UNWINDING THE ETHICAL CONCERNS OF NEWBORN SCREENING IN THE AGE OF GENOMIC MEDICINE

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ABSTRACT

The thesis begins by examining the history of the newborn screening (NBS) process in the United States and why it is the way it is today. The next section explores why certain genetic conditions, such as Long QT Syndrome (LQTS), do not fulfill requirements for the recommended uniform screening panel (RUSP). Lastly, ethical considerations of expanded NBS in the age of genomic technology are examined by highlighting the principles of autonomy, beneficence, equity, cost-effectiveness, privacy and trust. Overall, the NBS process benefits children by identifying serious rare diseases and intervening early to prevent harm; however, a deeper ethical analysis highlights some of the concerns with expanding mandatory, universal NBS in the age of precision medicine. The focus must be on educating the public and healthcare professionals about the NBS process and using evidence-based protocols for adding new conditions to the panel.

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CHAPTER 1: INTRODUCTION

Within the initial 24-48 hours of life, a newborn baby undergoes their "first test." A heel stick is obtained to collect a blood sample for the newborn screen (NBS) to check for possible metabolic, endocrine, and hematologic disorders before signs and symptoms appear. The majority of these disorders are hereditary, rare, and harmful causing developmental delay, morbidity or mortality if not treated early. The state mandated NBS, a public health initiative, is now routine in every hospital across the United States. However, the NBS was not done when my parents were born in the 1950's. When I was born in the 1990's there was no uniform screening panel resulting in major variability in the screening panels from one state to another. Some states screened for 30 different conditions, while others screened for fewer than 5 conditions. Currently, based on the American College of Medical Genetics (ACMG) Recommended Uniform Screening Panel (RUSP), which is supported by the Advisory Committee on Heritable Disorder in Newborns and Children (ACHDNC) and recommended by the Secretary of Health and Human Services (HHS), there are 35 core conditions and 26 secondary conditions that are endorsed for newborn screening (Health Resources & Services Administration [HRSA], 2020). States have the option to decide which conditions to screen for in their newborn screening program and most states have chosen to screen for most or all of the core conditions.

Technological advances, rapidly evolving knowledge, patient advocacy groups, and health issues that get politicized have fueled the rapid expansion of population genetic screening targeted at the youngest members of society. As screening for conditions within the RUSP expands, other heritable disorders, such as Long QT

Syndrome (LQTS), do not qualify for universal newborn screening. It is imperative to understand why universal screening is considered standard of care for some genetic conditions and not for others.

Newborn genetic screening is just that – screening. It is not a diagnostic exercise. It is designed to detect abnormal levels of metabolites in the blood of an asymptomatic newborn that *might* be evidence of a genetic disorder. Screening is not simply one event – it is a process to uncover an abnormal result. Abnormal results are then checked by repeat testing to either confirm the diagnosis or elucidate what was a false positive test result. As the NBS public health program continues to expand in an age of precision medicine, it is critical to consider the ethical implications of each facet of the program, including sample collection and storage, variability of the screening tests from state to state, confirmatory testing, and communication of results. It is just as important to understand how parents are being educated about NBS programs, what treatment options are available once a diagnosis is made, and the availability of short-term and long-term follow-up for these patients and families.

The field of genomics is quickly evolving, and the findings are being applied in the clinical setting for diagnostic, therapeutic, and even preventative purposes. Genomics is also having a significant impact on a baby's "first test" – the mandatory universal newborn screening panel – which has become standard of care. The NBS is a state-run public health screening program, designed by numerous stakeholders who are invested in the program for different reasons. Are these decision-makers building a fair, ethical genetic screening program for all children and their families? This thesis will examine the changes in the NBS program over time and the ethical concerns surrounding the newborn

screening process in the age of precision medicine. I will examine relevant cases I was involved in during my clinical training, review the current literature, and share insights from discussion with pediatricians. The NBS is about preventing impairment – the widespread search for genetic abnormalities that cause *harm* if not treated early. While I see the benefit in that application of NBS, I argue that it is unethical to initiate *mandatory universal* newborn screening for genetic variations with uncertain clinical significance in order to uncover "genetic imperfections" with no follow-up or interventions to offer patients or families.

CHAPTER 2: THE NEWBORN SCREENING STORY

Victory of the "Guthrie Test"

On October 17, 1961, President John F. Kennedy established the President's Panel on Mental Retardation, which was composed of experts from various fields, and they issued the "Report of the Task Force on Law" to address "research and manpower, treatment and care, education and preparation for employment, legal protection and development of federal, state and local programs" for the "naturally disabled" (President's Panel on Mental Retardation, 1963, p. 5). This Report grapples with topics such as mental illness, developmental disabilities, and intellectual disabilities. The task force struggles with definitions of normal and abnormal persons in relation to the law. Under section two entitled, "Mental Retardation: The Medical Context," the task force explains, "…it is possible that retarded children can become more retarded through failure to detect their condition early and to provide effective measures of treatment and training" (1963, p.17). On October 6, 1963 a panel of pediatricians at the Section on Child Development Meeting discussed the special call to action towards focusing on problems of development within their own practices or through their research (Knobloch, 1963).

Around this same time in the late 1950's and early 1960's, Robert Guthrie, an American microbiologist, cancer researcher, and active member of the New York State Association for Retarded Children, developed a test to detect Phenylketonuria (PKU), a rare autosomal recessive genetic disorder that occurs in 1 in 10,000 to 15,000 newborns in the United States (NIH, Genetics Home Reference: PKU, 2017; Guthrie, 1992). PKU is caused by a deficiency in the phenylalanine hydroxylase enzyme that is necessary to

break down the amino acid phenylalanine into tyrosine. The clinical manifestations of children with PKU include seizures as early as 24 hours after birth, albinism, "musty" odor of sweat and urine, failure to attain developmental milestones, and intellectual disability (ID) (NIH, Genetics Home Reference: PKU, 2017). Early treatment with low protein diet and phenylalanine-free amino acid supplements – that must be continued throughout a child's entire life – decreases the buildup of toxic metabolites leading to improved clinical outcomes. Guthrie's test required a drop of the baby's blood to be put on a piece of filter paper, which was then analyzed for signs of PKU by utilizing a bacterial inhibition assay (BIA) (Driscoll & McPherson, 2010; Guthrie, 1992). Early diagnosis of PKU through laboratory analysis of a newborn dried bloodspot screening (NDBS) allowed for immediate dietary intervention by phenylalanine restriction in the infant's diet to avoid long-term neurological deficits.

Guthrie's passion and motivation for early detection of metabolic conditions that cause intellectual and developmental delay stemmed from his personal experience of caring for a son with ID and niece with autism and ID. His niece was diagnosed with PKU at 15 months of age (Guthrie, 1992). Guthrie wrote an article titled, "The origin of newborn screening," for the first issue of the Journal, *Screening*, published in 1992, in which he opened with, "It began with our second child, John. He is mentally retarded. John stimulated me to go into research aimed at preventing mental retardation and developmental disabilities" (p. 5). From 1957 to 1961, Guthrie began collecting whole blood specimens on filter paper to trial his new screening test for PKU. With support from Dr. Alfred Yankhauer, the Director of Maternal and Child Health for New York State, Guthrie tested his BIA for phenylalanine on 3118 blood filter paper specimens

from residents at Newark State School for the mentally disabled (Guthrie, 1961). The same residents were screened for PKU utilizing the known, yet flawed urine ferric chloride method. Guthrie's results revealed that the whole blood BIA method identified the 17 PKU cases confirmed by the urine screening method, identified at least 2 PKU cases missed due to difficulty attaining a urine sample, and also identified one patient in which urine testing was negative 3 times yet "2 confirmatory blood level determinations gave values of 18-20 and 36-40mg per cent, respectively" (Guthrie, 1961, p. 863). Guthrie demonstrated that the blood filter paper BIA screening method could provide early identification of infants with PKU compared to the then gold standard urine ferric chloride method that had an increased number of false negatives.

The success of mandated neonatal screening for PKU highlights the importance of passionate individuals, fortunate timing, patient advocacy, and efficient systems to achieve change. In 1961, Guthrie began receiving newborn dried bloodspot specimens to screen for PKU from counties throughout New York (Guthrie, 1992). His passion for wanting to combat developmental and intellectual disabilities due to inborn errors of metabolism (IEM) resonated with public and governmental agencies. Guthrie met Dr. Arthur Lesser, the Director of the Maternal and Child Health Division of the U.S. Children's Bureau, at an annual American Public Health Association meeting and notes, "At that time the Children's Bureau was amply funded, particularly for projects to prevent mental retardation, because of the influence of President John F. Kennedy, who had a retarded sister. Dr. Lesser decided to provide the funds for a national trial to begin in 1962" (Guthrie, 1992, p. 8). Guthrie describes the process of developing a well-organized laboratory system as "a little factory" in which the screening kit is "'instant',

like instant coffee" to efficiently screen one million infants for PKU (1992, p. 9). Guthrie clearly wanted to expand PKU screening to allow basic laboratory employees to perform simple, timely PKU screening before permanent neurological damage could ensue.

Nevertheless, as a microbiologist, Guthrie knew he needed the support of the medical community, specifically pediatricians, to adopt his program of universal newborn screening for IEMs for it to be successful. Many pediatricians, such as Dr. Stanley W. Wright, Associate professor of Pediatrics at the University of California School of Medicine, were opposed to universal screening for rare diseases like PKU and thought the focus should be on identification of high-risk families with children already affected by PKU to allow for counseling and early detection of future children at risk (Wright, 1962). Despite resistance from the medical community, state mandated neonatal PKU screening grew with the help of patient advocacy groups such as the National Association for Retarded Children (NARC). Guthrie writes, "The role of the NARC cannot be overestimated in providing support for neonatal screening of PKU. During the 1962-67 period their state chapters vigorously lobbied for laws for PKU screening. By 1967, 37 states had such laws, almost all requiring this screening for newborn infants" (1992, p. 12). Based on this support, Guthrie's PKU test clearly was accepted as a mandated universal screening test for newborns across the United States. Using a simple heel prick to produce a NDBS specimen, screening for other IEMs such as Galactosemia, Maple Syrup Urine Disease (MSUD), and Homocystinuria soon became available (Guthrie, 1992).

Focus on NDBS as a Public Health Initiative

In the midst of Guthrie's successful and expanding NDBS platform, the World Health Organization (WHO) Scientific Group on Screening for Inborn Errors of Metabolism (IEM) met in Geneva in November 1967 to discuss "to consider whether and how screening programmes for such disorders could improve the health of mankind" (WHO Technical Report Series No. 401, 1968, p. 5). Around the same time, a 1968 WHO report written by Wilson, then Principal Medical Officer at the Ministry of Health in London, and Jungner, then Chief of the Clinical Chemistry Department of Sahlgren's Hospital in Sweden, issued 10 population screening criteria that have greatly influenced how the public health community thinks about screening programs (Jungner & Wilson, 1968). Wilson & Jungner's report focuses on the importance of screening for early detection of chronic diseases within developed countries where "an improvement in social conditions has been accompanied by a decline in communicable disease and by an apparent or real increase in degenerative and genetically determined disease" (1968, p. 15). The criteria set forth by Wilson and Jungner provide a solid framework for the development of screening programs for early detection of prevalent, treatable disorders within the general population.

