.

Medical advances in treating S,S-disease with prophylactic penicillin in the early 1980s (Gaston et al 1986) led to increased emphasis on NBS for SCD. The slow response of many programmes in recognizing the importance of early detection and treatment for SCD, and the unequal screening access across the country, led the National Institutes of Health to convene a 1987 consensus conference on newborn screening for SCD. After thoroughly investigating the scientific evidence, the conference jury recommended universal NBS for SCD (National Institutes of Health 1987). HRSA responded by providing start-up and expansion funding for programmes wishing to add SCD screening and over the ensuing three years, a large number of states added SCD to their screening panel (Therrell 1988). Despite these efforts, it was only in 2005 that SCD became a universal mandate in all 51 state programmes.

The late 1980s and early 1990s saw the introduction of DNA (McCabe et al 1987) and tandem mass spectrometry (MS/MS) (Millington et al 1990) technology into US NBS laboratories. Both RNA (Zhang and McCabe 1992) and DNA techniques were used for second-tier SCD testing (Descartes et al 1992; Jinks et al 1989) and DNA was used for second-tier cystic fibrosis (CF) testing (Gregg et al 1993). Use of MS/MS improved screening efficiency by allowing simultaneous screening for multiple numbers of amino acid, organic acid and fatty acid oxidation disorders (Chace et al 1993; Chace and Millington 1994; Rashed et al 1995). In some screening programmes, expansion during the 1990s also included infectious disease testing for such conditions as HIV (Comeau et al 1992) and toxoplasmosis (TOXO) (Hsu et al 1992).

Recognizing that policy issues were creating barriers to NBS expansion and access, HRSA funded the American Academy of Pediatrics (AAP) to convene a NBS Task Force in 1999, "in recognition that pediatricians and other primary care health professionals must take a lead in partnering with public health organizations to examine the many issues that have arisen around the state NBS programmes." The AAP Task Force was asked to review the issues and challenges facing state NBS systems and to make recommendations. Their report was extensive and outlined a national agenda for strengthening US NBS programmes (American Academy of Pediatrics 2000). Responding to Task Force recommendations, HRSA then contracted with the American College of Medical Genetics (ACMG) to develop a model decision-matrix for NBS programme expansion and to recommend a uniform screening panel for US NBS programmes. As a result, a relative scoring system was developed as one means of evaluating conditions to be included in programme mandates. Eighty-four conditions were evaluated by the ACMG working group, and 29 core conditions and 25 secondary targets (conditions that might be identified incidental to differentiating the core conditions, but lacking the evidence necessary to rank them as a core condition) were recommended as components of a US uniform NBS panel. The ACMG report (American College of Medical Genetics 2006) was forwarded to the US Secretary of Health and Human Services following its acceptance by the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children. No official action has yet been taken by the Secretary, although many NBS programmes have expanded in response to the report's recommendations.

NBS laboratory services were provided in three ways when NBS began—hospital laboratory, private pathology laboratory, or public health laboratory. Lack of profitability and liability issues caused hospital and private sector laboratories to defer to the public health system, and state public health laboratories evolved as the most cost-effective way to provide NBS laboratory testing. Some states with limited numbers of births and medical specialists, particularly in the west and northeast, found it cost-effective to contract with larger states for laboratory and selected clinical follow-up services. In some other states, contracts exist with university medical centre facilities or private pathology laboratories to provide testing services, and in at least two states a state public health laboratory and a medical centre laboratory combine to provide screening tests. Figure 1 illustrates the variation in current NBS laboratory activities in the US There are now four public health laboratories serving as 'regional' laboratories—Oregon, Massachusetts, Iowa and Colorado. The Iowa laboratory was able to absorb specimens from Louisiana during the Hurricane Katrina disaster in 2005 and this service continues today while the infrastructure in Louisiana is rebuilt

