Physician Knowledge and Confidence Regarding Newborn Screening for Spinal Muscular Atrophy

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Abstract

Spinal muscular atrophy (SMA) is an autosomal recessive condition resulting in progressive muscle weakness and atrophy. Newborn screening is a public health program which screens infants for treatable genetic conditions with the goal of implementing early intervention. SMA was added to Pennsylvania newborn screening in March of 2019 following the development of treatment. Several studies have revealed that primary care physicians (PCPs) have limited knowledge and confidence regarding newborn screening despite their important role in the process. The purpose of this study was to assess Pennsylvania PCPs' knowledge regarding SMA newborn screening and their confidence in caring for these patients.

A survey was distributed to PCPs in Pennsylvania inquiring about their experience, knowledge, level of comfort, and desire for more information regarding SMA newborn screening. The survey was faxed and emailed to PCPs included on the Pennsylvania Department of Health's list of those who have the potential to receive a newborn screening result for follow-up. The survey was also emailed to PCPs belonging to the Pediatric PittNet research network.

Of the 26 respondents, 18 (69.2%) reported having been involved in the care of a patient with SMA. Ten participants (45.5%) indicated they had received formal education related to SMA. PCP knowledge and level of comfort regarding SMA newborn screening was low. Knowledge of basic concepts was higher than knowledge of complex information regarding

treatment and follow-up. Physician confidence was particularly low for disclosing positive newborn screening results, discussing SMA with families, and ordering diagnostic testing. Both knowledge and comfort were higher in participants who reported having experience with patients with SMA, but this difference was more modest for comfort than for knowledge. Most respondents (91.3%) indicated they would find it beneficial to receive additional information regarding SMA.

The results of the study demonstrate that PCPs lack knowledge and confidence regarding caring for patients with SMA. They desire and could benefit from additional training. Better equipping our workforce to provide follow-up care for patients with SMA identified on newborn screening will ensure rapid referral to appropriate specialists. This will benefit both individual families and the field of public health.

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1.0 Introduction

Spinal muscular atrophy (SMA) is a genetic condition estimated to affect 1 in 10,000 live births (Prior 2008). It is characterized by progressive muscle weakness and atrophy caused by degeneration of motor neurons (Meldrum et al. 2007). Severe cases of SMA include loss of muscular control for respiration and lack of motor development in the early infantile form. The milder and later onset form of the disease is associated with muscle weakness and loss of ambulation later in life. Individuals with SMA are classified clinically into five subtypes depending on the age of onset and the motor milestones achieved (Carré and Empey 2016; Brunhilde Wirth 2000). SMA is the second most fatal autosomal recessive disorder and the leading genetic cause of infant mortality (Meldrum et al. 2007; Prior 2008). On December 23, 2016, the U.S. Food and Drug Administration (FDA) approved Nusinersen (trade named Spinraza) for the treatment of SMA (Aartsma-Rus 2017). A second treatment option, onasemnogene abeparvovec-xioi (Zolgensma), was later approved in May of 2019.

Newborn screening is a public health program aimed at early identification of children with severe and treatable genetic conditions. While states differ in their lists of conditions included on newborn screening, the Recommended Uniform Screening Panel (RUSP) is a list of conditions that the U.S. Department of Health and Human Services (HHS) Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) recommends that all states screen for. In July of 2018, SMA was added to the RUSP. This led to states across the country expanding their screening panels to include SMA, including Pennsylvania which began newborn screening for SMA beginning in March of 2019.

Primary care physicians (PCPs) have a crucial responsibility in state newborn screening programs, specifically in pursuing follow-up care for children with abnormal results, such as diagnostic testing and arranging treatment if necessary. However, due to the rarity of the conditions included on the RUSP, physicians may not be adequately prepared to manage the care of a child who receives an abnormal screening result for one of these conditions. Given the fact that SMA is the condition most recently added to the RUSP, this may be the case even more so for physicians involved in the care of an infant with a positive newborn screen for SMA. Resources to aid Pennsylvania physicians with SMA follow-up care are currently scarce; there is a lack of information and resources available regarding proper care for infants who receive an abnormal screening result.

This study aims to assess Pennsylvania PCPs' knowledge regarding SMA newborn screening and their confidence in caring for these patients. The goal is to identify gaps in PCP understanding of SMA and newborn screening in order to determine what interventions for further education may be successful. This will ultimately improve the care of patients with SMA. It is hypothesized that high numbers of PCPs do not have fundamental knowledge regarding SMA and therefore have limited confidence in caring for these patients.

1.1 Specific Aims

Specific Aim 1:

Distribute a survey to Pennsylvania PCPs which measures:

- Knowledge of the disease mechanisms and clinical presentation of SMA
- Understanding of SMA treatment options

- Familiarity with the process of identifying patients through newborn screening
- Level of confidence in being involved in the care of patients with SMA

Specific Aim 2:

Analyze survey data to assess trends in PCP knowledge and confidence regarding SMA newborn screening

Specific Aim 3:

Identify gaps in PCP knowledge and confidence in order to determine appropriate future efforts for additional information and training

2.0 Literature Review

2.1 SMA

SMA is a severe autosomal recessive condition caused by the degeneration of motor neurons which leads to progressive muscle weakness and atrophy. It has an estimated incidence of 1 in 10,000 live births, making it the most common genetic cause of mortality in infants and the second most common fatal autosomal recessive condition after cystic fibrosis (Prior 2008; Carré and Empey 2016).

Patients with SMA are classified clinically into one of five subtypes based on the age of onset and severity of clinical symptoms (Carré and Empey 2016; Wang et al. 2007). Type 0 is the most severe and typically presents prenatally with reduced fetal movement and joint contractures. Infants experience severe weakness at birth and rarely survive longer than six months due to respiratory challenges (Macleod et al. 1999; Dubowitz 1999). Type I, previously referred to as Werdnig-Hoffmann disease, includes an onset before six months of life with hypotonia and generalized weakness. These infants cannot sit independently and typically do not survive past two years of life (Oskoui et al. 2007; Finkel et al. 2014). Type II is characterized by onset between six and twelve months of life. Children are often able to sit, but cannot stand or walk independently. The life expectancy is unclear, but studies have shown a majority of individuals with type II living into their early twenties (Zerres et al. 1997). Type III, previously referred to as Kugelberg-Welander disease, is a milder form and consists of onset after 18 months of life. Patients typically learn to walk independently, but later lose this ability as the condition progresses. The life expectancy of individuals with type III is similar to that of the general population (Zerres et al.

1997). Type IV is the mildest form of the condition with onset during adolescence or adulthood. It is similar to type III and typically does not involve a shortened life expectancy (Zerres et al. 1997).

A significant amount of research has been devoted to understanding the complex genetic etiology of SMA. The condition was initially mapped to chromosome 5q13 in 1995 by two separate research groups and large deletions were reported in patients (Lefebvre et al. 1995; Rodrigues et al. 1995). The condition was subsequently found to be caused by homozygous deletions in the gene encoding the survival motor neuron (SMN) protein (Hahnen et al. 1995; Cobben et al. 1995). The SMN protein is expressed from two nearly-identical genes: *SMN1* located near the telomere on chromosome 5 and *SMN2* located downstream near centromere (Bürglen et al. 1996). *SMN2* differs from *SMN1* by a single nucleotide (C>T) in exon 7 at position 840. This polymorphism affects the splicing pattern by interfering with an exon splice enhancer (ESE). As a result, *SMN2* cannot create as much full-length SMN protein transcript as *SMN1* (Monani et al. 1999; Lorson et al. 1999; Ogino and Wilson 2004).

SMA is caused by a non-functioning *SMN1* gene, while a non-functioning *SMN2* gene does not result in a clinical phenotype (Lorson et al. 1999). Homozygous loss of *SMN2* has been reported in approximately 5% of controls in studies. Ninety six percent of patients with SMA have deletions in *SMN1*, while the other 4% have been deemed to have a cause unlinked to chromosome 5q13. Of the patients with *SMN1*-related disease, 96.4% have homozygous deletions of exon 7 or exons 7 and 8. The other 3.6% are compound heterozygotes with an *SMN1* deletion on one copy of the gene and a pathogenic sequencing variant on the other copy of the gene (Wirth 2000).

The literature does not reveal any recognized genotype-phenotype correlation between *SMN1* pathogenic variants and clinical course or severity. However, in the late 1990s and early

2000s, researchers recognized an apparent association between patients' clinical severity and *SMN2* copy number. Wirth et al. 1999 concluded that SMA phenotype was determined by the mutations on both *SMN1* alleles, as well as *SMN2* copy number (Wirth et al. 1999). Individuals in the general population carry a varying number of *SMN2* copies. Most individuals without SMA have been observed to have one or two *SMN2* copies. Smaller proportions of unaffected individuals have zero or three copies (14.4% and 4% respectively in one study) (Mailman et al. 2002). It has been estimated that <1% of individuals in the general population carry four *SMN2* copies (Ogino et al. 2004). For these reasons, SMA phenotype is more complicated than other autosomal recessive conditions and has not been fully understood.

In 1999, Wirth et al. tested the effect of *SMN2* copy number on phenotype by comparing six patients with the same mutation in *SMN1* (Y272C). Patients with type I SMA had two *SMN2* copies, those with type II had either two or three copies, and those with type III had three copies (Wirth et al. 1999). The hypothesis was further supported in 2002 when Feldkotter et al. revealed a novel method for quantitative analysis of *SMN1* and *SMN2* via real-time polymerase chain reaction (RT-PCR). The study performed analysis of 375 patients with SMA type I, II, or III. Results showed that 80% of patients with type I had one to two *SMN2* copies, 82% of patients with type II had three *SMN2* copies, and 96% of those with type III had three or four *SMN2* copies. These findings were used to predict the probability of patients with SMA to have a specific phenotype based on *SMN2* copy number. Calculations showed a greater than 99% chance for a patient with one *SMN2* copy to have type I, a 97% chance for a patient with two copies to also have type I, an 83% chance for patients with three copies to have type II, and an 84% chance for patients with four copies to have type III. Findings also supported an association between *SMN2* copy number and severity, or prognosis, within a subtype. In 113 patients with type I, the median

age of survival for those with one and two *SMN2* copies was 7 months and 8 months respectively. Those with three *SMN2* copies had a median survival age of 37.5 months (Feldkötter et al. 2002). A long-term study between 1995 and 2001 by Mailman et al. compared over 600 patients with type I and type III SMA and determined that the majority of those with type I had two *SMN2* copies while the majority of those with type III had three *SMN2* copies (Mailman et al. 2002).

In the following years, this phenomenon continued to dominate SMA research and findings supported its validity. Researchers proposed that this unique aspect of the condition could provide valuable prognostic information and be a target for the development of treatment (Prior et al. 2004).

2.2 Treatment of SMA

In December of 2016, Nusinersen (trade named as Spinraza) became the first U.S. Food & Drug Administration (FDA)-approved treatment for patients with SMA (Aartsma-Rus 2017). It was subsequently approved by the European Medicines Agency in June of 2017. The therapy involves the binding of antisense oligonucleotides to a splicing silencer in intron 7 of *SMN2,* which allows for inclusion of exon 7 and the production of full-length SMN protein. The drug does not cross the blood-brain barrier, thus requiring intrathecal administration directly into the cerebrospinal fluid (Gidaro and Servais 2019).

Nusinersen was first determined to enhance the survival of mice with severe SMA (Gidaro and Servais 2019). A phase 1 trial included twenty-eight individuals with SMA type 2 or 3 who were given a single dose of Nusinersen and no serious adverse events were reported. Several months later, patients showed increased SMN levels and clinical improvement from just the single

dose (Gidaro and Servais 2019). CHERISH, a double-blind phase 3 trial, was later conducted across several centers and included children with SMA type 2. Over 100 patients were randomly assigned to receive 12mg Nusinersen or a placebo. Outcomes were assessed by evaluating changes in Hammersmith Functional Motor Scale-Expanded, which measures motor function in non-ambulant individuals with SMA. Scores were assessed across fifteen months of drug administration. Of the Nusinersen group, 57% showed increased scores of at least three points, compared to 26% of those in the placebo group (Gidaro and Servais 2019). The ENDEAR study, a double-blind phase 3 trial evaluated the treatment in over one hundred patients aged seven months or younger with SMA type 1. Infants were randomized to receive four doses of intrathecal Nusinersen or placebo. No adverse drug-related events were observed and 40% of those in the Nusinersen group showed improved motor function. However, the condition of all individuals in the placebo group declined, which resulted in early termination of the study (Gidaro and Servais 2019). The NURTURE study is a currently ongoing phase 2 trial evaluating the use of Nusinersen in pre-symptomatic infants with SMA across multiple countries. It has been designed to evaluate patients during a five-year treatment period, as well as follow-up after treatment. At the time of reporting interim results, Nusinersen was being well-tolerated by all infants. All patients were aged 25 months or older and living without permanent ventilation. All children were able to sit independently and 88% were able to walk independently (De Vivo et al. 2019).

Several issues remain regarding the use of Nusinersen as a treatment for SMA. These concerns include limited data for use with SMA types 0 and 4, unknown long-term risks, varying responses between patients, and cost. While ample data exists for SMA types 1, 2, and 3, there is limited information about the efficacy of Nusinersen in infants with SMA types 0 and 4. Due to the severe progression of disease in individuals with type 0, families may decline the option of

treatment given the poor prognosis. Data about potential long-term risks to individuals treated with Nusinersen is also limited. Responsiveness to the drug has been observed to vary greatly among patients, but little is known about the determinants of such responses (Gidaro and Servais 2019). Concerns also surround the economic implications and availability of the drug. Biogen pharmaceuticals announced the cost of Nusinersen to be $750,000 for the first year of treatment and $375,000 for each subsequent year. The high price raises fear that certain payers will decline coverage of the drug, leading to disparities among those who are able to receive it and those who are not (Prasad 2018).

In addition to Nusinersen as an available treatment method, gene therapy has shown great promise in SMA patients. Vector-based gene therapy works to restore the deleted *SMN1* gene in affected individuals. This results in increased amounts of full-length SMN protein to support motor neurons (Phan et al. 2015). The AVXS-101, or scAAV9.CB.SMN, vector was designed for SMA gene therapy and animal model studies showed safety and efficacy (Rao et al. 2018). Multiple clinical trials have been initiated for AVXS-101, which include children of varying ages and with different SMA types and *SMN2* copy numbers. The trials showed safety and improved motor function in treated individuals. One of the observed side effects included elevated liver enzymes, but the therapy was deemed to be safe overall (Rao et al. 2018). In May of 2019, the FDA approved this therapy (trade named Zolgensma) as the first gene therapy for SMA. It is authorized for use in the treatment of children with SMA under two years of age (Commissioner 2019). The development of available treatment for SMA and its proven efficacy when initiated early has been a driving factor in support of the pre-symptomatic diagnosis of patients.

2.3 Newborn Screening

Newborn screening is a public health program which operates under the goal of early diagnosis and treatment initiation for patients with severe genetic conditions. It was initiated in the early 1960s when Dr. Robert Guthrie developed a screening test for phenylketonuria (PKU) through collecting blood samples on filter paper (Force et al. 2000). It was implemented in Massachusetts in 1962 as part of a voluntary study which demonstrated its feasibility for mass screening. In the following years, the majority of states had statues mandating newborn screening for PKU and state health departments were primarily responsible for executing the programs. Today, newborn screening programs occur in all U.S. states and are implemented by state public health agencies. Programs rely on five core components: screening, follow-up, diagnosis, treatment/management, and evaluation (Force et al. 2000). The education process is present throughout each of these components. Technological advancements, such as tandem mass spectrometry, have been critical to the progression of newborn screening programs and their ability to simply and accurately screen mass populations (Force et al. 2000).

The conditions included on newborn screening panels vary from state to state and change over time. A number of proposed criteria have become widely accepted for determining whether particular conditions should be added to the list of those screened for. In 1968, James Maxwell Glover Wilson, Principal Medical Officer at the Ministry of Health in London, and Gunner Jungner, Chief of the Clinical Chemistry Department of Sahlgren's Hospital in Sweden, published a report outlining criteria for population disease screening. These criteria have subsequently been revised to pertain specifically to newborn screening (Andermann 2008). Such criteria include an incidence frequent enough to justify population screening, early treatment that is effective and

economically sound, and screening and diagnostic testing which is technically feasible and safe for the infant (Force et al. 2000).

Although each state has its own procedure for adding conditions to its newborn screening panel, the RUSP is a list of early-onset, treatable genetic conditions that states are recommended to include. The HHS Secretary's ACHDNC is responsible for reviewing nominated conditions and voting on their addition to the RUSP. Organizations or individuals have the opportunity to nominate conditions to the ACHDNC for inclusion on the RUSP. Nominators are responsible for providing adequate information on the disorder, including available treatment, details of the screening test and follow-up diagnostic test, and results from a pilot study which identified at least one case. If the information provided warrants a formal evidence review, the nomination is sent to the ACHDNC's external Condition Review Workgroup (CRWG). The CRWG then conducts a thorough evidence review of both published and unpublished data regarding the benefits and harms of screening for the particular condition. The condition is assigned a rating based on the evidence review which the CRWG provides to the ACHDNC for their final decision (Shone 2019).

The RUSP contains 35 core conditions which all states are recommended to include on their newborn screening panels. It also includes 25 secondary conditions, which are clinically significant disorders that can be detected in the differential diagnosis of core conditions due to the screening mechanisms used (American College of Medical Genetics Newborn Screening Expert Group 2006). The most recent data published by the Centers for Disease Control and Prevention (CDC) reports that about 12,500 newborns of the 4 million who are screened each year are diagnosed with a core condition on the panel. This correlates to approximately 1 in 300 infants who receive a diagnosis through newborn screening each year ("CDC Grand Rounds" 2012).

Each state has its own legislation which determines the process for newborn screening, including follow-up. In Pennsylvania, blood is collected on a filter paper specimen card between 24 hours to 72 hours of age. The birthing facility or healthcare provider sends the filter paper to a laboratory contracted by the Pennsylvania Newborn Screening and Follow-Up Program (NSFP). Testing is typically completed within seven to ten days. Screening results are reported to the NSFP, the PCP, practitioner or midwife listed on the filter paper specimen card, and the birth facility. In the case of an abnormal screening result, the PCP listed on the filter paper card is then responsible for disclosing the results to the parents or guardians of the newborn and coordinating follow-up testing and care (PA Dept of Health Division of Newborn Screening and Genetics 2009).

2.4 Newborn Screening for SMA

With advancements in understanding SMA disease mechanisms and developing treatment came a push for including SMA in newborn screening programs. In the early 2000s, researchers began investigating the feasibility of mass screening for SMA in anticipation of treatment discovery, despite no established treatment to date. As no known biochemical marker for SMA exists, researchers investigated whether typical RT-PCR methods would be feasible for SMA screening. They designed a multiplex, real-time assay for identifying *SMN1* homozygous deletions. Using over 200 samples with known *SMN1* and *SMN2* copy numbers, they found the methods to have a sensitivity and specificity of 100% in the samples tested. A two-tiered approach to newborn screening for SMA was proposed, including RT-PCR analysis for all dried blood spots followed by competitive polymerase chain reaction (PCR) on a blood sample for those with positive results to confirm the homozygous *SMN1* deletion and determine *SMN2* copy number.

This demonstrated the technical feasibility of including SMA in newborn screening, with a need for still exploring the economic and ethical considerations (Pyatt and Prior 2006). Several other methods are also available for SMA screening using dried blood spots but are not being used as frequently. These include liquid microbead assays and high-resolution DNA melting analysis (HRMA) (Pyatt et al. 2007; Er et al. 2012).

SMA was initially proposed for inclusion on the RUSP in 2008. Small studies such as those discussed above had shown the feasibility and accuracy of SMA screening using dried blood spots. However, the ACHDNC denied the nomination due to lack of available treatment and evidence of feasibility on a larger scale from pilot studies at that time (Kraszewski et al. 2018).

Pilot studies were subsequently initiated to evaluate the feasibility of mass screening for SMA. In one study in New York state, nearly 4,000 women who had recently given birth in three different hospitals were consented to be enrolled. Routine blood spot cards sent to the New York Department of Health were used for the SMA screening. An *SMN1* genotyping assay detected heterozygotes and homozygotes for an exon 7 deletion. The assay was assessed using several control samples with known genotypes, which revealed 100% concordance. The procedure was repeated in instances when samples did not meet quality control or results indicated heterozygous or homozygous deletion. Researchers reported that 3.86% of samples required repeated testing, but estimated that this number would be between 1.5% and 3.7% in population-level implementation. Genetic counselors contacted parents of 59 identified heterozygous carriers of an *SMN1* deletion to discuss implications and next steps due to a New York state mandate that any detected variant be reported. The pilot study identified one infant with homozygous *SMN1* deletion, and parents were notified. This patient was brought to a nearby SMA clinical research center at age seven days and received Nusinersen treatment beginning at age fifteen days. As of

age twelve months, she was asymptomatic and had normal developmental milestones. At the time of publication, researchers noted that they were not aware of any false negatives or false positives to date (Kraszewski et al. 2018).

In an additional pilot study, researchers obtained over 40,000 de-identified dried blood spot samples previously collected from the Ohio Department of Health and used a liquid bead array to amplify for *SMN1* exon 7. Four homozygous deletions were identified and confirmed using competitive PCR. Researchers concluded that SMA newborn screening technology is able to accommodate large numbers of samples. Based on the methodology, they predicted the sensitivity of the screening to be approximately 95% to 98% given the fact that it would not detect compound heterozygotes with one *SMN1* deletion and one point mutation (Prior et al. 2010).

A pilot program at the National Taiwan University Hospital Newborn Screening Center was performed between 2014 and 2016. The program utilized RT-PCR using a dried blood spot to detect homozygous *SMN1* deletions. For those who screened positive, droplet digital PCR (ddPCR) using the dried blood spot and multiplex ligation-dependent probe amplification (MLPA) using whole blood was performed to confirm the result and determine *SMN2* copy number. Sensitivity and specificity of this screening method was determined to be 100% using nearly 3,000 samples of individuals with known *SMN1* and *SMN2* copy numbers. The pilot screened over 120,000 newborns, fifteen of which screened positive with RT-PCR. Eight of these were determined to be false positives by ddPCR and the other seven were confirmed positives with MLPA. Three of the patients affected with SMA had two *SMN2* copies, two patients had three *SMN2* copies, and the remaining two patients had four copies. Six of the seven affected infants were asymptomatic at the time of diagnosis. Those with two *SMN2* copies exhibited symptoms by their first follow-up visit. One of these patients was enrolled in a clinical trial by three weeks of

age. The children with three *SMN2* copies began showing symptoms around one year of age and one began receiving treatment through a clinical trial at six weeks of age. The patients with four *SMN2* copies had not shown symptoms as of their last follow-up visit with the pilot program. Researchers determined that five of the eight false positive results occurred from intragenic recombination. The program demonstrated the feasibility of newborn screening for SMA and the value of performing ddPCR to confirm RT-PCR preliminary screening results (Chien et al. 2017).

