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Improving and Assuring Newborn Screening Laboratory Quality Worldwide: 30-Year Experience at the Centers for Disease Control and Prevention

Víctor R. De Jesús, PhD, Joanne V. Mei, PhD, Carol J. Bell, BS, MT (ASCP), and W. Harry Hannon, PhD

Newborn screening is the largest population-based genetic screening effort in the United States. The detection of treatable, inherited congenital disorders is a major public health responsibility. The Centers for Disease Control and Prevention's (CDC's) Newborn Screening Quality Assurance Program helps newborn screening laboratories ensure that testing accurately detects these disorders, does not delay diagnosis, minimizes false-positive reports, and sustains high-quality performance. For over 30 years, the CDC's Newborn Screening Quality Assurance Program has performed this essential public health service, ensuring the quality and accuracy of screening tests for more than 4 million infants born each year in the United States and millions more worldwide. The Program has grown from 1 disorder in 1978 for 31 participants to more than 50 disorders for 459 participants in 2009. This report reviews the Program's milestones and services to the newborn screening community.
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In 1961, Dr Robert Guthrie introduced the collection of blood as dried spots on filter paper for testing newborns for the detection of phenylketonuria (PKU).[1,2] He coupled these specially collected specimens with a unique bacterial inhibition test that he developed for measurement of phenylalanine.[2] This combination of easily transportable specimens and an inexpensive test made large-scale testing for PKU possible. The first case of PKU detected by his procedure occurred in a pilot study in Niagara Falls City Health Department Laboratory (New York), after 800 newborns had been screened.[1] Guthrie's early publication, submitted in 1962,[2] described his method in detail and its application to testing blood spots obtained from newborns. It was initially rejected because another study published using his "inhibition method" had reported a high incidence of false-positive results and had recommended not using Guthrie's test for PKU screening.[3] Guthrie attributed the likely source of this difference in performance to the source of the filter paper used in the other study. Guthrie stated that the filter paper used by them was not absorbent enough to allow uniform spotting. He thought that Schleicher and Schuell Grade 903 filter paper was best suited for collection of uniform dried-blood spots (DBS), and indicated some minimal criteria for uniform performance of the filter paper.[2] Because of Guthrie's efforts, the successful introduction of DBS as a source for PKU screening eventually led to population-based screening of newborns nationwide using a few blood drops collected from a heel stick and absorbed into special filter paper.

Today, newborn screening (NBS) is the largest population-based genetic screening effort in the United States, and is primarily performed by state public health laboratories. The detection of treatable, inherited congenital disorders is a major public health responsibility. Screening tests are designed to differentiate asymptomatic newborns that may have a disease from those who may not. It is important to note that these screening tests alone are not intended to yield a diagnostic testing outcome. However, effective screening of newborns using DBS specimens collected 24-48 hours after birth and rapid follow-up diagnostic confirmation and treatment helps prevent mental retardation, premature death, and other adverse outcomes. State public health laboratories or other contracted NBS laboratories routinely screen DBS specimens for inborn errors of metabolism and other congenital disorders that require medical intervention. The Centers for

Newborn Screening Quality Assurance Program, Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, GA.

Address reprint requests to Víctor R. De Jesús, PhD, The Centers for Disease Control and Prevention, 4770 Buford Highway, NE Mail Stop F-19, Atlanta, GA 30341. E-mail: vdejesus@cdc.gov

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Disease Control and Prevention's (CDC's) Newborn Screening Quality Assurance Program (NSQAP) helps NBS laboratories improve testing accuracy, minimize unnecessary follow-up, and establish screening reliability. For >30 years, NSQAP has performed this essential public health service, ensuring the quality and accuracy of screening tests for >4 million infants born each year in the United States. The NSQAP is cosponsored by the Association of Public Health Laboratories (APHL).

All NBS testing is done in a screening laboratory that meets licensing standards specified by the Clinical Laboratory Improvement Amendments of 1988 or equivalent requirements as determined by the Centers for Medicare and Medicaid Services. As part of these requirements, a screening laboratory must meet certain criteria for quality control (QC). They must also participate in proficiency testing (PT) programs designed to evaluate the quality of laboratory performance on a periodic basis, using specimens in the dried blood matrix simulating the patient specimens tested. The NSQAP enables laboratories to meet the Clinical Laboratory Improvement Amendments quality assurance (QA) requirement for verifying test accuracy. It also provides technical guidance to participating laboratories to help assure that no screen-positive cases are misclassified during routine screening activities. Participation in NSQAP allows laboratories to gain testing confidence through an external QA program that provides comparisons of peer performance within and among methods.