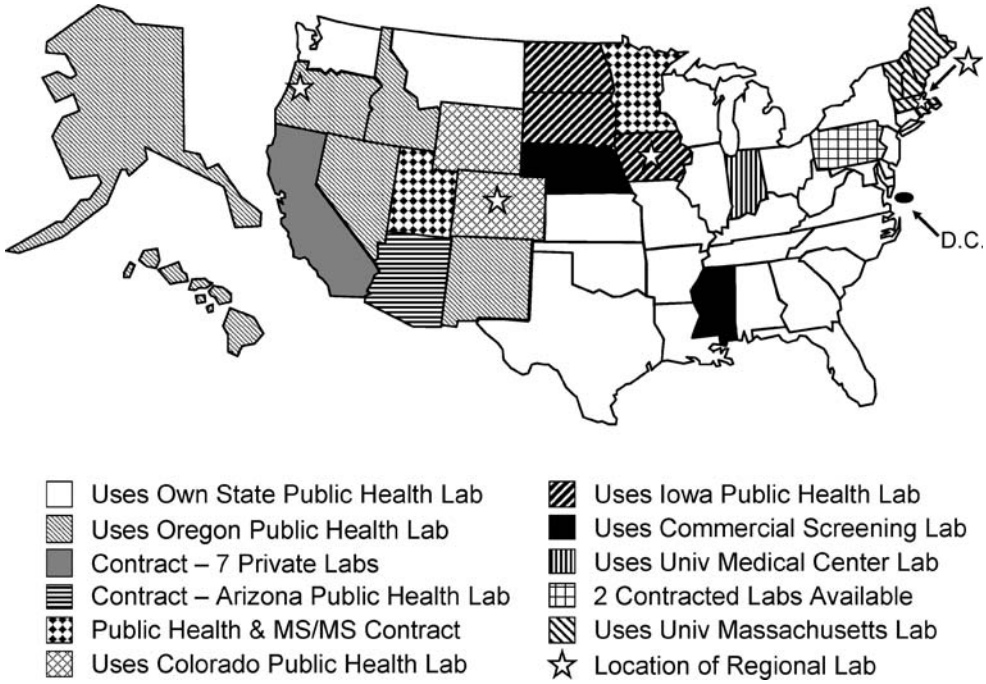

Fig. 1 Various NBS laboratory models in the USA

(Andersson et al 2006). The programmes in Utah and Minnesota both use the public health laboratory for some testing and a medical centre laboratory for MS/MS tests. California contracts with seven commercial laboratories that periodically must compete for the use of state-owned equipment and use testing protocols defined by the state. Nebraska, Mississippi and the District of Columbia each contract with the same commercial NBS laboratory, and this laboratory also provides testing for some hospitals in Pennsylvania, Louisiana, Maryland and the US Department of Defense (some military hospitals). The Montana programme provides optional MS/MS testing through a contract with the Wisconsin public health laboratory. A limited number of private and non-profit laboratories directly market supplementary tests (particularly MS/MS testing) to parents as a supplement to programmes where testing may not be fully comprehensive. In at least one state, parents must be informed of the availability of tests that might not be included in the state required screen.

Canada

Canada has a population of approximately 33.4 million (an increase of about 8 million since screening began) and occupies approximately 9.9 million km^2 (see Fig. 2). There are approximately 340 000 births annually (about the same as the state of Texas in the USA) Its federal parliamentary form of government is replicated in ten provinces, and the sparsely inhabited northern half of the country is divided into three territories of which one, Nunavut, is so large and sparsely populated that services are conveniently subdivided into three subdivisions—east, west and central. As previously noted, health is a provincial/territorial responsibility with costs shared by the federal and provincial governments.

Almost in parallel with the USA, the first NBS programme in Canada was established in 1963 in the province of Prince Edward Island. NBS expanded throughout the 1960s in Canada such that eight more provinces established NBS programmes by 1970 (see Table 2). Initial federal involvement in NBS was limited to funding for pilot studies. All screening was (and is) voluntary, and expansion and growth of programmes was most often due to individual or group initiative from outside of government. Because there was no sector in the Ministry of National Health and Welfare with specific responsibility for genetics, activities related to genetics and NBS became the responsibility of the Medical Research Council.

A 1971 survey of provincial health ministries found that the principal objective of the provincial screening programmes was detection of diseases amenable to treatment and was focused on PKU. The provinces of Manitoba and Quebec reported slightly broader programmes. Manitoba reported screening for other aminoacidopathies, galactosaemia and fructose intolerance, and Quebec reported screening for tyrosinaemia and galactosaemia from blood, and other

Fig. 2 Locations of various Canadian provinces and territories

aminoacidurias and meliturias from urine. Quebec also reported continually revising and updating its technology. The programme in the province of Prince Edward Island, while initially focused on PKU, also expanded its screening to include other aminacidopathies in 1973. Most provinces used centralized public laboratory services as a means of providing technical reliability, accuracy and uniformity. However, in some provinces screening tests were performed in hospitals, including 25% in Ontario and 100% in Newfoundland. Follow-up for positive tests depended on available expertise and was generally regionalized (Haworth et al 1974).

In large population areas such as Ontario, multiple diagnostic/treatment centres existed. Typically, NBS programme coordination was an assigned responsibility of the Maternal and Child Health Service of the Provincial Department of Health, including diagnostic and treatment services and diet subsidies. As an example of Canadian programme development, in Ontario (the province immediately adjacent to Guthrie's US hometown), many of the local hospitals began providing their own PKU screening services, paralleling activities that were occurring in the USA In 1965, The Ontario Minister of Health requested the cooperation of hospitals with maternity/nursery

Table 2 Date newborn screening was initiated in Canadian newborn screening programmes

Jurisdiction	Year newborn screening began	Jurisdiction	Year newborn screening began
Provinces		*Territories*	
Alberta	1967[a,b]	Northwest Territories	1965?[c]
British Columbia	1964[b]	Nunavut	
Manitoba	1965[b]	Eastern	1965?[c]
New Brunswick	1966[b]	Western	1965?[c]
Newfoundland and Labrador	1978[c]	Central	1965?[c]
Nova Scotia	1966[b]	Yukon	1970?[c]
Ontario	1965[b]		
Prince Edward Island	1963[b]		
Quebec	1969[b]		
Saskatchewan	1965[b]		

[a] Reference: Alberta Health and Wellness (2006).
[b] Reference: Haworth et al (1974).
[c] Exact date of beginning of programme is unknown.

services to establish a coordinated provincial NBS programme. Laboratory services were provided by the Ontario Public Health Laboratory in Toronto, or alternatively through local hospital laboratories. The Ontario Public Health Laboratory made Guthrie testing kits available to the hospital laboratories, and a summary of testing results was reported to the Maternal and Child Health Service at 6-month intervals. Financing was through the Provincial Hospital Insurance Program or through the Public Health Laboratory. An Advisory Committee including treatment center directors and a public health laboratory representative provided programme guidance (Hanley et al 1969). The 1973 Advisory Committee report confirmed the program's success noting a 94.5% screening rate from 1966 to 1971 and a positive benefit-to-cost ratio of at least 30:1 (Ontario Ministry of Health 1973).