In addition to the New York state pilot study being conducted, Massachusetts and Utah also began screening for SMA in 2018 despite the condition not being included on the RUSP. Minnesota, North Carolina, and Wisconsin were also in the preparation stages of implementing SMA screening at this time (Kemper et al. 2018).

Following the FDA's approval of Nusinersen and implementation of pilot programs, SMA was nominated for addition to the RUSP for a second time in 2018. The debate for including SMA in newborn screening programs involved arguments of several benefits and risks. Similar to benefits cited for newborn screening as a whole, supporters stressed early identification and diagnosis of patients with SMA to allow for earlier treatment. In the case of SMA, this could lead to improved motor function and survival outcomes. Other arguments for including SMA in newborn screening involved giving families more time to plan for the future, seek genetic counseling, and make family planning decisions (Kemper et al. 2018). For all these reasons, the argument for initiating newborn screening for SMA was strengthened by the support of both families affected by the condition (Boardman et al. 2017; Wood et al. 2014), as well as the general public (Rothwell et al. 2013).

Despite the vast benefits of newborn screening for SMA, arguments also existed against its inclusion. Such risks included the difficulty to predict phenotype and SMA type from genotype

screening and testing. Concerns were also raised regarding detected individuals being exposed to risks of treatment earlier in life, as well as the fact that some detected infants may not need treatment until later in life (Kemper et al. 2018). Uncertainty surrounding the management and treatment path of newborns diagnosed with later-onset cases of SMA has also made some individuals weary of screening (Phan et al. 2015).

After considering the benefits and risks outlined above, the ACHDNC recommended to the Secretary of HHS that SMA be added to the RUSP in July of 2018. The Secretary of HHS's approval subsequently initiated its incorporation into newborn screening programs across the country (Aartsma-Rus 2017). The committee of experts cited the vast potential public health impacts of screening, including its ability to detect about 364 newborns each year, to prevent 16-100 children with SMA type 1 from needing a ventilator each year, and to prevent 14-68 deaths due to SMA type 1 each year (Kemper et al. 2018).

Pennsylvania began screening for SMA in March of 2019 and, as of April of 2020, is one of 23 states which have implemented screening (Cure SMA 2019a; McCall n.d.). Thirteen additional states have adopted screening, but have not yet implemented the testing and three states are conducting screening pilots (McCall n.d.).

Screening is also showing success beyond the United States. Results from the first year of newborn screening in two federal states of Germany were recently reported. Twenty-two cases of SMA were identified in over 165,000 screened newborns. Two *SMN2* copies were identified in 45% of these cases, while 19% had three copies and 36% had four copies. Ten affected infants with either two or three *SMN2* copies began Nusinersen treatment before two months of age. Seven of these patients were asymptomatic at the time treatment was initiated and still had not exhibited muscle weakness as of their last evaluation between one month and one year of age. Two affected

infants with two *SMN2* copies did not undergo treatment due to insurance status and parental decision and their condition progressed rapidly with onset by three months of age (Vill et al. 2019). With this expansion comes a need for more established guidelines and treatment algorithms for the care of patients with SMA.

To address this need and the complications of phenotype variation by *SMN2* copy number, guidelines have been developed for the treatment of patients diagnosed through newborn screening. Clinicians, geneticists, and SMA advocates comprising the SMA Newborn Screening Multidisciplinary Working Group collaborated to create a treatment algorithm for newborn screening follow-up. Following diagnostic testing and *SMN2* copy number testing, the algorithm suggests that all patients with two and three *SMN2* copy numbers undergo immediate treatment. Physician discretion is recommended to determine if treatment would be beneficial for infants with one *SMN2* copy number if they are symptomatic at the time of diagnosis. The guidelines suggest that patients with four *SMN2* copies undergo regular monitoring with treatment being initiated when symptoms arise. Monitoring of these individuals should include many methods, such as electromyography (EMG), compound muscle action potential (CMAP), myometry, and physical and reflex examinations. The group also recommends the use of several motor function measurement scales, including the Children's Hospital of Philadelphia Infants Test of Neuromuscular Disorders (CHOP INTEND), the Hammersmith Infant Neurological Exam (HINE), the Hammersmith Functional Motor Scale - Expanded, six-minute walk tests, and the Bayley Scales of Infant and Toddler Development. Follow-up should occur every three to six months in infants under two years of age and every six to twelve months after age two years (Glascock et al. 2018).

The success that has been observed in screening thus far has provided a strong argument for future expansion to other states and areas of the world. The shift in attention to SMA that comes with such growth has revealed a limited understanding of the condition, both in the public and in clinicians (Moultrie et al. 2016).

2.5 Research on Physicians and Newborn Screening

Despite the fact that conditions on the RUSP are rare, most pediatricians and about one half of family physicians report caring for a child with a positive newborn screening result in the past five years (Kemper et al. 2006). However, several studies have revealed that physicians have limited knowledge of the conditions included on newborn screening. While data specific to physician understanding of SMA is lacking, studies have focused on other conditions, including cystic fibrosis, hemoglobinopathies, and hearing loss (McWalter et al. 2011; Oyeku et al. 2010; Stark et al. 2011; Topal et al. 2019). Researchers have concluded that physicians require more training for managing the care of a child with a positive newborn screen, including counseling the family, initiating diagnostic testing, and making subspecialty referrals (Kemper et al. 2006).

Studies investigating physician understanding of these conditions have included a combination of basic information about the condition (e.g. inheritance, symptoms), as well as more complicated information such as treatment and follow-up procedures (McWalter et al. 2011; Stark et al. 2011; Topal et al. 2019). Physicians have typically demonstrated a solid understanding of the more basic concepts (McWalter et al. 2011; Stark et al. 2011; Topal et al. 2019). In a survey of pediatricians in Hawaii, San Francisco, and Salt Lake City assessing knowledge of hemoglobinopathies and newborn screening, 89.4% of respondents had either “good” or “perfect”

scores, meaning they answered at least three out of the four questions correctly. However, authors cited that this could be due to the fact that the questions were simple, including information such as inheritance and basic clinical presentation (McWalter et al. 2011). Studies have shown that physicians have limited understanding and knowledge of more complicated information related to newborn screening (Stark et al. 2011; Topal et al. 2019). A survey of pediatricians in Illinois regarding newborn screening for sickle cell disease and cystic fibrosis revealed that while their basic knowledge of each condition was high, questions about the interpretation of newborn screening results were less understood (Stark et al. 2011). Similarly, in interviews and surveys of family physicians in Turkey about cystic fibrosis newborn screening, participants demonstrated a higher knowledge of basic information (such as inheritance and symptoms) than of more complex concepts (such as diagnosis and follow-up) (Topal et al. 2019).

Several studies have also determined that physicians tend to feel uncomfortable with handling newborn screening follow-up. Certain researchers have assessed comfort with newborn screening as a whole, while others have focused on specific conditions (Gennaccaro et al. 2005; Hayeems et al. 2013; Kemper et al. 2006; Moeller et al. 2006; Oyeku et al. 2010). In a survey of Massachusetts pediatricians, 42% reported feeling less than comfortable talking about the disorders on expanded newborn screening and 54% reported feeling less than comfortable disclosing newborn screening results (Gennaccaro et al. 2005). Similarly, Hayeems et al. (2013) surveyed PCPs and midwives involved in newborn care and determined that a minority felt they were up to date (18.5%) or confident (16.5%) with information about newborn screening (Hayeems et al. 2013). Another survey focused on PCPs' confidence in discussing newborn screening for hearing loss. Researchers found that many respondents reported being confident

talking about newborn screening results, but did not feel confident discussing follow-up care and treatment (Moeller et al. 2006).

An extensive study on physicians' attitudes about newborn screening, including level of comfort, was conducted by Kemper et al. (2006). Researchers surveyed nearly 350 pediatricians and family physicians who reported providing care for infants. The survey focused on five conditions: congenital hypothyroidism, PKU, sickle cell disease, cystic fibrosis, and medium-chain acyl-coenzyme A dehydrogenase deficiency (MCAD). Survey questions inquired about the clinicians' beliefs regarding who should be responsible for follow-up care, barriers to follow-up care, and which families should receive genetic counseling. The tool also assessed participants' knowledge of the conditions, potential resources, and the availability of genetic counseling. The percentage of respondents who reported not feeling competent to discuss positive newborn screening results varied depending on the condition. The condition that participants felt most uncomfortable with was MCAD, with 75% of pediatricians and 92% of family physicians indicating they are not competent to discuss positive MCAD newborn screening results. The majority of respondents also reported being uncertain what confirmatory test to order for PKU and MCAD. Based on their findings, researchers discuss concerns regarding variations in care, particularly between pediatricians and PCPs. They suggest that more rigid guidelines for follow-up care may help address these discrepancies. They also recognized that MCAD, one of the most recent conditions to be included in newborn screening at the time, was the one that providers felt least comfortable with (Kemper et al. 2006). This raises a need for more education and guidance for newborn screening as a whole, and particularly for more recently included conditions.

The only known experimental research of physician knowledge and comfort regarding newborn screening was conducted by Oyeku et al. (2010). Researchers distributed pre- and post-

test surveys to PCPs regarding their knowledge of newborn screening for sickle cell disease and their confidence in caring for patients with this condition. Participants completed the survey before and after either reviewing educational materials or attending interactive seminars on sickle cell disease and newborn screening (depending on their assigned intervention group). The survey covered a variety of topics, including follow-up for children with positive newborn screening results, knowledge of sickle cell disease management, and clinicians' self-efficacy in handling positive newborn screening results. To assess knowledge, the survey included clinical vignettes focusing on sickle cell disease screening, diagnosis, and treatment. For measuring confidence, participants were asked to rate their confidence in performing certain clinical tasks, including explaining sickle cell disease inheritance and family planning options for families affected by sickle cell disease. Participant knowledge of newborn screening follow-up practices increased for both the group attending the seminars and the group receiving printed educational materials. Confidence also increased after reviewing the educational materials or attending the seminars, but was a more modest increase than knowledge (Oyeku et al. 2010).

As PCPs have the opportunity to receive a positive newborn screen for SMA, it is important to determine whether they also lack knowledge and confidence for this particular condition. While there has been research on other conditions included on newborn screening, as described above, to date no study has evaluated physician knowledge and confidence regarding SMA.

3.0 Manuscript

3.1 Background

SMA is a severe autosomal recessive condition caused by the degeneration of motor neurons which leads to progressive muscle weakness and atrophy. It has an estimated incidence of 1 in 10,000 live births, making it the most common genetic cause of mortality in infants and the second-most common fatal autosomal recessive condition after cystic fibrosis (Prior 2008; Carré and Empey 2016).

The genetic etiology of SMA is complex. SMA is caused by a non-functioning *SMN1* gene, which is located on chromosome 5q13 and is normally responsible for coding the SMN protein (Cobben et al. 1995; Hahnen et al. 1995; Lefebvre et al. 1997; Lorson et al. 1999; Rodrigues et al. 1995). The *SMN2* gene is nearly identical to *SMN1* and only differs by a single nucleotide which prohibits it from producing as much fully functional SMN protein (Lorson et al. 1999; Monani et al. 1999). While loss of *SMN2* does not cause SMA, *SMN2* gene copy number has been shown to inversely affect the severity of SMA phenotype (B Wirth et al. 1999).

In December 2016, Nusinersen (Spinraza) became the first FDA-approved treatment for patients with SMA (Aartsma-Rus 2017). It was subsequently approved by the European Medicines Agency in June of 2017. The antisense oligonucleotide drug was the product of many years of research and clinical trial experimentation. The therapy involves the binding of antisense oligonucleotides to a splicing silencer in intron 7 of *SMN2*, which allows for inclusion of exon 7 and the production of full-length SMN protein (Gidaro and Servais 2019). In addition to Nusinersen, gene therapy has also shown great promise in patients with SMA. The FDA approved

the first gene therapy for SMA (trade named Zolgensma) in May 2019. It is authorized for use in the treatment of children with SMA under two years of age (Commissioner 2019). The development of available treatment and its proven efficacy when initiated early has been a driving factor in support of pre-symptomatic diagnosis of patients with SMA.

Newborn screening is a public health program which operates under the goal of early diagnosis and treatment initiation for patients with severe genetic conditions. Today, newborn screening programs occur in all U.S. states and are implemented by state public health agencies. Although each state has its own procedure for adding conditions to its newborn screening panel, the RUSP is a list of conditions that states are recommended to include. The ACHDNC is responsible for reviewing nominated conditions, voting on their addition to the RUSP, and making recommendations to the HHS Secretary (Shone 2019).

Each state has its own legislation which determines the newborn screening process, including follow-up. In Pennsylvania, blood is collected on a filter paper specimen card between 24 hours and 72 hours of age. The birthing facility or healthcare provider then sends the filter paper to a laboratory contracted by the Pennsylvania NSFP. Testing is typically completed within seven to ten working days. Screening results are reported to the NSFP, the PCP or midwife listed on the filter paper specimen card, and the birth facility. In the case of an abnormal screening result, the PCP listed on the filter paper card is responsible for disclosing the results to the parents or guardians of the newborn and coordinating follow-up testing and care (PA Dept of Health Division of Newborn Screening and Genetics 2009).

With advancements in understanding SMA disease mechanisms and developing treatment came pushes for including SMA in newborn screening programs. SMA was initially proposed for inclusion on the RUSP in 2008. Small studies had shown the feasibility and accuracy of SMA

screening using dried blood spots (Pyatt et al. 2007; Pyatt and Prior 2006). However, the ACHDNC denied the nomination due to lack of available treatment and evidence from pilot studies at that time (Kraszewski et al. 2018). Pilot studies were subsequently initiated to evaluate the feasibility of mass screening for SMA (Chien et al. 2017; Kraszewski et al. 2018; Prior et al. 2010). Following the FDA's approval of Nusinersen and implementation of pilot programs, SMA was nominated for addition to the RUSP for a second time in 2018. After considering the benefits and risks, the ACHDNC recommended to the Secretary of HHS that SMA be added to the RUSP in July of 2018. The Secretary's approval subsequently initiated its incorporation into newborn screening programs across the country (Aartsma-Rus 2017). Pennsylvania began screening for SMA in March of 2019 and, as of April of 2020, is one of 23 states which have implemented screening (Cure SMA 2019a; McCall n.d.).

This shift in attention to SMA has revealed a limited understanding of the condition, by both the public and clinicians (Moultrie et al. 2016). Despite the fact that conditions on the RUSP are rare, a survey distributed by Kemper et al. (2006) shows that most pediatricians and about one half of family physicians report caring for a child with a positive newborn screening result in the past five years. Research assessing physician knowledge of newborn screening and some included conditions has revealed that while physicians tend to understand basic concepts, they have limited knowledge of more complex information related to follow-up (McWalter et al. 2011; Stark et al. 2011; Topal et al. 2019). Studies have also found that most PCPs feel uncomfortable with handling newborn screening follow-up and lack confidence in this area of their practice (Gennaccaro et al. 2005; Hayeems et al. 2013; Kemper et al. 2006; Moeller et al. 2006; Oyeku et al. 2010). Researchers have thus concluded that PCPs require more training for managing the care of a child with a positive newborn screen (Kemper et al. 2006).

There have been no previous studies assessing physician knowledge or confidence regarding newborn screening for SMA. The goal of this project is to identify gaps in PCP understanding of SMA and newborn screening in order to develop interventions for further education and ultimately improve the care of these patients.

3.2 Methods

3.2.1 Study Participants

This study was designed to target PCPs who have the potential to receive newborn screening results from the state of Pennsylvania. The intent of the study was to focus on PCPs who may not have a history of extensive training surrounding genetics and SMA, but may still be involved in the care of patients with SMA. This population includes mostly PCPs practicing in Pennsylvania, as well as some in surrounding states. There are instances when children are born at a Pennsylvania facility, and thus receive Pennsylvania newborn screening results, but receive care from a PCP in a surrounding state.

The survey was distributed to 1,161 PCPs on a list obtained from the Pennsylvania Department of Health Division of Newborn Screening and Genetics. The list contains PCPs who could potentially receive an abnormal newborn screening result for follow-up. The survey was distributed in February 2020 via email to those for which email addresses were available and via fax for the others using the invitation in Appendix B.1. Emails and faxes were followed by a reminder which was sent two weeks after the initial invitation. A second reminder was sent to each individual two weeks following the first reminder, for a total of three correspondences. Following

distribution to these providers, an additional method for recruitment was pursued due to a low response rate.

In April 2020, the survey was distributed to providers in the University of Pittsburgh Clinical and Translational Science Institute's Pediatric PittNet research network. An approval letter for the study from Pediatric PittNet is included in Appendix B.3. The research network includes over 275 pediatric physicians in 31 different practices across 13 counties in southwest Pennsylvania. Practices involved in Pediatric PittNet include 26 Children's Community Pediatrics sites, a rural hospital-affiliated clinic, an independent pediatric practice, a federally qualified health center, University of Pittsburgh Medical Center (UPMC) Children's Hospital primary care centers, and the UPMC Children's Hospital Adolescent Medicine Clinic (Clinical and Translational Science Institute 2018). The survey invitation included in Appendix B.1 was emailed to members of the Pediatric PittNet research network. A reminder email was sent ten days following the initial invitation. A second reminder was emailed five days after the first reminder for a total of three correspondences. The survey was closed to participants on May 19, 2020.

3.2.2 Survey Development

The University of Pittsburgh Institutional Review Board (IRB) approved this study and survey (ID: 19090037) as an exempt study (Appendix A). The survey was developed in Qualtrics software, which was accessed through a University of Pittsburgh license. A copy of the survey is included in Appendix B.2. The survey included a total of 22 questions covering the following topics: level of experience with SMA (patient care, education, training), knowledge of SMA (genetic etiology, inheritance, phenotype, treatment, screening), level of comfort caring for patients with SMA (screening interpretation, follow-up testing, referrals), desire for more

information about SMA, and demographics. Responses were not required for individual questions and participants were able to withdraw from the survey at any point. The survey included various types of questions, such as multiple choice, text entry, and side-by-side matrix. The final question was a free response opportunity for participants to enter any additional comments. A pilot of the survey was administered to two pediatrics fellows at UPMC Children's Hospital of Pittsburgh.

3.2.3 Data Analysis

Descriptive statistics, including means and standard deviations, were performed using Microsoft Excel software. All surveys with responses to at least one question were included in the data analysis. Response proportions were calculated based on the number of total responses for each individual question.

To analyze responses to questions regarding knowledge of SMA (survey questions 4-13), a knowledge score was calculated for each respondent who answered at least one of these nine questions. Participants earned one point for each question correctly answered. For "select all that apply" questions (survey questions 7, 9, and 13), respondents earned one point for each correct item selected and one point was subtracted for each incorrect item selected. This scoring method was modeled after the one reported by M.R.J. Morgan, which was designed to discourage random guessing by including a penalty for incorrect choices (Morgan 1979). Questions that were answered with "Don't know" were counted as incorrect. Respondents did not earn any points for questions which were left blank. For survey question 8, responses that answered with "4" or "5" were deemed correct, since some sources state there are four types of SMA and some state there are five, depending on whether SMA type 0 is counted (Carré and Empey 2016; B. Wirth et al. 2006). A summary of the scoring methods utilized for each knowledge question is included in

Table 1. Participants were not given negative knowledge scores; the lowest possible score was 0. Possible knowledge scores ranged from 0 (all items incorrect for all questions) to 19 (all items correct for all questions).

Table 1 Scoring Method for Knowledge Questions

Survey Question	Response	Scoring
SMA is caused by pathogenic variants in which of the following genes? (Question #4)	SMN1	Earned 1 point
	SMA1, SMA2, SMN3, Don't Know	Earned 0 points
What pattern of inheritance does SMA follow (Question #5)	Autosomal recessive	Earned 1 point
	Autosomal dominant, X-linked dominant, X-linked recessive, Mitochondrial, Don't know	Earned 0 points
Patients with SMA can experience varying degrees of disease severity (True or False) (Question #6)	True	Earned 1 point
	False, Don't know	Earned 0 points
Which of the following factor(s) have been shown to impact the clinical presentation of patients with SMA? (Question #7)*	SMN2 gene copy number	Earned 1 point
	From which parent the more severe pathogenic variant was inherited, Whether pathogenic variants were inherited or were de novo mutations, Don't Know	Subtracted 1 point for each
How many subtypes of SMA exist? (Question #8)	4, 5	Earned 1 point
	2, 3, Don't know	Earned 0 points
Which of the following clinical symptoms have been observed in patients with SMA? (Question #9)*	Respiratory complications, Progressive muscle weakness and atrophy, Hypotonia, Feeding difficulties and poor growth, Joint contractures, Scoliosis	Earned 1 point for each
	Hepatosplenomegaly, Coloboma, Polydactyly, Cleft lip and palate	Subtracted 1 point for each
Nusinersen (marketed as Spinraza), the first FDA-approved treatment of SMA, works by which of the following mechanisms?	Antisense oligonucleotide therapy	Earned 1 point
	Enzyme replacement therapy, Substrate reduction therapy,	Earned 0 points

Table 1 Continued

(Question #10)	Small interfering RNA (siRNA) therapy, Don't know	
Administration of Spinraza occurs via which of the following? (Question #11)	Intrathecal injection	Earned 1 point
	Orally, Subcutaneous injection, Intramuscular injection, Don't know	Earned 0 points
Current SMA newborn screening methods only identify patients with severe, early-onset forms of the condition (True or False) (Question #12)	False	Earned 1 point
	True	Earned 0 points
Which of the following steps should be taken immediately upon identification of a patient with SMA through newborn screening? (Question #13)	Contact family to inform them of the newborn screening result, Consult with pediatric neurologist and geneticist, Evaluate the newborn for signs of neuromuscular disease, Initiate timely confirmatory/diagnostic testing, Provide family with basic information about SMA	Earned 1 point for each
	Order a chromosomal microarray for each of the patient's first-degree relatives, Conduct an audiology evaluation, Consult with a pediatric surgeon	Subtracted 1 point for each

* "Select all that apply" question

A comfort score was also calculated for each respondent who answered at least one part of question 14 to analyze level of comfort caring for patients with SMA. Each possible response was assigned a point value as shown in Table 2. Each participant's point values were averaged to calculate an overall comfort score. This approach was based on one of Mark Robinson's suggestions for scoring multi-item psychometric scales (Robinson 2018). Responses which were left blank or noted as "N/A" were not included in the average calculations. Possible comfort scores ranged from 0 (all items were N/A) to 5 (very comfortable with all items).