The WHO report on Screening for IEM (1968), conversely, stresses the unique aspects surrounding mass screening for heritable diseases. These distinct features include – importance of genotype compared to phenotype, preventative medicine for the patient vs. collection of scientific data for the good of public health, and the nature vs. nurture interaction (1968). The Scientific Group (1968) explains how most IEM are recessive disorders, thus homozygous individuals – those with two mutant alleles – have the disease phenotype while heterozygotes do not. "However, a specific environmental stress

or an appropriate loading test may result in the appearance of a measurable abnormality in a heterozygote; this generally happens, for instance, when excessive amounts of phenylalanine are administered to heterozygotes for phenylketonuria" (1968, p. 6). Genotypes, gene products, phenotypes, and the environment are inherently linked with one another which emphasizes the importance of understanding the pathophysiology and natural history of a disease process before screening protocols are in place to detect it. In regards to mass screening for IEM, the report states it "cannot be undertaken lightly," and points to Wilson & Jungner's criteria to guide communities with adequate resources, such as laboratories, clinical facilities for diagnosis, available treatment, education programs, and economic means to initiate widespread programs (1968, p. 42).

The United States did have adequate resources, technology, and advocacy to grow NDBS programs. In the 1970's and 1980's, state-run NDBS programs, such as those in Texas, New York, and California began to screen for more conditions and create computerized data management systems (Driscoll & McPherson, 2010). In response to the rapid expansion of NBDS programs, advances in the field of genetics, and a letter by the Chairman of the Social Issues Committee of the American Society of Human Genetics (ASHG), the National Research Council (NRC) issued a report in 1975 that set forth recommendations stating genetic screening should be undertaken "under controlled conditions" within a public health framework to allow for standardization and quality control (NRC, 1975, p. iv; p. 1).

The report continues to discuss how most genetic screening has been focused on high-risk groups in which there is a higher prevalence of disease (1975). The committee argues that selective screening for particular groups of people, such as Ashkenazi Jews

for Tay Sachs disease and African Americans for Sickle Cell Disease (SCD), might encourage discriminatory ideals "that we are at pains to eliminate from our society and that should be permitted to play no part in genetic screening" (1975, p. 242). Yet, the committee explains the main reason for selective screening is not based on discrimination – it is because of economic feasibility and the need for cheaper, more efficient screening systems for conditions in which early detection can lead to early interventions (1975, p. 242-243).

The call for efficiency was answered in the 1980's when computerized data management systems for NDBS programs were initiated to allow states to handle large amounts of NDBS samples being sent into the laboratory. A review article published in the *Journal of Medical Systems* in 1988 reveals that multiple states began using computerized tracking systems for various steps within the screening process (Meaney, 1988). The automated tracking techniques utilized by numerous states at that time ranged from specimen entry only to automated processes from specimen collection to follow-up (1988). A 1984 survey from the Illinois Department of Public Health determined 19 states had an "automated follow-up" protocol in place for some or all conditions within their newborn screening program (Meaney, 1988, p. 71). Additionally, costs and funding for laboratory materials, computerized systems, and proper follow-up remained a major concern as NDBS programs in the United States expanded in the 1980's (Meaney, 1988).

Other concerns around this same time stressed lack of consistency between state screening programs. For example, some states screened for SCD and others did not due to reservations about the utility of early detection, questions about carrier status, and ambiguity about who to screen (NIH, Consensus Conference, 1987). SCD is more

prevalent within the African American and African Caribbean populations. The Centers for Diseases Control and Prevention (CDC) estimates "about 1 in 13 black or African-American babies is born with sickle cell trait (SCT)" and "SCD occurs among about 1 out of every 365 Black or African-American births" (CDC, Data & Statistics on Sickle Cell Disease, 2019). During the 1980's, researchers, clinicians, and public health officials created programs to improve the healthcare of sickle cell patients (Prabhakar, Haywood, Molokie, 2010). Gaston et al. published results of the Prophylactic Penicillin Study (PROPS) that demonstrated prophylactic penicillin by four months of age in children with SCD greatly decreased the risk of pneumococcal septicemia (Gaston et al., 1986). The researchers concluded that "neonatal detection of sickle cell anemia should be a high priority, since it is the first step in the prevention of morbidity and mortality due to severe bacterial infections among young children with SS hemoglobinopathy" (Gaston et al., 1986, p. 1598). This study was the spark that began the battle for equitable newborn screening protocols for SCD.

The 1987 NIH Consensus Conference on "Newborn Screening for Sickle Cell Disease and Other Hemoglobinopathies" recommended state-mandated universal screening for SCD within a "comprehensive program for the care of sickle cell patients and their families" (p. 1209). Despite the NIH's recommendations and increased funding for SCD screening through the HRSA, newborn screening for SCD was not mandated in all states until 2005 (Driscoll & McPherson, 2010). The 1990's and early 2000's introduced novel technology that transformed Guthrie's original NDBS into the state-mandated public health newborn screen (NBS) program. With more scientific knowledge

and desire for genomic information in the start of the 21st century, questions about equity and uniform screening panels remained a major issue.

Mass Spectrometry and Expansion of the Newborn Screening Panel

The dried bloodspot cards allowed researchers to use different tools such as DNA extraction, RNA analysis, and second tier testing to provide more information that could lead to timelier diagnoses (Driscoll & McPherson, 2010). Yet, the most powerful force in the 1990's that changed newborn genetic screening was tandem mass spectrometry (MS/MS). Instead of performing a series of different tests on the NDBS cards for each specific disorder, MS/MS produced a panel of metabolites from one bloodspot. Acylcarnitines, organic acids, amino acids, and other metabolites could be easily identified and ratios or values produced to determine whether the levels are normal or abnormal. According to Tarini et al., between 1995 and 2005, the average number of conditions added to the NBS panel was 19 (2006). Furthermore, Tarini et al. emphasize the advantages of MS/MS – "quick (~1-2 minutes), relatively inexpensive ($10-30), and readily scalable, because increasing the number of conditions screened does not change the time or price substantially" (2006, p. 449). Nevertheless, questions surrounding false positives, cut-off values, non-pathological variations, and availability of treatment caused state governments to hesitate when deciding to apply this technology to their newborn screening programs (Bhattachatya, et al., 2014; Baily & Murray, 2009).

As NBS exploded in the 1990's with the advent of MS/MS, the use of dried bloodspots to screen for infectious diseases like HIV in some states, and discovery of technologies for newborn hearing screening, the US government called upon the American Academy of Pediatrics (AAP) to create recommendations to "strengthen" state

newborn screening programs (Newborn Screening Task Force Report, 2000). Governmental agencies and professional societies like the AAP helped build the newborn screening infrastructure; however, mandated screening for conditions still varied widely between states and no standard of care for newborn screening panels existed. States wanted to embrace the traditional Wilson & Jungner screening criteria but were simultaneously getting pressure to expand their screening panels based on groups who were advocating to use emerging technologies (Baily & Murray, 2009). There needed to be consensus with regard to uniform screening for all states that would balance screening for established diseases for which early intervention could reduce morbidity and mortality, and screening that employs newer genetic technology that may advance scientific discovery of rare inherited disorders.

Between 2002 and 2005, the ACMG developed the RUSP with support from the Maternal Child Health Bureau (MCHB) of the HRSA. The report states: "A total of 292 individuals determined to be generally representative of the regional distribution of the United States population and of areas of expertise or involvement in newborn screening provided a total of 3,949 evaluations of 84 conditions" (ACMG, 2006, p. 9). The conditions were assessed using a two-tiered approach consisting of surveys in which the respondents scored the conditions based on various criteria and then "evidence from the scientific literature" was incorporated with the survey outcomes (2006, p. 47). The 29 "primary target conditions" or "core panel" had scores 1,200 or above and were deemed "appropriate for newborn screening" (2006, p. 62). They fulfilled the criteria below:

> *"1) It can be identified at a period of time (24 to 48 hours after birth) at which it would not ordinarily be clinically detected. 2) A*

> *test with appropriate sensitivity and specificity is available. 3) There are demonstrated benefits of early detection, timely intervention, and efficacious treatment."* (ACMG, 2006, p. 29)

According to the ACMG working group, the 25 "secondary targets" are defined as conditions "identified while searching for the primary target…or a clinically significant condition that is likely to be detected when performing a comprehensive profile of a given group of biochemical markers" (2006, p. 29). There was much criticism from the bioethics and pediatric communities regarding ACMGs methodology and its decision to add conditions to the RUSP in which the natural history was not well known (Botkin et al., 2006; President's Council on Bioethics, 2008). President Bush's Council on Bioethics issued a paper in 2008 titled "The Changing Moral Focus of Newborn Screening" that discusses how the RUSP is a departure from the traditional screening framework set forth by Wilson & Jungner. A letter dated November 22, 2009 from R. Rodney Howell, the Chairperson of the ACHDNC at the time, to Secretary Sebelius of the HHS, discusses how "the [S]ACHDNC has many reservations about the final report from President Bush's Council on Bioethics" and asks the Secretary whether HHS will accept the recommendations (Howell, 2009, p. 2). In May 21, 2010, Secretary Sebelius accepted the RUSP "as a national standard for newborn screening programs and facilitate the adoption of [S]ACHDNC's Recommended Uniform Panel by all State newborn screening programs" (Sebelius, 2010, p. 1).

Despite the adoption of ACHDNC's Recommended Uniform Panel, states still voluntarily decide which conditions they will screen for; however, most states follow all recommendations on the core panel. The role of federal government is evident in the

establishment of the ACHDNC in February 2003, and further defines its role with the Newborn Screening Saves Lives Act of 2007, which has helped to fund and assist states in NBS activities (NIH, "Brief History of Newborn Screening," 2017). The ACHDNC has established protocols to propose new conditions to the panel and routinely assess the quality of state NBS programs.[i] Additionally, the ACMG has stayed involved in the newborn screening process by creating ACT sheets to help healthcare providers navigate the short-term follow-up procedures for genetic conditions.[ii] The interaction between the federal government, state legislature, and professional organizations such as the ACMG, along with MS/MS technology, played a pivotal role in facilitating the expansion of population-wide NBS in the United States.

Newborn Genetic Screening in the Age of Precision Medicine

Initial expansion of NBS and the call for a RUSP occurred at a time when society was focused on sequencing the entire human genome. In 1988 the NRC published a report titled *Mapping and Sequencing the Human Genome* in which recommendations were considered in regards to this "special effort" known today as the Human Genome Project (Olson, 2017, p. 4-5). The sequencing of 3 billion base pairs – or "letters" – within the human genome was completed in 2003. In 2011 the NRC published another report titled *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease* (Olson, 2017, p. 7). Maynard Olson, a chemist

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[i] The ACHDNC page on the HRSA website has an advisory notice that states: "The statutory authority of the Congressionally established Advisory Committee on Heritable Disorders in Newborns and Children (Committee) expired on September 30, 2019. All official business related to the Congressionally established Committee, including workgroup activities, is halted at this time."

[ii] https://www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms.aspx

and now Professor of Genome Sciences and Medicine at the University of Washington, served on both NRC committees and calls the 2011 report "a sequel' to the *Mapping and Sequencing* report (2017, p. 7). The "sequel" focuses on recommendations to use sequencing technology to improve health outcomes. President Obama announced the Precision Medicine Initiative "to understand how a person's genetics, environment, and lifestyle can help determine the best approach to prevent or treat disease" (NIH, Genetics Home Reference, 2015).