In Manitoba, the Guthrie test was first instituted in the Provincial Public Health Laboratory in 1964 with a small pilot project begun at the Winnipeg General Hospital. In January 1965, city-wide screening started and a year later the programme was expanded to the rest of the province. Because the Guthrie test only detected PKU, chromatographic methods for detecting other aminoacidopathies were evaluated (Efron et al 1964). A pilot project expanding NBS to other inborn errors of metabolism in Winnipeg began in 1966 and was expanded to the rest of the province for 3 months at the end of 1967. Following a 2-year suspension of the expanded testing, expanded screening (including PKU, detectable aminoacidopathies and galactosaemia) was reintroduced in April of 1969, replacing the Guthrie test. The NBS programme was extended at one point to test mentally retarded females of childbearing age, mentally retarded pregnant women and women who have given birth to mentally retarded children. While a federal grant initially paid for some follow-up and dietary services, these expenses were eventually assumed by the provincial government (Fox et al 1971).

In Quebec, there was also interest in NBS for a broader group of aminoacidopathies, and a study in nine metropolitan hospitals in Montreal between March 1965 and May 1967 showed that partition chromatography of capillary plasma specimens could be used for such screening. This study also pointed to a common problem in establishing efficient NBS protocols—how to implement successful patient recall. One of the significant conclusions of this study was the recognition that population-wide mass screening should not be established unless follow-up services to locate, retest, and follow children with positive initial test results could be provided (Clow et al 1969). The provincial NBS programme for PKU and tyrosinaemia (TYR) evolved in 1969 from a demonstration project organized by the heads of the paediatric departments of four university medical schools (Laval, McGill, Montreal, and Sherbrooke) with concurrence of the Ministry of Health and Social Affairs. In 1972, this programme became the Quebec Network for Genetic Medicine. Unlike the other provinces, which generally limited their follow-up services to provision of the low-phenylalanine diet, the Quebec network was more broadly structured and emphasized ambulatory care for patients. All laboratory screening services were centralized in two laboratories, one for dried blood spots and one for dried urine. For greater efficiency, patient retrieval, confirmatory testing, counselling and treatment were all performed within the network (Scriver et al 1978).

The 1971 survey of Health Ministries confirmed that some provincial governments paid for special dietary products, including facilitation and distribution. The more liberal policies were in Manitoba, British Columbia and Quebec. Case registries existed in most provinces as a means of enumerating and coordinating regional services. British Columbia and Alberta maintained extensive registries for handicapping conditions including inborn errors of metabolism. Only in Quebec was research and development formally included by the Ministry as a part of the screening programme (Haworth et al 1974). The inclusion of research and development in the Quebec programme ultimately resulted in many genetics and NBS advances of international importance including the groundbreaking work on NBS for CH (see below).

Because the Quebec Network of Genetic Medicine was sponsored by the academic community, the central laboratories were not confined to services as a state public health laboratory might be. Additionally, since government funds were involved, the government was represented on the advisory committee and the government received periodic reports of activities, as well as applications for new services and research and development projects. This granting mechanism encouraged activity by members of the advisory committee (Laberge 1980).

The availability of samples at a central laboratory facilitated their use in pilot studies. As a result, in 1971 and early 1972, Dussault (whose laboratory was located nearby) was able to develop a radioimmunoassay for thyroxine (T_4) from the eluate of filter paper blood spots (Dussault and Laberge 1973). A research

pilot funded by the Quebec Network of Genetic Medicine demonstrated the feasibility of adding screening for congenital hypothyroidism to an ongoing screening programme and confirmed the relatively high incidence of CH compared to PKU. In April 1974, NBS for CH was added to the Quebec NBS programme and made available to all newborns in Quebec (Dussasult et al 1975). Expansion of CH screening in the USA and France quickly followed, and the first international meeting on neonatal hypothyroid screening was held in Quebec in 1979 (Burrow and Dussault 1980). This meeting facilitated the relationship between Quebec and Massachusetts CH screeners that led to larger study populations and more comprehensive outcome reporting over relatively short periods (Fisher et al 1979).

The ability of the Quebec Network of Genetic Medicine to do research contributed to other studies of interest to the NBS community. The centralized urine screening laboratory at Sherbrooke provided a convenient means of evaluating urine screening as a way of detecting other inborn errors of metabolism (Lemieux et al 1988). Studies in neuroblastoma screening (Lemieux et al 1989) and screening for Duchenne muscular dystrophy (Lemieux et al 1987) were two other important examples of related research resulting from this network.

During the 1990s, activity in expanding NBS in Canada diminished. Most programmes maintained two-disorder (PKU and CH) screening programmes, and despite the fact that NBS advisory committees were recommending expansion to include screening for other conditions, including CAH and SCD, little expansion occurred. Likewise, as MS/MS technology allowed for significant NBS expansion, only Saskatchewan adopted the technology early. Until 2006, most provinces only screened for PKU and CH.