Quality Assurance Program Operations

The NSQAP provides comprehensive, multicomponent QA services that include PT and QC services for DBS testing to NBS laboratories, including >50 newborn disorders for 459 laboratories in 63 countries. NSQAP is not just a PT program, but a proactive, multicomponent QA program for a specialized area of public health testing. It provides external PT specimens for voluntary comparative assessment of laboratory performance, QC materials, filter paper quality assessment, special consultations, and technical assistance to public health and private laboratories. The PT data reporting is handled through an internet web site that permits participants to report their results online for each analyte and receive timely performance evaluation reports. It also allows storage and retrieval of archived data-report summaries.[4]

All PT and QC materials should simulate, as closely as possible, the actual specimens analyzed in the assay systems. CDC DBS materials are certified for homogeneity, accuracy, stability, and suitability for all NBS assays available from the various commercial sources. Intended to supplement the participants' method or kit QC materials, NSQAP QC materials provide an independent external resource that allows participants to monitor the long-term stability of commercial assay kits. PT for the assessment of clinical laboratories dates back to the 1940s.[5,6] NSQAP provides training in the preparation of DBS materials and test methods. The program staff also compiles and distributes 21 data reports annually for comparative and assessment use by participants. Laboratories that report false-negative results, indicating possible problems with their assays, are immediately contacted and provided consultations. If problems are not identified and corrected, laboratories would likely assume that their test results were accurate. They would continue testing newborns without correcting the problem, possibly missing or delaying case diagnosis. The potential catastrophic consequences of a delayed diagnosis underscore the need for prompt NSQAP consultative action.

Since its inception, NSQAP has provided NBS laboratories with quarterly panels of 5 blind-coded DBSs, and data are now returned to the program through an internet-based, secure reporting system. Reports of individual laboratory performance and summary data by analyte and method are available within 1 week of the close of the internet data-reporting deadline. Laboratories can retrieve their results as needed. For PT challenges, laboratories report the cut-off value for each analyte tested. There is a large degree of variability in cut-off values among laboratories (Fig. 1). Participating laboratories are evaluated on the decisions that identify test results requiring additional follow-up testing (out-of-range) vs those that do not (in-range). However, reported analytical values are an important component of the overall grading algorithm because specimen assessments are based on the expected analytical values. The NSQAP grading algorithm considers each laboratory's reported cut-off value.[7] On the basis of qualitative results (clinical assessments) for analytes or disorders, NSQAP summarizes annual false-positive and false-negative rates for laboratory PT challenges. In 2008, the false-positive rate for PT specimens was <1% for all screening analytes except decenoylcarnitinine (C10:1), a secondary marker for medium chain acyl-CoA dehydrogenase deficiency; immunoreactive trypsinogen (IRT), a primary marker for cystic fibrosis (CF); and succinylacetone (data not shown), a specific marker for tyrosinemia type 1. The false-negative rate for PT specimens was >1% for 4 of the 25 disorders or analytes monitored (tyrosine, C10, C16, and IRT) (Table 1). False-negative errors result in immediate notification from NSQAP so that the source of the error can be investigated, and steps can be taken to reduce the risk of a continuously occurring error. False-positive results are identified as a tool for the laboratory in examining their performance metrics. A decline in the PT false-negative rate was observed for the 6-year period from 2002 to 2008, which confirms the value of the NSQAP in improving laboratory performance.

NSQAP: The Dried-Blood Spot Program's Timeline

In 1975, the Committee for the Study of Inborn Errors of Metabolism, National Academy of Sciences, noted that better QC of PKU screening was vital, and recommended that a single laboratory within the CDC be responsible for maintaining the proficiency of the regional laboratories testing newborns.[8] In the late 1970s, NSQAP began its critical work

