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# **Newborn Screening for Spinal Muscular Atrophy: The Views of Affected Families and Adults**

[SMA Newborn Screening: Views of Affected Individuals]

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**ABSTRACT**

Spinal muscular atrophy (SMA) is one of the leading genetic causes of infant death worldwide. However, due to a lack of treatments, SMA has historically fallen short of Wilson-Jungner criteria. While studies have explored the acceptability of expanded newborn screening to the general public, the views of affected families have largely been overlooked. This is in spite of the potential for direct impacts on them and their unique positioning to consider the value of early diagnosis. We have previously reported data on attitudes towards pre-conception and prenatal genetic screening for SMA amongst affected families (adults with SMA (n=82) and family members (n=255)). Here, using qualitative interview (n= 36) and survey data (n= 337), we report the views of this same cohort towards newborn screening. The majority (70%) of participants were in favour, however, all sub-groups (except adults with type II) preferred pre-conception and/or prenatal screening to newborn screening. Key reasons for newborn screening support were: 1) the potential for improved support 2) the possibility of enrolling pre-symptomatic children on clinical trials. Key reasons for non-support were: 1) concerns about impact on the early experiences of the family 2) inability to treat. Importantly, participants did not view the potential for inaccurate typing as a significant obstacle to the launch of a population-wide screening programme. This study underscores the need to include families affected by genetic diseases within consultations on screening. This is particularly important for conditions such as SMA which challenge traditional screening criteria, and for which new therapeutics are emerging.

**Key Words: Spinal Muscular Atrophy, Newborn Genetic Screening, Bloodspot, Ethics, Social Implications.**

## INTRODUCTION

With recent developments in the field of genomics, for example, the increasing move towards next-generation sequencing in various aspects of healthcare [Soden and others 2014] and reproduction [Dondorp and others 2015] newborn screening practices are facing new challenges both in the UK and beyond [Botkin 2016; Botkin and Rothwell 2016; Botkin and others 2016]. Originally introduced in the UK in the 1950s with the primary purpose of offering early treatment for babies with the metabolic disorder Phenylketonuria (where early intervention drastically alters outcomes), newborn screening has not significantly altered in the UK since this time, despite the introduction of new techniques and approaches (e.g. Guthrie's bloodspot technique/ tandem mass spectrometry). Indeed, the list of conditions for which newborns are currently screened for within the UK (nine) remains modest compared to other European countries, or the USA, where in some states (e.g. Massachusetts), upwards of 60 conditions are screened for simultaneously [Downing and Pollitt 2008]. The inconsistent application of genetic screening in the international arena has been attributed to the lack of clear screening criteria. Indeed, it is increasingly acknowledged that traditional Wilson-Jungner criteria (now over 40 years old) do not adequately accommodate the very specific challenges posed by screening for genetic disorders [Andermann and others 2008]. In response to this, various attempts have been made to develop focused genetic screening criteria, however uptake has been inconsistent and there appears to be no universally accepted standards for genetic screening programmes [Walters 1992; Cornel and others 2012].

As the criteria used to guide genetic screening policies come under scrutiny, the views and perspectives of stakeholder groups set to be affected by them have gained significance. Various

studies have been undertaken exploring attitudes to expanded newborn screening, however these have tended to focus on the views of clinicians [e.g. [Hiraki and others 2006]] and/or (expectant) parents [e.g. [Hasegawa and others 2011]], with far less attention paid to the views of families living with conditions that are potential screening candidates (although there have been a few notable exceptions: Fragile X [Skinner and others 2003], Mucopolysaccharidoses [Hayes and others 2007] and Duchenne/Becker Muscular Dystrophy [Wood and others 2014]). This lack of consultation with affected families is surprising given that they are set to be directly impacted by the introduction of newborn screening, both through the change in public profile of the disease, but also through potential advances in research as affected children come to be enrolled earlier (and potentially pre-symptomatically) onto clinical trials. Aside from these impacts, families living with potentially screened-for conditions are also in a privileged position to consider the impact that an early diagnosis would have had for their lives, and consequently have much to offer studies considering the effects and desirability of expanded newborn screening [Wood and others 2014].