Table 2 Point Values for Responses to Survey Question 14

Survey Response	Point Value
Very uncomfortable	1
Somewhat uncomfortable	2
Neither comfortable nor uncomfortable	3
Somewhat comfortable	4
Very comfortable	5
N/A	Excluded

3.3 Results

Of the estimated 1,161 individuals to whom the survey was distributed, there were a total of 29 responses with at least one question answered. This is equivalent to a 2.5% response rate. Of the 29 responses, 20 respondents completed every question. Respondents who noted their medical specialty to be anything besides pediatrics or family medicine were excluded in order to avoid skewing results and affecting the generalizability of the study to primary care physicians. Three respondents noted other medical specialties and thus were excluded from data analysis. The final data analysis includes 26 responses.

3.3.1 Respondents

Table 3 summarizes demographic information from survey respondents who provided it. The information is divided into two categories: those who have been involved in the care of a

patient with SMA and those who have not. The majority of respondents, 77.3% (n=17), identified their gender to be female. The majority of providers had been practicing for 20 or more years. All respondents included in the data analysis indicated their medical specialty to be pediatrics (n=22). The majority (63.6%) indicated that their practice setting is a group practice (n=14). Of note, no participants were of the family medicine specialty, practiced in a private hospital, or were retired. All respondents practice in the state of Pennsylvania and are from 11 different counties. The county of practice with the highest number of respondents is Allegheny County.

Table 3 Demographic Information

	Has Cared for a Patient with SMA	Has Not Cared for a Patient with SMA	Total
Gender Identity			
Female	78.6% (11)	75.0% (6)	**77.3% (17)**
Male	14.3% (2)	25.0% (2)	**18.2% (4)**
Prefer not to say	7.1% (1)	0.0% (0)	**4.5% (1)**
Number of Years in Practice			
<5	7.7% (1)	12.5% (1)	**9.5% (2)**
5-9	30.8% (4)	12.5% (1)	**23.8% (5)**
10-14	23.1% (3)	12.5% (1)	**19.0% (4)**
15-19	23.1% (3)	12.5% (1)	**19.0% (4)**
20 or more	15.4% (2)	50.0% (4)	**28.6% (6)**
Medical Specialty			
Pediatrics	100.0% (14)	100.0% (8)	**100.0% (22)**
Practice Setting			
Academic	7.1% (1)	12.5% (1)	**9.1% (2)**
Group practice	71.4% (10)	50.0% (4)	**63.6% (14)**

Table 3 Continued

Hospital (public)	7.1% (1)	12.5% (1)	**9.1% (2)**
Individual practice	7.1% (1)	25.0% (2)	**13.6% (3)**
Other	7.1% (1)	0.0% (0)	**4.5% (1)**
State of Practice			
Pennsylvania	100.0% (14)	100.0% (8)	**100.0% (22)**
County/Region of Practice			
Allegheny County	50.0% (6)	42.9% (3)	**47.4% (9)**
Other Western PA Counties (Armstrong, Butler, Erie, Fayette, Westmoreland)	41.7% (5)	0.0% (0)	**26.3% (5)**
Other Eastern PA Counties (Bucks, Lackawanna, Luzerne, Montgomery, Montour)	8.3% (1)	57.1% (4)	**26.3% (5)**

3.3.2 Respondent Experience with SMA

Survey questions 1-3 were designed to assess participants' level of experience with SMA. Of the 26 respondents included in data analysis, 69.2% (n=18) indicated that they have cared for a patient with SMA. Of these providers who have cared for a patient with SMA, the majority (66.7%, n=10) indicated that they have provided primary care (Figure 1). The roles endorsed by respondents who report having been involved in the care of a patient with SMA are displayed in Figure 1. Due to participant answers to the "Other: please specify" response, two additional categories of physician involvement were created: residency and neonatal intensive care unit (NICU) involvement.

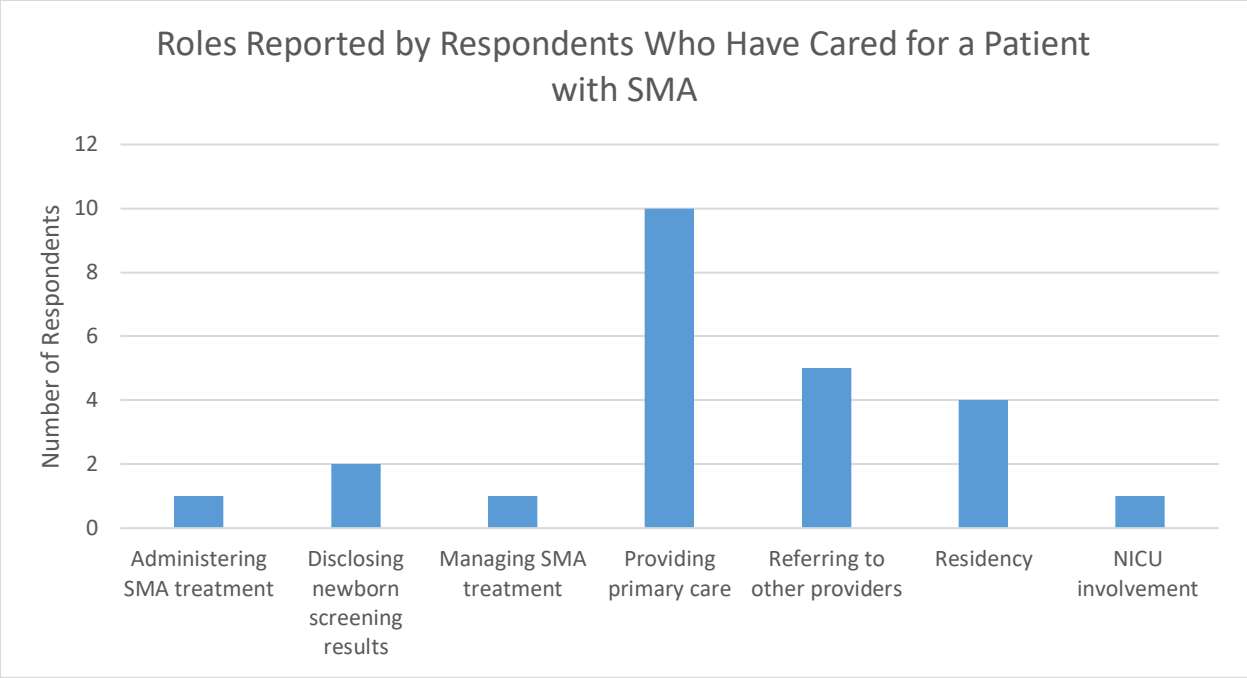

Figure 1 Roles Reported by Respondents Who Have Cared for a Patient with SMA

Ten respondents (45.5%) indicated they have received some formal training regarding SMA, while seven (31.8%) responded that they may have but do not remember. A summary of demographic information divided into those who have received formal SMA training, those who might have, and those who have not is provided in Table 11 (Appendix C).

Of all participants, 73.9% (n=17) responded that they have consulted at least one source for information related to SMA. The resource most frequently utilized was journal articles, with 64.7% (n=11) indicating that they have consulted journal articles for information about SMA. A majority of respondents (58.8%, n=10) also reported using websites for information about SMA (Figure 2). The numbers of respondents reporting having consulted each source are displayed in Figure 2. One respondent noted using the "Up To Date" resource for information, which was included in websites.

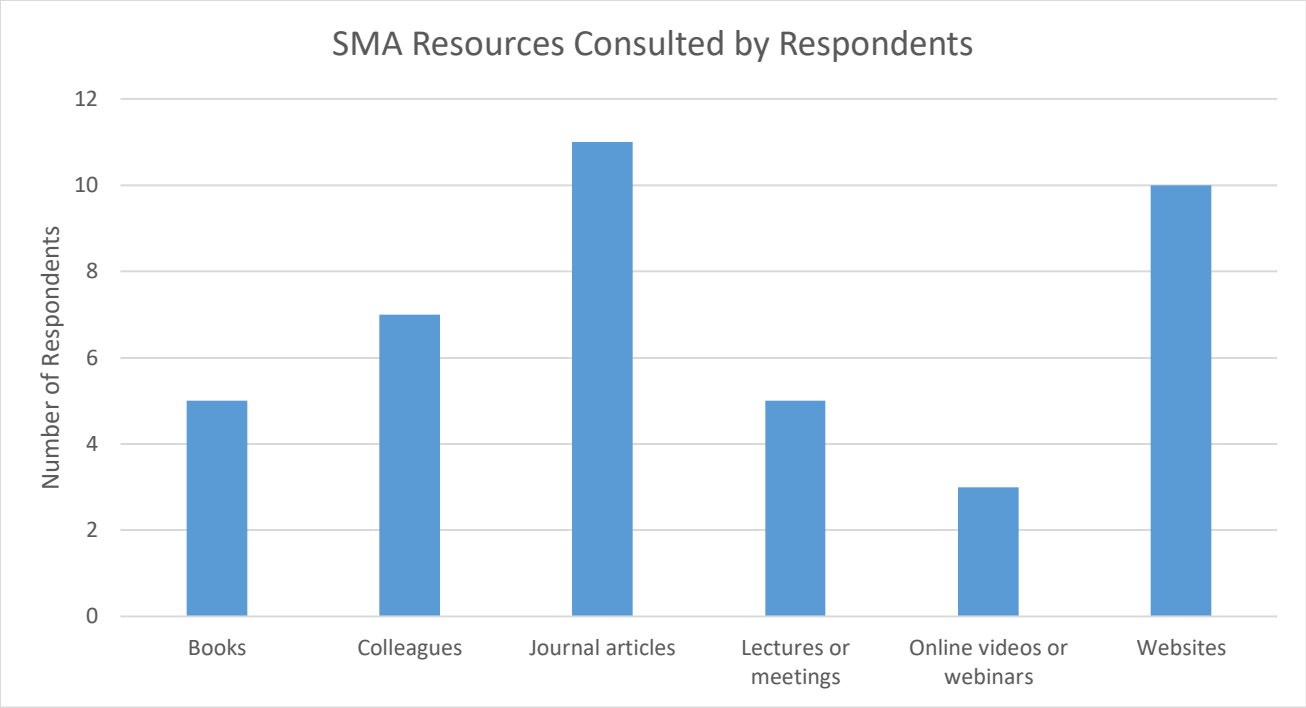

Figure 2 Resources Consulted by Respondents for Information Regarding SMA

3.3.3 Respondent Knowledge of and Level of Comfort with SMA

A knowledge score was calculated for each participant based on responses to survey questions 4-13 to assess their knowledge of SMA. Higher knowledge scores indicate more knowledge regarding SMA, as measured by this survey. Table 4 summarizes the total percentage of participants who answered each of the ten knowledge questions correctly. For the purposes of this calculation, "select all that apply" questions were only deemed correct if respondents selected all appropriate items and did not select any incorrect items. Table 12 (Appendix C) provides these percentages by providers who have cared for a patient with SMA compared to those who have not cared for a patient with SMA. Similarly, Table 13 (Appendix C) divides the data by those who have received formal SMA training, those who might have, and those who have not. Possible knowledge scores ranged from 0 to 19. The average knowledge score was 10.0 with a standard

deviation of 3.9. Knowledge scores of participants ranged from 1 to 18 (Table 5). A breakdown of average knowledge scores for those who provided demographic information is included in Table 5.

Table 4 Total Correct Responses to Knowledge Questions

Question	Percent Correct
SMA is caused by pathogenic variants in which of the following genes?	13.0% (3)
What pattern of inheritance does SMA follow?	47.8% (11)
Patients with SMA can experience varying degrees of disease severity (True or False)	91.3% (21)
Which of the following factor(s) have been shown to impact the clinical presentation of patients with SMA?*	18.2% (4)
How many subtypes of SMA exist?	39.1% (9)
Which of the following clinical symptoms have been observed in patients with SMA?* Select all that apply	17.4% (4)
Nusinersen (marketed as Spinraza), the first FDA-approved treatment of SMA, works by which of the following mechanisms?	8.7% (2)
Administration of Spinraza occurs via which of the following?	39.1% (9)
Current SMA newborn screening methods only identify patients with severe, early-onset forms of the condition (True or False)	26.1% (6)
Which of the following steps should be taken immediately upon identification of a patient with SMA through newborn screening?*	21.7% (5)

*In this table, answers to "select all that apply" questions were only deemed correct if the respondent marked all correct items and did not mark any incorrect items

Table 5 Average Knowledge and Comfort Scores of All Respondents

	Average Knowledge Score (Possible Scores Range 0-19)	**Average Comfort Score** (Possible Scores Range 0-5)
Gender Identity		
Female (n=17)	9.6 ± 3.2	2.5 ± 0.8
Male (n=4)	8.3 ± 4.2	2.8 ± 0.7
Prefer not to say (n=1)	16.0 ± 0	3.2 ± 0.0
Number of Years in Practice		
<5 (n=2)	8.0 ± 1.0	1.9 ± 0.3
5-9 (n=5)	12.0 ± 2.3	2.9 ± 1.0
10-14 (n=4)	10.0 ± 2.7	2.9 ± 0.6
15-19 (n=4)	8.8 ± 1.5	2.2 ± 0.4
20 or more (n=6)	7.5 ± 4.5	2.5 ± 0.9
Medical Specialty		
Pediatrics (n=22)	9.6 ± 3.6	2.6 ± 0.8
Practice Setting		
Academic (n=2)	8.5 ± 7.5	2.1 ± 1.1
Group Practice (n=14)	9.9 ± 2.6	2.6 ± 0.8
Hospital (public) (n=2)	11.0 ± 0.0	2.6 ± 0.3
Individual practice (n=3)	8.7 ± 4.8	2.9 ± 0.7
Other (n=1)	8.0 ± 0.0	1.8 ± 0.0
State of Practice		
Pennsylvania (n=22)	9.6 ± 3.6	2.6 ± 0.8
County of Practice		

Table 5 Continued

Allegheny County (n=9)	9.1 ± 4.9	2.5 ± 1.0
Other Western PA Counties (Armstrong, Butler, Erie, Fayette, Westmoreland) (n=5)	10.4 ± 2.7	2.8 ± 0.7
Other Eastern PA Counties (Bucks, Lackawanna, Luzerne, Montgomery, Montour) (n=5)	9.0 ± 1.8	2.7 ± 0.7

A comfort score was also calculated for each participant to assess level of comfort caring for patients with SMA. Higher comfort scores indicate more comfort caring for patients with SMA. Table 6 summarizes the participants' responses to each part of survey question 14, which was used to assess comfort. An overview of these responses for respondents who have provided care to patients with SMA is given in Table 14, Appendix C. A summary of responses for those who have not provided care to patients with SMA is shown in Table 15, Appendix C. Overall comfort scores ranged from 1 to 4.9 with an average comfort score of 2.7 and standard deviation of 0.9 (Table 5). Table 5 summarizes average comfort scores by demographic information of respondents.

Table 6 Summary of Responses to Comfort Questions (Survey Question #14)

	Very uncomfortable	**Somewhat uncomfortable**	**Neither comfortable nor uncomfortable**	**Somewhat comfortable**	**Very comfortable**	**N/A**
Interpreting a newborn screening report containing positive results	22.7% (5)	22.7% (5)	13.6% (3)	27.3% (6)	13.6% (3)	0.0% (0)
Discussing the genetic mechanism and inheritance of SMA with a	39.1% (9)	43.5% (10)	4.3% (1)	8.7% (2)	4.3% (1)	0.0% (0)

Table 6 Continued

patient's family						
Discussing the expected clinical course of SMA with a patient's family	30.4% (7)	52.2% (12)	4.3% (1)	8.7% (2)	4.3% (1)	0.0% (0)
Discussing available treatment options for SMA with a patient's family	36.4% (8)	50.0% (11)	4.5% (1)	4.5% (1)	4.5% (1)	0.0% (0)
Disclosing the results of a positive SMA newborn screen to a patient's family	13.6% (3)	40.9% (9)	13.6% (3)	22.7% (5)	9.1% (2)	0.0% (0)
Ordering diagnostic testing after a patient receives a positive SMA newborn screen result	27.3% (6)	54.5% (12)	9.1% (2)	4.5% (1)	4.5% (1)	0.0% (0)
Referring a newborn with SMA to the appropriate specialists	4.5% (1)	9.1% (2)	13.6% (3)	18.2% (4)	40.9% (9)	13.6% (3)
Providing primary care to a	9.1% (2)	22.7% (5)	13.6% (3)	18.2% (4)	31.8% (7)	4.5% (1)

Table 6 Continued

patient with SMA						
Referring the family of a patient with SMA to genetic counseling and explaining the genetic counseling process	4.5% (1)	13.6% (3)	13.6% (3)	22.7% (5)	36.4% (8)	9.1% (2)

The average knowledge score of respondents who reported having been involved in the care of a patient with SMA is 11.1, compared to an average score of 7.9 for those who have not. Participants who have been involved in the care of a patient with SMA have an average comfort score of 2.9, compared to an average score of 2.3 for those who have not. Figure 3 compares average knowledge and comfort scores for respondents who have provided care for a patient with SMA with those who have not provided care for a patient with SMA. A scatterplot illustrating the relationship between knowledge scores and comfort scores is provided in Figure 4. The correlation coefficient for this relationship is 0.7.

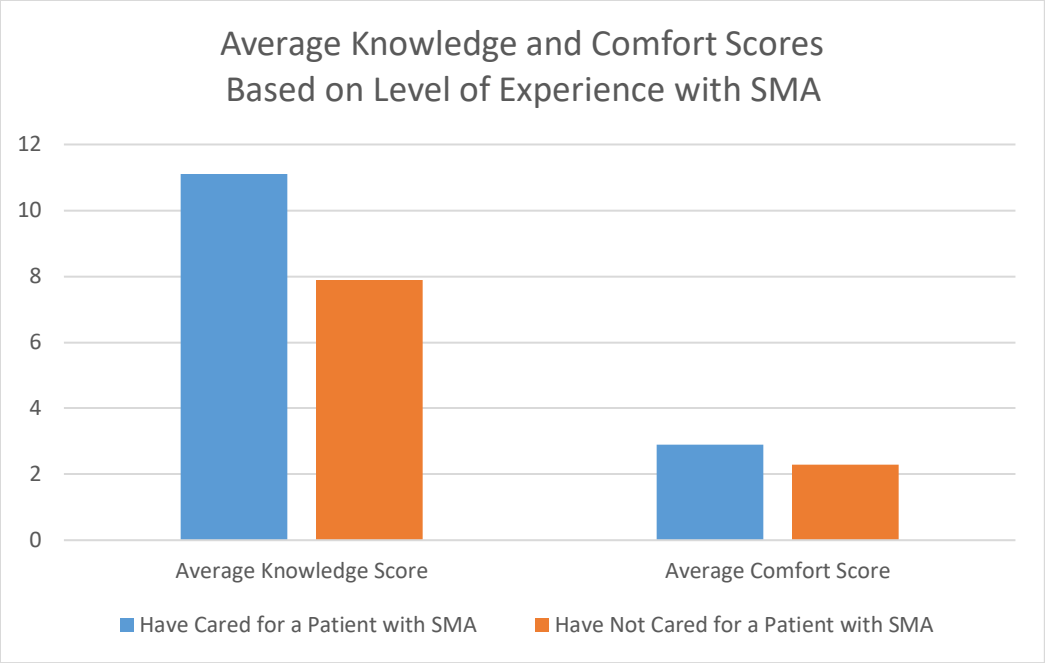

Figure 3 Average Knowledge and Comfort Scores Based on Level of Experience with SMA

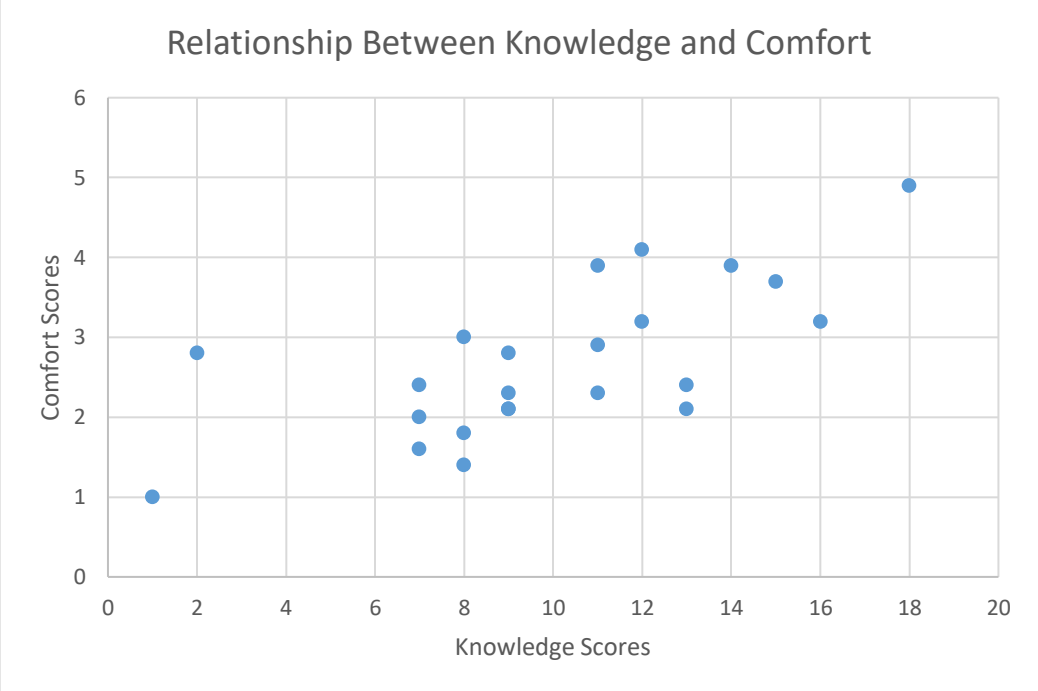

Figure 4 Relationship Between Knowledge and Comfort Scores

3.3.4 Respondent Desire for Further Training

Survey questions 15 and 16 assessed respondents' desires for additional education or information related to SMA. Overall, 91.3% (n=21) of participants responded that they would find it beneficial to receive additional training or information about SMA. Figure 5 summarizes the topics that these respondents indicated they would find helpful.