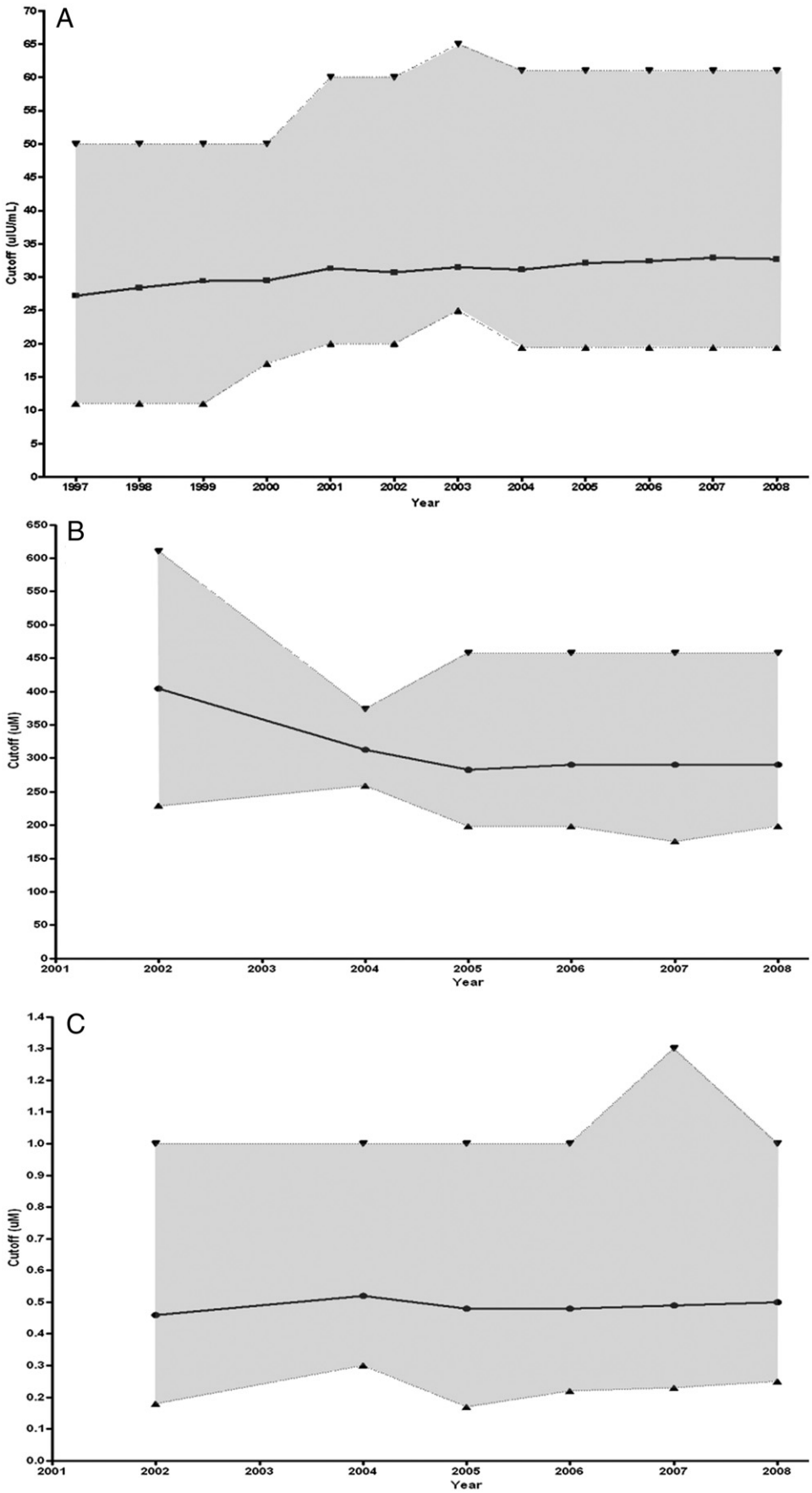

Figure 1 Cutoff ranges for selected analytes showing harmonization across time. (A) Thyroid-stimulating hormone (TSH), (B) Leucine (Leu), (C) Octanoylcarnitine (C8).

Table 1 Domestic False-Negative Rates (%) for 2003-2008

Disorder/Analyte	Year						Average 6-year False-Negative Rate
	2003	2004	2005	2006	2007	2008	
Phenylketonuria (phenylalanine)	0	0	0.8	0.6	0	1.1	0.4
Maple syrup urine disease (leucine)	0.8	0	0	0	0	0	0.1
Homocystinuria (methionine)	0	0	1.4	0	0	0	0.2
Maple syrup urine disease (valine)	1.8	0	0	0	0	0	0.3
Tyrosinemia I, II, III (tyrosine)	5.7	2.9	0	1.6	0.7	3.3	2.4
Citrullinemia (citrulline)	2.3	0	0	0	0	0	0.4
C3 Screen	0	1	0	1.9	0	0	0.5
C4 Screen	0	1.2	0	0.4	0	0	0.3
C5 Screen	0	1.2	1.7	0.8	0	0	0.6
C5DC Screen	0	0	0	3.7	0	0	0.6
C6 Screen	0	0	0	0	0.6	0	0.1
C8 Screen	0	0.7	0.6	0.6	0	0	0.3
C10 Screen	0	4.0	1.1	1.3	0	0	1.1
C14 Screen	0	1.4	1.1	0.7	0	0	0.5
C16 Screen	10.5	2.4	0	0.6	0	0	2.3
Hypothyroidism	0	0	0.6	0	0.5	0	0.2
Congenital adrenal hyperplasia	0.7	0.5	2.4	0.5	0	0	0.7
Galactosemia	0	1.5	2.2	0	1.1	0	0.8
Biotinidase deficiency	0	0	0.6	0	0.8	0	0.2
Galactosemia	0	0.5	0	0	0	0	0.1
Cystic fibrosis (IRT)	1.5	1.1	0	2.1	1.6	1.3	1.3

with 10 state public health laboratories testing for 1 disorder, congenital hypothyroidism.