This paper addresses this identified gap in literature by presenting attitudes towards newborn genetic screening amongst families and individuals living with a condition for which newborn genetic screening could feasibly soon be offered -Spinal Muscular Atrophy (SMA) [Phan and others 2015; Swoboda 2010]. SMA is a neuromuscular disorder and one for which newborn genetic screening has been described as particularly critical, not only because of the serious impact SMA has on families [Klug and others 2016] and the acknowledged difficulties with obtaining a timely diagnosis [Lin et al., 2015], but also because developing treatments for the condition requires children to be entered into clinical trials prior to the onset of symptoms, which is typically early in life [Prior and Nagan 2016; Swoboda 2010]. While a limited number of studies have been conducted

to explore public attitudes towards newborn genetic screening for SMA [Rothwell and others 2013], there is very little evidence on the views of affected families, bar one study which included the views of five parents of affected children [Wood and others 2014].

Spinal Muscular Atrophy (SMA) is an autosomal recessive neuromuscular disorder and is a leading genetic cause of infant death [Munsat and Davies 1992]. Although presenting symptoms are due to the loss of the alpha motor neurones of the spinal cord [Munsat and Davies 1992], recent reports have shown more systemic pathology [Somers and others 2016; Thomson and others 2016]. It is sub-classified into four main types, based on age of onset, severity and inability to reach defined motor milestones [Munsat and Davies 1992; Prior and Nagan 2016; Prior and others 2011; Prior and Russman 1993]. Type I SMA is the severe form, with onset within the first few months of life and death usually occurring before 18 months through respiratory failure [Munsat and Davies 1992]. Type II SMA (intermediate) is the most divergent form, with onset usually within the first two years of life [Munsat and Davies 1992]. The impact on lifespan for individuals living with type II is dictated by the degree of respiratory involvement, with affected individuals facing end of life events anywhere from adolescence to late adulthood. Although mildly progressive, type II disease pathways tend to involve long “static” periods where symptoms do not change significantly [Glanzman and others 2011; Munsat and Davies 1992]. Type III SMA is usually diagnosed after the age of 4 years, with the majority of able to sit and stand unaided [Dunaway and others 2012; Glanzman and others 2011; Munsat and Davies 1992; Oh and others 2011]. Type IV SMA is diagnosed in adulthood, with patients developing generalised muscle weakness [Clermont and others 1995]. In both type III and IV there is a gradual deterioration in abilities over time, although life span is usually unaffected [Burglen and others 1995; Clermont and others 1995; Munsat and Davies 1992].

While a limited number of studies have been conducted into public attitudes towards newborn genetic screening for SMA [Rothwell and others 2013], there is very little evidence on the views of affected families, bar one study which included the views of five parents of affected children [Wood and others 2014]. We have previously reported data from the UK SMA Screening Survey, which tested the views of 337 adults associated with SMA on three separate screening programmes: 1) Preconception Genetic Screening (PCGS); 2) Prenatal Genetic Screening (PGS); and 3) newborn genetic screening [Boardman et al., 2016]. Our initial study reported the data on PCGS and PNS; here we report the cohorts' views on newborn genetic screening. This is the largest to systematically describe the views of affected families on newborn genetic screening, but also details their perceptions of the key social and ethical debates it would involve.

## METHODS AND MATERIALS

An exploratory sequential mixed methods research design was adopted to address the complex and multi-faceted question of screening for SMA. This design involved the use of qualitative interviews (n= 36) which were used to inform the development of a survey which was subsequently administered to a larger sample of families and adults with SMA (n= 337), as set out below.

### Qualitative interviews

In-depth qualitative interviews were conducted with 36 people who either have SMA or have SMA in their family between January and May 2014, with ethical approval for the study being granted by the Biomedical and Scientific Research Ethics Committee in early January 2014. Participants were recruited through advertisements placed in the newsletter of the main support and advocacy group for families living with SMA in the UK, SMA Support UK. The interviews were designed to explore experiences with SMA, views around and previous/anticipated use of reproductive genetic technologies, as well as perceptions of newborn genetic screening for SMA.