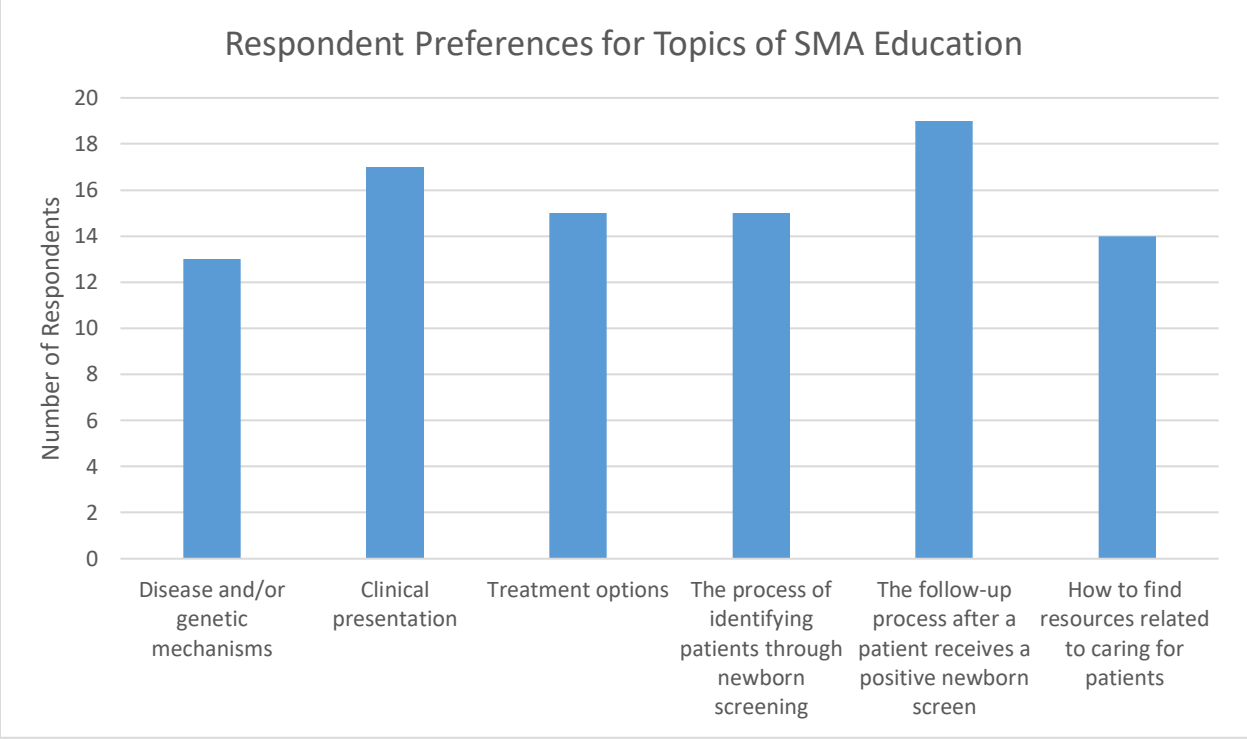

Figure 5 Respondent Preferences for Topics of SMA Education

3.4 Discussion

3.4.1 Response Rate

Studies utilizing surveys as a tool for data collection have varying response rates. Due to the demanding schedules of physicians and the fact that they are frequently approached to complete surveys, surveys of physicians have response rates about 10% lower than surveys of the general population (Cummings et al. 2001). Given these challenges, the low response rate in this study is not unexpected. A summary of research on physician survey response rates is included in Table 7. A review of 50 surveys of pediatricians revealed an average response rate of 68% (Cull et al. 2005). However, surveys of PCPs related to newborn screening reveal a lower response rate, which could be related to lack of interest or discomfort with the topic of newborn screening. Of ten surveys of PCPs regarding newborn screening, response rates range from 8.4% to 60.9% with an average response rate of 34.94% (Acharya et al. 2005; Bansal et al. 2019; Desposito et al. 2001; Gennaccaro et al. 2005; Hayeems et al. 2013; Kemper et al. 2006; Moeller et al. 2006; Oyeku et al. 2010; Ross and Visser 2012; Thompson et al. 2005). The low response rate of approximately 2.5% observed with the survey in this study could be attributed to the difficulties in obtaining email addresses for physicians, as well as the lack of incentives for participation. Physicians receiving the survey also may have limited interest in SMA and newborn screening or may have had the misconception that they could not participate unless they had received a positive newborn screening result for SMA.

Table 7 Summary of Research on Physician Survey Response Rates

Article	Methods	Primary Findings
(Ahlers-Schmidt et al. 2010) *Kansas Journal of Medicine*	- Authors initially administered surveys to 149 physicians by e-mail - Surveys were then faxed to non-respondents - Phone interviews were then attempted with physicians who had not responded by e-mail or fax	- Overall response rate of 68.5% - 48% of respondents answered by e-mail, 24.5% by fax, and 27.5% by phone
(Braithwaite et al. 2003) *Family Practice*	- Literature review of web-based surveys of health professionals - Authors distributed a web-based survey to general practitioners	- Of the 17 web-based surveys included in the literature review, 12 studies reported response rates, which ranged from 9-94% - The authors' survey had a response rate of 52.4% after five email reminders
(Brtnikova et al. 2018) *PLOS One*	- Internet and mail surveys of U.S. PCPs	- Internet surveys had a higher response rate than mailed surveys (74% vs. 62%)
(Cummings et al. 2001) *Health Services Research*	- Literature review of articles published between 1985 and 1995 using mailed surveys of physicians	- The average response rate of articles using mailed surveys was 61%
(Cunningham et al. 2015) *BMC Medical Research Methodology*	- Online survey distributed to 904 physicians of various medical specialties	- Overall response rate of 35% - The response rates varied by medical specialty: 46.6% for neurology/neurosurgery; 42.9% for internal medicine; 29.6% for general surgery, 29.2% for pediatrics, and 27.1% for psychiatry
(Flanigan 2008) *American Association for Public Opinion Research (AAPOR)*	- Literature review of articles published between 1987 and 2008 involving physician response to surveys	- Using web surveys alone resulted in lower response rates - Web surveys using an e-mail letter with a hyperlink to the survey may have more sampling error because physician e-mail addresses are not as accessible as physician addresses and phone numbers
(Lensing et al. 2000)	- Survey of Arkansas general practitioners, family physicians, and pediatricians	- Overall response rate of 59% - 47% of respondents completed the survey by fax,

T**able 7 Continued**

Evaluation & the Health Professions	- Participants were given the option of completing the survey by telephone, mail, or fax	28% by phone, and 25% by mail
(Nicholls et al. 2011) *Health Services Research*	- Survey of Alabama PCPs - Participants were given the option of completing the survey by telephone, fax, e-mail, or online	- 88% of surveys were completed by mail, 10% by fax, and 2% online - No surveys were completed by telephone or e-mail
(Weaver et al. 2019) *BMC Medical Research Methodology*	- Survey of physicians randomly selected from the Minnesota Board of Medical Practice - Physicians were randomly assigned to single mode (mail or web only) or mixed mode (mail and web)	- Overall response rate of 18.6% - No statistically significant different in response rate across modes

3.4.2 Demographics

Based on information from the Pennsylvania Department of Health's 2014 Pulse of Pennsylvania's Physician and Physician Assistant Workforce, the demographics of respondents are fairly similar to those of the physician workforce in the state (Pennsylvania Department of Health 2017).

Most respondents were female, which echoes the fact that the majority of physicians reporting a pediatric specialty in Pennsylvania are female (Pennsylvania Department of Health 2017).

Thirty-percent of participants in this study had been practicing medicine for 20 or more years while 45% of physicians in Pennsylvania who provide direct patient care have been practicing for 16+ years. The majority of providers reported their medical specialty to be pediatrics, which was the primary target group for this project and the specialty of the majority of individuals to whom the survey was distributed. Practice settings reported by respondents included public hospitals, individual practices, group practices, and academic, with a majority in group

practices (61.9%). Practice settings of physicians in Pennsylvania vary, with most located within a single specialty clinic or inpatient hospital (Pennsylvania Department of Health 2017).

While respondents spanned 11 different counties in Pennsylvania, Allegheny County contained the highest number of participants. This could be explained by the fact that the survey was developed in Allegheny County. In addition, the majority of providers in the Pediatric PittNet research network are located in Allegheny County and 16 (62%) of the responses included in the data analysis were received after the survey was distributed to this group. According to the Pennsylvania Department of Health, Allegheny County has high physician density; there are over 300 physicians practicing direct patient care per 100,000 population in Allegheny County (Pennsylvania Department of Health 2017).

Demographic information was fairly similar among physicians who have been involved in the care of a patient with SMA compared to those who have not been involved in the care of a patient with SMA.

3.4.3 Level of Experience with SMA

Most respondents (69.2%) reported that they have been involved in the care of a patient with SMA. This could result from providers who are familiar with SMA being more likely to participate in the survey compared to those who are not.

Surveys of PCPs regarding newborn screening have revealed that most providers have received at least one positive result for a condition on their state's panel (Kemper et al. 2006; Thompson et al. 2005). SMA is a rare condition with a reported incidence of 1 in 10,000 (Carré and Empey 2016). However, data from SMA newborn screening pilot programs have revealed that the incidence may be higher than prior reports (Kraszewski et al. 2018; Vill et al. 2019). Specific

to Pennsylvania, Cure SMA reports that an estimated 12 children are born with SMA annually and approximately 431 individuals were living with SMA in the state as of 2019 (Cure SMA 2019b). According to the Pennsylvania Department of Health, 12 newborns received a positive SMA newborn screening result between March 1, 2019 and April 20, 2020. The total number of newborns screened during this time period was 148,911, revealing an incidence of approximately 1 in 12,400 in this sample (J. Shover, personal communication, April 21, 2020). This data only encompasses the one year that SMA has been included on Pennsylvania newborn screening thus far. Future reports may reveal higher or lower numbers of diagnoses per year.

Ten respondents (45.5%) indicated that they have received some formal education related to SMA. Treatment for SMA was developed in recent years, meaning that attention has not been given to broad screening until recently. This may explain why the majority of participants reported either not receiving formal education related to SMA or not remembering if they have.

Respondents reported having consulted a variety of resources for information related to SMA: books, colleagues, journal articles, lectures or meetings, online videos or webinars, and websites. The resources utilized by the most providers were journal articles and websites. Six physicians (26.1%) reported that they have not consulted any sources of information about SMA. A survey of pediatricians in Massachusetts regarding newborn screening revealed that the majority of participants had obtained information about newborn screening from colleagues. Several also consulted medical journals, websites, and books for newborn screening-related information (Gennaccaro et al. 2005). Based on the fact that knowledge scores were low among participants in this study, it may be beneficial to invest in developing more resources for providers to learn about SMA and newborn screening.

3.4.4 Knowledge of and Comfort with SMA

Despite their growing role in genetic screening and testing, several studies have revealed that PCPs lack important knowledge of genetics concepts and feel inadequately prepared to carry out tasks related to genetics (Baars et al. 2005; Hofman et al. 1993; Holtzman 1993; Metcalfe et al. 2002). This is the only known study which has investigated PCP knowledge and comfort regarding SMA. However, other studies have surveyed physicians about their knowledge of and comfort with other conditions included on newborn screening. Such studies have focused on a variety of conditions, including hemoglobinopathies, cystic fibrosis, PKU, congenital hypothyroidism, MCAD, and hearing loss (Kemper et al. 2006; McWalter et al. 2011; Moeller et al. 2006; Oyeku et al. 2010; Stark et al. 2011; Topal et al. 2019).

Knowledge scores were low across participants in this study, with only one question (question 6) having a majority of correct responses. This could be related to the fact that SMA has only recently been added to newborn screening, meaning that PCPs may not have had reason to be familiar with the condition before now. The percentage of correct answers varied across questions. More basic questions about inheritance and clinical presentation were more often answered correctly, while few respondents correctly answered more complex questions about newborn screening, genetic etiology, and treatment. This mimics the findings of other studies which have found that while participants achieve high scores with basic knowledge questions, they exhibit inadequate knowledge of the complex considerations of newborn screening and follow-up care (McWalter et al. 2011; Stark et al. 2011; Topal et al. 2019).

Reported comfort levels with being involved in the care of patients with SMA were also low in this study. The average comfort score across all respondents was 2.7, which is closer to "uncomfortable" than to "comfortable." This mirrors what has been found in similar studies

assessing physician confidence with newborn screening and with conditions included on screening panels (Gennaccaro et al. 2005; Hayeems et al. 2013; Kemper et al. 2006; Moeller et al. 2006). A survey of pediatricians in Massachusetts revealed that 42% were less than comfortable discussing disorders included on expanded newborn screening and 54% were less than comfortable disclosing newborn screening results (Gennaccaro et al. 2005). In a survey of PCPs and midwives involved in newborn care, a minority of respondents reported being up to date or confident with newborn screening-related topics (Hayeems et al. 2013). Physicians in this study reported higher levels of confidence with roles they might encounter more frequently in their practice, such as making appropriate referrals, explaining genetic counseling, and providing primary care. Roles more specific to SMA, such as ordering diagnostic testing and discussing treatment, were associated with lower comfort levels.

While some studies have revealed that experience with patients may contribute to knowledge more than additional training, educational interventions have been successful (McWalter et al. 2011; Oyeku et al. 2010). Oyeku et al. conducted pre- and post-test surveys before and after primary care clinicians received a randomized intervention for information about sickle cell disease and newborn screening (mailed educational materials or interactive seminars). The authors found that both the knowledge and confidence of physicians moderately increased following interventions (Oyeku et al. 2010). This suggests that additional training and education may be successful in increasing physician knowledge of and confidence with SMA newborn screening.

Knowledge scores were fairly similar across respondent demographics. It was hypothesized that providers in counties near larger cities (such as Allegheny County) may have higher knowledge scores due to more exposure to the condition, but this was not the case. Comfort

scores were also fairly consistent across demographics, with the reported comfort of physicians who have been in practice for less than five years being slightly lower than that of physicians who have been practicing longer. Other studies of physician knowledge of genetics concepts have revealed that graduating from medical school more recently and working in a specialty which involves exposure to genetics are significant predictors of a higher level of knowledge (Hofman et al. 1993; Holtzman 1993).

The scatter plot between knowledge and comfort scores (Figure 4) and correlation coefficient of 0.7 indicate that there is a positive correlation between knowledge and comfort; as knowledge of SMA increases, the level of comfort caring for patients with SMA tends to increase as well. The average knowledge score appeared higher among physicians who have provided care for a patient with SMA (11.1) compared to those who have not (7.9). The average comfort score also appeared slightly higher among those who have experience caring for a patient with SMA (2.9 compared to 2.3). This is what was hypothesized as those who have more experience with the condition likely have more knowledge of it. However, statistical analysis could not be used to make comparisons among groups due to the small sample size. The fact that comfort scores did not appear to be even higher among those who have cared for a patient with SMA could mean that there are other factors besides level of experience that impact confidence level.

3.4.5 Further Training

The majority of participants in this survey (91.3%, n=21) indicated that they would find it beneficial to receive additional training and education related to caring for patients with SMA. Other studies have revealed that providers favor the opportunity to receive educational resources related to newborn screening, particularly those that are printed, concise, and action-related (Davis

et al. 2006; Gennaccaro et al. 2005; Moeller et al. 2006; Thompson et al. 2005). Of the participants in this survey, the majority indicated they would like information about disease mechanisms, clinical presentation, treatment, how patients are identified through newborn screening, the follow-up process after a positive newborn screen, and how to find resources. The topic most commonly desired by providers was information about follow-up when an infant has a positive newborn screen for SMA. One study which conducted focus groups and interviews with health care professionals who provide prenatal or newborn care found that desired topics for further training included definitions, incidences, and treatment information about conditions included in newborn screening (Davis et al. 2006). In a survey of family physicians in Minnesota, participants indicated that information they would find helpful includes procedures for abnormal screens and condition-specific treatment and follow-up information (Thompson et al. 2005).

Given PCPs' lack of sufficient knowledge and confidence regarding newborn screening, efforts have been aimed at developing additional training and educational resources. For conditions included on the RUSP, the American College of Medical Genetics and Genomics (ACMG) lists two resources on their website: an ACTion (ACT) sheet and an algorithm. The ACT sheet is a focused summary including a description of the condition, the short-term actions the physician needs to take for follow-up of an abnormal screening result, and links to additional resources. The algorithm shows the steps involved in reaching a final diagnosis ("ACT Sheets and Algorithms" n.d.; Committee 2008; Weismiller 2017). However, developing such materials can be a timely process and typically are not available when a condition is first included in newborn screening. Despite being added to the RUSP in 2018, there is a lack of resources for PCPs specific to SMA.

Resources with additional information about SMA and newborn screening have been compiled for families, but lack some relevant information for physicians (Michigan Newborn

Screening Program n.d.; Muscular Dystrophy Association 2019; Newborn Screening Ontario n.d.; "Spinal Muscular Atrophy | Baby's First Test | Newborn Screening | Baby Health" n.d.). While some resources about SMA newborn screening have been developed for healthcare providers, most are not in the preferred format of physicians, are aimed towards a specific population (rather than a broader audience), or lack crucial information (Cure SMA n.d.; Mayo Clinic Laboratories 2019; "Medical Home Portal - Spinal Muscular Atrophy" n.d.; Minnesota Newborn Screening Program 2018). While these materials provide an important foundation, the results of this study and others show that there is a need for further efforts focused on actionable steps regarding newborn screening follow-up.

3.4.6 Limitations of the Study

There are several limitations to this study. The predominant limitation was the small sample size of physicians who responded to the survey. The low response rate could be due to the methods of survey distribution and potential lack of interest in the topic. Given the small sample size, it was not appropriate to conduct inferential statistics. Therefore, statistically significant trends or differences among groups could not be determined. The conclusions of this study rely on the descriptive statistics that were conducted.

Another limitation is a lack of information regarding which method of distribution respondents received the survey through. Since the survey was anonymous and did not include a question regarding how the respondent was invited to participate, there is no data about which methods of distribution were successful. Such data could have provided helpful information for future studies.

Given the small sample size, the findings may not be generalizable to all PCPs in Pennsylvania. Since nearly half of respondents (9) were located in Allegheny County, results may not be as generalizable to other areas of the state, especially those that are demographically different from Allegheny County. As Allegheny County is a large county with several healthcare resources, its demographics may not match other regions of Pennsylvania, such as the more rural counties.

Limitations also exist due to the fact that not all respondents completed the survey in entirety. Analyzing partially completed surveys allowed for the maximization of data, but limited the conclusions of some questions.

An additional limitation is that survey questions did not distinguish between types of SMA. Different types of SMA can have vastly different clinical presentations. The survey question inquiring about symptoms of SMA was intended to cover all types of SMA, but if respondents were only thinking of the most common subtypes, they would not have answered correctly.

The survey tool utilized in the study was not evaluated for its validity in measuring physician knowledge and confidence regarding SMA newborn screening. In order to do so, the survey could have been distributed to a sample of physicians with knowledge of and experience with SMA in order to determine whether they earn high scores.

The study could have introduced selection bias in that individuals who have an interest in or are familiar with newborn screening or SMA may have been more likely to participate. However, this was attempted to be minimized with the survey invitation which stressed that baseline familiarity with the topics was not necessary for participation.

The use of a survey for data collection could introduce self-reporting bias in that reported information could be inaccurate. Response bias also could result from respondents answering

questions with the answer they believe researchers are seeking. For example, this could be apparent with the question inquiring whether participants would benefit from receiving additional information about SMA. However, response bias was attempted to be minimized by the use of anonymity.

3.4.7 Future Directions

Several studies have demonstrated that PCPs have limited knowledge of and confidence with topics related to newborn screening (Gennaccaro et al. 2005; Hayeems et al. 2013; Kemper et al. 2006; Moeller et al. 2006; Oyeku et al. 2010; Stark et al. 2011; Topal et al. 2019). This study provides the first known information about physicians' knowledge and confidence regarding SMA specifically. The results of this study provide preliminary evidence indicating that physicians may benefit from additional training or resources related to SMA newborn screening.

Future research could focus on gathering more specific data about the type of information and format of information that physicians desire. While the results of this survey indicate that physicians would find it beneficial to have more information about SMA mechanisms, treatment, presentation, and newborn screening, future studies could explore other possible topics. Other studies have found that physicians prefer concise printed materials about newborn screening (Davis et al. 2006; Thompson et al. 2005). However, this study did not inquire about the desired format of information related to SMA and future studies could do so.

It would also be beneficial to understand which experiences and information physicians find most helpful in increasing their comfort levels with providing care for patients with SMA. If practical experiences are more beneficial than additional information, efforts may need to be focused in medical training rather than educational materials.

While this information was done on a state-wide scale, future efforts could focus on physicians on a national or international level. Having information about SMA knowledge and comfort among physicians across a larger landscape could inform where to focus larger educational efforts.

Other researchers have benefited from conducting experimental studies which assess physician knowledge and confidence before and after educational intervention (Oyeku et al. 2010). Once educational materials are developed for SMA, the field may benefit from conducting similar research to determine the impact of such materials. While this type of research is more resource-intensive, it is likely the most effective way to determine which mode(s) of education are most successful in preparing physicians to be involved in the newborn screening process.

3.5 Conclusion

This study examined Pennsylvania PCPs' baseline level of knowledge and comfort regarding newborn screening for SMA. It provides the first reported information on physician knowledge of the basics of SMA, knowledge of follow-up and treatment for SMA, level of comfort providing care for patients with SMA, and desires for additional information related to SMA.