Methods

In the USA, the federally funded National Newborn Screening and Genetics Resource Center (NNSGRC) serves as a national focal point for NBS information. A cooperative agreement between HRSA and the Department of Pediatrics of the University of Texas Health Science Center at San Antonio, provides direction for the NNSGRC's activities. As part of its responsibilities, the NNSGRC maintains an information website (http://genes-r-us.uthscsa.edu), various information exchange listservs, and a national NBS information database (National NBS Information System (NNSIS)). All US programmes are asked to voluntarily report selected programme information to the NNSIS as a tool for programme evaluation, including descriptive programme details, abbreviated case-specific information (without patient identifiers) and summary laboratory testing data. Currently, all 51 (50 states and the District of Columbia) programmes report to the system, although there are some variations in the timeliness of reporting. The APHL co-sponsors the NNSIS through a Memorandum of Understanding, and its members support the system through data sharing. A large number of reports are available from the system and may be accessed by both programmes and the public.

The NNSGRC maintains a listing of US NBS programme managers. This listing was used as a source of programme contact for data reported in this paper. Historic information was extracted from published government reports and data in the NNSIS. All accumulated descriptive and historic programme information was clarified and validated through e-mail and telephone contact with programme managers.

Because no centralized NBS resource exists in Canada, Canadian NBS programme information was extracted from various published reports and personal contacts. Building on a recent general survey of NBS status in Canada by Hanley (Hanley 2005), a more detailed survey of the current status of NBS was conducted by one of us (J.A.) in collaboration with the US Centers for Disease Control and Prevention (CDC). The survey was modelled after the Hanley survey for consistency, and the questions used were prepared in collaboration with the CDC. Sources likely to have factual knowledge of the requested information were identified in each jurisdiction and asked to participate. Summary information was published on two public websites: the Canadian Organization for Rare Disorders (http://www.cord.ca/index.php/site/resources/newborn_screening) and the NNSGRC (http://genes-r-us.uthscsa.edu/CA_nbsdisorders.pdf). Online display of the screening information produced useful feedback, resulting in clarification of some of the posted information. Further clarification and validation included e-mail and telephone contact with provincial and territorial NBS programme managers.

Results and discussion

The United States of America

Approximately 4 million births occur annually in the USA and essentially all neonates receive some form of NBS. Exact compliance data regarding screening are

not generally available since the data systems of most programmes are not yet integrated in such a manner that birth certificates are linked to screening information. Selected data elements considered to be useful for programme comparison and evaluation, and developed by working groups of NBS professionals, are collected through a voluntary national reporting system. This system, which has evolved over the years from a questionnaire reporting system to a real-time online system, is maintained by the NNSGRC and is available to the general public (http://www2.uthscsa.edu/nnsis). NBS programmes are requested to input confirmed diagnosed cases as they are identified. Laboratory testing data can be input daily, but most choose to report it annually. Two programmes have automated download of laboratory data on a weekly schedule.

Table 3 provides summary data for programmes in the US NBS system. The latest validated census data are given in column 2 to provide a comparative picture of the population distribution. Birth statistics (column 3) are reported to state birth registrars and then to the National Center for Health Statistics. Final data are not usually available for several years. As a result, the birth data reported in Table 3 are from 2004, the latest data available. Since all programme requirements apply only to births within a jurisdiction, the birth data reported are by occurrence (birth location) and not by residence (official location of family).

As a result of the relatively early hospital discharge in the USA, certain analytical procedures may exist in the USA that differ from countries in which screening occurs later. For example, many US programmes use T_4 as the primary screening test for CH in an effort to avoid high recall rates that could result from TSH testing on specimens collected during the first 24 hours as a consequence of a biological TSH surge. Early hospital discharge is still an issue despite the fact that hospitals are required to honour a mother's request to stay in the hospital for up to 48 hours after birth. All US programmes require a specimen to be recollected in instances where the programme has determined that an invalid test may result. In most programmes, this means that a specific age at time of collection has been defined below which biological immaturity may invalidate one or more tests. Column 4 shows how programmes vary in this regard. While most programmes define 24 hours of age as the cut-off for obtaining a properly timed specimen, a few still use 48 hours for this limit and one uses a limit of 12 hours. Nine programmes mandate that a repeat newborn screen be collected on all newborns, usually at 1–2 weeks of age, and several other programmes strongly recommend it such that over 80% of newborns receive two screens. Nationally, approximately 25% of all newborns receive a second newborn screen. The published data on the yield of cases from second screening is limited and favours detection of endocrine conditions.

Most US NBS programmes derive part or all of their funding from fees. The amounts of the fees vary widely as shown in column 5 of the table. A few programmes continue to obtain full support from tax revenues. Health care financing in the USA includes various payer systems including private insurance and a type of government insurance for the poor (Medicaid). In addition to the varying support from insurance and Medicaid, a federal programme for children with special health care needs also provides funds to states that can be used for NBS. Two recent reviews and a federal report for Congress outline the US NBS financing issues in detail (US General Accounting Office 2003; Johnson et al 2006; Therrell et al 2007). The fees listed in the table generally reflect some but not all of the costs of NBS, and a full financing picture is not possible without knowing the extent of other available funds that might be integrated into the NBS funding stream and the extent of services provided. Fees are therefore not directly proportional to the number of conditions included in the screening mandate nor to the services offered. Their tabulation here shows only the wide variation across the country.