Feero and Gutmacher explore the connections between "Genomics, personalized medicine, and pediatrics" to examine how genomic technology impacts the pediatric population (2014). In regards to newborn screening, Feero & Gutmacher note that the NIH initiated a program in 2013 to begin pilot studies in four hospitals assessing the feasibility, clinical outcomes, and ethical implications of using genetic sequencing technology in the newborn period (2014; see NIH News & Events, September 4, 2013). The evolution and expansion of NBS public health programs in the United States has been heavily influenced by political pressures and scientific discoveries. If President Kennedy had not issued a panel focused on issues related to individuals with developmental and intellectual disabilities, would newborn screening for PKU been implemented so quickly or even at all? The quest for genomic knowledge greatly influences the world today. Despite these scientific forces pushing for using newborn screening as a platform to generate scientific data in pursuit of new discoveries, it is paramount that universal mandated newborn screening continues to be focused on its fundamental mission of preventing harm to infants by the recognition and early intervention of treatable genetic disorders.

CHAPTER 3: UNIVERSAL SCREENING FOR LONG QT SYNDROME

There is controversy surrounding universal screening for Long QT Syndrome (LQTS), a disorder of the cardiac conduction system leading to fatal arrhythmias that is believed to affect about 1:2500-1:5000 people (Tristani-Firouzi, 2015). This condition is associated with various genetic mutations involving cardiac ion channels, most commonly mutations in KCNQ1 and KCNH2 (Tristani-Firouzi, 2015). Tester and Ackerman review the link between genetic cardiac channelopathies and sudden infant death syndrome (SIDS) following Schwartz et al.'s controversial 1998 report that concluded: "Prolongation of the QT interval in the first week of life is strongly associated with SIDS. Neonatal electrocardiographic screening may permit the early identification of a substantial percentage of infants at risk for SIDS, and the institution of preventative measure may therefore be possible" (Schwartz et al, 1998, p. 1709; Tester & Ackerman, 2005). Preventative measures that have been shown to decrease the incidence of sudden death in patients with LQTS include beta blockers and implantable cardioverter/defibrillators (ICDs) (Tristani-Firouzi, 2015). Tester and Ackerman determine genetic cardiac ion channel mutations account for about 5% of SIDS among Caucasian infants and 2.9% among Black infants, noting this is based on only one cohort and needs to be replicated in different populations (Tester & Ackerman, 2005).

It is evident some association exists between LQTS and SIDS. LQTS has a higher incidence than PKU. Additionally, relatively inexpensive medication can reduce the risk of sudden death from this genetic condition. The ACMG report "Toward a Uniform Screening Panel and System" briefly mentioned ECG screening for LQTS in regards to being "considered for application to universal newborn population screening" (2006, p.

18). It is not on the RUSP and, based on the benefit/risk assessment of universal screening for LQTS, why is this so? There are arguments both for and against universal screening of LQTS based on clinical experience, cost-saving analyses, and patient advocates; yet, this condition does not fulfill requirements to justify screening an entire population.

One of the key reasons for the limitation of widespread newborn screening for LQTS cited in the literature is the absence of a "suitable" screening test – a qualification needed to complete Wilson & Jungner's "Principles of Early Disease Detection" (1968, pgs 26-27). LQTS is a pathology involving abnormalities in the ventricular repolarization of the heart. Electrocardiograms (ECGs) are utilized to assess the electrical conduction and rhythm of the heart leading to muscle contraction and blood circulation. The QTc interval of the ECG is used as a screening tool for LQTS. The QTc is calculated by "dividing the QT measurement by the square root of the preceding RR interval"; thus, altering the QT value based on the heart rate (Tristani-Firouzi, 2015, p. 1054). Tristani-Firouzi highlights the issues with this method – Bazett's formula – the standard approach to evaluate ventricular repolarization:

> *"Bazett's correction is notoriously inaccurate at elevated heart rates typical of the normal newborn (130-170 bpm). Moreover, the QT measurement itself has a low signal-to-noise ratio; the end of a T wave can be difficult to determine in a noisy signal (typical of a crying newborn) …Finally, the QTc measurement is cumbersome, time-consuming and can be difficult to accurately measure, even in adults"* (2015, p. 1054).

Criticism surrounding neonatal ECG screening for LQTS is based on both the broad distribution of normal QTc measurements and the lack of a clear correlation between LQTS and SIDS – an important connection needed to understand how treatment will prevent infant mortality.

Additional studies have looked at alternative methods to identify those newborns at risk for LQTS. A study conducted at the Mayo clinic looked at prolonged QTc measurements [average of 475 ms or greater from 24-hour QTc interval monitoring] using continuous monitoring with three-lead placement in 589 hospitalized neonates in the NICU from day 3 to day 7 of life (Kaemingk et al., 2020). The study (2020) found that 33 out of 589 infants screened positive on continuous monitoring and 30 of those 33 infants had follow-up 12 lead ECGs. None of these 30 infants had two ECGs with evidence of prolonged QTc, resulting in a positive predictive value (PPV) of continuous monitoring of 0% (Kaemingk et al., 2020). This research (2020) reveals continuous 3-lead ECG monitoring is a poor tool to identify those at risk of LQTS, resulting in unnecessary parental anxiety and unwarranted hospital costs.

The literature also discusses cost-effectiveness of screening for LQTS and screening in high risk groups or for before participation in athletics. An article from a group at Harvard in the *Journal of Pediatrics* (2000) compares the cost-effectiveness (life-years) of no screening, universal screening and high-risk neonatal ECG screening for LQTS (assuming efficacy of treatment and association between LQTS and SIDS) (Zupancic et al., 2000). The study (2000) discusses many interesting points about treatment efficacy, pathophysiology, need for additional trained cardiologist to read pediatric ECGs, and sensitivity/specificity relating to cost-effectiveness. Overall, in terms

of universal screening the study concludes, "…although the cost-effectiveness ratios are very good, the size of such programs is monumental, and the resulting $335-million-dollar cost would drain resources from many other slightly less cost-effective but smaller programs, thus creating equity problems" (Zupancic et al., 2000, p. 488). In terms of the high-risk neonatal group, researchers mention how the risk factors for SIDS may be different than those for LQTS, making it difficult to define those at high-risk (Zupancic et al., 2000).

Some countries have initiated mandatory ECG screening before participating in sports (Italy) or school-based ECG screening protocols (Japan). Tristani-Firouzi (2015) notes ECG screening for student athletes is more likely to expose other cardiac abnormalities, such as hypertrophic cardiomyopathy, compared to LQTS. Furthermore, the American Heart Association states that mandatory pre-participation ECGs are unnecessary (Tristani-Firouzi, 2015). Based on the findings above, LQTS is an example of a condition for which multiple factors – underlying pathophysiology, accuracy of screening tests, and cost-effectiveness of universal screening – must first be sorted out before a decision is made regarding implementation of mandatory screening protocols.

There are many genetic conditions that do not meet Wilson & Jungner's traditional screening criteria and are not part of the NBS panel in the United States. There is a growing interest, however, in adding various genetic conditions to the NBS panel and each of these cases is unique. One such example is included in a chapter in *Ethics and Newborn Genetic Screening* (Bailey & Murray, 2009) dedicated to a genetic condition that does not meet screening requirements – Duchenne Muscular Dystrophy (Ross, 2009, p. 106-124). In the age of genomic medicine, and based on pressure from patient

advocacy groups (in this case, the Parent Project Muscular Dystrophy [PPMD]), pilot studies such as the one in New York State began to screen 100,000 babies for DMD with parental consent over a two-year period to assess appropriateness for the RUSP (New York Department of Health, 2019 Press Releases). According to the New York Department of Health, "two therapies for DMD have been FDA-approved, and there are many more in the pipeline with ongoing clinical trials" (2019, p. 1). This fact may have been another reason for this pilot project to assess the merit of newborn screening for DMD. As advances in genetic screening continue, along with new discoveries in drugs, biologics, and medical devices, groups will be advocating for more genetic conditions to be added to the RUSP; this will require critical thinking and keen bioethical analyses to guide decision making in how best to balance NBS programs both today and in the future.

CHAPTER 4: THE EXPANDED NBS PROCESS – ETHICAL ANALYSIS

The implementation of MS/MS allows screening of a large panel of genetic conditions with one blood sample. The ACMGs RUSP has sanctioned expansion of newborn genetic screening using MS/MS technology. This type of "multiplex testing" is used to screen for IEM, such as fatty acid oxidation defects, amino acid disorders, and organic acid disorders (ACMG, 2006, p. 19). Separate platforms are used to screen for other disorders, such as endocrine disorders like CH and hemoglobinopathies like SCD. Expanded screening opens up the process to screen newborns for metabolites indicative of genetic disorders that might not have recognized treatment options. There has been support for more conditions to be added to the RUSP, and NIH pilot studies are assessing whole exome sequencing (WES) at birth. The technology has clearly arrived, but should we be using it to detect abnormalities in a baby's genome before we fully understand the significance and before the symptoms become apparent? Another key question is whether a genetic abnormality will even become apparent – in other words, are we screening for disease (harm) or normal variation (imperfection)? It is not as simple as it seems. Genetics is a complicated science and expanding newborn genetic screening in the age of precision medicine to include genomic technology requires very careful consideration of how it will affect children, their families, and society at large.

Bioethical concerns regarding newborn genetic screening is not a new subject. A 1975 report by the NRC highlights these concerns in the chapter, "Ethical Aspects of Genetic Screening." The President's Council on Bioethics in 2008 analyzes issues related to newborn screening. Baily and Murray published a book in 2009 titled *Ethics and Newborn Genetic Screening*. Finally, Tarini and Goldenberg published an article in 2012

which discusses the "Ethical Issues with Newborn Screening in the Genomics Era." Bioethics is largely based on perspective. It examines situations based on various vantage points and through different lenses to try and understand why things are the way they are within the realm of medicine, health, disease, and wellness. Bioethics exposes inequities or problems within society – how certain situations lift some people up while knocking others down – and offers solutions to address these inequities. The principles of autonomy, beneficence, equity, cost-effectiveness, privacy and trust will be analyzed using the various sources mentioned above to highlight the complex nature of expanded newborn genetic screening.

Autonomy/Agency

Autonomy is the process of making decisions for oneself. Children do not have the capacity to make decisions for themselves; thus, parents are the decision-makers. Informed consent – the process of telling patients or decision-makers the risk and benefits of a test or intervention – is necessary to make knowledgeable decisions. The 2000 AAP Newborn Screening Task Force Report states "parents should receive information (on behalf of their children) about newborn screening…pregnant women should be made aware of the process and benefits of newborn screening and their right of refusal before testing, preferably during a routine third trimester prenatal care visit" (AAP, 2000, p. 387). The recommendation also discusses the need for supplementary education in the hospital after the baby is born (AAP, 2000). Furthermore, the AAP (2000) asserts that newborn screening does not require written parental consent, unless the infant undergoes "investigational" screening tests (p. 387). In addition, written documentation is necessary if parents decline screening of their newborn infant (AAP, 2000).