The expansion of NSQAP services to NBS laboratories began in 1978, when the Health Resources and Services Administration (HRSA) provided funds to launch the program and became its sponsor. NSQAP distributed the first thyroxine and thyroid-stimulating hormone QC materials in DBS that year, after a 1-year pilot study to create DBS QC materials for congenital hypothyroidism screening (Table 2). In January 1979, Dr Guthrie sent a letter to CDC encouraging and supporting expansion of the program to provide DBS materials for more disorders, including PKU. The first PT survey for PKU occurred in 1980, followed by distribution of QC materials for phenylalanine in 1983. That same year, the NSQAP Filter Paper Evaluation Project was established in response to complaints about filter paper reliability and reproducibility. NBS filter paper quality was assessed using a DBS-based quantitative radioisotopic test to measure and monitor filter paper performance characteristics under a standardized protocol. This project ultimately resulted in the creation of a national standard for blood collection on filter paper. Initially, a product of the National Committee for Clinical Laboratory Standards , the standard is now in its fifth edition as a product of the Clinical and Laboratory Standards Institute (CLSI). The standard (CLSI LA4-A5) addresses issues associated with specimen collection, the filter paper collection device, and the transfer of blood onto filter paper.[9] On the basis of sustained compliance with the performance parameters specified in LA4-A5, the Food and Drug Administration (FDA) has currently registered 2 commercial sources of filter paper for blood collection.

Table 2 Timeline for the Addition of Disorders to NSQAP

1978	Congenital hypothyroidism
1980	Phenylketonuria
1988	Galactosemia, HIV seroprevalence
1990	Congenital adrenal hyperplasia
1991	Sickle cell disorders
1992	Maple syrup urine disease
1995	Homocystinuria
1997	Biotinidase
2000	Fatty acid and organic acid disorders
2002	Cystic fibrosis/IRT, diabetes type 1
2005	Toxoplasmosis
2006	2nd Tier congenital adrenal hyperplasia
2007	Cystic fibrosis DNA mutation panel
2008	Succinylacetone, lysosomal storage disorders
2009	2nd Tier maple syrup urine disease

In 1988, NSQAP distributed the first galactosemia PT survey and its first infectious disease DBS materials. Human immunodeficiency virus type 1 (HIV-1) DBS QC materials and PT challenges were created as part of a seroprevalence survey among childbearing women.[10] The first galactose QC materials were distributed in 1989. That same year, NSQAP celebrated its 10th anniversary with an enrollment of 75 laboratories in 4 countries, and offered QA materials for 8 disorders and 5 analytes.

The first congenital adrenal hyperplasia (CAH) PT survey, using 17-α-hydroxyprogesterone, was conducted in 1990, and in 1991, the first CAH QC materials were distributed to program participants worldwide. Another program milestone was achieved in 1991, when identification of sickle cell

disease and other hemoglobinopathies was added to the QA program. Inclusion of these conditions in NBS had been recommended after the results of research that indicated that pneumococcal sepsis in young children with sickle cell anemia was reduced by as much as 84% through early identification and treatment.[11]

NSQAP has had a long-standing relationship with the APHL dating to the program's initiation in 1978. A Memorandum of Understanding was formally signed in October 1992, which produced formal sponsorship and paved the way for the establishment of an APHL QA/QC/PT Subcommittee. The Subcommittee is charged with advising NSQAP on its NBS-related activities and the needs of the public health community. The QA/QC subcommittee comprises representative members from state public health laboratories across the country.

In 1994, NSQAP achieved another major milestone by establishing a QA program for DNA confirmation, using DBS specimens for hemoglobins A, S, C, E, and D. This work was initiated using HRSA start-up funds, and allowed NSQAP to expand into DNA testing, as technology became available in screening and diagnostic laboratories. NSQAPs non-DNA expansion continued in 1995, with PT survey for homocystinuria, and made available QC materials for methionine. Building on earlier success with its hemoglobins program, DNA testing for CF was established at the NSQAP laboratory in 1997. The CF DNA program coincided with the publication of the proceedings of a January 1997 workshop that discussed the benefits and risks associated with NBS for CF, and developed public health policy concerning such screening.[12] Additionally, in 1997, the first biotinidase deficiency PT survey was initiated, bringing the total to 17 disorders and 13 analytes covered by NSQAP. In 1998, NSQAP celebrated its 20th anniversary of service to NBS laboratories in the United States and 33 other countries by providing DBS QA materials to 198 laboratories, including 163 QC and 151 PT participants. However, after nearly 20 years of support, HRSA ended its NSQAP funding and sponsorship.