The remainder of Table 3 illustrates the variation between programmes relative to the conditions screened. Four conditions, PKU, CH, GAL and SCD are universally included in all programmes, although the screening procedures and testing algorithms differ from programme to programme. Essentially all programmes have MS/MS testing available and the few that do not are in the process of approving expansion. Because MS/MS testing allows for comprehensive or targeted analyte detection, the conditions screened for can be selectively limited. Some programmes reported having limited screening mandates either because they selected the MS/MS detectable conditions (usually because of unavailable curative treatment), or because they did not wish to imply that screening would detect all cases of a particular condition. In the latter case, a full scan MS/MS protocol may exist and the cases detected and reported may in fact be similar to those in programmes listing these conditions as mandates. In Table 3, programmes have been grouped into three basic categories for each condition or group of conditions: (1) those mandating screening for all detectable conditions; (2) those whose mandate restricts the conditions screened; and (3)

Table 3 Program demographics and screened conditions in US newborn screening programmes (conditions marked as mandated may not yet be available in limited instances—implementation status available: http://genes-r-us.uthscsa.edu.)

Jurisdiction	Program demographics				Conditions included in current newborn screening mandate														
	Population (1 April 2000 – Census Data)[a]	Births (2004–latest official counts available)[b]	Repeat specimen required – all or age at time of collection	Current screening fee	Congenital hypothyroidism	Phenylketonuria	Galactosaemia	Sickle cell diseases	Congenital adrenal hyperplasia	Biotinidase deficiency	Cystic fibrosis	G6PD deficiency	MS/MS detectable			Toxoplasmosis	HIV	Other–Krabbe disease
													Other amino acid disorders	Fatty acid oxidation disorders	Organic acid disorders			
Alabama	4 447 100	58 383	<24h	$139.33	•	•	•	•	•	•			†	†	†			
Alaska	626 932	10 268	<48h	$55.00	•	•	•	•	•	•	•		†	†	•			
Arizona	5 130 632	93 876	All	$30.00[c]	•	•	•	•	•	•	•		†	†	†			
Arkansas	2 673 400	37 840	<24h	$14.83	•	•	•	•										
California	33 871 648	545 758	<12h	$78.00	•	•	•	•	•	•	•		†	†	•			
Colorado	4 301 261	68 797	All	$59.00	•	•	•	•	•	•	•		†	•	•			
Connecticut	3 405 565	42 545	<24h	$28.00	•	•	•	•	•	•	†		†	†	†		‡	
Delaware	783 600	12 080	All	$78.00	•	•	•	•	•	•	•		†	†	†			
District of Columbia	572 059	14 794	<24h	No Fee	•	•	•	•	•	•	•	•	†	•	•			
Florida	15 982 378	218 218	<24h	$15.00	•	•	•	•	•	•	•		†	†	†			
Georgia	8 186 453	140 117	<24h	$40.00	•	•	•	•	•	•	•		†	†	†			
Hawaii	1 211 537	18 297	<24h	$47.00	•	•	•	•	•	•			†	†	•			
Idaho	1 293 953	21 949	<48h	$25.00	•	•	•	•	•	•			†	†	•			
Illinois	12 419 293	177 417	<24h	$47.00	•	•	•	•	•	•			†	†	†		‡	
Indiana	6 080 485	87 942	<48h	$74.50	•	•	•	•	•	•			•	•	†			
Iowa	2 926 324	38 527	<24h	$77.00	•	•	•	•	•	•	•		•	†	•			
Kansas	2 688 418	40 449	<24h	No Fee	•	•	•	•	•	•	•		†	†	†			
Kentucky	4 041 769	54 085	<24h	$53.50	•	•	•	•	•	•	•		†	†	†			
Louisiana	4 468 976	65 572	<48h	$30.00	•	•	•	•	•	•			†	†	†			
Maine	1 274 923	13 733	<24h	$52.00	•	•	•	•	•	•			†	†	†			
Maryland	5 296 486	70 538	<24h	$42.00	•	•	•	•	•	•	•		†	†	†			
Massachusetts	6 349 097	79 405	<24h	$54.75	•	•	•	•	•	•	†		†	†	†	•		
Michigan	9 938 444	128 585	<24h	$56.83	•	•	•	•	•	•	•		†	•	•			
Minnesota	4 919 479	70 618	<24h	$61.00	•	•	•	•	•	•	•		•	•	•			

