Recognizing 50 Years of Innovative Newborn Screening in North Carolina

Lou F. Turner, Sara Beckloff, Ann Grush

Newborn screening is a critical, preventive health program for early identification of disorders in newborns. Early detection, diagnosis, and treatment of certain genetic or metabolic disorders can significantly reduce death, disease, and associated disabilities. North Carolina has been instrumental in the development of innovative technologies used in newborn screening programs.

In December 2016, the North Carolina Division of Public Health celebrated the 50th anniversary of the implementation of a population-based newborn screening program. Although 1963 is nationally recognized as the birth of newborn screening, testing was initiated across the country beginning in the early-to-mid-1960s with most programs starting in 1965 [1]. At its inception, newborn screening focused on phenylketonuria (PKU), an autosomal recessive disorder which affects brain development and leads to profound intellectual impairment that would require institutionalization if left untreated. At that time, screening efforts employed the Guthrie Method, a manual microbiological-based method, which was developed in 1963 by Dr. Robert Guthrie, a microbiologist researcher from the State University of New York at Buffalo. Dr. Guthrie also introduced a system for collection and transportation of blood specimens on filter paper which lead to cost-effective, wide-scale genetic screening [2]. Concurrently, in North Carolina, Drs. John Hill and George Summer, clinical pediatric researchers at the University of North Carolina at Chapel Hill (UNC), were also working on adapting an automated fluorometric biochemical method to detect phenylalanine, an analyte of interest for PKU, in newborns [3]. North Carolina became a national leader as the first state laboratory to utilize the automated fluorometric method developed at UNC.

With $52,000 appropriated by then-Governor Terry Sanford toward the North Carolina State Laboratory of Public Health in 1964, and continuing funding provided by the General Assembly, pilot studies were conducted through 1965 and North Carolina began testing newborns from all 100 counties on a voluntary basis in January 1966. The compliance rate soon reached 97%, which exceeded testing rates in states with mandatory testing. This success would contribute to public health and clinical hospital pediatric leaders' early efforts to inform and educate all of North Carolina's health care providers about newborn screening [4]. Three babies were diagnosed with PKU in the first year of testing. Historical correspondence from the state laboratory archives noted that in the first year, the total program costs per year were equivalent to the costs for maintaining one child in an institution during their lifetime [5].

A second major breakthrough in newborn screening also had its beginnings in North Carolina. In the late 1990s Drs. David Millington and Steve Kahler, researchers at Duke University, began using powerful tandem mass spectrometry (MS/MS) to study blood spots of newborns and to screen for amino acid disorders. The application of MS/MS to newborn screening replaced the automated fluorometric method of screening for PKU and is now being used as a major component of expanded newborn screening testing both nationally and internationally. MS/MS can simultaneously screen for over 30 different metabolic conditions, with new conditions continually being added to the platform [6]. Once again, North Carolina was at the forefront of newborn screening. The State Laboratory of Public Health was the first state laboratory to use this method for newborn screening. In 2008, Dr. Neil Kirkman, a renowned clinical pediatric specialist and longtime chief of the Division of Genetics and Metabolism at UNC (1965-1991), compiled a historical review of the North Carolina newborn screening program that outlined these early efforts and innovative successes from 1966 through 2007 [7].

Since that time, the testing panel for newborn screening has evolved and Table 1 denotes the disorders North Carolina screened for as of 2018. To date, North Carolina has been unofficially steered by the American College of Medical Genetics (ACMG) guidelines for newborn screening, the Recommended Uniform Screening Panel (RUSP), when determining which disorders to add to its screening panel. As of September 2018, the RUSP included 35 core conditions and 26 secondary conditions. Many states are also tasked with providing follow-up to infants identified through newborn screening programs, including ensuring

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TABLE 1.
Disorders Screened for in the North Carolina Newborn Screening Program and 2017 Incidence Rates