Agency is the *ability* or *capacity* to make those decisions for oneself. The Stanford Encyclopedia of Philosophy (SEP) examines the broad concept of agency and its use "to denote the performance of intentional actions" (Schlosser, 2019, p. 1). Agency is action based on beliefs, intentions, desires, personal relationships, and experience. Both timely parental autonomy and agency are vital to allow the newborn screening process to occur. Parents must be informed and understand many different aspects about the process, such as what the initial screening panel includes, when repeat resting may be needed, if confirmatory testing is needed, and what all this means for their child. Nevertheless, the newborn screen is mandatary and happens in the hospital in the first 24-48 hours after birth when the infant is constantly being evaluated and parents are excited, distracted, and often exhausted. In addition, each state has different informed consent/education protocols, and these are not standardized either. Thus, NBS can easily take place without a family being aware and/or fully understanding what it is about because the doctor says it's the right thing to do (Evans, et al., 2019; Kelly et al., 2016). Kelly et al. argue "ensuring that appropriate education is provided and that parents are making truly informed decisions is at best a challenge, and at worst a near impossible task" (2016, p. 8). The 1975 NRC report also highlights the challenges of informed consent in mass genetic screening programs when the "screener" has certain self interests in mind (1975, NRC, p. 196-197). There are numerous barriers preventing parents from clearly understanding the NBS process, the tests being done, and the consequences of foregoing screening. Some of these barriers include a general lack of parental knowledge about the NBS process, the complexity of over 50 genetic conditions on the screening

panel, different levels of health literacy, insurance concerns, language differences, and lack of familiarity dealing with the healthcare delivery system.

The Newborn Screening Education Best Practices Framework, a project supported by the HRSA of the DHHS, offers a multi-step approach which states can utilize to develop educational resources and systems of implementation for their local communities (Evans et al., 2019). The framework (2019) highlights important questions such as: "what is the overall goal of education?", "why does the issue need to be addressed?", "who is the target audience?", "what special considerations are necessary for the target population?", and "what is the best modality for the target population?" (Evans et al., 2019, Figure 1)[iii] These questions stress the importance of unique educational outreach methods that are tailored to the target population. The conclusion of the 2019 education framework states, "As the field of molecular and genetic testing expands, the capabilities of NBS grow as well…new challenges caused by language and culture may arise as screening capabilities spread" (Evans et al., 2019, p. 8-9). Steps have been taken to increase parental education for culturally and geographically diverse backgrounds with the use of Spanish brochures, social media, phone apps, and more outreach from NBS screening programs to the community. However, in the age of precision medicine, the expansion of NBS panels to include DNA-based screening platforms and conditions with no effective treatment will generate even more information that will require additional educational efforts.

[iii]PDF version of the Best Practices Framework from Baby's First Test: https://www.babysfirsttest.org/sites/default/files/NBS%20Best%20Practice%20Framework_Final_0.pdf

The NBS is unique in that states can ignore a parent's decision to decline newborn screening, taking away their autonomy and agency. NBS is technically a mandatory test – the state can override parental autonomy under the "individualized child welfare/child benefit model" (Tarini & Goldenberg, 2012, p. 384). Tarini & Goldenberg (2012) explore this issue by emphasizing the principle of *parens patriae*, which is Latin for "parent of his or her country" (Cornell Law School, "*parens patriae*"). The state can technically require newborn screening if they believe forfeiting the test would lead to more harm than good to the child. Tarini & Goldenberg (2012) discuss a case in Nebraska where the principle of *parens patriae* was upheld which led to temporary removal of the child by DHHS from the home until the newborn screen results returned. According to the legal documents, Joel Anaya was born at home on September 2, 2007 and appeared to be healthy (276 Neb. 825, 2008). His parents refused the newborn screen when approached by a DHHS newborn screening staff member. The Anayas "stated that the taking of a blood sample from Joel was contrary to their sincerely held religious beliefs, and they unsuccessfully challenged the newborn screening statues as violative of their right to the free exercise of religion under Neb. Const. art. I, & 4" (276 Neb. 825, 2008, p. 829). The Nebraska newborn screening statute required each newborn to be screened for 8 disorders – "congenital primary hypothyroidism, hemoglobinopathies, biotinidase deficiency, congenital adrenal hyperplasia, cystic fibrosis, phenylketonuria, medium-chain acyl co-a dehydrogenase (MCAD) deficiency, and galactosemia" (276 Neb. 825, 2008, p. 827; Neb Rev. Stat. & 71-519). Despite this experience in Nebraska, most states allow parents to refuse NBS for religious or other reasons and will respect this decision.

The belief that newborn screening is in the child's best interest and should be mandated is similar to the argument surrounding vaccine requirements. A panel of vaccines are mandatory to attend school in the United States; however, parents can refuse based on state statutes within vaccination laws that grant opposition on the basis of religious or "philosophic" reasons. Malone & Hinman write a chapter highlighting the importance of mandatory vaccinations in the prevention of serious communicable diseases, titled "Vaccination Mandates: The Public Health Imperative and Individual Rights" in which they argue "on both *parens patriae* and police power grounds the US Supreme Court sees a compelling state interest in mandating vaccination of children because of the health threat to the community and to the children themselves" (Malone & Hinman, 2007, p. 275). Both the required vaccination program and NBS demonstrate the ethical dilemma when individual liberty of a child (as decided by a parent) and the public welfare are in conflict. In both cases, most states do not necessarily "force" these interventions onto a child when parents do not consent for NBS or vaccinations.

In examining the issue of autonomy within the scope of NBS and vaccine programs, there appears to be three different approaches that can be taken: 1) voluntary/optional informed consent in which it is entirely up to the guardian to opt in or out; 2) a "mandatory" test that must be offered and given to every child, unless parents choose to 'opt out' based on religious or philosophical reasons; and, 3) mandatory/required/compulsory testing that always overrides parental decision making and authority. The second approach lies along a spectrum of how easy or difficult it is for a parent to opt out – demonstrating the struggle between values of individual liberty and public safety. The higher the benefit-risk ratio for a test or intervention, the harder it

should be to opt out, undermining parental autonomy and individual liberty for the benefit of public welfare.

On the other hand, what if a parent wants even more genetic screening or testing done for their child. Does a parent have the right to know and within what framework can this be done? This approach explores the idea of allowing parents to have even more options to uncover genetic variation in their child's genome. Duane Alexander, then director of the National Institute of Child Health and Human Development (NICHD), and Peter C. van Dyck argue in their 2006 article, "A Vision of the Future of Newborn Screening," an expanded and uniform newborn screening protocol should be put in place to allow technologies such as MS/MS and DNA microarrays to screen for a greatly expanded panel of genetic disorders in newborns even if effective treatment does not exist (Alexander & van Dyck, 2006). Alexander & van Dyck (2006) argue that the central principle of screening programs – availability of effective treatment – should be questioned:

> *"That tenet served a useful purpose in the early years of newborn screening, but it is now being challenged as outmoded because it fails to consider other benefits of diagnosis in the newborn period and dooms us to continued ignorance and unavailability of treatment because affected individuals are not identified until they exhibit symptoms, too late for effective preventative interventions to be tested or applied"* (p. S352).

Alexander & van Dyck (2006) emphasize the need for organized, private registries of those children with genetic conditions, additional education, and infrastructure if this

expansion were to take place. They highlight the need for informed consent "at least for screening for the conditions for which there is not yet an effective treatment" (2006, p. S352). Alexander & van Dyck (2006) embrace the technological imperative – using novel technology because it exists and we can – to uncover genetic variation.

Parents can freely exercise their right to uncover their child's genetic makeup with direct to consumer (DTC) genetic tests; however, the AAP and FDA urge parents to "talk about DTC test results with a health care provider before making any decisions" (Korioth, 2019, p. 1). The line is blurred, and the situation becomes complex when parents want to know about medical conditions that might not show up until a child is an adult, such as Alzheimer's disease or Huntingdon's disease. I believe it is ethical for parents to voluntarily screen their infant for genetic disorders of childhood that don't have valid treatment options because they have the right to know as guardians and caretakers. However, they do not have the right to screen or test for genetic predisposition of disorders that will not manifest until later on in life (at least after 18 years old) because it is in direct interference with an individual's future autonomy, when those individuals *do* have the capacity to make self-governing decisions.

Tarini & Goldenberg (2012) argue that the mandatary nature of the NBS under the principle of *parens patriae* conflicts with screening for disorders without effective treatment. The child welfare model claims that states require NBS because early detection of IEM, such as PKU, for example, will lead to dietary intervention and, ultimately, normal development. Harm has been avoided to the infant by *early detection and intervention*. Forgoing early detection of PKU through the NBS would lead to more harm than good for the baby. If the state requires screening for disorders without

treatment, harm (in the form of developmental delay, morbidity, or mortality) may be delayed but is inevitable. Plus, no effective intervention exists. The question – why are we mandating universal NBS in the first place? – lies in one's perspective. For Alexander & van Dyck (2006), they believe expansion of the NBS for disorders without effective interventions will support further research, leading to innovation and new treatments for these disorders. For parents, perhaps they want to have answers and avoid the diagnostic odyssey of trying to figure out what is wrong with their child once symptoms appear. Tarini & Goldenberg (2012) argue "a broader definition of benefit" – one that does not only focus on an individual child's health – "becomes ethically and socially problematic within this existing child welfare/child benefit framework that justifies mandatory screening" (p. 384). I agree *mandatory* NBS should be for conditions with effective interventions that show direct benefit to the newborn. On the other hand, parents, not the state, should decide if they want to screen for disorders without valid interventions where the benefit is focused on families, society, and research. The principles of autonomy and beneficence are inherently linked in NBS. The bioethical concept of beneficence will be discussed in the next section.

Beneficence

Beneficence is the principle of doing good. Furthermore, it can be defined as "a normative statement of a moral obligation to act for the others' benefit, helping them to further their important and legitimate interests, often by preventing or removing possible harms" (Beauchamp, 2019, p. 1). The notion of acting "for the others' benefit" and "removing possible harms" raises the question – who is the subject of this benefit? In terms of the NBS process, is it helping the individual infant, the family, and/or society as

a whole? In December 2008, the President's Council on Bioethics published a comprehensive report that examines "The Changing Moral Focus of Newborn Screening." This was based on meetings that were held which brought together experts in the fields of public health, genetics, bioethics, and pediatrics to examine the ethical dilemma of expanding newborn genetic screening outside the traditional screening criteria. The Council's report (2008) examines the shift in perspective of benefit and purpose of the NBS after the ACMGs RUSP was introduced in 2005.

Chapter two of the President's Council on Bioethics NBS report (2008) focuses on the question: "Is the expansion recommended by the ACMG consistent with the classical ethical principles of screening, or does it represent a radical departure?" (p. 21). There seems to be two distinct perspectives on the definition of benefit with regard to the newborn screening process. One perspective is that NBS should directly benefit the individual child (with indirect benefits to family and society) and this represents the "classical ethical principles of screening" set forth by Wilson & Jungner (1968) that highlight the need for effective treatments of those conditions in the screening panel. Alexander & van Dyck's (2006) position represents the conflicting point of view that an expanded approach to newborn genetic screening that includes conditions without a known prognosis or a proven treatment should be done for the broader benefit to families, society, and ultimately biomedical research. Identifying newborns with mutations in disease-associated genes can provide answers to families seeking to understand what is wrong with their child and, at the same time, generate data to develop a database to enable us to learn more about these conditions. This information could help lead to

possible discoveries of treatments to help those children afflicted by these genetic disorders and other advancements for future generations.