Mississippi	2 844 658	41 562	<24h	$70.00	•	•	•	•	•	•	•		†	†	†					
Missouri	5 595 211	78 591	<24h	$50.00	•	•	•	•	•	•	•		†	†	†					
Montana	902 195	11 526	<24h	$42.70	•	•	•	•	†	†	†		†	†	†					
Nebraska	1 711 263	26 446	<24h	$35.75	•	•	•	•	•	•	•		†	†	†					
Nevada	1 998 257	34 780	All	$60.00	•	•	•	•	•	•			†	†	•					
New Hampshire	1 235 786	14 198	<24h	$40.00	•	•	•	•	•	•	•		†	†		•				
New Jersey	8 414 350	112 232	<24h	$71.00	•	•	•	•	•	•	•		†	†	†					
New Mexico	1 819 046	27 798	All	$32.00	•	•	•	•	•	•	•		†	†	†					
New York	18 976 457	251 562	<24h	No Fee	•	•	•	•	•	•	•		†	•	•			•	•	
North Carolina	8 049 313	120 588	<24h	$14.00	•	•	•	•	•	•			†	†	†					
North Dakota	642 200	9 408	<24h	$42.50	•	•	•	•	•	•	•		•	†	•					
Ohio	11 353 140	149 481	<24h	$55.16	•	•	•	•	•	•	•		†	†	†					
Oklahoma	3 450 654	50 223	<24h	$98.70	•	•	•	•	•		•		†	†						
Oregon	3 421 399	46 454	All	$54.00	•	•	•	•	•	•	•		†	†	†					
Pennsylvania	12 281 054	144 498	<24h	No Fee	•	•	•	•	•	†	†	†	†	†	†					
Rhode Island	1 048 319	13 582	<24h	$110.00	•	•	•	•	•	•	•		†	†	†					
South Carolina	4 012 012	54 232	<24h	$42.00	•	•	•	•	•	•	•		†	†	†					
South Dakota	754 844	11 803	<24h	$99.99	•	•	•	•	•	•	†		†	†	†					
Tennessee	5 689 283	84 855	<24h	$47.50	•	•	•	•	•	•			†	•	†					
Texas	20 851 820	387 337	All	$29.50[d]	•	•	•	•	•	•	•		†	†	†					
Utah	2 233 169	51 835	All	$65.00	•	•	•	•	•	•			•	†	†					
Vermont	608 827	6 262	<24h	$33.30	•	•	•	•	•	•			†	†	†					
Virginia	7 078 515	101 826	<24h	$53.00	•	•	•	•	•	•	•		†	†	†					
Washington	5 894 121	81 390	<24h	$67.50	•	•	•	•	•	•	•		†	†						
West Virginia	1 808 344	21 305	<48h	No Fee	•	•	•	•	•	•	•		†	†	†					
Wisconsin	5 363 675	69 014	<24h	$69.50	•	•	•	•	•	•	•		†	†	•					
Wyoming	493 782	6 326	All	$70.00	•	•	•	•	•	•	•		†	†	†					
Totals	281 421 906	4 118 907			51	51	51	51	48	47	34	1				2		1	1	

• Indicates full population screening mandate—for MS/MS indicates mandate for all detectable conditions.
† Indicates available but not full population mandate—for MS/MS indicates that all detectable conditions are either not mandated or not included in the analytical interpretation.
‡ Law requires newborn to be screened if mother not screened during pregnancy. Not considered a part of the newborn screening programme.
[a] Reference: http://www.census.gov/population/cen2000/tab02.xls; accessed May 20, 2007.
[b] Reference: National Center for Health Statistics data available http:www2.uthscsa.edu/nnsis; accessed May 20, 2007.
[c] Second and successive screens at $40.00 each.
[d] Second and successive screens at $29.50 each.

those not screening for any condition. These classifications provide an indication as to whether or not the programme is all-inclusive, restrictive, or only beginning. A more complete description of the conditions screened is available online at http://genes-r-us.uthscsa.edu. For the non-MS/MS conditions, the delineations also reflect the extent of a programme's screening policies—comprehensive, restrictive, developing.

Canada

NBS in Canada is a complex system of provincial and territorial programmes varying in the numbers of conditions screened, available health technology, methods of organization and financing, and programme-related services. Canada's ten provinces and three territories are responsible for NBS as part of their constitutional authority for health, with the exception of federal jurisdiction for the health of aboriginals and the military. There is a distinct absence of nationwide reporting of NBS information in Canada, and there is only limited public reporting of NBS information at the provincial and territorial levels. There has been no participation in NBS by the federal government in recent years, and there is no national strategy for NBS and no national standards or guidelines for system performance exist.

The material differences in NBS among the 13 provinces and territories of Canada are greater than variations across the USA (see Table 4). The number of conditions included in routine screening ranges from a high of 38 in Saskatchewan to a low of 5 in British Columbia and the Yukon, and 6 in Manitoba, Nunavut (Kivilliq), and Newfoundland and Labrador. Four provinces, one territory and two-thirds of another territory screen for more than 15 conditions. Only one province includes screening for SCD, and one province includes CF screening, although two others are in the planning phase for CF screening. Six of the eight provincial NBS laboratories have MS/MS capability.

Unlike most US states, only one province, Saskatchewan, has a law mandating NBS and it applies to two conditions: PKU and CH. For other conditions and in the other jurisdictions, NBS relies on standards of practice to drive availability. No professional health organization in Canada has taken a public position on NBS in recent years, although the Garrod Association, an organization of metabolic professionals, is considering a position calling for national NBS standards (T. Rupar, personal communication, 2007).