Interviews were either completed over the telephone (n= 31) or face-to-face (n=5), depending on the participants' preferences and geographical location. The interview recordings were transcribed verbatim (with names and identifiers removed or changed) and the data analysed using qualitative data analysis software, Nvivo10. A constructivist approach to grounded theory data analysis was used in order that the participants' own meanings and interpretations guided the analysis, rather than those of the researcher. Initially, 'open coding' of the data was carried out which was largely descriptive, before hierarchical coding was undertaken. A process of coding, refinement of concepts (through data interpretation), followed by re-coding was carried out over



a period of five months until ‘theoretical saturation’ had occurred [Glaser 1967]. The qualitative analysis was completed by an experienced qualitative researcher, under the supervision of two senior academic mentors with expertise in qualitative methodology.

### **SMA Screening Survey (UK)**

The SMA Screening Survey (UK) was developed directly from the qualitative data in order to ensure that the priorities of SMA families were reflected in the survey questions. The survey assessed views on preconception genetic screening (PCGS), prenatal genetic screening (PGS) and newborn genetic screening. The survey is based on single sentence ‘attitude/belief’ statements, which were in turn developed into quantitative survey questions through the use of a Likert scale [Mitchael]. As such, the 7 key themes from the qualitative analysis were therefore used to delineate the key domains of the survey. These broad domains were then transformed into single sentence ‘attitude/belief’ statements, which were in turn developed into quantitative survey questions through the use of a Likert scale [Mitchael]. In this way, the qualitative analysis directly informed the content of the survey (see Table 1 for a list of statements). Questions designed to capture demographic information from respondents (such as educational attainment, religious faith and ethnicity) were either directly replicated from, or appear as modified versions of, questions used in the 2011 UK Census survey.

As well as the underpinning qualitative work, the survey was also passed through three expert panels, made up of professionals working with families affected by SMA (SMA Support UK/ SMA Patient Registry) as well as people living with SMA themselves. Ethical approval for the survey was

granted (separately to that for the qualitative interviews) by the Biomedical and Scientific Research Ethics Committee in July 2014.

Quantitative data collection was carried out over a period of ten months, from 1<sup>st</sup> September 2014 to 30<sup>th</sup> June 2015. Two versions of the survey were made available, an online version (hosted on a secure website) and a paper copy. The survey was via UK SMA Support and the Imaging Future research website.

Potential participants were invited to complete the survey if they were aged 18 or over and either had SMA themselves, or at least one diagnosis of SMA in the family. People affected by one the variant forms of SMA (Spinal Muscular Atrophy and Respiratory Distress, Spinal Bulbar Muscular Atrophy) were also invited to take part. No restrictions were placed on the type of family members invited to take part: step-, adopted and fostered family members were included. The recruitment strategy for family members was kept broad (and included non-biological relatives) as the social relationship to the person with SMA was considered as important as the biological relatedness of the person. Whilst the SMA Screening Survey (UK) also included questions on pre-conception and prenatal screening, due to the very specific social and ethical issues pertaining to these types of screening (i.e. those of selective reproduction), primarily data on attitudes to newborn genetic screening are reported in this paper. The pre-conception and prenatal screening data are discussed elsewhere [Boardman and others 2016]. The survey was distributed to families living with SMA through SMA Support (by post and online) and through the research projects website (Imaging Futures).

### **Statistical Analysis**

The attitudes of families and adults with SMA towards newborn genetic screening were compared to determine if there were any statistical differences. The following sub-group analyses were performed: All participants were analysed collectively to identify any overriding trends (all participants). Responses from families (all) and adults with SMA (all) were compared to determine if living the disease altered views. Sub-analyses on participants associated with the three most prevalent childhood forms of SMA (type I, II and III) were then performed. Responses from families associated with type I were compared with responses from families with milder forms (type II/III SMA (combined), type II alone and type III alone)- to determine if severity altered families views. Responses were compared between families and adults with SMA, to determine if the relationship to SMA affects views (when severity is standardised). This analysis was split into three: 1) type II-associated participants; 2) type III-associated participants and 3) type II/III combined (the combined analysis was performed to facilitate logistic regression analysis based on the relatively low number of adults with SMA in the two sub-groups. Finally, responses from adults with type II were compared to adults with type III, and responses from type II families were compared to type III families. This assessed whether the severity and age of diagnosis impacts views, and whether any differences were seen in both families and adults living with the disease. For the sub-group analysis, families members associated with more than one form of the disease were classified according the most severe form within their family (e.g. a family associated with type I and II would be classified as a type I family).