The notion of using NBS for the sake of scientific knowledge is reminiscent of the Tuskegee Study. The United States Public Health Service began the "Tuskegee Study of Untreated Syphilis in the Negro Male," in 1932 which enrolled 399 black men believed to have syphilis and 201 black men as controls to "determine the progression of disease, the effectiveness of treatments at different stages, and modes of disease transmission" (Norrgard, 2008, p.1). The study continued until 1972 even though penicillin was discovered in the 1940's and was shown to be very safe and effective for the treatment of syphilis (Norrgard, 2008). The uncovering of what really happened during this study in terms of human experimentation results in major modifications in the regulation of human subjects in research, such as the National Research Act in 1974, the Belmont Report of 1979, and the establishment of institutional review boards (IRBs) (Norrgard, 2008). This was the start of dedicated efforts to protect human subjects participating in research studies from both a legal and ethical perspective, and the measures taken to protect human subjects have been strengthened over the years. Transforming NBS from one that directly benefits the health of infants to expanding the process to what could essentially be viewed as a universal, mandated population research study may result in unintended consequences, such as the identification of a growing list of genetic disorders for which there is little understanding of the fate of those patients in the setting of little understanding of how to treat those conditions. This requires critical thinking regarding how and when it is appropriate to expand the panel of NBS.

The President's Council on bioethics (2008) argues that the 29 core conditions (20 of those detectable by MS/MS) and the 25 secondary conditions (22 detectable by MS/MS) within the RUSP brought forth by the ACMG fall outside the traditional screening framework.[iv] The Council on Bioethics (2008) examines how the ACMG focuses on maximizing MS/MS technology – using its "full profile mode" to look for all possible "clinically significant" metabolic disorders in asymptomatic infants, regardless of understanding of the natural history of a disease or availability of effective treatment options (p. 42). The ACMG (2006) justifies this view based on the broader concept of benefit that mostly includes society at large and the biomedical research community. The Council (2008) scrutinizes the ACMG working group's decision-making algorithm and summarizes the ethical transformation and expansion in NBS:

> *"…the ACMG working group has effectively recommended mandatary newborn screening for two categories of conditions: the relatively small number of treatable and well understood disorders that satisfy the classical Wilson-Jungner criteria, and the potentially much larger set of untreatable and poorly understood disorders that fall short of those criteria but are detectable by multiplex screening…Hitherto, for diseases that were poorly understood or for which no effective treatment was available, we as a nation have not been in the habit of subjecting individuals to compulsory screening merely for research purposes. In the wake of the ACMG report and its enthusiastic reception by the states, our*

[iv] 6 primary condition and 1 secondary condition have been added to the RUSP since its initiation

> *approach to newborn screening seems to be heading into* ***uncharted territory****"* (p. 49)

Despite support from the March of Dimes, AAP, HRSA, and numerous other organizations, there was back then, and there still is today, resistance to the ACMGs recommendation that emphasizes a broader concept of benefit to mandated NBS.

Healthcare providers and public health officials criticize this "uncharted territory" of newborn screening established by the ACMG due to lack of evidence-based studies that demonstrate clear efficacy of conditions in the RUSP, poor methodology in the development of the RUSP, harms of false positives, and lack of insight into the ethical and legal consequences in the ACMG working group's report (Botkin et al., 2006). Jeffrey Botkin and collaborators, including Murray and Baily from the Hastings Center, offer their opinion in the 2006 article titled, "Newborn Screening Technology: Proceed with Caution." Botkin et al. (2006) argue that it is obvious many children and their families have benefited from newborn screening since its initiation over 40 years ago; however, PKU for example – "a model condition" – even has its own faults in regards to the efficacy of its screening program (p. 1793). The article mentions the need for "insurance coverage for ongoing specialty care and special diets" in addition to difficulty of following the PKU diet "because of its poor palatability, high cost, and limits on insurance coverage in many policies" (Botkin et al., 2006, p. 1793). The goal of the NBS is to improve health outcomes for children. Botkin et al. (2006) reveal how even for a "model condition" like PKU, its success as an effective screening program should be tempered by the challenges of managing the children who screen positive for this condition.

Botkin and colleagues (2006) offer four recommendations focused on "a research-paradigm" NBS program that allows for data collection and an evidence-based approach rather than purely observational verification or "expert opinion" (Botkin et al., 2006, p. 1797; ACMG, 2006, p. 11). The goal of this framework is to "determine if the uniform panel is clinically useful and valid" (Botkin et al., 2006, p. 1798). Botkin et al. (2006), Kelly et al. (2016), and the Council on bioethics (2008) all agree that it is unethical to mandate universal screening of newborns for disorders that are not well-understood, have an unclear benefit-risk ratio, and/or do not have effective treatments. Yet, the Council stresses "gains in biomedical knowledge from expanded screening programs should not be ignored" (p. x). This position supports the consensus that pilot studies with "voluntary, informed consent of the infant's parents" should be enacted for those conditions outside the traditional screening platform to benefit biomedical research and society as a whole (Council on Bioethics, 2008, p. x).

The goal of NBS is to improve health outcomes for children. This goal can be interpreted based on who the beneficiary is – whether that be the newborn children being tested, future children, or society as whole. Another variable in this ethical question is what is meant by "effective treatment"? The council on bioethics (2008) dissects the ACMG working groups conclusion (2006): "…effective treatment was available that could prevent all (for 4 conditions), most (ten), or at any rate, some (fifteen) of the disease symptoms…Finally, for 25 of the 29 core conditions, the ACMG concluded that the available treatment was efficacious at preventing mortality, independent of any reduction in morbidity" (2008, p. 36). The concept of "effective treatment" can be interpreted in different ways. While a treatment might not prevent all disease symptoms,

it could prove beneficial for “most” or “some” of the symptoms if averted through early detection and intervention.

Most people would agree that if an infant has a positive screening test and receives a diagnosis through DNA-based testing of a rare genetic condition, then everything should be done to prevent the devastating effects of that rare genetic disease. However, what if that child with a genetic mutation remains totally healthy without any intervention? The council on bioethics (2008) highlights this potential for clinical uncertainty, especially amongst the secondary conditions, such as organic acid disorder 2-methylbutyryl-coenzyme A dehydrogenase deficiency (2-MBG), an extremely rare disorder most often found in individuals of Hmong ancestry, an ethnic group in East and Southeast Asia. Symptoms can range from severe developmental delay, seizures, and cerebral palsy to someone with the disorder being completely asymptomatic. According to the council (2008), “only five cases of 2-MBG had been described worldwide when the state of Wisconsin, in 2000, added 2-MBG to its mandatory newborn screening panel” (p. 39). Between 2000 and 2006, twenty-seven infants in Wisconsin were diagnosed with 2-MBG, most undergoing modified diets; however, the council notes, “parental compliance with this diet was quite variable” (2008, p. 39). “As of 2007, all of the Wisconsin children who had been diagnosed at birth with 2-MBG were normal, healthy, and asymptomatic” (Council on Bioethics, 2008, p. 39). It is unclear whether the dietary modifications lead to prevention of symptoms or these children would remain asymptomatic without intervention. Other secondary conditions such as short-chain acyl-coA dehydrogenase deficiency (SCADD) pose the same challenge around clinical significance and the benefit-harm ratio of labeling these children (many within one ethnic

group) with a life-long disease (van Maldegem et al., 2010). Many countries, such as the United Kingdom and the Netherlands, do not believe these secondary conditions (like 2-MBG and SCADD) qualify for neonatal screening.[v]

In contrast to the ACMGs mandatory RUSP of core and secondary conditions, Massachusetts currently uses a two-tiered model consisting of a required panel with 32 conditions (25 by-product conditions) and a voluntary/optional panel with 8 conditions (6 by-product conditions) ("Newborn Screening in Massachusetts"). This two-tired model emphasizes the distinction between conditions that have a high benefit-risk ratio – those that are mandatory – and others that have an unclear benefit-risk ratio, which need pilot studies with parental informed consent before initiation of universal neonatal screening. One issue with this approach is deciding what to do with "by-product" findings. These findings refer to information revealed about other "clinically significant" disorders when using multiplex screening for a specific panel of conditions. ACMG recommends mandatory reporting of all "clinically significant" results regardless of availability of effective treatment and knowledge of the natural history of the disease (2006, p. 30). This policy is clearly evident in their full-profile approach to MS/MS technology, and their recommendation that mandatory newborn screening should be obtained for all conditions in the core and secondary panel (ACMG, 2006). Disclosure of by-product findings may be challenging in the two-tired model when information is exposed about conditions in both the required and voluntary panels, yet the parent did not give consent for the voluntary NBS disorders. The council on bioethics (2008) recommends options, such as

[v] https://www.metabolicsupportuk.org/newborn-screening/ [UK screens for 9 disorders at 5 days of age]

informed consent to disclose incidental findings and only reporting the results if more is learned about a condition which would then move it to the required panel (p. 103-104). I believe these are fair alternatives that allow parents to have autonomy, while simultaneously releasing information to benefit the welfare of a child. The Bioethics and Legal Workgroup for the Newborn Screening Translational Research Network published an article in 2018 looking at which "ethical, legal, and social implications" (ELSI) should be addressed in pilot studies (Goldenberg et al., 2019). Qualitative studies such as this are critical to uncover what problems need to be addressed in the NBS process for new conditions before they are added to the RUSP for mandatory, population-wide newborn screening.

There appears to be some disconnect surrounding the definition of "effective treatment" and "clinical significance" between state governments that decide what to screen, public health officials who run the NBS process, and the primary care pediatricians on the front lines ordering the testing. The divide is based on whether the emphasis is more on the direct benefit of a child or the benefit of society at large. It is evident that the NBS process is complex and that there are many stakeholders in this process. It should also be even clearer that all these stakeholders must come together, focus on the newborn infant population, and find common ground in order to establish equitable screening protocols that best serve the needs of this population and the families caring for them.

Equity

The words "equity" and "disparity" are often used within the healthcare field without a much clarity as to what they really mean. The ACMG comments on the

newborn screening landscape in their report: “It is important that universal access to this screening and its central public health focus are maintained, while efforts move forward to bring uniformity and *equity* to State screening efforts” (2006, p. 15). The ACMG report (2006) uses the term ‘equity’ in terms of uniform screening programs such that each state should use the same panel to ensure early detection and treatment of genetic diseases. Equity is much more than uniformity; it encompasses the ability to recognize unique circumstances and perspectives to allow people to achieve their full potential.

The Boston Public Health Commission examine how health inequities and health disparities are essentially the same thing referring to “differences in the presence of disease, health outcomes, or access to health care between population groups”; however, health inequities are considered when the difference is “unfair, avoidable, and rooted in social injustice” (“Health Disparities vs. Health Inequities”). There is a webinar on www.babysfirsttest.org entitled “Health Equity in Newborn Screening” that discusses equity concerns within current newborn screening programs in regards to follow-up testing and long-term care (Baby’s First Test, 2018). An example of health inequity could be a pregnant, non-English speaking woman from a low socioeconomic background who does not have access to prenatal care, which results in inadequate education about the newborn screening process. If she does not know what the newborn screen is or what to do about abnormal results, there might be lapse in care for her newborn baby or possibly a lack of access to care given her situation. This example highlights how marginalized populations are more likely to be pushed out of the healthcare system, resulting in poor health outcomes. Health inequities like this must be addressed in NBS programs to

overcome the unjust racial, educational, societal, and institutional barriers that some populations are faced with.