The study found that physicians in Pennsylvania have limited knowledge about SMA newborn screening, particularly when it comes to more complex topics like treatment and follow-up. Physicians also lack comfort being involved in the care of patients with SMA, especially with discussing SMA and disclosing results to families, as well as ordering diagnostic testing.

Physicians who have been involved in the care of a patient with SMA have higher levels of knowledge and comfort with SMA. This indicates that practical experience with SMA or

medical training may help increase physician knowledge and comfort. The majority of physicians desire additional information and indicate that having this information cover a variety of topics related to SMA and newborn screening would be helpful. Based on these results, distributing SMA-specific resources to providers may help increase their knowledge and confidence regarding the condition.

Increasing physician knowledge and confidence regarding SMA may prepare them to provide care for patients with SMA, thus improving outcomes for these patients. PCPs also may be the first line of contact for families whose infant receives a positive newborn screen. If physicians are more adequately prepared and comfortable discussing SMA with families, it may also impact the psychosocial outcomes for these families.

This study fits into the larger base of research regarding lack of physician knowledge and comfort about newborn screening, while also providing the first insight into SMA specifically. Continuing to conduct research about successful interventions and create avenues for additional training and education for physicians will help to fill this gap in providing care to patients with genetic conditions identified on newborn screening.

4.0 Research Significance to Genetic Counseling and Public Health

SMA has a significant disease burden; it has an estimated incidence of 1 in 10,000 live births, making it the most common genetic cause of mortality in infants and the second-most common fatal autosomal recessive condition after cystic fibrosis (Prior 2008; Carré and Empey 2016). Newborn screening is one of the most far-reaching public health programs in the country. PCPs are an essential stakeholder in the program through their responsibility to coordinate follow-up care for patients and families who receive abnormal newborn screening results.

The three core functions of public health are assessment, policy development, and assurance. Each core function contains respective essential public health services. Within the core function of assurance, the essential service addressed by this project is assuring a competent workforce ("CDC - National Public Health Performance Standards - STLT Gateway" 2019). This study aims to identify and fill gaps in physician understanding of SMA and the newborn screening process. Results of the study will guide future efforts in education and training to prepare PCPs to effectively care for patients and families who receive a diagnosis of SMA as a result of newborn screening. Proper preparation of primary care practices to handle newborn screening follow-up may ultimately contribute to more prompt treatment and effective care, leading to a lower disease morbidity and mortality.

Newborn screening programs consist of five crucial components: screening, follow-up, diagnosis, management, and evaluation. PCPs, including pediatricians and family physicians, play an important role in the follow-up process and "have a responsibility to ensure that any infant with a positive or equivocal screen result is located, retested, and has a diagnosis confirmed or excluded" (Force et al. 2000). The goal of newborn screening is to identify infants with treatable

genetic conditions as soon as possible in order to provide them with life-saving and timely interventions. In order for this to happen, physicians are responsible for executing follow-up diagnostic testing to either confirm a diagnosis or clarify a false positive screening result. Due to the relatively rare nature of conditions included in newborn screening programs, such as SMA, PCPs are not always adequately prepared for handling positive results before they arise. Since SMA was recently added to the RUSP and state newborn screening panels, educational materials and resources for healthcare providers are still scarce compared to the volume of resources for other conditions.

This project works to address that problem by assessing the current status of physician knowledge and comfort regarding caring for patients with SMA. Results of the study will provide important information regarding the need for SMA-related educational and training materials for physicians. Providing PCPs with these materials before they receive an abnormal newborn screen for SMA will help to increase preparedness and save time when the result arises. These resources and increased preparedness also may improve PCP confidence being involved in SMA newborn screening follow-up. Improving physician confidence will allow newborn screening programs to run more effectively and may also allow infants who are newly diagnosed with SMA to receive better care, thus decreasing the burden of this disease in populations.

In the context of diagnosis of a genetic condition following a newborn screening result, genetic counselors often engage in follow-up conversations with families covering topics such as genetic etiology, recurrence risk, treatment, family planning, and more. In many cases, the family's first experiences with the diagnosis before speaking with a genetic counselor comes from the PCP. Therefore, conversations with PCPs have the opportunity to shape the family's understanding of and psychosocial reaction to the diagnosis. Allowing families to have an appropriate and

comfortable experience with the newborn screening and diagnostic process will allow genetic counselors to contribute to families' experiences in a meaningful way. Providing care for families dealing with a diagnosis of a genetic condition requires a team approach involving physicians, genetic counselors, and other healthcare professionals. Ensuring that one part of the team is adequately prepared will influence the work of the rest of the team. Setting PCPs up for success in providing care for families affected by SMA will allow genetic counselors to more efficiently carry out their role in also caring for these families.

5.0 Public Health Essay: Resources for SMA Newborn Screening Follow-Up

5.1 Background

5.1.1 Newborn Screening

Newborn screening is a public health program with the goal of early diagnosis and treatment initiation for patients with severe genetic conditions, which was started in the early 1960s (Force et al. 2000). A detailed review of the newborn screening process, including which conditions are screened for and variations by state, is included in the study above. In Pennsylvania, the state newborn screening program relies heavily on many stakeholders, including the Pennsylvania Newborn NSFP, birthing facilities, and PCPs (PA Dept of Health Division of Newborn Screening and Genetics 2009).

5.1.2 Newborn Screening for SMA

As discussed in detail in the study above, SMA was ultimately included on the RUSP in July of 2018 following the development of FDA-approved treatment (Nusinersen) and proven feasibility in pilot programs (Aartsma-Rus 2017). This subsequently initiated its incorporation into newborn screening programs across the country, including Pennsylvania which began screening for SMA in March of 2019.

5.1.3 Role of the PCP in Newborn Screening

PCPs play a crucial role in newborn screening programs, particularly in communicating results to families and facilitating interventions in the event of abnormal screening results. When newborns receive positive screening results, appropriate follow-up includes parental education, medical examinations, and relevant interventions and treatment. While the time frame of the follow-up process depends on the condition involved, the initial focus is locating the infant with an abnormal result and implementing diagnostic testing and management. In terms of long-term care, the PCP plays a central role in managing care alongside other experts in the condition (Kaye and Genetics 2006). Depending on the particular condition, the physician's role in long-term care may vary. In some cases, the PCP provides most of the routine care. In other cases, the family sees a subspecialist for routine care, but may still rely on the PCP for emergent situations if the subspecialist is located at a distance. Either way, the PCP should continue to collaborate with subspecialists to ensure coordinated and comprehensive care (Committee 2008). In order for such procedures to be effectively implemented, PCPs should be familiar with expanded newborn screening and the included conditions (Weismiller 2017). Proper follow-up of abnormal newborn screening results is crucial and can help reduce morbidity and mortality associated with these conditions (Kaye and Genetics 2006).

It is also important to consider that the PCP may be the first line of contact for families of infants who receive abnormal newborn screening results (Kaye and Genetics 2006). Families are often understandably anxious during the time immediately following an abnormal result and may take it upon themselves to consult outside resources, such as the internet. Frequent communication from the PCP, including condition-specific information and support, can help to provide clarification, avoid confusion, and build trust (Committee 2008). Therefore, these physicians must

be familiar with the condition and comfortable communicating the meaning of the result and next steps to the family (Kaye and Genetics 2006).

With advances in technology and the diagnosis and treatment of rare genetic conditions has come increased opportunities for newborn screening. One challenge that this presents is the need for PCPs to be comfortable with several different conditions and prepared to provide follow-up care for infants who receive positive newborn screening results. As newborn screening panels expand, the likelihood that a physician will eventually receive an abnormal screening result continues to increase, requiring that all physicians are prepared to manage an unfamiliar condition (Committee 2008).

In 2008, the Newborn Screening Authoring Committee published recommendations for pediatricians in light of the recent expansion of newborn screening programs. The committee recommended that pediatric practices work to prepare for abnormal newborn screening results prior to when they arrive by familiarizing themselves with their state's newborn screening program and included conditions. Upon receiving an out-of-range screening result, the committee recommends that the PCP promptly review resources for the respective condition and consults their state newborn screening program for further guidance. The committee indicates that the most important actions to be taken by the PCP include contacting the family, determining the proper time to evaluating the infant, making appropriate referrals to other specialists, conducting confirmatory testing, initiating treatment, educating parents about the condition, and reporting findings back to the state newborn screening program (Committee 2008).

Despite the fact that conditions on the RUSP are rare, a 2006 survey shows that most pediatricians and about one half of family physicians report caring for a child with a positive newborn screening result in the past five years. However, several studies have demonstrated the

lack of physician knowledge and confidence regarding newborn screening in general, as well as specific conditions included on newborn screening (Gennaccaro et al. 2005; Hayeems et al. 2013; Kemper et al. 2006; McWalter et al. 2011; Moeller et al. 2006; Oyeku et al. 2010; Stark et al. 2011; Topal et al. 2019). In the study described above, knowledge and level of comfort with SMA newborn screening were low. A majority of participants did not correctly identify SMA disease mechanisms, symptoms, or treatment and follow-up processes. Most reported that they would feel uncomfortable disclosing the results of a positive newborn screen for SMA, discussing SMA with families, and ordering follow-up testing.

The literature also reveals that lack of knowledge and confidence may interfere with physicians' ability to execute their responsibilities related to newborn screening. A survey of over 800 pediatricians, family physicians, and midwives in Ontario distributed by Hayeems et al. (2013) assessed current practices and beliefs regarding providing information to families whose newborns receive positive newborn screening results. While the majority of providers agreed that it is their responsibility to provide general information about the particular condition (73.5%), only a minority of providers endorsed doing so (27.7%). Similarly, 64.2% of providers agreed that they should provide brochures to families, but only 15.3% reported that they did. Providers indicated that insufficient time, compensation, and training were contributing barriers to providing these services to families. Only 18.5% of providers indicated that they were up to date on information regarding newborn screening, while 16.5% indicated they were confident regarding their knowledge of newborn screening (Hayeems et al. 2013).

Given this gap in knowledge and confidence, researchers have suggested that PCPs may benefit from more preparation for managing the care of a child with a positive newborn screen.

This includes information about counseling the family, initiating diagnostic testing, and making subspecialty referrals (Kemper et al. 2006).

5.1.4 Physician Resources for Newborn Screening

Several resources have been developed for physicians in order to facilitate their important role in the newborn screening follow-up process. Providing resources for physicians to navigate newborn screening aims to improve health outcomes for children who receive positive newborn screening results (Committee 2008).

ACMG publishes resources to assist physicians with handling an abnormal newborn screening result in collaboration with the National Coordinating Center for the Regional Genetics Networks (NCC) and with support from the Health Resources and Services Administration (HRSA) Maternal and Child Health Bureau (MCHB). For conditions included on the RUSP, ACMG lists two resources on their website: an ACT sheet and an algorithm. The ACT sheet is a focused summary including a description of the condition, differential diagnoses, the short-term actions the physician needs to take for follow-up of an abnormal result, reporting requirements, and links to additional resources. The second page of the ACT sheets also contains websites to assist physicians in identifying specialists for referrals. The algorithm shows the steps involved in reaching a final diagnosis for the condition ("ACT Sheets and Algorithms" n.d.; Committee 2008; Weismiller 2017).

In addition to resources developed by ACMG, fact sheets for several disorders have also been published by *Pediatrics*. These fact sheets developed by the American Academy of Pediatrics Committee on Genetics include relevant information for each disorder, such as incidence, clinical manifestations, pathophysiology, inheritance, screening, follow-up and diagnostic testing, and

management (Kaye 2006). Additional guidance also exists for metabolic conditions that are included in newborn screening. The New England Consortium of Metabolic Programs provides acute illness protocols developed at Boston Children's Hospital on their website which include information for healthcare professionals treating newborns at risk for severe metabolic conditions ("Acute Illness Materials « New England Consortium of Metabolic Programs" n.d.).

Given the clear need to provide PCPs with resources related to newborn screening, studies have investigated how physicians would prefer to receive such information. Researchers have determined that as opposed to intensive training on newborn screening, physicians prefer short handouts and resources that provide succinct information to guide them in educating parents and providing care to infants (Davis et al. 2006; Gennaccaro et al. 2005; Thompson et al. 2005).

Davis et al. (2006) conducted focus groups and interviews across several states with the following groups of individuals: healthcare professionals providing prenatal care or care for newborns, parents of infants who received an abnormal newborn screening result, and state newborn screening program professionals. In the focus groups with health care providers, researchers asked what their current practices were in discussing newborn screening with parents, as well as what the providers believed they needed more information about and how they would like to receive that information. The focus groups and interviews revealed that participants had limited knowledge regarding their state's newborn screening program: none of the providers had read their state's newborn screening program brochure and several indicated that they did not know all of the disorders screened for in their state. In order to fill this knowledge gap, the participants indicated they wanted enough information to educate parents and determine whether follow-up or repeated testing is necessary. Several participating healthcare providers indicated that it would be helpful to have a printed copy of some essential information about newborn screening, including

definitions, incidence, and treatment of included disorders and additional resources for themselves and for families (Davis et al. 2006).

A survey of family physicians and pediatricians in Minnesota by Thompson et al. (2005) assessed preferences regarding the content and format of a newborn screening quick reference resource to be developed by the Minnesota Department of Health. Of the 80 survey respondents, 83% were interested in receiving a quick reference resource and the majority preferred that the information be provided as a laminated handout. Participants recommended that the resource include a variety of information, such as the actions that a physician should take following an abnormal newborn screening result, the newborn screening program's protocol for an abnormal result, and treatment and follow-up information for specific conditions (Thompson et al. 2005).

Similarly, Gennaccaro et al. (2005) mailed surveys to pediatricians listed in the *2000 Massachusetts Healthcare Directory* to assess their preparedness to discuss newborn screening results with families and the preferred format to receive educational materials related to newborn screening. Of the 190 participants, the majority (73%) preferred that information related to newborn screening be sent as printed materials in the mail, such as short reviews and brochures. A minority of respondents indicated that they preferred other methods of education, such as seminars, websites, email, and phone calls (Gennaccaro et al. 2005).

In the study described above, the majority of participants (91.3%) indicated that they would find it beneficial to receive further education about SMA. Respondents indicated that they desire information about SMA mechanisms, clinical presentation, newborn screening processes, and newborn screening follow-up procedures. The topic most desired by physicians was follow-up procedures after a child receives a positive newborn screen for SMA. This indicates that PCPs

could benefit from additional resources for SMA newborn screening and specifically prefer information about follow-up steps that need to be taken.

Despite the fact that SMA was added to the RUSP in July of 2018, as of April of 2020 ACMG has not published an ACT sheet or algorithm for this condition. The Pennsylvania Department of Health also has not published any condition-specific resources for SMA newborn screening. This leaves physicians in Pennsylvania who receive an abnormal screening result for SMA without a quick reference resource for providing follow-up care.

5.1.5 Specific Aims

5.1.5.1 Specific Aim #1

The first goal of this study is to explore the locations of Pennsylvania healthcare providers involved in newborn screening follow-up care, meaning they have the potential to receive an abnormal newborn screening result. This analysis will provide information for where educational efforts regarding SMA newborn screening should be focused. Specifically, the study will:

1. Explore whether providers receiving Pennsylvania newborn screening results are concentrated in certain counties or regions
2. Investigate whether certain types of providers tend to be located in specific regions
3. Examine whether there is an association between county population size and the number of newborn screening follow-up providers in a county
4. Determine whether there is an association between county per capita income and the number of newborn screening follow-up providers by population size

5.1.5.2 Specific Aim #2

The second goal of this study is to compile the most applicable information from the literature for physicians who provide follow-up care to patients who receive an abnormal newborn screening result for SMA. The information will be filtered and organized to create an educational resource for PCPs.

5.2 Methods

5.2.1 Specific Aim #1

The data set being analyzed is the Pennsylvania Department of Health Division of Newborn Screening & Genetics' primary care provider library. The library was provided by the Pennsylvania Department of Health and contains listings of clinicians who have the potential to receive an abnormal Pennsylvania newborn screening result for follow-up. The entire list was utilized for this analysis and includes other health professionals in addition to physicians (such as midwives). The data set contains a variety of information about each clinician, such as type of practice, a description, practice name, location, and contact information.

Additional information to supplement the data set was collected. Zip codes for each provider in the library were used to record county location using a zip code database obtained from unitedstateszipcodes.org ("Pennsylvania Zip Codes" n.d.). Information was also collected regarding population size and per capita income for each county included in the data set. Population sizes utilized were 2018 estimates developed by the Pennsylvania State Data Center based on 2010 census data (Pennsylvania State Data Center 2019). Per capita income for each

county was also gathered using 2010 census data ("American Fact Finder" n.d.). Provider type was deciphered for each listing in the data set using information such as the practice name and description. Each provider was sorted into one of five categories: family medicine/community clinics, pediatrics clinics, individual/private practitioners, hospitals, or other.

Maps created in this preliminary data analysis were generated through the use of two separate tools. Google My Maps was used to plot the locations of providers. Density maps by county were created through the web tool mapchart.net.

Given the non-normal distributions of variables, a nonparametric statistical test was used to analyze the relationship between county population size and number of providers. The same test was also used for analyzing per capita income. For this analysis, the number of providers was divided by population to represent providers per capita and control for population size. Variables for each analysis were plotted on scatter plots and Spearman correlation tests were run using Stata software. These analyses were performed only for counties in Pennsylvania, excluding those in the other seven states. This is due to the fact that the state newborn screening program of focus is Pennsylvania and there are only a small number of providers located in the bordering regions of other states. The fact that there are a low number of providers outside Pennsylvania is likely not due to factors such as population size or per capita income.

5.2.2 Specific Aim #2

5.2.2.1 Review of the Literature

Multiple resources that include information related to SMA and newborn screening were consulted to conduct a detailed review of the literature and to create an educational guide for PCPs. Using PubMed and Google, multiple sources related to SMA and newborn screening follow-up

were reviewed in regard to their content and format. These resources included journal articles, guidelines from professional groups, and other educational materials that have been published. Key phrases that were used in searches include: “SMA newborn screening follow-up,” “SMA newborn care,” “SMA positive newborn screen,” and “SMA newborn screening resources.” Search results were preliminarily broadly reviewed to determine whether they were relevant to the project. Those that were determined to be relevant and useful are described in the results section.

Certain ACT sheets from ACMG were also reviewed to provide a framework for the content to be included in the educational material developed in this project. The ACT sheets that are included in this review are those for carrier screening for SMA, newborn screening for Duchenne and Becker muscular dystrophy, and newborn screening for cystic fibrosis.

5.2.2.2 Creation of the Educational Resource

Information from the sources described above was used to create the resource for PCPs. A quick reference handout was made to be used by physicians who receive a positive newborn screening result for SMA. The format and content of the resource was informed by clinical guidelines, SMA-specific resources, and ACT sheets that were reviewed.

5.2.2.3 Readability Evaluation

In order to assess the readability of the created resource, the text was entered into the ReadablePro tool from readable.com. The tool analyzes text for readability using popular algorithms, including the Flesch-Kincaid and Gunning-Fog scores. ReadablePro also assesses writing for text quality by considering long sentences, complex words, clichés, adverbs, passive voice, tone, and sentiment.

5.3 Results

5.3.1 Specific Aim #1

5.3.1.1 Demographics

The majority (93.16%) of providers included in the data set are located in Pennsylvania. Sixty-one of the state's 67 total counties contain at least one newborn screening follow-up provider. Clinicians are also located in seven additional states surrounding Pennsylvania, including New Jersey, New York, Maryland, Delaware, West Virginia, Ohio, and Virginia. The percentages of providers located in each state are included in Table 8.

Table 8 Pennsylvania Newborn Screening Follow-Up Providers By State

State	Number of Providers	Percentage of Total Providers
Pennsylvania	1,240	93.16%
New Jersey	38	2.85%
New York	13	0.98%
Maryland	12	0.90%
Delaware	10	0.75%
West Virginia	9	0.68%
Ohio	8	0.60%
Virginia	1	0.08%
TOTAL	1,331	100%

5.3.1.2 Location of Providers

A plot of all 1,331 providers in the primary care provider library is shown in Figure 6. Figure 7 shows a density map which portrays how many providers are located within each county in the eight states included in the data set. Similar to Figure 6, Figure 8 includes all providers in the data set, but distinguishes provider type by color. As can be observed in Figure 8, the majority of providers conducting newborn screening-follow up for Pennsylvania are either part of a family medicine/community clinic or pediatrics practice. A smaller portion of practitioners work in an individual practice or hospital setting. A few providers fit into the other category, for example, those who are part of a midwife organization.