In each of the sub-group analyses, the individual questions were assessed and then responses correlated against support for screening. For each question the number of “agree’ v

“other” responses were reported and statistical differences between the subgroups were assessed using a chi-squared analysis (Graphpad Prism software, v6). Associations between positive “agree” responses to each question were assessed using binary logistic regression (performed against survey Q20I (I would support a newborn genetic screen for SMA)). Logistic regression was performed using SPSS v22 (IBM).

## RESULTS

The cohort characteristics have been previously reported [Boardman and others 2016]. Briefly, of the 337 participants, 255 were family members of people with SMA (75.7%) and 82 had SMA themselves (24.3%). Most participants were female (74.4%); aged between 35-55 years (52%); were not educated to degree level (63.8%); were religious (55%); were parents (82%); had lived/were living with someone with SMA (82%) and had experience with SMA types 0, I or II (69.4%). The remainder of the sample (31.6%) were affected by rarer forms of SMA (e.g. type IV).

Overall, 70% of survey participants were in favour of newborn genetic screening, with no statistical differences between any of the analysed sub-groups (**Table I-II**). However, the overall levels of support were lower than the previously reported levels of support in the same participants for both preconception genetic screening (77%) and prenatal screening (76%) [Boardman and others 2016].

Interestingly, while the majority of participants agreed that newborn genetic screening was important because it would lead to better support for children and families, would extend life expectancy, would help research by enabling children to enrol on clinical trials earlier and would prevent the difficulties for a child triggered by a later diagnosis (**Table I-II**), there were differences between the individual subgroups. Fewer family members than adults with SMA believed newborn genetic screening would result in better support (81% v 93%,  $p=0.01$ ; **Table I-II**); this difference was predominantly due to differences seen between type II families and adults living with type II SMA (76% v 100%,  $p=0.009$ ; **Table I-II**). There was also a considerable dichotomy between families and adults with SMA regarding extended life expectancy, with fewer type II family members thinking it

would increase compared to adults living with type II (37% v 74%;  $p=0.01$ ; **Table I-II**). Interestingly, there were also fewer type III patients than type II patients who thought life expectancy would increase (45% v 74%,  $p=0.0009$ ; **Table I-II**). In comparison, there was general uniform agreement across all subgroups that newborn genetic screening will enable early enrolment on clinical trials and that it will enable parents to make informed decisions about future pregnancies (**Table I-II**).

A lower proportion of type II family members thought newborn genetic screening would spare them some of the difficulties associated with a later diagnosis for the child (57%); this was significantly lower than for both adults with type II SMA (81%;  $p=0.03$ ; **Table I-II**) and type III families (82%;  $p=0.04$ ; **Table I-II**). In addition, proportionately more families associated type I SMA compared with type II families thought that an earlier diagnosis would prevent families enjoying life before symptoms emerge (53% v 32%;  $p=0.02$ ; **Table I-II**).

One of the key questions is whether newborn genetic screening is important, even without the ability to accurately type SMA. This is one of the central reasons why the UK National Screening Committee (NSC) rejected instigation of SMA screening programme. Therefore, it is important to note that the majority of participants from all sub-groups thought the importance of an early diagnosis out-weighed the accurate ability to type (using current methods). However, support was generally lower in families v adults with SMA (63% v 79%,  $p=0.01$ ; **Table I-II**); although the differences were not significant when type II and III individual comparisons were made; when these groups were merged there were significantly fewer type II/III families than adults with type II/III who thought diagnosis at birth was important without the ability to type (59% v 78%;  $p=0.01$ ; **Table I-II**).

Univariate logistic regression analysis confirmed the direct comparison analysis (**Table III-IV**). All family sub-groups who supported newborn genetic screening generally thought it would improve support, extend life expectancy, enable early enrolment on clinical trials, would make the diagnosis easier for parents to accept, spare difficulties associated with a later diagnosis and allow informed decisions regarding future pregnancies (indicated by a positive odds ratio;  $p < 0.05$ ; **Table III**). In comparison, while adults with type II/III (combined sub-group) agreed it would lead to better support and allow informed decisions on future pregnancies, there was no general agreement that it would increase life expectancy, allow early enrolment on trials (although this was approaching significance;  $p = 0.09$ ; **Table IV**), would make diagnosis easier to accept or would spare children the difficulties associated with a later diagnosis (**Table IV**). All adult and family subgroups in favour of NEWBORN GENETIC SCREENING predominantly thought it was important, even if type could not be determined (**Table III-IV**). Regarding negative drivers, participants in favour of newborn genetic screening did not agree that it was unethical (as there is no therapy) or that it would interfere with the early bonding process; this was consistent for all sub-groups analysed where there were enough responses to perform a statistically relevant logistic regression (**Table III-IV**).