The council on bioethics (2008) acknowledges some of the similarities between state-run NBS programs, such as “privacy and confidentiality policies”, allowing parents to decline screening, and dissemination of NBS educational material to inform parents about the screening process (p. 19). Nevertheless, there are important differences between each program. The council on bioethics highlights three main differences: “quality of parental education”, the price of the screening test, and the timing/number of initial screening tests (p. 19-20). There are more similarities than differences in general NBS practices across state lines; however, as Tarini & Goldenberg (2012) point out, there is “One Nation, 51 Programs” (p. 382). These differences in NBS practices between the states can cause inconsistencies in health outcomes for newborn infants across the United States.

As the NBS panel expands to over 50 conditions now, educating parents about the NBS panel and process is getting more difficult, with uncertainties around what group or society should lead the educational efforts and when should the educational information be disseminated. The American College of Obstetricians and Gynecologists (ACOG) committee opinion No. 481 (2011) is consistent with AAPs recommendation that NBS education should take place during prenatal visits. However, Tarini & Goldenberg (2012) highlight how these recommendations are not always consistent with state regulations and what is actually happening in hospitals and doctor’s offices.

Additionally, the price of the newborn screen varies from state to state. The Pennsylvania NBS page on babysfirsttest.org states that the cost for the nine conditions

on the “mandatory screening panel” is covered by “state appropriations” through the Department of Health. In addition, the 27 additional disorders on the “mandatory follow-up panel” and point-of-care screenings, such as tests for critical congenital heart disease [CCHD] and hearing, should be covered by insurance. However, the babysfirsttest.org website and further Pennsylvania Department of Health documents suggest that the panel of conditions differs based on birthing facility and out of pocket costs may vary (PA Department of Health, “Frequently Asked Questions,” 2017). In comparison, the Massachusetts NBS page declares “The NBS cost is $133.90 per child and is covered by most insurances” (Baby’s First Test, “Massachusetts”). Additionally, the HRSA website notes the conditions in the RUSP are “part of the comprehensive preventive health guidelines” under section 2713 of the Public Health Service Act, requiring insurance to cover the costs of those tests (HRSA, 2020). Based on this, it seems like it would be hard to discern what the out-of-pocket costs of NBS are from state to state, especially for someone not versed in the healthcare system, and that these costs vary from state to state.

In regards to the timing of the initial screening tests, some states, such as Pennsylvania, require one test to be done between 24-48 hours of life (after 24 hours of feeding) while other states, such as Maryland require two initial screening tests, one after 24 hours of feeding (usually day of hospital discharge) and another “collected by a healthcare provider when a baby is greater than 7 days old, ideally between 10 days and two weeks” (Baby’s First Test, “Maryland”). The Maryland NBS page on babysfirsttest.org defends the necessity of a second screen, asserting it is a more sensitive protocol to pick up Congenital Hypothyroidism (CH), and two screening tests are also required for the IRT/IRT system for Cystic Fibrosis (CF) that began in 2006. When

examining each state's NBS program, there appears to be many differences – mostly small variations – in the timing of when the screening tests are done. One major difference, however, from state to state is the varying number of disorders on the NBS panel, despite having a RUSP. The sum total of this analysis suggests that states decide what screening tests they want to do and how they communicate the process.

Despite existence of the RUSP and states adopting it to varying degrees, we have not reached a state of equity within the newborn screening process. The capability to universally screen newborns for genetic conditions represents significant advancement in the age of precision medicine but this can only be beneficial for all infants if the screening tests are valid, results are clearly communicated, and patients and families have access to treatment if available. There is still debate today about which screening tests should be done and how the diversity of ethnic backgrounds impacts the selection of which genetic tests are most relevant.

Falling Through the Cracks: CF and Fatty Acid Oxidation Defects

CF is an autosomal recessive disorder caused by a mutation in chloride ion channels resulting in lung, pancreas, and digestive dysfunction. It is more prevalent in Caucasians, occurring in 1 in 2,500 to 3,500 white newborns compared to 1 in 17,000 African Americans and 1 in 31,000 Asian Americans (Genetics Home Reference, CF). Early diagnosis and intervention improve health outcomes. Since every newborn in the US is screened for CF, then equitable tests and follow-up protocols must be in place to provide adequate healthcare to all children, regardless of race, ethnicity, or socioeconomic status.

A 2008 article in the *Journal of Pediatrics* entitled, "Newborn Screening for Cystic Fibrosis: A Lesson in public health disparities" describes the different methods for CF newborn screening – IRT/IRT vs. IRT/DNA vs. IRT/DNA/IRT vs. IRT/IRT/DNA vs. IRT/PAP – and their different false negative rates between ethnicities (Ross, 2008).[vi] For example, some states require two elevated IRT results before a diagnostic sweat chloride test is indicated, while other states require an elevated IRT and one DNA mutation (Ross, 2008). Additionally, El Hajj and colleagues wrote an article in 2019 entitled, "Equity in genetic newborn screening," that uses CF as a model condition to investigate ways to create "equitable panels" that searches for all CF-causing mutations "under a limited budget" (El Hajj et al., 2019, p. 1). Both articles highlight the need to reduce false negatives which could have significant consequences given the severity of the disease. Ross (2008) discusses how "physicians are reassured by a negative screening test even though it is not meant to be diagnostic" (p. 308). Therefore, children with a false negative screening result, based on the screening protocol in that state, might not obtain a diagnostic workup for CF and continue along a diagnostic odyssey which would result in a delay in receiving appropriate interventions.

Prevention of false negative screening results in ethnic minorities is imperative to avoid health inequities. As ethnic heterogeneity in our society increases, Ross (2008) discusses the need for a diverse panel of mutations in the IRT/DNA method. The delta F508 mutation is the most common, "found in 72% of the US Non-Hispanic Caucasian CF population, but in much lower percentages of patients with CF from other ethnicities

[vi] IRT = immunoreactive trypsinogen; PAP = pancreatic associate protein

(Hispanic Caucasian, 54%; African American, 44%; Asian American, 39%; Ashkenazi Jewish, 31%)" (Ross, 2008, p. 309). If mutations that occur at lower frequencies within minority populations are not tested for, there will be missed diagnoses of CF amongst children in these communities in the newborn period. Ross (2008) examines how the ACMG CF Carrier Screening Working Group created a panel of 25 mutations in 2001. Between 2001 and 2008, the panel has expanded to include 20 additional mutations that occur at lower frequencies, usually within minority populations (Ross, 2008). Nevertheless, Ross (2008) emphasizes, "Adding mutations will improve sensitivity but decrease specificity. The selection of mutation panels, then, is not a simple medical decision" (p. 309). As more genotypes are uncovered and added to the DNA-based screening panel to reduce false negatives in minority populations, new questions arise regarding carrier status and diagnostic criteria for CF.

In 2017, the CF Foundation published a report titled "Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation" to create recommendations "to clarify diagnostic criteria and terminology for other disorders associated with CFTR mutations" (Farrell et al, 2017, p. S4). Clarity is needed because 1) the NBS is identifying more asymptomatic infants and 2) there are differences in CFTR dysfunction between individuals. Ross's article (2008) and the CF Foundation's recommendations (2017) highlight the emerging challenges in newborn screening for CF given the heterogeneity of the underlying genetics of the disorder as well as the phenotypic expression of the disease across different ethnic and minority populations.

Screening newborns for fatty acid oxidation defects (FAOD) demonstrates inherent challenges in NBS itself, based on the complexity and heterogeneity of this

group of disorders, which can be further complicated by ethnic, socioeconomic, and environmental factors. With the advent of MS/MS, FAOD are screened using ratios of acylcarnitines within dried bloodspots, which can be indicative of abnormalities of fatty acid (FA) breakdown in the mitochondria for cellular energy. During one of my clinical rotations, I encountered a 4-year-old boy from North Philadelphia with developmental delay presenting to the hospital with recurrent hypoglycemic episodes and elevated creatine phosphokinase (CPK), an indicator of rhabdomyolysis or muscle breakdown, suggestive of a FAOD not properly identified on the NBS. How did this boy fall through the cracks of the NBS system? If identified when he was a newborn, proper diagnosis and interventions could have prevented his recurrent symptoms and changed the trajectory of his medical condition, possibly reducing his pain and suffering and that of his family.

The literature reveals similar case studies to the one I experienced, further highlighting the challenges with screening for FAOD, such as valid acylcarnitine ratios, timing of NDBS collection, influence of stressors (such as infection) on pathophysiology, and confirmatory biochemical plasma levels (see Dowsett et al., 2017; Edmondson et al., 2017). For example, a 2017 article published in the *International Journal of Neonatal Screening* reveals a similar case study in which an 18-month-old male was considered to have a false-positive screening for a FAOD; nevertheless, during hospitalization his diagnosis of carnitine palmitoyltransferase 1A (CPT1A) deficiency was confirmed by gene sequencing (Dowsett et al., 2017). The researchers state, “There have been reports of disorders of long-chain fatty acid oxidation being missed by newborn screening. Patients with fatty acid oxidation defects can have normal biochemical profiles in the absence of physiologic stressors. It is therefore possible to have an abnormal newborn

screen but normal confirmatory metabolic testing" (Dowsett et al., 2017, p. 4) A case study in 2017 discusses a missed case of another FAOD, in which a 4-year-old girl with normal NBS presented with muscle breakdown in the setting of fevers and upper respiratory infection (Edmondson et al., 2017). Further genetic testing revealed a homozygous mutation for carnitine palmitoyltransferase-II (CPTII) deficiency. The case studies above highlight the complexity of newborn screening for FAOD and how the results can be affected by several variables.

Ideally, NBS should not miss diagnosing infants with harmful genetic conditions. Yet, there is not a one size fits all approach. Each disease process is unique and, the more we learn with regard to genomics, the more we appreciate the heterogeneity of disease processes and underlying etiologies. Additionally, every patient is unique and brings to the testing encounter a different baseline based on his/her genetic makeup, environmental and socioeconomic situation, health status and belief system. Families, such as the one I met on my clinical rotation, may face barriers, such as health literacy and poor follow-up, that can impede timely diagnosis and intervention for their newborn. Evidence-based protocols and valid assessment algorithms are necessary for conditions like FAOD that are screened by MS/MS. Even with such protocols in place, the NBS process still needs to recognize the vast diversity of the newborn population it is serving and the obstacles some families face.

Advocacy, Advocacy, Advocacy!

Public health initiatives do not occur in a vacuum. Policy decisions are made by people or groups of people that are influenced by the world around them. Advocates, predominantly family members of someone affected by a specific genetic disease, are

major players who have a significant impact on the decision-making process. Each condition has its own advocacy network usually made up of several organizations that are committed to the same cause. For example, the main advocacy organization for CF is the Cystic Fibrosis Foundation and its website has a page dedicated to advocacy that explains all the ways to get involved and raise awareness in order "to ensure that the CF community receives support from federal and state decision makers across the country."[vii] Sicklecelldisease.org, supporting the SCD community, also has numerous resources dedicated to advocacy and the efforts that are in place to "establish the national infrastructure to ensure that individuals diagnosed with SCD receive appropriate follow-up services including counseling, education materials and access to a medical home."[viii] There are numerous similar examples that demonstrate the power of advocacy and how it can to sway legislation in one direction or another. For example, Vince and Robin Haygood, parents of a child with MCAD, greatly influenced Mississippi's genetic advisory committee (GAC) and other state legislators to expand NBS to 30 disorders using MS/MS technology in 2002 (Clayton, 2009, p. 127).