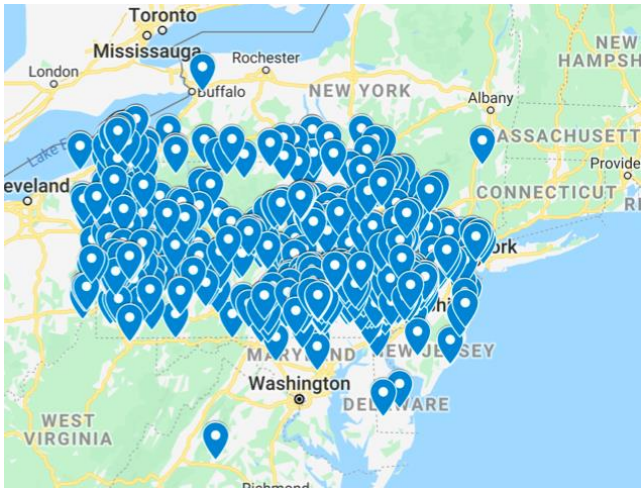

Figure 6 Locations of Pennsylvania Newborn Screening Follow-Up Providers

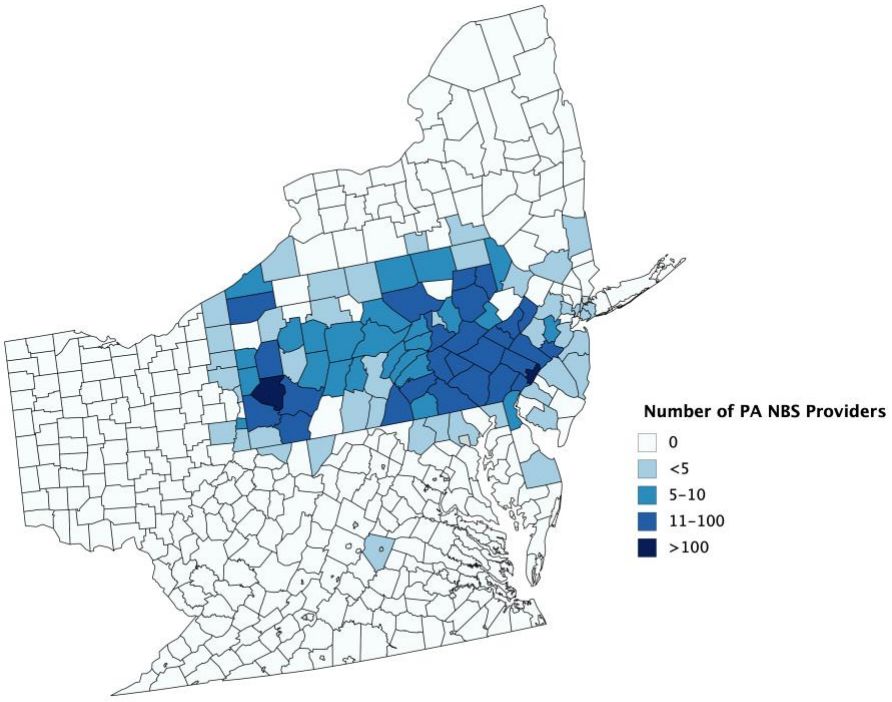

Figure 7 Pennsylvania Newborn Screening Follow-Up Providers by County

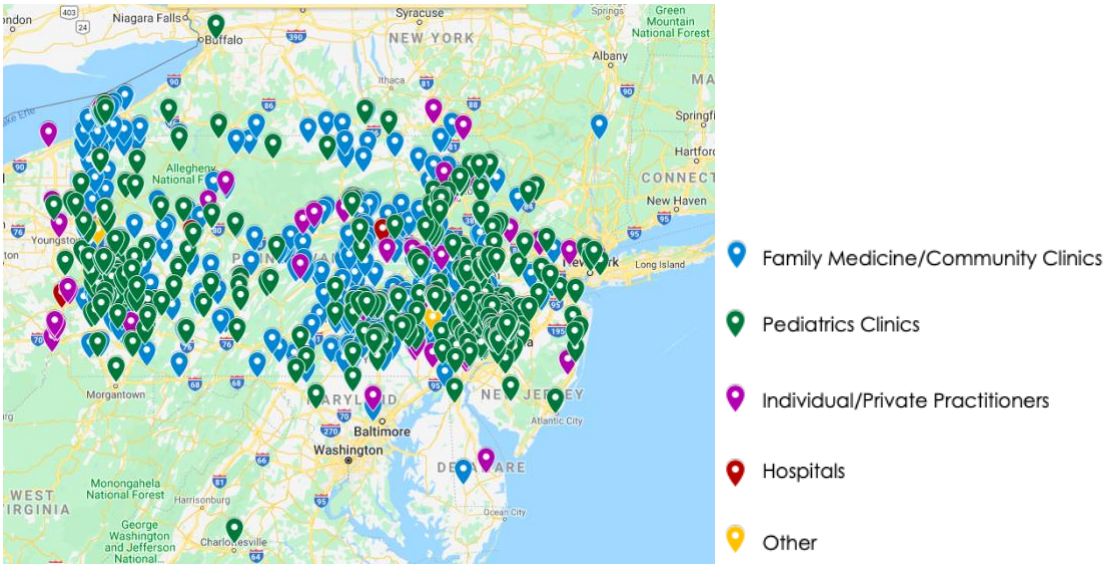

Figure 8 Locations of Pennsylvania Newborn Screening Follow-Up Providers by Provider Type

5.3.1.3 County Population Size and Per Capita Income

The relationship between county population size and number of providers can be visualized in Figure 9. A Spearman's rho of 0.81 ($p < 0.001$) was calculated for this correlation. Figure 10 shows the relationship between county per capita income and the number of providers per capita. A Spearman's rho of -0.18 ($p = 0.1723$) was calculated for this relationship. A summary of these results is included in Table 9.

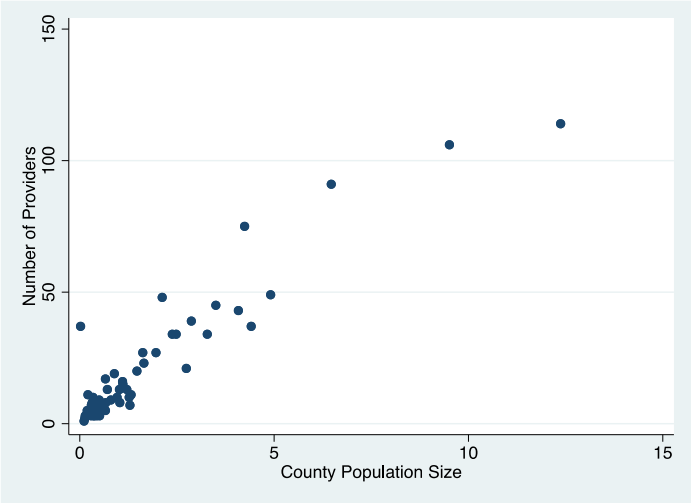

Figure 9 Scatterplot of County Population Size and Number of Providers

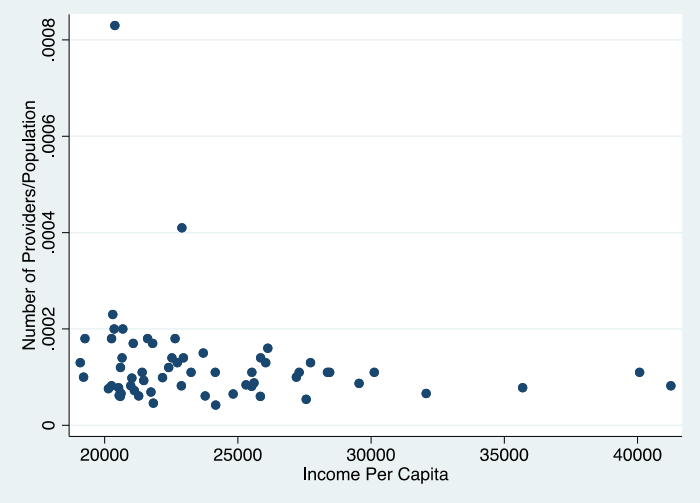

Figure 10 Scatterplot of County Income Per Capita and Number of Providers

Table 9 Summary of Spearman Correlation Results

	Number of Providers Per County	Number of Providers/ County Population
County Population Size	$\rho = 0.81$ (p-value < 0.001)	
County Income Per Capita		$\rho = -0.18$ (p-value = 0.1723)

5.3.2 Specific Aim #2

5.3.2.1 SMA Clinical Guidelines

Searches conducted in PubMed and Google revealed two sets of clinical guidelines that are applicable to the care of infants diagnosed with SMA from a positive newborn screening result.

In 2004, an International Conference on the Standard of Care for SMA established a committee of experts to develop a consensus statement regarding the care of individuals with SMA. The committee published clinical guidelines in 2007 which were subsequently widely adopted across the field. In 2018, the committee published updated guidelines following years of improvements and advancements, including clinical trials and approved treatment. The updated guidelines are divided into two parts which collectively cover nine topics: diagnosis and genetics, physical therapy and rehabilitations, orthopedic and bone care, nutrition, pulmonary care, acute care in the hospital setting, other organ system involvement, medication, and ethics and palliative care. Leaders from Europe and the United States conducted working groups for each topic consisting of relevant experts, including parents, caregivers, and patients. Guidelines from the American Academy of Pediatrics (AAP) were used for analyzing the results of the working groups and forming the clinical recommendations (Mercuri et al. 2018).

The clinical guidelines divide patients with SMA into three separate categories, acknowledging that care will not look the same for all patients with SMA. Patients with type 1 SMA are referred to as "non-sitters." Patients with type 2 or type 3 SMA who have lost ambulation are called "sitters." Finally, those who have type 3 SMA and are still ambulant are referred to as "walkers" (Mercuri et al. 2018).

At the time they were developed, the guidelines state that diagnostic testing is typically prompted by clinical signs of SMA. A diagnosis can be confirmed by molecular genetic testing of the *SMN1* and *SMN2* genes and typically does not require muscle biopsy. Gold standard genetic testing is quantitative analysis of both genes using MLPA, quantitative PCR (qPCR), or next-generation sequencing (NGS). Absence of both *SMN1* copies confirms a diagnosis of SMA. If one copy of *SMN1* is present and the phenotype is consistent with SMA, the remaining *SMN1* gene should be sequenced in order to look for another mutation. If both copies of *SMN1* are present, sequencing should only be done if there is a remarkable phenotype or consanguinity. Assessing *SMN2* copy number is not essential to reach a diagnosis, but should be routinely done as it can inform the severity of the phenotype and affect eligibility for treatment or clinical trials. The committee also stresses the importance that families receive genetic counseling and psychological support at the time of diagnosis (Mercuri et al. 2018).

The guidelines recommend that management follow a multidisciplinary approach given the fact that SMA is a complex disorder and involves several different elements of care. The team providing care will likely involve several professionals and should be coordinated by a physician knowledgeable about SMA (usually the neurologist). The experts discuss the aspects of a physical examination for an individual with SMA, which focuses on neuromuscular and musculoskeletal evaluation and should be conducted every six months to monitor changes and response to

interventions. The examination assesses strength and range of motion, as well as motor functional scales (Mercuri et al. 2018).

In regard to physical therapy and rehabilitation, the committee explains that there has recently been increasing evidence to show that taking a proactive approach by incorporating these sessions into routine care can be beneficial. The specific care plan will vary for all patients and may include braces, orthoses, or exercises. Pulmonary management has also recently shifted to a more proactive approach. Clinic visits are recommended every three months for non-sitters and include pulse oximetry, capnography, and sleep studies. Certain pulmonary interventions may include airway clearance, ventilation, and medications. Spine deformity management is dependent upon the findings of a spinal x-ray, but may include monitoring, bracing, or surgery (Finkel et al. 2018).

The patient's care team should also include an expert nutritionist for nutritional management and assistance with swallowing and gastrointestinal dysfunction. Among other necessary evaluations and interventions, nutritional management should include regular growth assessments and evaluations for gastrointestinal symptoms (Mercuri et al. 2018).

The guidelines describe detailed protocols and considerations for transport to medical facility, emergency department evaluations, and medical care in a hospital setting. The committee stresses that respiratory support should be a top priority and the multidisciplinary team should always be contacted to assist with acute care (Finkel et al. 2018).

In response to some of the most crucial developments since the initial guidelines were published, the updates address the approved treatment Nusinersen (Spinraza). The committee explains that since the drug is intrathecally administered, post-procedural monitoring is crucial (Finkel et al. 2018).

The experts involved in forming these guidelines conclude that efficient management requires several specialists and the goal should be to improve quality of life and reduce the burden of disease by paying attention to individual patient concerns (Finkel et al. 2018).

In addition to the clinical guidelines by the International Conference on the Standard of Care for SMA, the SMA Newborn Screening Multidisciplinary Working Group also published a recommended treatment algorithm for infants with a positive SMA newborn screen in 2018. The working group was supported by the advocacy organization Cure SMA and was comprised of fifteen individuals, including clinicians with SMA expertise and patient advocates. The group participated in an online survey, as well as a moderated discussion (Glascock et al. 2018).

The group focused on determining which individuals with SMA should be treated immediately and which should be monitored with the goal of initiating treatment later in life. The treatment algorithm that was developed focuses on genotype but acknowledges that treatment initiation is ultimately up to the discretion of the attending physician. The algorithm recommends that all individuals with three or less copies of *SMN2* receive treatment immediately, as these patients will likely have SMA type 1 or type 2 (Glascock et al. 2018).

On the other hand, the group was evenly divided in regard to whether treatment should be immediately initiated for patients with four copies of *SMN2* or should be deferred until mild symptoms have appeared. However, they did reach consensus that patients with more than four copies of *SMN2* should not be treated immediately. They recommend that the timing of treatment initiation should depend on physician judgment and the patient's and the family's preferences. When treatment is not immediately administered, the patient should receive routine follow-up care, ideally by a neuromuscular specialist. The group specifies that this follow-up should occur every three to six months until the patient is two years of age and should occur every six months to one

year afterwards. This will ensure that symptoms are detected in rare cases of SMA types 1 and 2 with more than four *SMN2* copies. Follow-up should involve a variety of assessments that are sensitive to early changes in pre-symptomatic infants, such as CMAP and EMG, as well as physical examinations and motor functional scales. Physicians should also educate families and caregivers about signs and symptoms to be cognizant of in the patient. Such signs include changes in movement, feeding, or breathing, fatigue, loss of motor function, and more. For infants whose previous testing reports more than four *SMN2* copies, they should receive testing that can identify their exact copy number. This allows for more of an understanding of when phenotypic symptoms may appear and when treatment may need to be initiated.

5.3.2.2 SMA Educational Resources

PubMed and Google searches revealed several educational materials related to SMA. After preliminarily reviewing several, eight resources were deemed to be most relevant to this project in terms of content and format. Those eight resources are reviewed below and in Table 10.

Baby's First Test is a national newborn screening educational website which provides information and resources about newborn screening programs and conditions included on newborn screening. Baby's First Test provides an educational web page geared towards the general public for conditions included on newborn screening, such as SMA ("Spinal Muscular Atrophy | Baby's First Test | Newborn Screening | Baby Health" n.d.). The Muscular Dystrophy Association (MDA) has also created a four-page SMA information guide for patients and families including information about causes, symptoms, and treatment (Muscular Dystrophy Association 2019).

Medical Home Portal is a source of information for families and healthcare providers about children with special health care needs. The resource provides information for nationwide audiences, as well as information specific to six states: Idaho, Montana, Nevada, New Mexico,

Rhode Island, and Utah. They provide web pages for several "newborn disorders," one of which is SMA (Hart 2019).

Cure SMA is a prominent advocacy organization aimed at eradicating SMA by funding research and supporting families. The organization has published several educational booklets for families and health care providers covering various topics. The main resource reviewed for the purposes of this project was a guide for healthcare professionals entitled "What You Need to Know and Do About an SMA Diagnosis from Screening" (Cure SMA n.d.).

Certain laboratories involved with SMA newborn screening have also published relevant resources. Mayo Clinic Laboratories developed a "Newborn Screening Act Sheet" for SMA as defined by the patient having zero functioning copies of *SMN1* (Mayo Clinic Laboratories 2019).

While action sheets for SMA are still scarce in the United States, state newborn screening programs in Michigan and Minnesota have published resources for SMA. Michigan's information sheet that was reviewed is targeted to families, while Minnesota's is specifically aimed towards healthcare providers (Michigan Newborn Screening Program n.d.; Minnesota Newborn Screening Program 2018). Ontario's newborn screening program has also published an SMA information sheet for families whose infant receives a positive newborn screen (Newborn Screening Ontario n.d.).

A more detailed review of the format and contents of each of these seven resources is included in Table 10 below.

Table 10 Summary of Published SMA Resources

PUBLISHING ORGANIZATION	*RESOURCE*	*FORMAT*	*TARGET AUDIENCE*	*INCLUDED CONTENT*

Baby's First Test	Spinal Muscular Atrophy webpage
	
	("Spinal Muscular Atrophy | Baby's First Test | Newborn Screening | Baby Health" n.d.)
		Webpage	Families	• SMA overview
				  • Incidence
				  • Symptoms/early signs
				  • Treatment
				  • Expected outcomes
				  • Causes
				• Follow-up testing
				  • Importance of testing
				  • Goals of testing
				• Support services
				  • Cure SMA
				  • Spinal Muscular Atrophy Foundation
				  • ACMG's clinical services support engine
				  • NSGC's "Find a Genetic Counselor"
				  • "Learn About Spinal Muscular Atrophy" website
				• References
				  • GeneReviews
				  • National Human Genome Research Institute
				  • National Organization for Rare Disorders

Table 10 Continued

				• Cure SMA • Genetics Home Reference • Genetic and Rare Diseases Information Center

Cure SMA	Guide for Healthcare Providers: What You Need to Know and Do About an SMA Diagnosis from Screening
	
	(Cure SMA n.d.)
		Booklet (12 pages)	Healthcare providers	• SMA overview
				  • Incidence/carrier frequency
				  • Inheritance
				• Cause
				  • SMN protein description
				• Types
				• Diagnosis
				  • Newborn screening
				  • Referral to pediatric neurologist or other neuromuscular disease specialist
				  • Confirmatory genetic testing
				  • *SMN2* copy number testing
				• Presentation and symptoms
				  • Focus on Type 1 SMA
				• Predicting the severity of SMA
				  • *SMN2* gene copy number
				• Treating SMA
				  • Spinraza
				  • Zolgensma
				  • Importance of early treatment
				• Living with SMA
				  • Food and nutrition
				  • Adaptive equipment
				  • Breathing and coughing

Table 10 Continued

				• Common recommendations and referrals

Mayo Clinic Laboratories	Newborn Screening Act Sheet for Spinal Muscular Atrophy: Zero Functioning Copies of *SMN1*
	
	(Mayo Clinic Laboratories 2019)
		Act Sheet (1 page)	Physician receiving newborn screen	• Condition description
				  • Inheritance
				  • Cause
				  • *SMN2* as predictor of severity
				• Medical emergency – take the following actions
				  • Contacting the family
				  • Consulting with pediatric neurologist/geneticist
				  • Evaluating the newborn
				  • Initiating diagnostic testing and management
				  • Providing the family with information
				• Diagnostic evaluation
				• Clinical expectations
				  • Symptoms
				  • Incidence
				  • Treatment options
				• Additional information
				  • Genetics Home Reference
				  • Genetic Testing Registry
				  • Baby's First Test

Medical Home Portal	Spinal Muscular Atrophy webpage	Webpage	Parents and healthcare providers	• Other names • Diagnosis coding • Disorder category • Screening • Testing method

Table 10 Continued

	(Hart 2019)			• Overview of SMA
				  • Symptoms
				  • Types
				  • Long-term outlook/life expectancy
				• Incidence
				• Inheritance
				• Prenatal testing
				• Clinical characteristics
				• Follow-up testing after positive screen
				• Primary care management
				  • Upon notification of the positive screen
				  • Coordinate urgent evaluation and testing with pediatric neurology
				  • Contact family
				  • If the diagnosis is confirmed
				  • Educate family
				  • Treatment
				  • Specialty care collaboration
				• Resources
				  • For professionals
				  • GeneReviews
				  • OMIM
				  • For parents and patients
				  • Genetics Home Reference
				  • Genetic Alliance
				  • Services for patients and families
				  • Genetic Testing Registry
				  • Services in Medical Home Portal partner states

Table 10 Continued

Michigan Newborn Screening Program	Spinal Muscular Atrophy Family Fact Sheet
	
	(Michigan Newborn Screening Program n.d.)
		Information sheet
		(1 page)
			Families	• What is a positive newborn screen?
				  • Newborn screening process
				• What is SMA?
				  • Cause
				  • Inheritance
				• What problems can SMA cause?
				  • Types
				  • Symptoms
				• What is the treatment for SMA?
				  • Care team
				  • FDA approved treatments
				  • Management and support
				• Resources and support
				  • Michigan Newborn Screening Nurse Consultant
				  • SMA Newborn Screening Coordinating Center
				  • Children's Special Health Care Services
				  • Genetics Home Reference
				  • National Organization for Rare Disorders
				  • Baby's First Test

Minnesota Newborn Screening Program	*SMN1* Absent Provider Fact Sheet
	
	(Minnesota Newborn Screening
		Information sheet
		(1 page)
			Physician receiving newborn screen	• Next steps
				  • Within one business day
				  • Consult with neurologist
				  • Contact family
				  • Evaluate infant
				  • Refer to pediatric neurologist
				• Review with family
				  • Follow-up plan

Table 10 Continued

	Program 2018)			• Signs/symptoms • False positives • Unlikely • Differential diagnosis • Incidence of SMA • Clinical summary • Cause • Types • Treatment
Muscular Dystrophy Association (MDA)	Spinal Muscular Dystrophy Fact Sheet (Muscular Dystrophy Association 2019)	Information guide (4 pages)	Patients & Families	• SMA overview • Incidence • Cause/genetic etiology • Involvement of the *SMN2* gene • Signs/symptoms • Nervous system • Lung • Gastrointestinal • Skeleton and muscle • Heart • Newborn screening /inclusion on RUSP • Types of SMA • Other forms of SMA • Spinal muscular atrophy with respiratory distress (SMARD) • Distal SMA • Prognosis • Treatment/management • Nusinersen (Spinraza) • Muscle relaxants • Botulinum toxin

Table 10 Continued

				• Antidepressants and anxiolytics • Occupational therapy • Speech-language pathology • Respiratory devices • Assistive technology products • Braces • Gastrostomy tube • Glossary
Newborn Screening Ontario (NSO)	Spinal Muscular Atrophy – Information Sheet (Newborn Screening Ontario n.d.)	Information sheet (2 pages)	Families	• Importance of screening • What is SMA? • Symptoms and early signs • Types • Incidence • Screening positive for SMA • Follow-up testing • Treatment • Follow-up tests and monitoring • Nusinersen • Gene therapy (Zolgensma) • Living with SMA • Importance of early treatment

5.3.2.3 ACT Sheets

Three ACMG ACT sheets determined to be most applicable to this project were reviewed: SMA carrier screening, Duchenne/Becker muscular dystrophy newborn screening, and cystic fibrosis newborn screening.

All three ACT sheets are two pages in length. Each ACT sheet contains a description of the condition, immediate actions to be taken, and additional information and resources. Condition descriptions include a variety information, such as the incidence, cause, clinical symptoms, and age of onset. Each ACT sheet provides resources, some of which are specific to the condition and some of which are common across all conditions. Resources provided with each ACT sheet include the Genetic Testing Registry, GeneReviews, and ACMG's Find a Genetic Service webpage (American College of Medical Genetics and Genomics 2012a; American College of Medical Genetics and Genomics 2012b; American College of Medical Genetics and Genomics 2019).

The SMA carrier screening ACT sheet provides an overview of carrier screening and a section regarding reproductive implications, including a description of autosomal recessive inheritance. Listed actions for a positive SMA carrier screen are fairly broad, but include informing the individual of his or her result, referring the patient to genetic counseling, and offering genetic testing to the partner. The ACT sheet provides a link to the Claire Altman Heine Foundation, an SMA-specific resource (American College of Medical Genetics and Genomics 2012a).