There are currently ten NBS laboratories in Canada with most located in paediatric academic health centres. Nine of these laboratories provide DBS testing and one in Quebec specializes in testing urine specimens. The three Maritime Provinces of New Brunswick, Nova Scotia and Prince Edward Island utilize a regional NBS laboratory in Halifax, with New Brunswick the latest to join the regional effort in April 2007. In the case of New Brunswick, the biochemical lab in St. John continues to receive and analyze bloodsports for PKU and CH while a single bloodspot is sent to the regional facility in Halifax for MS/MS analysis. The Yukon Territory utilizes NBS laboratory services in British Columbia and the Northwest Territories utilizes the laboratory in Alberta. The vast size and population scarcity in Nunavut Territory provide distinct NBS challenges and, as a result, the westerly Kitikmeot region uses the Alberta laboratory, the central Kivalliq region uses the Manitoba laboratory, and the easterly Baffin region uses the Quebec laboratory. This means that in the Kitikmeot region, screening includes 19 conditions, in the Kivalliq region it includes 6 conditions, and in the Baffin region it includes 25 conditions.

Newborn screening in Quebec is somewhat unique, with two screening laboratories in operation since 1971. The provincial programme is a DBS programme for PKU and CH using a hospital-based NBS laboratory in Quebec City. There is also a urine screening programme that screens for more than 25 abnormalities in urine amino and organic acids (Auray-Blais et al 2003). Parents of newborns are asked to collect a urine specimen on day 21 of life and mail the specimen to the Sherbrooke screening laboratory. Compliance is approximately 90% and, if a retest is requested, retest compliance is approximately 99%. Of the 25 conditions screened, 12 are included in the core conditions listed by the ACMG (American College of Medical Genetics 2006).

Between March 2006 and May 2007, NBS activity in Canada rose significantly. In March 2006, approximately 71% of Canadian newborns were being offered screening for six or fewer conditions (8 2/3 of 13 jurisdictions) with no provincial screening for SCD or CF. In three provinces there was screening for only 3 conditions and only a single province was offering an extensive screening panel of 36 conditions reaching approximately 3.5% of newborns, and only four of eight provincial laboratories were using MS/MS technology. In late 2006 Ontario became the first province to screen for SCD, and in April 2007 Alberta became the first to screen for CF. Both Ontario and Saskatchewan announced plans to add CF later in 2007. NBS programme reviews began in three provinces (British Columbia, Manitoba and Quebec) and six of

Table 4 Program demographics and screened conditions in Canada blood spot newborn screening programmes

Jurisdiction	Program demographics			Conditions included in current newborn screening mandate										
	Population 1 July 2006[a]	Births (2004 – latest official counts available)[b]	Location of screening laboratory	Congenital hypothyroidism	Phenylketonuria	Galactosaemia	Sickle cell diseases	Congenital adrenal hyperplasia	Biotinidase deficiency	Cystic fibrosis	Other	MS/MS detectable		
												Other amino acid disorders	Fatty acid oxidation disorders	Organic acid disorders
Provinces														
Alberta	3 375 800	41 056	Alberta	•	•			•	•	•	†	†	†	†
British Columbia	4 310 500	40 565	British Columbia	•	•	•						†	†	
Manitoba	1 177 800	13 864	Manitoba	•	•	•		•	•	‡				
New Brunswick	749 200	6 924	Nova Scotia	•	•							†	†	†
Newfoundland and Labrador	509 700	4 451	Newfoundland and Labrador	•	•							†	†	
Nova Scotia	934 400	8 700	Nova Scotia	•	•							†	†	†
Ontario	12 687 000	132 769	Ontario	•	•	•	•	•	•	•		†	†	†
Prince Edward Island	138 500	1 390	Nova Scotia	•	•							†	†	†
Quebec	7 651 500	75 347	Quebec	•	•							†	†	†
Saskatchewan	985 400	12 012	Saskatchewan	•	•	•		•	•	•		†	•	†
Territories														
Northwest Territories	41 900	698	Alberta	•	•	•		•	•	•				
Nunavut – Kitimeot Region			Alberta	•	•			•	•	•		†	†	†
Nunavut – Kivalliq Region	30 800	754	Manitoba	•	•	•		•	•					
Nunavut – Baffin Region			Quebec	•	•							†	†	†
Yukon	31 200	364	British Columbia	•	•	•						†	†	
Totals	32 623 500	338 894												

• Indicates that full population screening is available—for MS/MS indicates testing for all detectable conditions.
† Indicates that all detectable conditions are not included in the analytical interpretation.
‡ Selected screening in males for Duchenne muscular dystrophy.
[a] Reference: http://www40.statcan.ca/101/cst01/demo02a.htm; accessed 31 March 2007.
[b] Reference: http://www40.statcan.ca/101/cst01/demo04a.htm; accessed 31 March 2007.

eight provincial NBS laboratories now use MS/MS technology.

Perhaps the most significant impact on NBS services was the decision in 2006 by the Ontario Health Minister to take Ontario from 'worst to first' in providing NBS to Canadian newborns. Ontario's population of 13 million (39% of Canadian births) makes it the most populous province in Canada; until 2006, NBS there included only CH and PKU. Recent NBS expansion activities were prompted by consumer, professional and media pressure accompanied by an emergency investigation by the Ontario Ombudsman (an independent government investigator with powers of subpoena, search, entry and seizure) into whether the Health Ministry had failed to properly administer NBS. The Ontario Health Minister has now publicly committed to implement the core panel of 29 screening conditions recommended by the ACMG. NBS laboratory testing was transferred from the Ontario Public Health Laboratory to a paediatric academic centre in Ottawa through a bidding process, and two dedicated research positions were added to the NBS staff. The Ontario programme is well underway in its expansion efforts, and as a result of the Ombudsman's activities there NBS inquiries by the Ombudsman of British Columbia have begun.