The introduction of tandem mass spectrometry (MS/MS) as a viable technique for detecting phenylalanine in DBS,[13] revolutionized the practice of NBS for metabolic disorders. Recognizing the need for best practices guidelines for MS/MS use in NBS Laboratories, the National Newborn Screening and Genetics Resource Center, in collaboration with NSQAP/CDC and HRSA, convened a workshop in June 2000, attended by approximately 50 participants from public and private health agencies and universities. Workshop participants examined concerns about integrating MS/MS technology into ongoing NBS activities, and published a report[14] to assist policymakers, program managers, and laboratorians in informed decision making. In 2001, the NSQAP launched a pilot PT survey for laboratories testing DBS by MS/MS for amino acid, fatty acid oxidation, and organic acid disorders. In 2002, NSQAP brought MS/MS detectable analytes into PT evaluation status, using cutoff decisions and presumptive case classifications for participant grading. Additionally, the program began distributing the first galactose-1-phosphate uridyl transferase PT survey and specimens for IRT. In 2003, NSQAP offered the first PT survey for DNA confirmatory testing for CF. The program's expansion continued in 2005, when a pilot PT survey for *Toxoplasma gondii* antibodies was launched for laboratories performing toxoplasmosis screening.

Acquisitions of MS/MS technology by NBS laboratories in early 2000, presented a unique challenge to incorporate MS/MS into NBS. With this new technology and its multianalyte capability, NBS programs could now detect several disease biomarkers simultaneously from a single specimen aliquot. Additionally, an increased potential for second-tier testing to improve specificity of traditional screening tests was now available. The American College of Medical Genetics (ACMG), because of a HRSA contract, recommended a uniform panel of conditions for inclusion by all state NBS programs.[15] The expert working group recommended 54 conditions (29 core conditions—including hearing screening—and 25 secondary targets) for implementation in all state NBS programs. This "uniform panel" was subsequently endorsed by the Secretary of Health's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children. To date, all states have expanded to include at least the core biochemical tests. NSQAP initiated and continuously expanded its coverage of MS/MS detected analytes in its QA services; all analytes were identified in the uniform panel. In 2006, NSQAP launched a CAH PT pilot survey in support of laboratories evaluating second tier MS/MS-based CAH testing.[16] This procedure involves detecting secondary steroid markers and establishing a clinical algorithm for identification of CAH-affected newborns.

In 2007, NSQAP expanded its DNA mutation panel for CF PT surveys. Mutations were added to the IRT PT program, thereby providing CF screening laboratories with QA materials for primary and secondary CF assays. This enhanced the NSQAPs expertise in molecular biology-based technology, while establishing a solid foundation to assist participating laboratories with their DNA-based screening assays. NSQAP celebrated its 30th anniversary in 2008 by launching a PT survey for succinylacetone, a specific marker for tyrosinemia type 1,[17,18] and a pilot program for lysosomal storage disorders detected by MS/MS,[19,20] in collaboration with the Newborn Screening Translation Research Initiative at CDC. Currently, the total number of laboratories and countries served by NSQAP for all facets of the program are 547 laboratories in 78 countries (Table 3), covering over 50 disorders and 48 analytes (Table 4). The NSQAP coverage by the end of 2009 will include 52 of the 54 analytes in the ACMG uniform panel and 2 infectious diseases not in this panel, in addition to other analytes currently used in pilot studies for possible inclusion in the uniform panel, for example, severe congenital immunodeficiencies. NSQAP annually produces approximately a million DBS to meet the QA and PT needs of its participating laboratories worldwide.

Filter Paper (Blood Collection Device) Quality Assurance

Beginning with Guthrie's report in 1963,[2] the special filter paper matrix for blood collection for NBS has periodically

Table 3 Participating Countries in the Newborn Screening Quality Assurance Program (N = 78[a])