	RUSP Disorder	Year started testing in NC	Confirmed cases in 2017	Confirmed cases per 100,000 newborns
Endocrine Disorders	**Core Conditions**			
	Primary congenital hypothyroidism	1979	56	47
	Congenital adrenal hyperplasia	1989	3	3
Hemoglobin Disorders	Hemoglobinopathies	1987	134	113
Other Disorders	**Core Conditions**			
	Biotinidase deficiency	2004	1	1
	Critical congenital heart disease	2014	155	131
	Cystic fibrosis	2009	30	25
	Classic galactosemia	1988	6	5
	Glycogen storage disease type II (Pompe)			
	Hearing loss	2000	185	157
	Severe combined immunodeficiencies	2017		
	Mucopolysaccharidosis type 1			
	X-linked adrenoleukodystrophy			
	Spinal muscular atrophy due to homozygous deletion of exon 7 in SMN1			
	Secondary Conditions			
	Galactose epimerase deficiency			
	Galactokinase deficiency			
	T-cell related lymphocyte deficiencies			
Metabolic Disorders	***Amino Acidopathies - Core conditions (AA)***		5	4
	Argininosuccinic aciduria (ASA)	2015	2	2
	Citrullinemia type I (CIT)	1999		
	Maple syrup urine disease (MSUD)	1999	1	1
	Homocystinuria (HCY)	1999		
	Classic phenylketonuria (PKU)	1999	2	2
	Tyrosinemia type I (TYR I)	2015b		
	Amino Acidopathies - Secondary conditions (AA)			
	Argininemia (ARG)	2015		
	Citrullinemia type II (CIT II)	1999		
	Hypermethioninemia (MET)	1999		
	Benign hyperphenylalaninemia defect (H-PHE)	1999		
	Biopterin defect in cofactor biosynthesis [BIOPT (BS)]	1999		
	Biopterin defect in cofactor regeneration [BIOPT (REG)]	1999		

appropriate diagnosis, treatment, and ongoing evaluation. In many cases, education (professional and consumer) is also a program responsibility, along with counseling and provision of other ancillary services. In North Carolina, the follow-up component of the newborn screening program is provided by genetic counselors from the Children and Youth Branch of the Women's and Children's Health section of the North Carolina Division of Public Health. These consultants track abnormal screening results and assist families with re-screening or referrals to clinical specialists for confirmation testing, diagnosis, and treatment. Pediatric specialists at UNC and Duke University primarily focus on those patients with certain metabolic and genetic disorders. UNC provides the metabolic follow-up for MS/MS disorders and Dr. Joseph Muenzer of UNC is a world-renowned expert on mucopolysaccharides. Duke University also has Dr. Rebecca Buckley, the world-renowned medical expert on severe combined immunodeficiency disorder (SCID), and Dr. Priya

TABLE 1. *continued*
Disorders Screened for in the North Carolina Newborn Screening Program and 2017 Incidence Rates

	RUSP Disorder	Year started testing in NC	Confirmed cases in 2017	Confirmed cases per 100,000 newborns
	Amino Acidopathies - Secondary conditions (AA) continued			
	Tyrosinemia type II (TYR II)	1999		
	Tyrosinemia type III (TYR III)	1999		
	Organic Acid Disorders - Core conditions (OA)		7	6
	Propionic acidemia (PROP)	1999	1	1
	Methylmalonic acidemia (MUT) (methylmalonyl-CoA mutase)	1999		
	Methylmalonic acidemia (Cbl A,B) (cobalamin disorders)	1999		
	Isovaleric acidemia (IVA)	1999	1	1
	3-Methylcrotonyl-CoA carboxylase deficiency (3-MCC)[3]	1999	2	2
	3-hydroxy 3-methylglutaric aciduria (HMG)	1999		
	Holocarboxylase synthetase deficiency (MCD)	1999		
	β-ketothiolase Deficiency (bKT)	1999	1	1
	Glutaric acidemia type 1 (GA1)[3]	1999	1	1
	Organic Acid Disorders - Secondary conditions (OA)			
	Methylmalonic acidemia with homocystinuria (Cbl C,D)	1999	1	1
	Malonic acidemia (MAL)	2015		
	Isobutyrylglycinuria (IBG)	1999		
	2-methylbutyryl glycinuria (2MBG)	1999		
	3-methylglutaconic aciduria (3MGA)	1999		
	2-methyl-3-hydroxybutyric aciduria (2M3HBA)	1999		
	Fatty Acid Oxidation disorders - Core conditions (FAO)		16	14
	Carnitine uptake defect/carnitine transport defect (CUD)[3]	2015	2	2
	Medium chain acyl-CoA dehydrogenase deficiency (MCAD)	1999	7	6
	Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)	1999	1	1
	Long-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency (LCHAD)	1999		
	Trifunctional protein deficiency (TFP)	1999	2	2
	Fatty Acid Oxidation Disorders - Secondary conditions (FAO)			
	Short-chain acyl-CoA dehydrogenase deficiency (SCAD)	1999	2	2
	Glutaric acidemia type II (GA II)	1999		
	Medium-chain ketoacyl-CoA thiolase deficiency (MCAT)			
	Carnitine palmitoyltransferase type II deficiency (CPT II)	1999	1	1
	Carnitine acylcarnitine translocase deficiency (CACT)	1999	1	1