Advocacy is a driving force in the setting of public policy. Yet, one must consider who is represented amongst the voices in these powerful groups. Genetic variation is clustered within ethnicities; thus, it is possible that not all causes and all genetic disorders have the same access to the legislators who are involved in setting NBS policy. Citrin & Modell (2009) highlight the need to investigate race and ethnicity within NBS screening

[vii] https://www.cff.org/Get-Involved/Advocate/

[viii] https://www.sicklecelldisease.org/our-initiatives/newborn-screening-follow-program/

to ensure all voices are heard (Citrin & Modell, 2009). Recommendations from the Communities of Color and Genetics Policy project (CCGP) stress the importance of representation within advisory committees, community-based organizations, non-discriminatory policies, and trust in public health agencies (Citrin & Modell, 2009).

Cost-Effectiveness

Advocates fight for awareness, resources, and money. There is a finite amount of resources and money; thus, is widespread screening of asymptomatic newborns for genetic conditions an effective use of funding? NBS is on the CDC's list of "Ten Great Public Health Achievements" between 2001 and 2010 (Domestic Public Health Achievements Team, CDC, 2011). According to the NIH, there are about 4 million births each year in the United States, of which about 12,500 newborns each year are diagnosed with a genetic condition on the core panel detected by NBS ("About Newborn Screening," 2017). Clearly, the NBS process improves health outcomes in the pediatric population. Studies show the NBS using MS/MS is cost effective; however, certain assumptions are made, such as quality of the screening tool (low number of false positives and false negatives) and effectiveness of timely diagnosis/intervention (Carroll & Downs, 2006). Grosse discusses the shortcomings of cost-effectiveness analysis (CEA) in newborn screening as there is insufficient data so the findings reported for CEA for many disorders are merely speculative (Grosse, 2009). It is important to assess CEA within pilot studies for each disorder separately, especially before a program expands, in order to have a data driven approach based on what adverse effects are prevented by screening, early diagnosis, and intervention. Politicians and researchers should not add another disorder onto the NBS MS/MS panel simply because it is inexpensive to do so.

These decisions must come from evidence-based data to ensure that the utilization of resources is well placed and distributed equitably.

Privacy/Trust

Obtaining the dried blood spots for NBS requires trust between the public and healthcare community. Based on past experiences, this trust has sometimes been questioned by members of minority communities. This is because of certain situations in which the medical or public health community did not treat minority populations in a fair and ethical manner, such Tuskegee, Henrietta Lacks, and the Havasupai Tribe study. There have also been legal cases in Texas, Minnesota, and Indiana that expose mistrust surrounding retention of residual dried bloodspots for research or quality control measures without explicit parental consent (Lewis, 2014). The Screening Saves Lives Reauthorization Act of 2014 now requires states to have informed consent policies "for use and storage of their states' DBS if they are being used for federally funded research" (Kelly et al., 2016, p. 4). Informed consent is necessary because genetic material can't be de-identified, thus the residual blood spots represent human subject research. In addition, there are laws, such as the Genetic Information Nondiscrimination Act (GINA), that was passed in 2008 to prevent health insurance companies and employers from discriminatory policies based on NBS results or genetic information. However, babysfirsttest.org states "life insurance, long-term care, and disability insurance are not covered by GINA" ("Insurance and Planning," 2018). Since the start of NBS in the 1960's, there have been numerous legal statutes put in place to protect the privacy of all families. Continued assessment and input from all stakeholders in the community are necessary to increase trust in the NBS process.

Ethical Conclusion: Education and Evidence-Based Protocols

On a macro level, NBS programs are similar across state lines and benefit children by identifying serious rare diseases and intervening early to prevent harm and preserve health for newborns. The above ethical analysis of expanded universal NBS dives deeper into concerns surrounding autonomy, beneficence, equity, cost-effectiveness, and privacy/trust. Even though all states have required screening for at least 29 of 35 core conditions, each state has a unique panel (emphasizing "full profile mode" MS/MS technology) and organization that oversees its NBS program. Unifying the NBS into one system for the entire country would be beneficial and help to achieve an equitable approach; however, just as there are barriers to universal healthcare in the United States, there are numerous obstacles for a federally funded, national NBS program. Therefore, the focus now must be on education for the existing program and pilot studies to support an evidence-based approach to expansion of NBS. The pilot studies include both an objective approach and ethical considerations in the analyses of their findings to help guide the recommendation of which genetic disorders would be appropriate to add to the NBS panel for all states to use. There are excellent education materials online, such as babysfirsttest.org; however, more education is needed for primary care pediatricians and parents, especially those with low health literacy, low trust in the healthcare delivery system, and/or additional barriers to accessing healthcare. Pediatricians play a central role in this process and need to be able to explain what conditions are on the panel for their state and how the *NBS process* works because they coordinate most of a child's care after birth. Nevertheless, history exposes two facts: 1)

policy is dynamic and 2) the quest for knowledge is constant. What must be done to ensure ethical newborn genetic screening in the future?

CHAPTER 5: THE FUTURE OF NBS – THIRST FOR INFORMATION

This thesis has reviewed the historical aspect of NBS and discussed the ethical considerations of the NBS process related to rare genetic diseases. While the central theme has been the preservation of health, as with all ethical issues, there is a delicate balance between that tenet and one which is well known to medicine: *primum non nocere* or first, do no harm.

As the NBS moves toward expansion in the age of genomic medicine, the council on bioethics (2008) considers how its growth represents a "Faustian imperative driving the search of genetic knowledge back to earlier and earlier points along life's path" (p. 78). Ethical principles should not disappear to obtain knowledge. This goal of helping children reach their full potential within an ethical screening framework must be maintained in the face of NBS expansion. Compared to population-wide screening during the immediate newborn period for well recognized disorders that are part of the standard panel, genetic screening can be done at different points throughout one's lifespan when there is "perceived need," for which screening can be more selective based on a child's signs and symptoms (Council on Bioethics, 2008, p. 6). *The future of newborn genetic screening requires focus on education and using technology thoughtfully – not mandating screening for conditions at birth that may or may not be clinically significant.*

The expansion of the RUSP has slowed down for now; nevertheless, changing political climates, technological advances, and increased patient advocacy have the power to transform the NBS process into something that looks like the movie GATACA – sequencing the entire genome at birth looking for "good" or "bad" characteristics, susceptibility to various diseases later on in life, and ultimately, "genetic imperfections."

This truly would bring us into "uncharted territory." One could argue that we are already moving in that direction with Prenatal Genetic Diagnosis (PGD) done during the prenatal period, which offers the potential for "designer babies." In the new realm of genomic medicine, the quest to define an ethical approach to universal newborn screening must be informed by empirical information and thoughtful analysis, so that the NBS does not get out ahead of what medicine is able to manage. Keeping the thirst for genetic discovery in check will allow the NBS program to maintain the balance between the preservation of health and *primum non nocere*.

REFERENCES

276 Neb. 825, (2008) "Nebraska Advance Sheets in re Interest of Anaya," <https://biotech.law.lsu.edu/cases/reporting/Anaya.pdf>.

American College of Medical Genetics (ACMG) Newborn Screening Expert Group, "Newborn Screening: Toward a Uniform Screening Panel and System," 2006. <https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/reports-recommendations/reports/uniform-screening-panel-system.pdf>.

American College of Obstetricians and Gynecologists Committee on Genetics, "Committee Opinion No. 481: Newborn Screening," *Obstetrics & Gynecology*, 2011; 117(3):762-5. DOI:10.1097/AOG.0b013e31821478a0.

Baby's First Test, "Health Equity in Newborn Screening Webinar," April 25, 2018. <https://www.babysfirsttest.org/newborn-screening/resources/health-equity-in-newborn-screening-webinar>.

Baby's First Test, "Insurance and Planning," 2018. <https://www.babysfirsttest.org/newborn-screening/insurance-and-planning>.

Baby's First Test, "Maryland," <https://www.babysfirsttest.org/newborn-screening/states/maryland>.

Baby's First Test, "Massachusetts,"<https://www.babysfirsttest.org/newborn-screening/states/massachusetts>.

Baby's First Test, "Pennsylvania,"<https://www.babysfirsttest.org/newborn-screening/states/pennsylvania>.

Baily, Mary Ann, Murray, Thomas H. *Ethics and Newborn Genetic Screening*, The Johns Hopkins University Press, 2009.

Beauchamp, Tom, "The Principle of Beneficence in Applied Ethics", *The Stanford Encyclopedia of Philosophy* (Spring 2019 Edition), Edward N. Zalta (ed.). <https://plato.stanford.edu/archives/spr2019/entries/principle-beneficence/>.

Bhattacharya, Kaustuv, Wotton, Tiffany, Wiley, Veronica. "The evolution of blood-spot newborn screening," *Transl Pediatrics*. 2014; 3(2): 63-70.

Boston Public Health Commission, "Health Disparities vs. Health Inequities," <https://www.bphc.org/whatwedo/health-equity-social-justice/what-is-health-equity/Pages/Health-Disparities-vs.-Health-Inequities.aspx>.

Botkin, J. R., Clayton, E. W., Fost, N. C., Burke, W., Murray, T. H., Baily, M. A., … Ross, L. F. (2006). Newborn Screening Technology: Proceed With Caution. *Pediatrics*, *117*(5), 1793 LP – 1799. http://doi.org/10.1542/peds.2005-2547.

Carroll, Aaron E., Downs, Stephens M., "Comprehensive Cost-Utility Analysis of Newborn Screening Strategies," *Pediatrics*, 2006; 117;S287, DOI: 10.1542/peds.2005-2633H<https://pediatrics.aappublications.org/content/pediatrics/117/Supplement_3/S287.full.pdf>.

CDC, Data & Statistics on Sickle Cell Disease, 2019 <https://www.cdc.gov/ncbddd/sicklecell/data.html>.

Citrin, T. & Modell, S. M., "Racial/Ethnic Communities and Newborn Screening Policies," 2008, *Ethics and Newborn Genetic Screening*.

Clayton, E.W., (2009). "Lessons to be Learned from the Move Toward Expanded Newborn Screening," *Ethics and Newborn Genetic Screening*.

Cornell Law School, "*Parens patriae*," <https://www.law.cornell.edu/wex/parens_patriae>.

Domestic Public Health Achievements Team, CDC, "Ten Great Public Health Achievements – United States, 2001-2010," May 20, 2011, *Morbidity and Mortality Weekly Report*, 60(19);619-623, <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6019a5.htm>.

Dowsett, L., Lulis, L., Ficicioglu, C., & Cuddapah, S. (2017). Utility of Genetic Testing for Confirmation of Abnormal Newborn Screening in Disorders of Long-Chain Fatty Acids: A Missed Case of Carnitine Palmitoyltransferase 1A (CPT1A) Deficiency. *International journal of neonatal screening*, *3*(2), 10. https://doi.org/10.3390/ijns3020010.

Driscoll, Carlie J., McPherson, Bradley. *Newborn Screening Systems: The Complete Perspective*. Plural Publishing, Inc. 2010.

Edmondson, A. C., Salant, J., Ierardi-Curto, L. A., & Ficicioglu, C. (2017). Missed Newborn Screening Case of Carnitine Palmitoyltransferase-II Deficiency. *JIMD reports*, *33*, 93–97. https://doi.org/10.1007/8904_2016_528.

El Hajj, H, Bish, DR, Bish, EK. Equity in genetic newborn screening. *Naval Research Logistics*. 2019; 1– 21. https://doi.org/10.1002/nav.21882.