Argentina	Hungary	Portugal
Armenia	Iceland	Russia
Australia	India	Saudi Arabia
Austria	Ireland	Senegal
Belgium	Israel	Singapore
Brazil	Italy[b]	Slovak Republic
Cambodia	Japan	South Africa
Canada	Kazakhstan	South Korea
Chile	Kenya	Spain
China	Kyrgyzstan	Sweden
Colombia	Latvia	Switzerland
Costa Rica	Lebanon	Tajikistan
Cote d'Ivoire	Lithuania	Taiwan
Cuba	Luxembourg	Tanzania
Czech Republic	Malaysia	Thailand
Denmark	Malawi	Turkey
Dominican Republic	Mexico	Uganda
Egypt	Netherlands	Ukraine
Estonia	New Zealand	United Arab Emirates
Ethiopia	Nicaragua	United Kingdom
Finland	Norway	United States
France	Pakistan	Uruguay
Germany	Panama	Uzbekistan
Greece	Peru	Venezuela
Guatemala	Philippines	Vietnam
Haiti	Poland	Zambia

[a]Includes laboratories receiving DBS services for HIV antibodies and lysosomal storage disorders.
[b]First international participant (May 1978).

created analytical performance issues. As a vital service to the NBS community, NSQAP evaluates NBS filter paper's absorption characteristics and other parameters for all manufactured lots of filter papers from manufacturers with FDA clearance (approval). According to a mutual voluntary agreement, the filter paper manufacturer provides NSQAP with statistically valid sample sets from different reels of the unprinted filter paper production lot for evaluation, using NSQAPs standardized procedures.[9] The manufacturer has the responsibility for establishing its own parallel evaluation laboratory. NSQAP's evaluation results are provided for comparison with those of the primary evaluator. Agreement is achieved between the 2 evaluation sources before a new production lot of filter paper is released for printing and distribution.

DBS collection requires the use of special grades of commercially manufactured paper, as a unique whole blood collection matrix for NBS and other related applications. Because the paper punch is a volumetric measurement for an analytical method, a high degree of uniformity is essential to minimize variance from the lot-to-lot filter paper transitions for specimens, calibrators, QC materials, and unknown samples.[9] In the Unites States, only papers from sources cleared by the FDA are acceptable for blood collection for NBS tests. Critical to proper and effective use of this matrix is an ongoing assessment and evaluation of new production lots as they are manufactured, as well as the monitoring of problems identified with individual lots in use by NBS programs.

NSQAP's evaluation parameters were established in 1980, with voluntary cooperation from the manufacturer of Grade 903 paper. Figure 2 shows the results from NSQAP's evaluation of Grade 903 paper for 30 years. Lysed red blood cells were originally used for the evaluations to control for heterogeneity due to cell lysis; but for the last 20 years, both lysed and intact red blood cell preparations have been used for these evaluations. The 2 methods serve as a cross check for performance comparison. Figure 2 shows that 3 lots of paper were outside the expected performance criteria in 1981, and this created great concern for the testing community until the manufacturer re-established the performance quality of the paper. This event firmly established the need for continued monitoring of the filter paper before its distribution.

NSQAP chose to monitor the following parameters: absorption volume, absorption time, physical appearance, and homogeneity, to ensure consistency among production lots, before a new lot is distributed to the user community. From earlier studies, NSQAP established a working protocol, a QC

Table 4 List of Biomarkers Covered by NSQAP (2009)

Biotinidase	Free Carnitine (C0 low)	Tetradecenoylcarnitine (C14:1)
Thyroxine	Propionylcarnitine (C3)	3-Hydroxypalmitoylcarnitine (C16OH)
Thyroid-stimulating hormone	Malonylcarnitine (C3DC)	Palmitoylcarnitine (C16)
17 α-Hydroxyprogesterone	Isobutyrylcarnitine (C4)	Immunoreactive trypsinogen (IRT)
Total galactose	3-Hydroxybutyrylcarnitine (C4OH)	CF DNA Mutation Panel
Uridyltransferase (GALT)	Isovalerylcarnitine (C5)	Hemoglobinopathies
Citrulline	Glutarylcarnitine (C5DC)	SS, SC, SD, SE mutations
Phenylalanine	3-Hydroxyisovalerylcarnitine (C5OH)	Diabetes Type 1 risk mutations
Leucine	Tiglylcarnitine (C5:1)	Toxoplasmosis (IgG, IgM)
Valine	Hexanoylcarnitine (C6)	HIV type 1 antibodies
Methionine	Octanoylcarnitine (C8)	Creatine kinase (DMD)
Arginine	Decanoylcarnitine (C10)	Androstenedione
Tyrosine	Decenoylcarnitine (C10:1)	Cortisol
Succinylacetone	Myristoylcarnitine (C14)	11-Deoxycortisol
α-Glucosidase (GAA)	α -Galactosidase (GLA)	21-Deoxycortisol
β-Galactosidase (GALC)	Acid β-Glucocerebrosidase (ABG)	Acid sphingomyelinase (ASM)