The newborn screening ACT sheets for Duchenne and Becker muscular dystrophy and cystic fibrosis contain differential diagnoses, diagnostic evaluation information, and clinical considerations (American College of Medical Genetics and Genomics 2012b; American College of Medical Genetics and Genomics 2019). The Duchenne and Becker muscular dystrophy newborn screening ACT sheet provides six actions that providers are recommended to take. These include

contacting the family, giving the family basic information about the condition, obtaining a family history, consulting with a neuromuscular specialist, referring to genetic counseling, and reporting the findings to the state newborn screening program. Links to some condition-specific organizations are provided, as well as a link to the Duchenne and Becker muscular dystrophy carrier testing ACT sheet (American College of Medical Genetics and Genomics 2019). The newborn screening ACT sheet for cystic fibrosis contains similar information, including five action steps to be taken and links to relevant cystic fibrosis-related organizations. The actions listed for cystic fibrosis are contacting the family, contacting the Cystic Fibrosis Center for a consultation with a specialist, conducting a sweat test, making referrals for a clinical evaluation and genetic counseling, and reporting findings to the state newborn screening program (American College of Medical Genetics and Genomics 2012b).

5.4 SMA Resource for PCPs

Review of the literature and resources above revealed that there is a lack of adequate resources for PCPs regarding follow-up for SMA newborn screening. The majority of resources that exist are geared towards patients and their families. The few resources that target physicians lack detailed information about SMA, as well as follow-up procedures for a positive SMA newborn screen.

Information from the review was used to address this gap by creating the following resource to be used by PCPs who receive a positive newborn screening result for SMA (Figure 11). The resource contains immediate steps that physicians can take after receiving the result, as well as some broad information about SMA. Providing physicians with this information about the

condition is intended to help supplement their knowledge of SMA, as well as assist them in educating families. As physician surveying has revealed that they favor succinct handouts, that is the approach that was taken with the format of this resource (Gennaccaro et al. 2005; Thompson et al. 2005; Davis et al. 2006).

SPINAL MUSCULAR ATROPHY
Information for Primary Care Physicians

OVERVIEW OF SPINAL MUSCULAR ATROPHY (SMA)

Spinal muscular atrophy (SMA) is a severe genetic condition caused by the degeneration of motor neurons, leading to progressive muscle weakness, decreased mobility, and early death in some cases.

Incidence
1 in 10,000

Inheritance
Autosomal recessive

Cause
SMA is caused by a non-functioning *SMN1* gene. Patients with SMA usually have deletions in both copies of the *SMN1* gene. The number of *SMN2* gene copies that the individual has is associated with the clinical severity of SMA. Patients with more *SMN2* copies have a better prognosis.

Clinical Signs/Symptoms (not observed in all individuals with SMA)
- ◊ Hypotonia
- ◊ Progressive muscle weakness
- ◊ Respiratory difficulty
- ◊ Poor feeding
- ◊ Weak cry

Subtypes
Cases of SMA are classified into one of five subtypes (type 0 – type 4) based on the age of onset and severity of symptoms. Type 0 is the most severe subtype and type 4 is the least severe. Types 1 and 2 are the most common.

Treatment
There are currently two FDA-approved drug therapies for SMA:
- ◊ Spinraza (nusinersen) - an antisense oligonucleotide (ASO) therapy administered through intrathecal injection
- ◊ Zolgensma - a gene therapy injection which replaces absent *SMN1* gene

Patients with SMA typically receive care from several specialists, including:
- ◊ Neurology
- ◊ Genetics
- ◊ Orthopedics
- ◊ Respiratory/Pulmonary

◊ Nutrition
◊ Gastroenterology

FOLLOW-UP TESTING

Genetic testing of the *SMN1* and *SMN2* genes

NEXT STEPS

◊ Contact the family to inform them of the newborn screening result and inquire about symptoms
◊ Initiate follow-up testing and clinical evaluation (with assistance from a pediatric neurologist and/or geneticist)
◊ Refer the family to a pediatric neurologist who provides treatment for SMA
◊ Refer the family to genetic counseling
◊ Educate the family about the basics of SMA and next steps

ADDITIONAL INFORMATION AND RESOURCES

Providers

◊ Cure SMA (https://www.curesma.org/about-sma-for-hcps/)

◊ Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care (https://doi.org/10.1016/j.nmd.2017.11.005)

◊ Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics (https://doi.org/10.1016/j.nmd.2017.11.004)

◊ GeneReviews (https://www.ncbi.nlm.nih.gov/books/NBK1352/)

◊ Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening (https://doi.org/10.3233/JND-180304)

Families and Patients

◊ Baby's First Test (https://www.babysfirsttest.org/newborn-screening/conditions/spinal-muscular-atrophy)

◊ Cure SMA (https://www.curesma.org)

◊ Genetics Home Reference (https://ghr.nlm.nih.gov/condition/spinal-muscular-atrophy)

Figure 11 SMA Resource for PCPs

5.4.1 Readability Evaluation

As measured by the ReadablePro tool on readable.com, the resource above earned an overall score of C. The Flesch-Kincaid grade level was 10.4, while the Gunning Fog tool revealed a slightly lower grade level of 9.8. Other readability grade level tools reported grade levels varying from 5.4 to 13.2. The Flesch Reading Ease tool, which rates writing on a scale of 0 to 100, reported a score of 32.2 for this document. The Common European Framework of Reference for Languages (CEFR) level was B2, meaning the text will generally be understood by adults with conversational English.

In terms of text quality, ReadablePro pointed to some spelling and grammar issues, the majority of which are misunderstood medical terms. The tool also highlighted the fact that 21% of sentences contain >20 syllables as a potential issue. Other potential issues with text density included average characters per word, syllables per word, words per sentence, words per paragraph, and sentences per paragraph.

ReadablePro estimates that the text should be readable for 82% of the addressable audience, equating to 70% of the general public. The tone is considered formal and the sentiment is slightly negative. The tool estimates that the resource's reading time is 1 minute and 35 seconds, while speaking time is 2 minutes and 51 seconds. A copy of the ReadablePro report is provided in Appendix D.

5.5 Discussion

5.5.1 Specific Aim #1

As hypothesized, there is a higher concentration of newborn screening follow-up providers in certain regions of Pennsylvania, leaving other areas with a lack of providers. As Figure 7 shows, the two counties with the most providers are Allegheny County and Philadelphia County. The majority of other counties with the highest numbers of providers are located on the eastern and western ends of the state in areas surrounding Allegheny and Philadelphia County. Counties with low numbers of providers or no providers are mostly positioned throughout the center of the state and the northern regions of the state. Figure 8 portrays the distribution of providers throughout Pennsylvania.

These findings raise concern about access to PCPs with experience in newborn screening follow-up, particularly for families living in the central region of the state. Patients living in this region who receive an abnormal newborn screening result may not receive as timely or adequate follow-up care as infants living in other regions. Additionally, this provides information about where educational efforts regarding newborn screening and SMA should be prioritized. Education and training could be particularly successful in the eastern and western areas of the state given the density of providers located there. However, such education could also benefit the central region of the state. Physicians in this region may lack experience with patients with abnormal newborn screening results and therefore may benefit from additional information or training. Future research directions may focus on evaluating the preparation level that clinicians in these areas have regarding newborn screening, as well as the availability of educational materials.

A map containing data from the 2010 census is shown in Figure 12 and outlines population sizes across the state's 67 total counties ("Decennial Census Datasets" n.d.). Counties with higher population counts are concentrated in the southeast and southwest of Pennsylvania, while the central and northern regions of the state are less populated. Comparison to Figures 6, 7, and 8 reveals a potential correlation between population size and the number of providers.

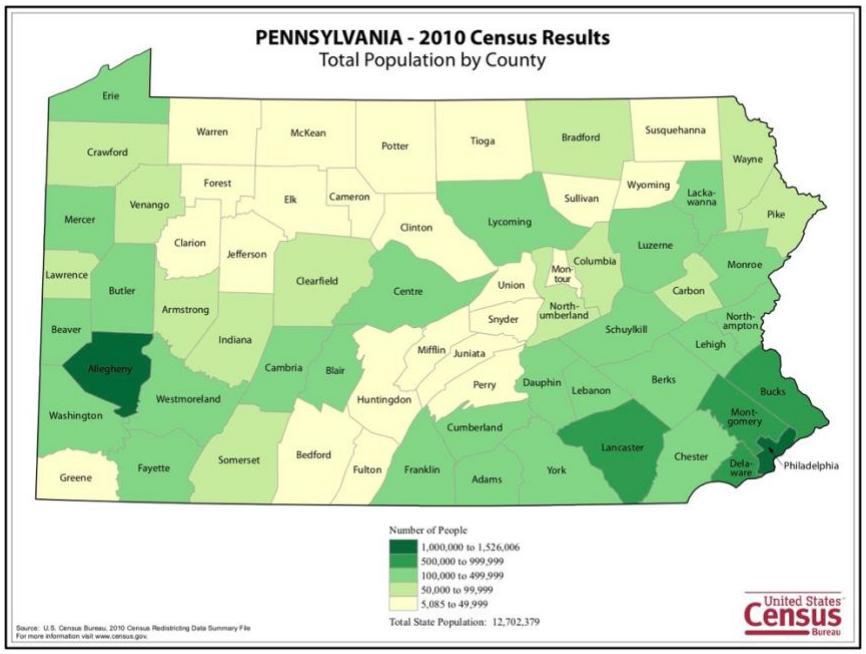

Figure 12 Population Sizes of Pennsylvania Counties According to 2010 Census Results

Statistical analyses confirm this strong positive correlation between county population size and number of providers (shown in Figure 9 and Table 9). The Spearman rho of 0.81 ($p<0.001$) indicates a statistically significant strong positive relationship, meaning that as county population size increases, the county's number of providers also increases. This is a logical finding, as more children would be expected to receive abnormal screening results in the more populous areas of the state. A future research direction could be to evaluate the relationship between the number of

children who screen positive for a condition on Pennsylvania's newborn screening panel and the number of providers.

However, the relationship between county per capita income and number of providers per capita (shown in Figure 10 and Table 9) does not indicate the presence of a statistically significant association. Thus, the results of this study imply that as county income per capita varies, it does not have a direct effect on the number of providers. One explanation for this could be that more providers tend to be located near large hospital systems in the state, which are not necessarily located in counties with the highest per capita income levels.

While similar research has not been conducted in regard to newborn screening or SMA, studies of general access to healthcare in Pennsylvania have yielded comparable results. Figure 13 portrays geographic areas of Pennsylvania determined to be primary care health professional shortage areas (HPSAs) by HRSA as of 2015. HRSA defines HPSAs according to different criteria, such as the ratio of population to the number of full-time equivalent physicians in a certain area, distance, and accessibility (Joint State Government Commission 2015). Comparison of Figure 13 to Figure 7 reveals that HPSAs tend to be located in counties with lower numbers of newborn screening follow-up providers. Both maps depict a shortage of providers around the central and northern regions of the state. Areas including Pittsburgh, Philadelphia, and the northeastern region contain more sufficient clinician coverage.

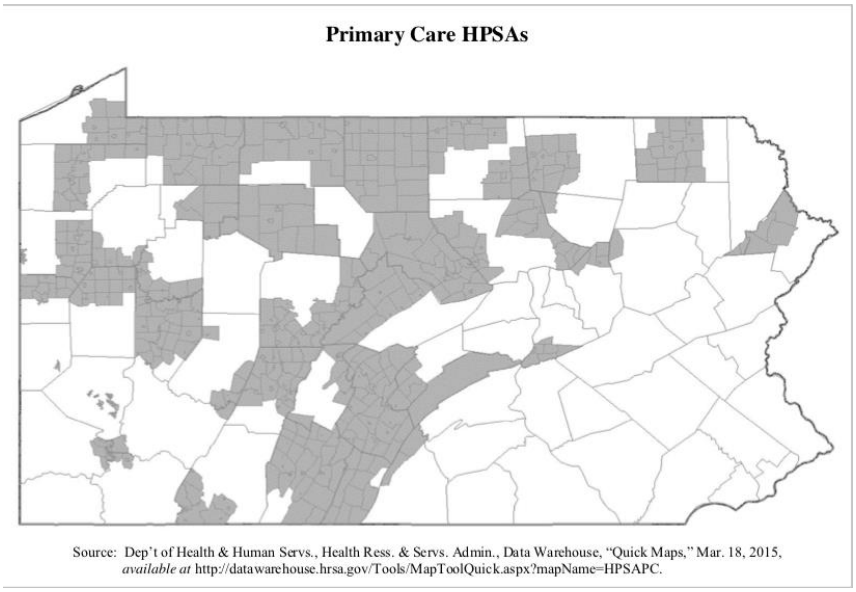

Figure 13 HPSAs in Pennsylvania as of 2015

The numbers of physicians per 100,000 population in each county in Pennsylvania as of 2012 are mapped in Figure 14 (Joint State Government Commission 2015). Overall, the map does echo the density of providers in Allegheny County and Philadelphia County. However, this map also shows high concentrations of providers in certain counties in the southeastern, central, and northwestern parts of the state. The abundance of providers in Montour County is likely explained by the presence of Geisinger Health System, while that of Dauphin County can likely be attributed to the city of Harrisburg. Figure 7 shares these trends in terms of the amount of newborn screening follow-up providers, but not quite to the magnitude displayed in Figure 14.

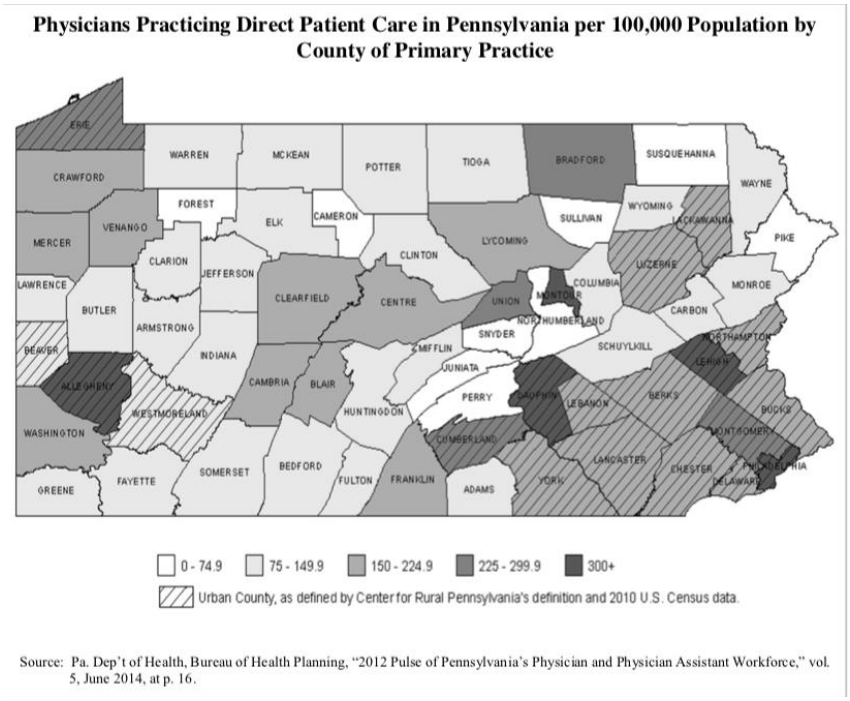

Figure 14 Physicians Practicing Direct Patient Care in Pennsylvania per 100,000 Population by County of Primary Practice

This data analysis includes limitations. First, there is minimal information regarding collection of the data. Depending on the methods used, there is a possibility that the data set does not include a complete picture of all providers involved in newborn screening follow-up for Pennsylvania. Additionally, without knowing when the provider library was most recently updated, there is a possibility that it includes providers who are no longer practicing or involved in newborn screening follow-up. In addition, focusing on the state level as opposed to the national level limits the number of variables that can be analyzed. Information regarding access to health care or other variables that could have been relevant in this analysis is more limited at the county level compared to the state level. Future research focused on gathering such data related to health indicators in Pennsylvania counties could greatly benefit studies such as this one.

5.5.2 Specific Aim #2

The SMA clinical guidelines contain several details and protocols not immediately relevant to PCPs. In most cases, the pediatric neurologist or other specialist familiar with SMA is responsible for coordinating treatment. The PCP's role comes with referring the infant to necessary specialists for timely follow-up and educating the family on the basics of the condition and next steps. Resources created for SMA and other newborn screening conditions have focused on providing concise overviews regarding the condition and next steps for providers to take. It is intended that the resource created for this project could be utilized by PCPs who receive a positive newborn screening result for SMA.

The readability of the created resource, as measured by the ReadablePro tool from readable.com, seems appropriate for the intended audience. Some issues the assessment points to are in resource names, meaning that the readability of the actual text is likely higher than the score indicates. Organizations such as the American Medical Association (AMA) recommend that patient resources be written at or below the 6th grade level (Weiss 2003). While physicians are of a higher education level than the average patient, investigating readability can still be informative about the approachability and convenience of the document. While the readability grade levels and scores of this resource would be too high for a patient population, they seem appropriate for physicians. Some unavoidable medical phrases and terms negatively affect readability and text quality as measured by this tool. Some text quality issues, such as the syllables per sentence, may affect physicians' desire to read the entire document. However, a reading time of 1 minute and 35 seconds seems ideal for a physician who has limited time and may be in an urgent situation to provide follow-up for an infant with a positive newborn screen. This resource allows physicians to receive important information in under two minutes, rather than having to spend time reviewing

the literature and compiling it on their own. It may be beneficial for future studies to investigate the effects of readability on physicians' understanding of and desire to utilize educational materials.

Physician preparation before receiving a positive newborn screening result is crucial. Being prepared by having resources prior to receiving an abnormal result will save time and allow providers to take more prompt next steps. Given the recent addition of SMA to newborn screening, future efforts should focus on assessing SMA-specific resources, such as the one produced in this project. Evaluating existing resources and their use by primary care practices will provide implications for creation of future resources and interventions.

Appendix A University of Pittsburgh Institutional Review Board Approval

University of Pittsburgh
Institutional Review Board

Human Research Protection Office
3500 Fifth Avenue, Suite 106
Pittsburgh, PA 15213
Tel (412) 383-1480
www.hrpo.pitt.edu

APPROVAL OF SUBMISSION (Exempt)

Date:	October 25, 2019
IRB:	STUDY19090037
PI:	Stephanie Betts
Title:	A survey of physicians' knowledge and confidence regarding newborn screening for spinal muscular atrophy (SMA)
Funding:	None

The Institutional Review Board reviewed and approved the above referenced study. The study may begin as outlined in the University of Pittsburgh approved application and documents.

Approval Documentation

Review type:	Initial Study
Approval Date:	10/25/2019
Exempt Category:	(2)(ii) Tests, surveys, interviews, or observation (low risk), (2)(i) Tests, surveys, interviews, or observation (non-identifiable)

Approved Documents:	• SBetts_thesis_survey.docx, Category: Data Collection; • HRP-721 - WORKSHEET - Exemption_Tests Surveys Public Behavior_Version_0.01.docx, Category: IRB Protocol; • Thesis survey script.pdf, Category: Recruitment Materials;

As the Principal Investigator, you are responsible for the conduct of the research and to ensure accurate documentation, protocol compliance, reporting of possibly study-related adverse events and unanticipated problems involving risk to participants or others. The HRPO Reportable Events policy, Chapter 17, is available at http://www.hrpo.pitt.edu/.

Clinical research being conducted in an UPMC facility cannot begin until fiscal approval is received from the UPMC Office of Sponsored Programs and Research Support (OSPARS).

If you have any questions, please contact the University of Pittsburgh IRB Coordinator, Teresa McKaveney.

Please take a moment to complete our Satisfaction Survey as we appreciate your feedback.

Pitt_510_Exempt

Appendix B Survey Materials

Appendix B.1 Survey Invitation

Hello,

My name is Stephanie Betts and I am a current graduate student in the Genetic Counseling Program at the University of Pittsburgh.

You are invited to complete a questionnaire as part of a Masters level research study I am conducting. The purpose of the study is to learn about the knowledge and self-efficacy of physicians in Pennsylvania regarding the care of patients with spinal muscular atrophy (SMA) in light of its addition to the Pennsylvania Newborn Screening Panel in March of 2019.

This survey is open to any licensed physician who may receive Pennsylvania newborn screening results. The results of the survey will be recorded and compiled anonymously. Participation in the study is voluntary and there is no direct benefit to respondents. Potential risks include any discomfort in answering survey questions and minimal risk for breach of confidentiality.

The survey should take about *5-10 minutes* to complete and can be accessed by visiting http://bit.ly/SMA_survey.

If you have any questions or concerns about this study, please feel free to contact Stephanie Betts at sjb148@pitt.edu.

Thank you for your consideration!
Stephanie Betts
University of Pittsburgh Genetic Counseling Program

Appendix B.2 Qualtrics Survey

Survey

Start of Block: Default Question Block

You are invited to complete a questionnaire as part of a Masters level research study being conducted by a genetic counseling student at the University of Pittsburgh.
The purpose of the study is to learn about the knowledge and self-efficacy of physicians in Pennsylvania regarding the care of patients with spinal muscular atrophy (SMA) in light of its addition to the Pennsylvania Newborn Screening Panel in March of 2019. This survey is open to any licensed physician who may receive Pennsylvania newborn screening results. The results of the survey will be recorded and compiled anonymously. Participation in the study is voluntary and there is no direct benefit to respondents. Potential risks include any discomfort in answering survey questions and minimal risk for breach of confidentiality. The survey should take about 5-10 minutes to complete. If you have any questions or concerns about this study, please feel free to contact Stephanie Betts at sjb148@pitt.edu.

Questions 1-3 will ask about your level of experience with Spinal Muscular Atrophy (SMA).

Q1 Have you ever been involved in the care of a patient with SMA?

- ○ Yes
- ○ No

Q1a How have you been involved in the care of these patient(s)?

Select All That Apply

- [ ] Providing primary care
- [ ] Disclosing newborn screening results
- [ ] Referring to other providers
- [ ] Managing SMA treatment
- [ ] Directly administering SMA treatment
- [ ] Other (please specify) _____

Q2 Have you ever received formal education related to SMA, either during medical school or additional training?

- ○ Yes
- ○ No
- ○ Maybe, I don't remember

Q3 Which of the following sources have you consulted for information related to SMA, if any?