We compared the levels of support for newborn genetic screening against support for two alternative programmes (preconception genetic screening (PCGS) and prenatal genetic screening (PGS)). As reported here and elsewhere [Boardman and others 2016], in general there is more support for PCGS and PGS than newborn genetic screening in all analysed sub-groups (**Table V**). The kappa analysis suggests there is a minimal-weak agreement within each sub-group; this is important, because it highlights that participants are not simply in-favour of all tests- instead there are subtle differences between the different groups that reflect their views and experiences. As

highlighted in the analysis, adults with type II SMA are the only sub-group that preferentially support newborn genetic screening over the other groups (**Table V**). This is in keeping with our previous report, which demonstrates these participants have a comparatively positive view on their condition, believing they have fulfilling lives and can have a valuable impact on society [Boardman and others 2016]. Therefore, their support for newborn genetic screening is understandable, because it is the one test that would not result in fewer children with type II SMA being born (this was highlighted in our previous study as one of the main reasons adults with type II SMA were opposed to PCGS and PGS programmes) [Boardman and others 2016].



## DISCUSSION

Screening newborns for conditions in the absence of effective treatments has been described as ethically problematic, not least because the direct benefits to the child of undergoing such screening are limited [Schmidt and others 2012; Timmermans and Buchbinder 2010; Tluczek and others 2011]. Moreover, newborn genetic screening carries multiple risks for that child, not only in terms of the widely discussed (and sometimes long-term) physical and psychological risks of indeterminate or false positive/negative results [Schmidt and others 2012; Timmermans and Buchbinder 2010; Tluczek and others 2011], but also in terms of the inherent risks of clinical trial enrolment in relation to experimental therapies. It is noteworthy that for the majority of people who participated in this study the possibility of facilitating clinical trials was seen as a positive reason to support screening. This support of trials was fairly even across all types of SMA as well as between family members and adults with SMA (**Table I**). It is unclear whether participants perceived a direct benefit to trial enrolment for SMA children or whether they accepted the indirect benefits, but the importance of supporting such trials, as well as the earlier introduction of support and healthcare, the importance of an earlier diagnosis and the benefits in terms of future reproductive decisions all featured as positive drivers for newborn genetic screening support (**Table I**).

The importance of early SMA diagnosis and trial enrolment has been elevated recently following the preliminary reports from a phase 2, open-label, dose-escalation study of Nusinersen (an antisense oligonucleotide that modifies *SMN2* RNA splicing) [Chiriboga and others 2016; Finkel and others 2016; Hache and others 2016]. The trial involved 20 participants, with 2-3 copies of *SMN2* and age of onset ranging from 21-154 days [Finkel and others 2016]. Data from this trial demonstrated that pre-symptomatic infants at high genetic risk of Type I SMA responded well to

Nusinersen, achieving motor milestones in timelines more consistent with normal development [Finkel and others 2016]. These findings suggest that improved outcomes (motor function, achieved motor milestones and increased time to ventilation) would be achieved if pre-symptomatic patients (identified through newborn screening) could be enrolled and treated with Nusinersen (or similar ASOs). This therapeutic has been approved by the U.S. FDA and may be prescribed for newborns with high genetic risk for Type I SMA.

For the 30% of the sample who were not openly in favour of newborn genetic screening for SMA, concerns about parent-child bonding and the ethics of a newborn programme in the absence of treatments emerged as key reasons for their non-support. The newborn screening literature highlights the detrimental impact that an unsought and serious diagnosis can have on the early parent-child relationship in terms of bonding and levels of parental stress [al-Jader and others 1990; Grob 2008]. Given the gravity of an SMA diagnosis, the lack of available treatments and difficulties associated with accurate prognostic information, it is perhaps unsurprising that this issue would also emerge as significant for families affected by SMA.