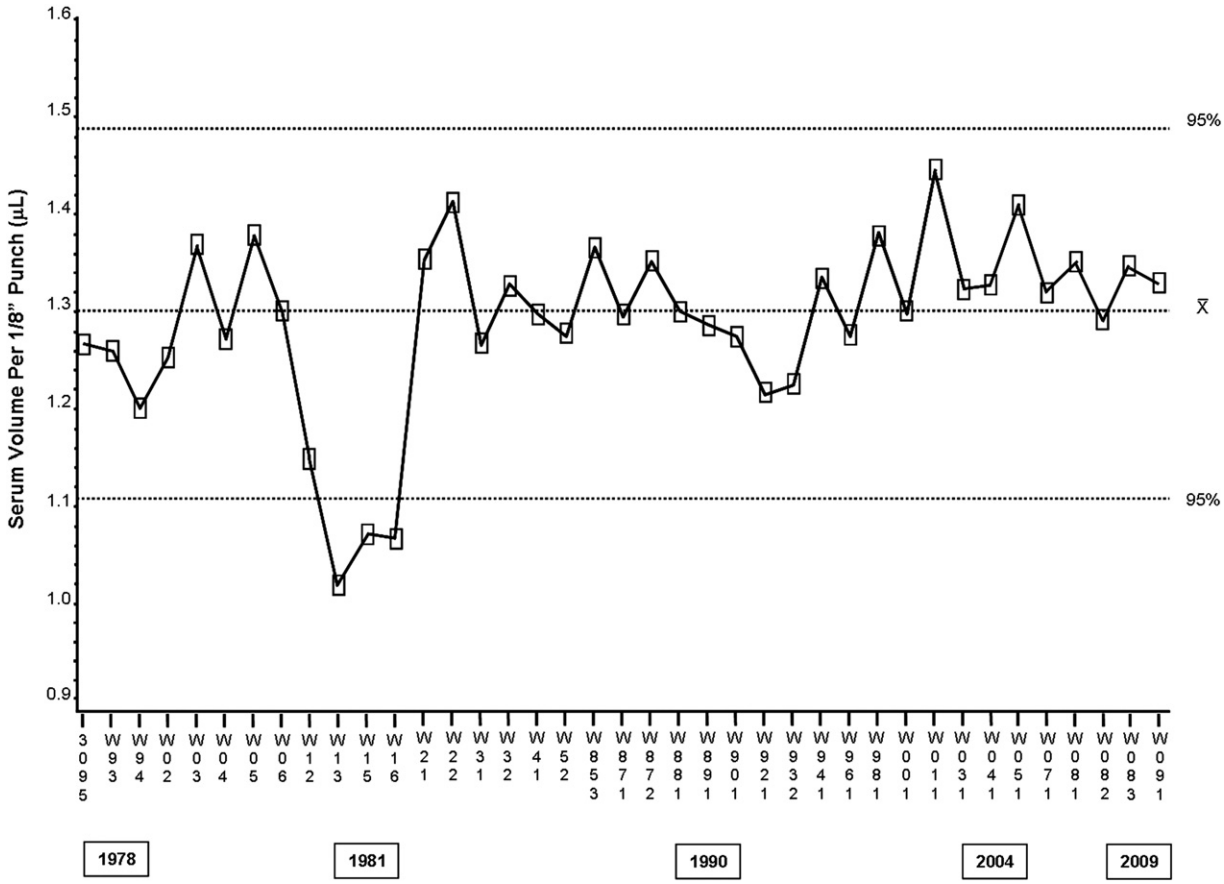

Figure 2 Evaluation of Grade 903 Blood Collection Filter Paper: 1978-2009.

system for evaluation, and the set of parameters and performance expectations to monitor for criteria adherence on a routine basis. This protocol became a part of the CLSI's Approved Standard in 1982. NSQAP has applied this protocol for troubleshooting filter paper problems, evaluating new production lots, and assessing proposed products from new manufacturers for almost 30 years.

Future Directions

Infectious Diseases Testing and Surveillance Using Dried Blood Spots

Infectious disease testing in the United States has used newborn DBSs to estimate the seroprevalence of HIV in childbearing women[10] and to screen newborns for *T. gondii* exposure.[21] These assays detect specific antibodies made against the infectious agents. The NSQAP played a lead role in assuring the quality of testing for the national HIV seroprevalance survey of childbearing women for 10 years, and continues to provide QA materials and services for laboratories using DBS for HIV screening. QA services for toxoplasmosis testing were introduced in 2005, although only a few programs in the United States included this test in their screening panel. Additionally, NBS for congenital cytomegalovirus infection, which is a leading cause of sensorineural hearing loss and developmental disability in children, has been proposed for Unites States hospitals and public heath programs.[22] NSQAP has implemented research efforts into the development of DBS QA materials for cytomegalovirus screening.