Select All That Apply

- [ ] Online videos or webinars
- [ ] Lectures or meetings
- [ ] Journal articles
- [ ] Books
- [ ] Websites (GeneReviews, Genetics Home Reference, NORD, etc.)
- [ ] Colleagues
- [ ] Other (please specify) _____
- [ ] I have not consulted any sources for information related to SMA

The next part of the survey (questions 4-16) will ask about your current knowledge of SMA and level of comfort caring for patients with SMA.

Q4 SMA is caused by pathogenic variants in which of the following genes?

- ○ SMA1
- ○ SMA2
- ○ SMN1
- ○ SMN3
- ○ Don't know

Q5 What pattern of inheritance does SMA follow?

- ○ Autosomal dominant
- ○ Autosomal recessive
- ○ X-linked dominant
- ○ X-linked recessive
- ○ Mitochondrial
- ○ Don't know

Q6 Patients with SMA can experience varying degrees of disease severity.

- ○ True
- ○ False
- ○ Don't know

Q7 Which of the following factor(s) have been shown to impact the clinical presentation of patients with SMA?

- [ ] From which parent the more severe pathogenic variant was inherited
- [ ] SMN2 gene copy number
- [ ] Whether pathogenic variants were inherited or were de novo mutations
- [ ] Don't know

Q8 How many subtypes of SMA exist?

- ○ 2
- ○ 3
- ○ 4
- ○ 5
- ○ Don't know

Q9 Which of the following clinical symptoms have been observed in patients with SMA?

Select All That Apply

- [ ] Hepatosplenomegaly
- [ ] Respiratory complications
- [ ] Progressive muscle weakness and atrophy
- [ ] Coloboma
- [ ] Polydactyly
- [ ] Hypotonia
- [ ] Feeding difficulties and poor growth
- [ ] Cleft lip and palate
- [ ] Joint contractures
- [ ] Scoliosis

Q10 Nusinersen (marketed as Spinraza), the first FDA-approved treatment of SMA, works by which of the following mechanisms?

- ○ Enzyme replacement therapy
- ○ Substrate reduction therapy
- ○ Antisense oligonucleotide therapy
- ○ Small interfering RNA (siRNA) therapy
- ○ Don't know

Q11 Administration of Spinraza occurs via which of the following?

- ○ Orally
- ○ Subcutaneous injection
- ○ Intrathecal injection
- ○ Intramuscular injection
- ○ Don't know

Q12 Current SMA newborn screening methods only identify patients with severe, early-onset forms of the condition.

- ○ True
- ○ False
- ○ Don't know

Q13 Which of the following steps should be taken immediately upon identification of a patient with SMA through newborn screening?

Select All That Apply

- [ ] Order a chromosomal microarray for each of the patient's first-degree relatives
- [ ] Contact family to inform them of the newborn screening result
- [ ] Consult with pediatric neurologist and geneticist
- [ ] Conduct an audiology evaluation
- [ ] Evaluate the newborn for signs of neuromuscular disease
- [ ] Initiate timely confirmatory/diagnostic testing
- [ ] Provide family with basic information about SMA
- [ ] Consult with a pediatric surgeon

Q14 Please indicate how comfortable you would feel performing each of the following tasks based on your current level of SMA knowledge (i.e. without receiving additional education or doing additional research).

	Click to write Column 1					
	Very uncomfortable	Somewhat uncomfortable	Neither comfortable nor uncomfortable	Somewhat comfortable	Very comfortable	N/A

Interpreting a newborn screening report containing positive results	○	○	○	○	○	○
Discussing the genetic mechanisms and inheritance of SMA with a patient's family	○	○	○	○	○	○
Discussing the expected clinical course of SMA with a patient's family	○	○	○	○	○	○
Discussing available treatment options for SMA with a patient's family	○	○	○	○	○	○
Disclosing the results of a positive SMA newborn screen to a patient's family	○	○	○	○	○	○
Ordering diagnostic testing after a patient receives a positive SMA newborn screen	○	○	○	○	○	○

result						
Referring a newborn with SMA to the appropriate specialists	○	○	○	○	○	○
Providing primary care to a patient with SMA	○	○	○	○	○	○
Referring the family of a patient with SMA to genetic counseling and explaining the genetic counseling process	○	○	○	○	○	○

Q15 Would you find it beneficial to receive additional training and/or education related to caring for patients with SMA?

- ○ Yes
- ○ No

Q16 For which topics related to SMA would additional information be helpful?

Select All That Apply

- [ ] Disease and/or genetic mechanisms of SMA
- [ ] Clinical presentation of a patient with SMA
- [ ] SMA treatment options
- [ ] The process of identifying patients with SMA through newborn screening
- [ ] The follow-up process after a patient receives a positive newborn screen for SMA
- [ ] How to find resources related to caring for patients with SMA
- [ ] Other (please specify) _____

Questions 17-21 will ask for demographic information.

This is the final portion of the survey.

Q17 Gender

- ○ Male
- ○ Female
- ○ Other
- ○ Prefer not to say

Q18 How many years have you practiced post-training?

- ○ <5
- ○ 5-9
- ○ 10-14
- ○ 15-19
- ○ 20 or more

Q37 In which state do you practice?

▼ Pennsylvania ... Other

Q19 In which county do you practice?

_____

Q20 What is your medical specialty?

- ○ Family Medicine
- ○ Genetics
- ○ Pediatrics
- ○ Other (please specify) _____

Q21 How would you describe your practice setting?

- ○ Hospital (private)
- ○ Hospital (public)
- ○ Group practice
- ○ Individual practice
- ○ Academic
- ○ Retired
- ○ Other (please specify) _____

Q22 The questionnaire is finished. However, if you have any additional comments, please include them below.

_____

_____

_____

_____

_____

End of Block: Default Question Block

Appendix B.3 Pediatric PittNet Approval Letter

University of Pittsburgh

Clinical and Translational Science Institute
Forbes Tower, Suite 7057
Meyran and Sennott Streets
Pittsburgh, PA 15260
412-692-5900

April 28, 2020

RE: Physician Understanding of Newborn Screening for Spinal Muscular Atrophy (SMA)

Dear Ms. Stephanie Betts:

I am pleased to inform you that your study, identified above, has been **APPROVED by Pediatric PittNet for survey distribution by Pediatric PittNet staff via email to network providers.** Pediatric PittNet is the University of Pittsburgh Clinical and Translational Science Institute (CTSI) pediatric practice-based research network. The Pediatric PittNet protocol review committee has determined that your IRB-approved study aligns well with the network's mission and is feasible to include in this practice.

As a participating Pediatric PittNet investigator, we ask that you support the network goal of improving children's health through enhanced collaboration between investigators and practitioners by providing feedback about practice- and/or practitioner-specific study data and major study findings. We will contact you in the future to assist you in sharing your study findings with our network providers and practice staff.

Additional requirements for study coordinators:
1. On a weekly basis, track and report the number of subjects recruited from network practices. Please email to pedspitt@pitt.edu **and cc Carrie Fascetti at** christopherc@upmc.edu
2. Include Pediatric PittNet and the CTSI grant in all publications resulting from this study citing "The project described was supported by the National Institutes of Health through Grant Number UL1TR001857"
3. Send the citation and a full copy of all accepted manuscripts resulting from research supported by Pediatric PittNet

A Pediatric PittNet program manager will contact you in the near future to plan inclusion of your study in network practices.

If you have any questions, please contact:

Alex Mykita, MA
CTSI Pediatric PittNet
412-864-3458
aam140@pitt.edu

Sincerely yours,

Stacey Engster, MD, MS
Medical Director, CTSI Pediatric PittNet
Assistant Professor of Pediatrics and Clinical & Translational Science
University of Pittsburgh School of Medicine
Children's Hospital of Pittsburgh of UPMC
General Academic Pediatrics

Appendix C Additional Results

Table 11 Supplemental Demographic Data

	Has Received Formal SMA Training	Might Have Received Formal SMA Training	Has Not Received Formal SMA Training	Total
Gender Identity				
Female	77.8% (7)	75.0% (6)	75.0% (3)	**76.2% (16)**
Male	22.2% (2)	25.0% (2)	0.0% (0)	**19.0% (4)**
Prefer not to say	0.0% (0)	0.0% (0)	25.0% (1)	**4.8% (1)**
Number of Years in Practice				
<5	0.0% (0)	0.0% (0)	25.0% (1)	**5.0% (1)**
5-9	33.3% (3)	28.6% (2)	0.0% (0)	**25.0% (5)**
10-14	11.1% (1)	14.3% (1)	50.0% (2)	**20.0% (4)**
15-19	33.3% (3)	0.0% (0)	25.0% (1)	**20.0% (4)**
20 or more	22.2% (2)	57.1% (4)	0.0% (0)	**30.0% (6)**
Medical Specialty				
Pediatrics	100.0% (9)	100.0% (7)	100.0% (5)	**100.0% (21)**
Practice Setting				
Hospital (public)	22.2% (2)	0.0% (0)	0.0% (0)	**9.5% (2)**
Group practice	66.7% (6)	57.1% (4)	60.0% (3)	**61.9% (13)**
Individual practice	11.1% (1)	28.6% (2)	0.0% (0)	**14.3% (3)**
Academic	0.0% (0)	14.3% (1)	20.0% (1)	**9.5% (2)**
Other	0.0% (0)	0.0% (0)	20.0% (1)	**4.8% (1)**
State of Practice				

Table 11 Continued

Pennsylvania	100.0% (9)	100,0% (7)	100.0% (5)	**100.0% (21)**
County of Practice				
Allegheny County	57.1% (4)	42.9% (3)	40.0% (2)	**47.4% (9)**
Other Western PA Counties (Armstrong, Butler, Erie, Fayette, Westmoreland)	14.3% (1)	28.6% (2)	40.0% (2)	**26.3% (5)**
Other Eastern PA Counties (Bucks, Lackawanna, Luzerne, Montgomery, Montour)	28.6% (2)	28.6% (2)	20.0% (1)	**26.3% (5)**

Table 12 Correct Responses to Knowledge Questions Based on Level of Experience with SMA

Question	Percent Correct	
	Has Cared for a Patient with SMA	**Has Not Cared for a Patient with SMA**
SMA is caused by pathogenic variants in which of the following genes?	20.0% (3)	0.0% (0)
What pattern of inheritance does SMA follow?	53.3% (8)	37.5% (3)
Patients with SMA can experience varying degrees of disease severity (True or False)	100% (16)	71.4% (5)
Which of the following factor(s) have been shown to impact the clinical presentation of patients with SMA?*	28.6% (4)	0.0% (0)
How many subtypes of SMA exist?	40.0% (6)	37.5% (3)
Which of the following clinical symptoms have been observed in patients with SMA?* Select all that apply	20.0% (3)	12.5% (1)
Nusinersen (marketed as Spinraza), the first FDA-approved treatment of SMA, works by which of the following mechanisms?	13.3% (2)	0.0% (0)
Administration of Spinraza occurs via which of the following?	46.7% (7)	25.0% (2)
Current SMA newborn screening methods only identify patients with severe, early-onset forms of the condition (True or False)	33.3% (5)	12.5% (1)
Which of the following steps should be taken immediately upon identification of a patient with SMA through newborn screening?*	13.3% (2)	37.5% (3)

*In this table, answers to "select all that apply" questions were only deemed correct if the respondent marked all correct items and did not mark any incorrect items

Table 13 Correct Responses to Knowledge Questions Based on Formal SMA Training

Question	Percent Correct		
	Has Received Formal SMA Training	**Might Have Received Formal SMA Training**	**Has Not Received Formal SMA Training**
SMA is caused by pathogenic variants in which of the following genes?	20.0% (2)	14.3% (1)	0.0% (0)
What pattern of inheritance does SMA follow?	60.0% (6)	28.6% (2)	40.0% (2)
Patients with SMA can experience varying degrees of disease severity (True or False)	100.0% (10)	71.4% (5)	100.0% (5)
Which of the following factor(s) have been shown to impact the clinical presentation of patients with SMA?*	20.0% (2)	14.3% (1)	20.0% (1)
How many subtypes of SMA exist?	50.0% (5)	28.6% (2)	40.0% (2)
Which of the following clinical symptoms have been observed in patients with SMA?* Select all that apply	10.0% (1)	14.3% (1)	40.0% (2)
Nusinersen (marketed as Spinraza), the first FDA-approved treatment of SMA, works by which of the following mechanisms?	10.0% (1)	0.0% (0)	20.0% (1)
Administration of Spinraza occurs via which of the following?	50.0% (5)	0.0% (0)	60.0% (3)
Current SMA newborn screening methods only identify patients with severe, early-onset forms of the condition (True or False)	30.0% (3)	14.3% (1)	40.0% (2)
Which of the following steps should be taken immediately upon identification of a patient with SMA through newborn screening?*	40.0% (4)	0.0% (0)	20.0% (1)

*In this table, answers to "select all that apply" questions were only deemed correct if the respondent marked all correct items and did not mark any incorrect items

Table 14 Comfort Question Responses of Participants Who Have Cared for a Patient with SMA

	Very uncomfortable	Somewhat uncomfortable	Neither comfortable nor uncomfortable	Somewhat comfortable	Very comfortable	N/A
Interpreting a newborn screening report containing positive results	20.0% (3)	26.7% (4)	6.7% (1)	26.7% (4)	20.0% (3)	0.0% (0)
Discussing the genetic mechanism and inheritance of SMA with a patient's family	20.0% (3)	60.0% (9)	6.7% (1)	6.7% (1)	6.7% (1)	0.0% (0)
Discussing the expected clinical course of SMA with a patient's family	20.0% (3)	46.7% (7)	6.7% (1)	20.0% (3)	6.7% (1)	0.0% (0)
Discussing available treatment options for SMA with a patient's family	21.4% (3)	57.1% (8)	7.1% (1)	7.1% (1)	7.1% (1)	0.0% (0)
Disclosing the results of a positive SMA newborn screen to a patient's family	7.1% (1)	42.9% (6)	0.0% (0)	35.7% (5)	14.3% (2)	0.0% (0)
Ordering diagnostic testing after a patient	14.3% (2)	57.1% (8)	14.3% (2)	7.1% (1)	7.1% (1)	0.0% (0)

Table 14 Continued

receives a positive SMA newborn screen result						
Referring a newborn with SMA to the appropriate specialists	0.0% (0)	7.1% (1)	21.4% (3)	0.0% (0)	57.1% (8)	14.3% (2)
Providing primary care to a patient with SMA	7.1% (1)	7.1% (1)	14.3% (2)	21.4% (3)	42.9% (6)	7.1% (1)
Referring the family of a patient with SMA to genetic counseling and explaining the genetic counseling process	0.0% (0)	14.3% (2)	21.4% (3)	7.1% (1)	42.9% (6)	14.3% (2)

Table 15 Comfort Question Responses of Participants Who Have Not Cared for a Patient with SMA

	Very uncomfortable	**Somewhat uncomfortable**	**Neither comfortable nor uncomfortable**	**Somewhat comfortable**	**Very comfortable**	**N/A**
Interpreting a newborn screening report containing positive results	28.6% (2)	14.3% (1)	28.6% (2)	28.6% (2)	0.0% (0)	0.0% (0)
Discussing the genetic mechanism and inheritance of SMA with a	75.0% (6)	12.5% (1)	0.0% (0)	12.5% (1)	0.0% (0)	0.0% (0)

Table 15 Continued

patient's family						
Discussing the expected clinical course of SMA with a patient's family	50.0% (4)	50.0% (4)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Discussing available treatment options for SMA with a patient's family	62.5% (5)	37.5% (3)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Disclosing the results of a positive SMA newborn screen to a patient's family	25.0% (2)	37.5% (3)	37.5% (3)	0.0% (0)	0.0% (0)	0.0% (0)
Ordering diagnostic testing after a patient receives a positive SMA newborn screen result	50.0% (4)	50.0% (4)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Referring a newborn with SMA to the appropriate specialists	12.5% (1)	12.5% (1)	0.0% (0)	50.0% (4)	12.5% (1)	12.5% (1)
Providing primary care to a patient with SMA	12.5% (1)	50.0% (4)	12.5% (1)	12.5% (1)	12.5% (1)	0.0% (0)
Referring the family of a patient with SMA to genetic counseling and	12.5% (1)	12.5% (1)	0.0% (0)	50.0% (4)	25.0% (2)	0.0% (0)

Table 15 Continued

explaining the genetic counseling process						

Appendix D Physician Resource Readability Evaluation

Text readability report generated on **2020-06-10 15:52**.

Readability Grade Levels	
Flesch-Kincaid Grade Level	10.4
Gunning Fog Index	9.8
Coleman-Liau Index	13.2
SMOG Index	11.2
Automated Readability Index	8.7
FORCAST Grade Level	12.6
Powers Sumner Kearl Grade	5.4
Rix Readability	7.0
Raygor Readability	0.0
Fry Readability	0.0

Text aimed at a general public audience should be around grade 8 to 10.

ReadablePro Rating
C

Readability Scores	
Flesch Reading Ease	32.2
CEFR Level	C2
IELTS Level	8+
Spache Score	4.3
New Dale-Chall Score	8.7
Lix Readability	45.4
Lensear Write	88.0

Text Quality		
Spelling Issues	10	3%
Grammar Issues	3	6%
Sentences > 30 Syllables	7	13%
Sentences > 20 Syllables	11	21%
Words > 4 Syllables	13	4%
Words > 12 Letters	0	0%

Writing Style		
Passive Voice Count	3	2%
Adverb Count	3	1%
Cliché Count	0	0%

Text Statistics

Text Composition		
Adjectives	43	12%
Adverbs	3	1%
Conjunctions	27	8%
Determiners	37	10%
Interjections	0	0%
Nouns	238	67%
Proper Nouns	57	16%
Prepositions	42	12%
Pronouns	2	1%
Qualifiers	0	0%
Verbs	34	10%
Unrecognised	2	1%
Non-Words	8	2%

Text Statistics	
Character Count	2026
Syllable Count	709
Word Count	357
Unique Word Count	182
Sentence Count	53
Paragraph Count	48

Text Statistics Averages	
Characters per Word	5.7
Syllables per Word	2.0
Words per Sentence	6.7
Words per Paragraph	7.4
Sentences per Paragraph	1.1

Timings	
Reading Time	1:35
Speaking Time	2:51

Content Composition

Tone	
« Formal	Conversational »

Formal

Sentiment	
« Negative	Positive »

Negative

Keyword Density

Keyword Density - 1 Word	
SMA	3.53%
is	1.36%
gene	1.36%
family	1.09%
SMN1	1.09%
Patients	1.09%
type	0.82%
severe	0.82%
muscular	0.82%
copies	0.82%
care	0.82%
atrophy	0.82%
are	0.82%
SMN2	0.82%
weakness	0.54%

Keyword Density - 2 Words	
the family	1.09%
with SMA	0.82%
of SMA	0.82%
muscular atrophy	0.82%
family to	0.82%
SMN1 gene	0.82%
Patients with	0.82%
type 4	0.54%
the most	0.54%
the SMN1	0.54%
spinal muscular	0.54%
severity of	0.54%
pediatric neurologist	0.54%
of spinal	0.54%
muscle weakness	0.54%

Keyword Density - 3 Words	
the family to	0.82%
spinal muscular atrophy	0.54%
of the SMN1	0.54%
of spinal muscular	0.54%
muscular atrophy Part	0.54%
management of spinal	0.54%
gene Patients with	0.54%
and management of	0.54%
a pediatric neurologist	0.54%
SPINAL MUSCULAR ATROPHY	0.54%
SMN1 gene Patients	0.54%
Refer the family	0.54%
Patients with SMA	0.54%
Diagnosis and management	0.54%

Text Issues Highlighted

Please note that you can find the key for the colours used to highlight issues in this text on the first page of this report, in the "Text Quality" and "Writing Style" sections.

SPINAL MUSCULAR ATROPHY

Information for Primary Care Physicians

OVERVIEW OF SPINAL MUSCULAR ATROPHY (SMA)

Spinal muscular atrophy (SMA) is a severe genetic condition caused by the degeneration of motor neurons, leading to progressive muscle weakness, decreased mobility, and early death in some cases.

Incidence

1 in 10,000

Inheritance

Autosomal recessive

Cause

SMA is caused by a non-functioning SMN1 gene. Patients with SMA usually have deletions in both copies of the SMN1 gene. The number of SMN2 gene copies that the individual has is associated with the clinical severity of SMA. Patients with more SMN2 copies have a better prognosis.

Clinical Signs/Symptoms (not observed in all individuals with SMA)

Hypotonia

Progressive muscle weakness

Respiratory difficulty

Poor feeding

Weak cry

Subtypes

Cases of SMA are classified into one of five subtypes (type 0 – type 4) based on the age of onset and severity of symptoms.

Type 0 is the most severe subtype and type 4 is the least severe. Types 1 and 2 are the most common.

Treatment

There are currently two FDA-approved drug therapies for SMA:

Spinraza (nusinersen) - an antisense oligonucleotide (ASO) therapy administered through intrathecal injection

Zolgensma - a gene therapy injection which replaces absent SMN1 gene

Patients with SMA typically receive care from several specialists, including:

- Neurology
- Genetics
- Orthopedics
- Respiratory/Pulmonary
- Nutrition
- Gastroenterology

FOLLOW-UP TESTING

Genetic testing of the SMN1 and SMN2 genes

NEXT STEPS

- Contact the family to inform them of the newborn screening result and inquire about symptoms
- Initiate follow-up testing and clinical evaluation (with assistance from a pediatric neurologist and/or geneticist)
- Refer the family to a pediatric neurologist who provides treatment for SMA
- Refer the family to genetic counseling
- Educate the family about the basics of SMA and next steps

ADDITIONAL INFORMATION AND RESOURCES

Providers

- Cure SMA (https://www.curesma.org/about-sma-for-hcps/)
- Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care (https://doi.org/10.1016/j.nmd.2017.11.005)
- Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics (https://doi.org/10.1016/j.nmd.2017.11.004)
- GeneReviews (https://www.ncbi.nlm.nih.gov/books/NBK1352/)
- Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening (https://doi.org/10.3233/JND-180304)

Families and Patients

- Baby's First Test (https://www.babysfirsttest.org/newborn-screening/conditions/spinal-muscular-atrophy)
- Cure SMA (https://www.curesma.org)
- Genetics Home Reference (https://ghr.nlm.nih.gov/condition/spinal-muscular-atrophy)

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