Conclusion

North American NBS programmes are continuing to expand in areas other than dried blood spot screening, most notably, newborn hearing screening (Brown et al 2001; Joint Commission on Infant Hearing 2000; National Institutes of Health 1993). With an overall incidence of approximately 1:300 for unilateral and bilateral hearing loss combined, screening for this condition is more productive than any other condition currently included in NBS (Therrell and Hannon 2006). NBS systems in both the USA and Canada also are continuing their activities in improving data information systems. This is particularly true in the USA, where there is intense effort from both the federal government and professional medical organizations (i.e. AAP) to establish user-friendly electronic medical records and Internet reporting of screening results. Emphasis is also being placed on shared child health data from public health programmes through linked and integrated information systems as a means of increasing record-keeping efficiency (Therrell 2003). This in turn has led to more sophisticated methods of quality assurance for various system components and increased opportunities to provide quality improvements to the system (Therrell and Hannon 2006). The increased capability to screen for more conditions has also led to complex ethical, legal and social discussions (Botkin et al 2006). Not only may some of these conditions not have treatments available to substantially change the course of the condition, but some may not occur until later in life (adult onset) (American Academy of Pediatrics 2001; Spada et al 2006).

Not surprisingly, the countries with the longest history of NBS have perhaps the largest number of complexities in their systems. Even without national NBS policies, NBS is available for all newborns in both the USA and Canada, but uniform access to and availability of screening do not exist. While screening requirements differ from programme to programme, there is now some agreement in the USA regarding which conditions should be included in all programmes, and there are increasing discussions in Canada. Where public programmes are deficient in both countries, private supplemental screening exists. Consumers and health professionals in both countries have influenced the NBS policy making process so that many more newborns have the availability of expanded NBS, which often exceeds 50 conditions in the USA and is growing in Canada.

The NBS activities in some of the Canadian provinces during the past year are particularly noteworthy. Up until now, very few programme changes have occurred in Canada since the beginnings of screening in the 1960s and 1970s. During the last year or so, almost all provinces have acquired the capability to use MS/MS for metabolic screening, and the addition of SCD and CF in Ontario and CF in Alberta, respectively, indicates renewed attention to other screening conditions. The use of some provincial NBS laboratories to provide services for others is also important. As in the USA, the resources do not exist in all areas of Canada to provide the needed testing and follow-up services. It will be important in the future to maintain the momentum and to revisit the more traditional screening conditions not yet included in some programmes—CAH, BIO, GAL. To achieve equality of NBS services across Canada will take time, as in the USA, but perhaps it can move more quickly learning from the mistakes of others.

Research efforts in the public and private sector continue to develop new testing methods and expansion of screening is inevitable. NBS for the lysosomal storage diseases (LSDs) has already begun with

screening for Krabbe disease in the New York NBS programme using MS/MS (Li et al 2004). Ongoing since October of 2006, the Krabbe disease screening programme has identified several potential cases of infantile Krabbe disease, with one successful bone marrow transplantation recently reported. The NBS protocol evolving there will be useful as others consider screening for this condition. NBS screening for severe combined immunodeficiency disease (SCID) is under development (Chan and Puck 2005; McGhee et al 2005a,b) and a pilot screening programme is in its initial phase in Wisconsin. NBS for Type I diabetes is also being studied (Carmichael et al 2003) in at least two different states, and NBS for Duchenne muscular dystrophy is a topic of continuing research interest at the CDC (http://www.cdc.gov/ncbddd/duchenne/documents/NBS_Lay_Report.pdf).

Improving the sensitivity and specificity of the NBS experience is an ongoing concern of most NBS programmes. In addition to more objective performance metrics (Rinaldo et al 2006), second-tier testing of a selected number of potentially positive specimens is continually under review. Filter paper DNA techniques to analyse for SCDs and CF are two successful second-tier processes that have been refined since their development in the 1990s. Currently, second-tier MS/MS testing using steroid profiling for CAH (Lacey et al 2004; Minutti et al 2004) and succinylacetone analysis for tyrosinaemia type I (Magera et al 2006) are under review in some programmes. Other analytical testing platforms are also of interest as more efficient laboratory screening procedures, including Luminex™ testing and DNA micro chips (Green and Pass 2005). The value of a routine second screen at 1–2 weeks of age is also an issue of particular interest in the USA where it is already mandated in nine states (see Table 3), and a US national prospective/retrospective study is underway to evaluate this screening policy.

It is a certainty that NBS will continue to expand in both the USA and Canada, as in the rest of the world. While both countries seek equitable national programmes of maximum benefit, local politics and economics continue to play a large role in the services available. Financing issues are important concerns, as are adequate human resources to supply appropriate short- and long-term follow-up and care. Successful national NBS policies will require cooperative efforts between consumers, health professionals and politicians. These efforts appear to be moving steadily forward in both countries and hopefully they will continue to result in improved NBS in both.

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