Role of Technologies in Newborn Screening

DBS technologies for NBS have evolved over time, and now encompass all clinical platforms from bacterial inhibition assays to many types of immunochemical assays to multiplexed methods, such as MS/MS, multimarker high performance liquid chromatography testing for hemoglobinopathies, and multianalyte immunoassays for HIV antibodies, hepatitis C antibodies, and hepatitis B antigens[23,24] to polymerase chain reaction. The NSQAP stays current with technological advances and plans for development of QA materials and services that will best meet requirements for the newly developed measurement systems, for example, lab-on-a-chip technologies.[25]

NBS activities have conventionally been influenced by emerging technologies, and NSQAP strives to stay in the forefront of technological and scientific developments to improve its role in providing QA services to NBS Laboratories. The program now works closely with a select group of molecular biologists, who have expertise in understanding how genetics and changes in DNA are associated with important public health issues, such as diabetes, kidney disease, birth defects, and asthma. Many NBS laboratories either use or are

considering the addition of DNA-based testing as second-tier testing to confirm positive screening results or enhance specificity of testing for disorders in the ACMG uniform panel (eg, galactosemia, CAH). Second-tier DNA-based testing is currently used by most state public health screening programs for CF screening,[26] as well as in confirmatory testing of Krabbe disease in New York State.[27] As a result, NSQAP is building on its CF QA program to create, certify, and distribute DBS materials that laboratories can use, to ensure that these DNA tests meet technical proficiency goals.

In addition to the goal to increase QA services for DNA-based tests, NSQAP aims to expand the availability of DBS QA materials for all the core and secondary target conditions listed by the ACMG report.[15] The increased availability of commercial and academic synthetic sources of many of the acylcarnitine compounds has enabled NSQAP to acquire and incorporate them into its DBS production schedule. In 2010, the program will offer DBS QC and PT materials for 27 of the 28 core disorders that are tested using DBS (excludes hemoglobin S/β-thalassemia) and for 24 of the 25 secondary target disorders (excludes 2,4-dienoyl-CoA reductase deficiency); when source materials are located, these remaining 2 markers will be added in the near future. The latest additions to NSQAP panels include 3-hydroxypalmitoylcarnitine (C16OH), 3-hydroxybutyrylcarnitine (C4OH), tiglylcarnitine (C5: 1), and arginine, which are primary markers for long-chain L-3-hydroxyacyl-CoA-dehydrogenase deficiency, medium/short chain acyl-CoA-dehydrogenase deficiency, β-ketothiolase deficiency, and argininemia, respectively. NSQAP will continuously focus on achieving the QA needs for all analytes detected in NBS for disorders identified in recommended panels and those in pilot testing programs.

The Newborn Screening Saves Lives Act, which was signed into law in 2008,[28] indirectly provided support to secure a funding source for the NSQAP that resulted in improved technology resources and increased staff, and other capabilities to better serve the NBS public health community. The bill identifies CDC's role under "Laboratory Quality" while endorsing and expanding the activities of NSQAP to respond to the QA needs for NBS laboratories. Furthermore, additional monies were obtained to fund grants for state pilot studies for severe congenital immunodeficiencies disorders and for development of second-tier tests for enhanced specificity in state programs. This legislative bill also required the development of a national contingency plan for NBS, which is to be used by states, regions, or consortia of states in the event of a public health emergency. In 2008, a planning meeting of stakeholders was held at CDC in collaboration with HRSA, and a report of the group's recommendations is expected to be issued in late 2009. As part of these efforts for contingency planning, APHLs QA/QC NBS Subcommittee developed a generic NBS collection card for use in emergency situations. The blood collection cards have been printed and are housed at CDC. NSQAP will be responsible for assuring the continuous performance of the blood collection filter paper during storage. Request for the emergency cards will be made through the APHL office.

Conclusions

The NSQAP with its many facets is designed to help screening laboratories achieve excellent technical proficiency and maintain confidence in their performance while processing large volumes of specimens daily. The program continually strives to produce certified DBS materials for reference and QC analysis, to improve the quality and scope of services, and to provide immediate consultative and technical assistance. Over 10 million DBS QA materials have been distributed globally during 30 years of operation. Through NSQAPs interactive efforts with the program's participants, it aspires to meet their growing and changing NBS needs, always with an eye on future technological advances. The accuracy of screening tests marks the difference between life and death for many infants; in other instances, identifying newborns with a disorder means that they can be treated, and thus avoid lifelong disability or cognitive impairment. Thousands of newborns and their immediate families have benefited from reliable and accurate testing that has been accomplished by a network of screening laboratories and the NSQAP.

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