Kishnani, the world-renowned expert in Pompe (glycogen storage disease type II). Some conditions are overseen by pediatric specialists at the other medical schools across the state.

Recent improvements in the North Carolina newborn screening program include the process by which newborn specimens are transported to the North Carolina State Laboratory. With support from the state, all birthing centers can now send specimens overnight via United Parcel Service (UPS), which negates mailing costs as a deterrent to timely transport and testing for newborns in North Carolina. Additionally, staff members in the newborn screening laboratory have moved to a six-day work week, allowing them to receive and process specimens on Saturdays and select holidays, continuing to improve the testing turnaround time for these critical specimens.

The North Carolina State Laboratory began a collaborative relationship with Research Triangle Institute (RTI) in 2016. RTI serves as an administrative liaison to secure grant funding for newborn screening research and advanced test-

ing methodologies. Funding obtained through this collaboration has facilitated pilot studies for several new disorders.

The North Carolina newborn screening laboratory was also selected by the Association of Public Health Laboratories (APHL) and the Centers for Disease Control and Prevention (CDC) as a host site for the Ronald Laessig Memorial Fellowship. This is a competitive fellowship in which every two years state newborn screening programs compete to be designated as a host laboratory. This fellowship has enabled the laboratory to utilize targeted next-generation sequencing to provide better predictions for cystic fibrosis.

During the 2018-2019 legislative session, the North Carolina General Assembly provided support for adding three new conditions to the state newborn screening program: Mucopolysaccharidosis Type I (MPS I), Pompe, and X-linked adrenoleukodystrophy (X-ALD) [8]. Along with funding support for new instrumentation, staff, and start-up costs for these conditions, this will permit implementation of these new parameters in the North Carolina newborn screening laboratory. The new legislation also increases the fee for newborn screening to fully cover all the new and existing costs associated with both the testing and the follow-up program. Originally, these costs were fully supported with appropriations until 2002 when the legislature approved the use of a $10.00 fee to offset state and federal (Medicaid) funding for newborn testing. Since that time, when new testing parameters have been added, new fees have been implemented to cover new testing costs. Noted in Table 2 is the historical timeline of fees charged for the program.

The role and scope of newborn screening is ever expanding. While traditionally it was only concerned with a few inborn errors that led to intellectual handicap, the North Carolina newborn screening program now includes disorders that can cause premature death, immune deficiency, hearing disorders, and heart problems. With recent legislation, future policy decisions regarding the program will officially be made based on conditions that are added to the RUSP. Although this provides for a science-based decision mechanism for adding new conditions, this new legislation also mandates using a currently cumbersome and time-consuming rule-making process in order to implement any future new conditions to the North Carolina newborn testing panel. It will take time to determine if this new process will help or hinder future innovations in the state's newborn screening program. NCMJ

TABLE 2.
History of Fees for NC Newborn Screening Program

Start Date	End Date	Newborn Screening Invoice Fees
11/1/2002	8/31/2005	$10.00
9/1/2005	7/31/2008	$14.00
8/1/2008	6/30/2016	$19.00
7/1/2016	6/30/2018	$44.00
7/1/2018	Present	$128.00

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