Concerns about the impact of newborn genetic screening on the early experiences of the family were also evident in attitudes towards the impact of a pre-symptomatic diagnosis. Significantly more type I and type III family members than any other sub-group agreed that newborn genetic screening would prevent families from enjoying care-free time with their baby before their SMA symptoms emerged. It is perhaps unsurprising that this issue was particularly pronounced for families living with type I and III, given the extremely curtailed life expectancy of infants with type I SMA and the relatively long period of time before the onset of symptoms in the case of type III SMA.

Sub-analyses of families and adults with SMA reveal evidence to suggest that the reasons underpinning non-support differed across the types, as well as between family members and adults with SMA. Family members with experience of types I SMA who did not want newborn genetic screening did so not out of a rejection of screening *per se*, but rather because they wanted screening in a different form. Our data highlight that 22% of adults with type II SMA reject all forms of screening for SMA. It is noteworthy that this view was not evidenced amongst adults with type III SMA, and seems to be related to the perceptions of the condition amongst adults with type II. Shakespeare postulates that people with fixed impairments from birth or early childhood are often better adjusted to their disabilities than those whose impairments are later onset, fluctuate, or involve periods of decline or deterioration [Shakespeare 2006]. For those who have always lived with their impairment, and set their lives up around its existence, the concept of screening and cure may be deemed secondary to the broader social and political goals of equality and an open, inclusive society for people with disabilities. It has recently been report that adults with more clinically severe forms of SMA reported higher quality of life and perceptions of the condition than those with milder and adult onset forms of SMA [Kruitwagen-Van Reenen and others 2016]. Our study demonstrates that these differing perceptions of the condition emerged within our sample, but also that they translated into negative attitudes towards screening and SMA prevention.

In spite of this identified resistance amongst a sub-set of adults with type II SMA, newborn genetic screening emerged from the SMA Screening Survey (UK) as the least divisive. Indeed, the vast majority of participants were positive about the newborn genetic screening's potential to improve the lives of people with SMA. The fact newborn genetic screening elicited far

less resistance from the adults with type II SMA is likely because it will not increase the number of SMA-related terminations [Boardman and others 2016]. Rather, newborn genetic screening lends itself to a model of disease prevention that relies on early identification and amelioration of disease symptoms rather than the more ethically complex approach of avoiding the affected individuals from being born.

There are potential limitations in this study. Due to confidentiality and data protection issues, no identifiable data were asked of individuals who participated in the SMA Screening Survey (UK), including IP addresses (where the survey was completed online). This meant that there was no mechanism in place to prevent an individual completing multiple surveys. Moreover, there was no way of verifying that the participant fitted the inclusion criteria to participate in the survey. Participants were furthermore accessed through a national support group, personal networks and a patient registry rather than neuromuscular clinics, which may have introduced bias. Due to the very poor prognoses associated with types 0 and I SMA, the adults with SMA who participated in the survey were largely affected with clinically milder forms of the disease (although two participating adults reported that they had a diagnosis of type I SMA, and all types of SMA can be associated with significant disability and disease burden), which may have impacted on how the disease was presented and the differences in perceptions of quality of life associated with SMA between adults living with it and parents of babies who died of types 0 or I SMA. Our analysis grouped responders as “families” or “adults with SMA”. This means we have not reported whether there are differences between close (parents, siblings) and distant (cousins, uncles etc) family members. This was because the low numbers involved for some of the family members reduced the significance of the analysis. This data will be reported elsewhere in a separate manuscript.

In conclusion, this study highlights that for families living with SMA, newborn genetic screening is viewed favourably by the majority of respondents, irrespective of the current lack of treatment for SMA and irrespective of the screen's ability to determine the type of SMA affecting the infant. This finding is in contrast to policy reviews and criteria where the absence of accurate typing and treatment for SMA are seen as fatal flaws to screening implementation [Cartwright 2012]. It is also in contrast to attitudes towards other forms of screening for SMA (pre-conception and prenatal), where inability to determine type was controversial, particularly among adults with type II SMA [Boardman and others 2016]. Unlike pre-conception and prenatal screening, which potentially involve the prevention, or termination, of lives affected by SMA [Boardman and others 2016], NEWBORN GENETIC SCREENING, through its focus on early detection, is the least emotive, and consequently the least divisive, form of screening for SMA. It has, furthermore, been identified by the SMA research community as the form of screening most likely to yield the most progress in terms of treatment development, through its concomitant increase in infants participating in clinical trials [Phan and others 2015].

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