Evans, Adrianna, et al. "A Newborn Screening Education Best Practices Framework: Development and Adoption," *International Journal of Neonatal Screening*, 2019, 5, 22.

Farrell, Philip M. et al, "Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation," *The Journal of Pediatrics*, 2017, vol 181S: S4-S15.e1. <https://www.jpeds.com/article/S0022-3476(16)31048-4/pdf>.

Feero, Gregory W. and Gutmacher, Alan E. "Genomics, personalized medicine, and pediatrics," *Acad Pediatr*. 2014; 14(1): 14-22.

Gaston, Marilyn, et al. "Prophylaxis with Oral Penicillin in Children with Sickle Cell Anemia: A Randomized Trial," *The New England Journal of Medicine*, 1986, vol 314, no. 25: 1593-1599.

Goldenberg, A. J., Lloyd-Puryear, M., Brosco, J. P., Therrell, B., Bush, L., Berry, S., … Network, for the B. and L. W. of the N. S. T. R. (2019). Including ELSI research questions in newborn screening pilot studies. *Genetics in Medicine*, *21*(3), 525–533. http://doi.org/10.1038/s41436-018-0101-x.

Grosse, S. D. "Cost-Effectiveness as a Criterion for Newborn Screening Policy Decisions," 2009, *Ethics and Newborn Genetic Screening*.

Guthrie, Robert. "Blood Screening for Phenylketonuria**,"** *JAMA.* 1961;178(8):863. doi:10.1001/jama.1961.03040470079019.

Guthrie, Robert. "The origin of newborn screening," *Screening*, vol 1 (1), 1992, pgs 5-15.

Health Resources & Services Administration [HRSA], "Recommended Uniform Screening Panel," Advisory Committee on Heritable Disorders in Newborns and Children, February 2020, <https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html>.

Howell, R.R., November 22, 2009. <https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/reports-recommendations/adoption-all-state-rusp.pdf>.

Kaemingk B.D., Ulrich T.J., Li M., Carey W.A, Ellsworth M.A., "Universal Electrocardiographic Screening for Long QT Syndrome in Hospitalized Neonates," *American Journal of Perinatology*, 2020; 37(3):322-325. doi: 10.1055/s-0039-1678605.

Kelly, N., Makarem, D. C., & Wasserstein, M. P, "Screening of Newborns for Disorders with High Benefit-Risk Ratios Should Be Mandatory," *The Journal of Law, Medicine & Ethics*, 2016 June; 44(2):231-240. https://doi.org/10.1177/1073110516654133.

Knobloch, Hilda. Report on the President's Panel on Mental Retardation: A Call for Action by the Pediatric Profession, *Am J Dis Child.* 1964;108(3):315. doi:10.1001/archpedi.1964.02090010317015.

Korioth, Trisha, "Want to test your child with a direct-to-consumer genetic test? Read this first," AAP News, December 26, 2019. <https://www.aappublications.org/news/2019/12/26/parentplus122619>.

Lewis, M. H. (2015). Lessons from the Residual Newborn Screening Dried Blood Sample Litigation. *The Journal of Law, Medicine & Ethics*, *43*(1_suppl), 32–35. https://doi.org/10.1111/jlme.12211.

Malone, Kevin & Hinman, Alan. (2009). Vaccination Mandates: The Public Health Imperative and Individual Rights. Law in Public Health Practice. 262-284. <https://www.cdc.gov/vaccines/imz-managers/guides-pubs/downloads/vacc_mandates_chptr13.pdf>.

Meaney, F. John. "Computerized Tracking for Newborn Screening and Follow-up: A Review," *Journal of Medical System*, Vol. 12, No. 2, 1988.

Neb Rev. Stat. & 71-519, "Screening test; duties; disease management; duties; fees authorized; immunity from liability," <https://nebraskalegislature.gov/laws/statutes.php?statute=71-519>.

NIH, Eunice Kennedy Shriver National Institute of Child Health and Human Development, "How many newborns are screened in the United States?" 2017, About Newborn Screening. .<https://www.nichd.nih.gov/health/topics/newborn/conditioninfo/infants-screened>.

NIH, Eunice Kennedy Shriver National Institute of Child Health and Human Development, "Brief History of Newborn Screening," 2017 <https://www.nichd.nih.gov/health/topics/newborn/conditioninfo/history>.

NIH, Genetics Home Reference, "Cystic Fibrosis," <https://ghr.nlm.nih.gov/condition/cystic-fibrosis#>.

NIH, Genetics Home Reference, "Phenylketonuria," <https://ghr.nlm.nih.gov/condition/phenylketonuria>.

NIH, Genetics Home Reference, "What is the Precision Medicine Initiative?" 2015.<https://ghr.nlm.nih.gov/primer/precisionmedicine/initiative>.

National Institutes of Health, "Newborn Screening for Sickle Cell Disease and Other Hemoglobinopathies," Consensus Conference, 1987, *JAMA*, Vol 258, No. 9, 1205-1209.

National Institutes of Health, "NIH program explores the use of genomic sequencing in newborn healthcare," News & Events, September 4, 2013. <https://www.nih.gov/news-events/news-releases/nih-program-explores-use-genomic-sequencing-newborn-healthcare>.

National Research Council (NRC) Committee for the Study of Inborn Errors of Metabolism (SIEM), *Genetic Screening: Programs, Principles, and Research*, National Academy of Sciences, 1975. Retrieved from https://books.google.com/books?id=xUArAAAAYAAJ.

"Newborn Screening in Massachusetts: Information for You and Your Baby," New England Newborn Screening Program. <https://nensp.umassmed.edu/sites/nensp.umassmed.edu/files/English.pdf>.

Newborn Screening Task Force, "Newborn Screening: A Blueprint for the Future," *Pediatrics*, 2000, vol. 106, No. 2. https://pediatrics.aappublications.org/content/pediatrics/106/Supplement_2/386.full.pdf.

New York State Department of Health, "The New York State Department of Health Announces Duchenne Muscular Dystrophy Newborn Screening Pilot," 2019 Press Releases, October 1, 2019. <https://www.health.ny.gov/press/releases/2019/2019-10-01_dmd_newborn_screening_pilot.htm>.

Norrgard, K., "Human subjects and diagnostic genetic testing," *Nature Education*, 2008, 1(1):82.

Olson, Maynard V. “A Behind-the-Scenes Story of Precision Medicine,” *Genomics Proteomics Bioinformatics*, 2017; 15(1): 3-10.

Pennsylvania Department of Health, “Frequently Asked Questions,” October 2017<https://www.health.pa.gov/topics/Documents/Programs/Infant%20and%20Children%20Health/11-17_DOH_BFH_NBS_FAQS.pdf>.

Prabhakar, Hari, Haywood Jr., Carlton, Molokie, Robert. “Sickle Cell disease in the United States: Looking back and forward at 100 years of progress in management and survival,” *American Journal of Hematology*, 2010, 85:346-353.

The President’s Council on Bioethics, “The Changing Moral Focus of Newborn Screening,” Washington, DC, December 2008. <https://repository.library.georgetown.edu/handle/10822/559367>.

The President’s Panel on Mental Retardation, “Report of the Task Force on Law,” 1963 <https://mn.gov/mnddc/parallels2/pdf/60s/63/63-ROT-PPMR.pdf>.

Ross L. F. (2008). Newborn screening for cystic fibrosis: a lesson in public health disparities. *The Journal of pediatrics*, *153*(3), 308–313. https://doi.org/10.1016/j.jpeds.2008.04.061.

Ross L. F. (2009). “Newborn Screening for Conditions that Do Not Meet the Wilson and Jungner Criteria: The Case of Duchenne Muscular Dystrophy,” *Ethics and Newborn Genetic Screening.*

Schlosser, Markus, "Agency", *The Stanford Encyclopedia of Philosophy* (Winter 2019 Edition), Edward N. Zalta (ed.). <https://plato.stanford.edu/archives/win2019/entries/agency/>.

Sebelius, Kathleen. May 21, 2010. <https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/reports-recommendations/response-rusp-20100521.pdf>.

Schwartz, Peter John, et al. “Prolongation of the QT Interval and the Sudden Infant Death Syndrome,” *N Engl J Med* 1998; 338:1709-1714. DOI: 10.1056/NEJM199806113382401.

Tarini, Beth A., et al. “State Newborn Screening in the Tandem Mass Spectrometry Era: More Tests, More False-Positive Results,” *Pediatrics*, 2006, vol 118, No. 2, 448-456.

Tarini, B. A., & Goldenberg, A. J. (2012). Ethical Issues with Newborn Screening in the Genomics Era. *Annual Review of Genomics and Human Genetics*, *13*(1), 381–393. http://doi.org/10.1146/annurev-genom-090711-163741.

Tester, David J., Ackerman, Michael J. "Sudden infant death syndrome: How significant are the cardiac channelopathies?" *Cardiovascular Research*, Volume 67, Issue 3, August 2005, Pages 388–396. https://doi-org.libproxy.temple.edu/10.1016/j.cardiores.2005.02.013.

Tristani-Firouzi, Martin. "Revisiting the challenges of universal screening for long QT syndrome," *Journal of Electrocardiology*, 2015, vol. 48, pgs. 1053-1057.

van Maldegem, B. T., Wanders, R. J. A., & Wijburg, F. A. (2010). Clinical aspects of short-chain acyl-CoA dehydrogenase deficiency. *Journal of Inherited Metabolic Disease*, *33*(5), 507–511. http://doi.org/10.1007/s10545-010-9080-z.

Wilson, J. M. G., Jungner, G. "Principles and Practice of Screening for Disease," *Public Health Paper No. 34*, WHO, 1968.

Wright, Stanley W. "Mass Screening for phenylketonuria," *The Journal of Pediatrics*, 1962;61(4):651-652.

World Health Organization Technical Report Series No. 401, "Screening for Inborn Errors of Metabolism," 1968.

Zupancic, J. A. F., Triedman, J. K., Alexander, M., Walsh, E. P., Richardson, D. K., & Berul, C. I. (2000). Cost-effectiveness and implications of newborn screening for prolongation of QT interval for the prevention of sudden infant death syndrome. *The Journal of Pediatrics*, *136*(4), 481–489.

APPENDIX A: COMPARISON OF SCREENING CRITERIA

Wilson & Jungner (1968) *-General mass screening criteria within public health framework*	***WHO Scientific Group on Screening for IEM (1968)*** *-Grouping of IEM for general screening*	***ACMG Report (2006)*** *-Criteria for core conditions on the NBS panel*
Condition should be an important health issue	*Group A* Conditions for which there is a well-defined screening test and a fairly uniform policy of management once the disease has been identified	It can be identified at a period of time (24 to 48 hours after birth) at which it would not ordinarily be clinically detected
Accepted treatment for patients with recognized disease	*Group B* Conditions in which the abnormal gene can regularly be identified but in which the condition only becomes symptomatic in a specific environment	A test with appropriate sensitivity and specificity is available
Facilities for diagnosis and treatment available	*Group C* A miscellaneous category which includes conditions for which more information is needed before they will fit easily into a routine screening programme	There are demonstrated benefits of early detection, timely intervention, and efficacious treatment
Recognizable latent or early symptomatic stage		
Suitable test or examination		
Test should be acceptable to the population		
Natural history of the conditions, including development from latent to declared disease, should be adequately understood		
Agreed policy on whom to treat as patients		
Cost of case-finding should be economically balanced		
Case-finding should be a continuing process and not a "once and for all" project		