Population Screening For Spinal Muscular Atrophy: A Mixed Methods Study Of The Views Of Affected Families

[SMA Screening: Views of Affected Families]

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ABSTRACT

Autosomal recessive conditions are a significant health burden with few treatments. Population carrier screening has been suggested as a means to tackle them. Little is known about the views of affected families despite the potential for direct impacts on them. Data is presented on attitudes amongst families affected by Spinal Muscular Atrophy (SMA) towards two population screening programmes, pre-conception and prenatal. Data were gathered through qualitative interviews (n= 36) and a survey (n=337). Eighty-two survey participants had SMA and 255 were family members. The majority were in favour of screening (75%). Reasons for supporting pre-conception screening support were a belief that it would reduce SMA-related terminations and raise awareness of SMA in the population. For prenatal screening, reasons for support included a belief in the importance of informed decision-making and the need to reduce suffering. Key reasons for non-support of pre-conception screening included concerns about carrier stigmatisation and social engineering. For prenatal screening, concerns focused on the collateral loss of high quality of life lives affected by SMA. This study highlights that those affected by SMA are predominantly in favour of screening, although pre-conception screening is most favoured. Whilst family members and adults with SMA had largely consistent views, perceptions varied according to the severity (type) of SMA, with those affected by SMA type II the least likely to support screening. These findings suggest that screening for SMA is a complex issue for affected families, underscoring the need to consider and include their views when planning and implementing screening programmes.

Key Words: Spinal Muscular Atrophy, Genetic Screening, Mixed Methods, Ethics.

INTRODUCTION

Autosomal recessive conditions, although individually rare, account for approximately 20% of infant mortality worldwide [Bell, 2011]. The vast majority of autosomal recessive conditions have severe presentations, relatively high carrier frequencies in the general population and little, if any, effective treatments, fuelling the case for their prevention through the use of population screening programmes. Indeed, advances in genetic screening technology capability- including next generation sequencing (NGS)- permit screening for whole 'panels' of conditions (50+ conditions) simultaneously, and studies are currently underway in the international arena exploring the feasibility of such panel screens for use by the general public [Plantinga, 2016; Leo et al., 2016].

Within the UK NHS healthcare system, genetic testing for autosomal recessive carrier status is usually only offered to people with a family history of that condition. 'Cascade' testing (testing of blood relatives of identified carriers/ affected individuals) is then usually offered in a step-wise fashion to map the dispersion of the disease-causing trait through a family's bloodline [Morris, 2004]. For the vast majority of people, therefore, the diagnosis of an autosomal recessive disease in their child remains the most common way that they discover their carrier status. This is, furthermore, usually an unforeseen event, as the diagnosis will often be the first in the family's known history.

Through the earlier provision of genetic information (either in the pre-conception or prenatal period), it is argued, genetic screening programmes can enhance and expand the reproductive options of these carrier couples whilst also reducing the number of (unanticipated)

births of children with genetic disease [Cornel et al., 2014]. Through the use of pre-conception screening, carrier couples may make use of genetic technologies in their *first* (rather than subsequent) pregnancies, relieving their reproductive decisions of the constraints associated with already having a child with a serious genetic disease [Human Genetics Commission, 2011]. Pre-conception screening also extends the reproductive options of carrier couples. Unlike those couples identified through the diagnosis of their child, such couples would have the option to abstain from reproduction altogether, or to reproduce with a different (non-carrier) partner.

A key concern associated with genetic screening programmes, however, is that they bestow significant- and potentially burdensome- reproductive decisions on members of the general population who have no previous knowledge, experience, or *a priori* risk of the condition for which they will be tested [McClaren et al., 2008]. In spite of this, studies have consistently demonstrated favourable attitudes towards expansive genetic screening among the general public [Plantinga et al., 2016; Archibald et al., 2009], reflecting a widespread social and cultural belief in the significance and benefits of gaining increasing amounts of genomic information [Middleton et al.,1998; 2016].

Whilst work has been undertaken to gauge the attitudes of the general public towards genetic screening, far less attention has been paid to the views of families with experience of the conditions for which screening could be offered, with a few notable exceptions [Pisnoli et al., 2016; Maxwell et al., 2014; Skinner et al., 2003]. However, affected families represent an important stakeholder group; such families possess expert 'experiential knowledge' [Abel & Browner, 1998] of the condition in question and unparalleled insight into the realities of its day-to-day impact. This

expert knowledge is of direct relevance to policy decision-making around which conditions should, and should not be, included in genetic screening programmes.

Aside from policy implications, the paucity of research on the views of affected families towards population screening is concerning because such families are set to be directly- and potentially significantly- impacted by their introduction [Kellog et al., 2016]. Such impacts might include changes in public attitudes towards the condition [Stotko, 2009], reductions in research funding for treatments and social isolation as a consequence of a reduced birth-rate of people with the same condition.

This paper addresses this identified gap in evidence and understanding by exploring the views of affected families and individuals towards population level pre-conception and prenatal genetic screening using one particular autosomal recessive disorder, Spinal Muscular Atrophy (SMA), as an example.

Background

SMA has been identified as the most common genetic cause of infant death worldwide [Munsat et al., 1992]. It is usually caused by either a point mutation (a single nucleotide is altered) or a deletion mutation (a section of DNA is missing) of the SMN1 gene, located on chromosome 5 [Clermont et al., 1998; Burglen et al., 1995]. It is characterised by loss of the alpha motor neurones of the spinal cord (neurones required to transmit nerve impulses from the brain to muscle), resulting in symmetrical and progressive atrophy of the voluntary muscles of the limbs and trunk, as well as weakening of the inter-costal muscles (muscles used to support breathing). It is sub-

classified into distinct ‘types’ (0-IV), based on the age of onset and severity (measured by achievement of gross motor milestones, primarily sitting and walking) [Lunn et al., 2008] (***table I***). From these types, the disease trajectory can be estimated, including anticipated life expectancy, which varies drastically across the different types of SMA. Babies diagnosed with Type 0 or I SMA typically have a significantly shortened lifespan, with death occurring either before, or shortly after, birth (in the case of Type 0) or by 18 months (Type I). Children diagnosed with Type II are usually never able to walk or sit independently, but their impairment typically remains relatively static over the life course, and lifespan is typically near-normal. Types III and IV onset later, and ambulation is often achieved before onset of the disease, which is in late childhood (Type III) or adulthood (Type IV). These milder forms of SMA involve gradual deterioration in abilities over time, but lifespan is usually unaffected.

Whilst the typing system for SMA has long been used as a shorthand for disease severity both within and without the medical profession, it is also acknowledged that this way of categorising SMA results in types with a high degree of overlap between them and broad ranges of disease severity within them [Dubowitz, 1991]. Pilot studies using *SMN2*-copy number to type SMA at diagnosis, have been reported. These include a pre-conception screening programmes in the USA [Prior et al., 2010] and a prenatal screening programme in Taiwan [Su et al., 2011]. These reports suggest that while most patients can be stratified by *SMN2* copy number, the overlap means patients in the boundaries between diseases can be mis-typed. Indeed, attempts to refine the classifications through linking genetic findings, primarily copy number, to disease severity have thus far been unable to adequately explain the co-occurrence of different types of SMA within one family, and it is now more widely accepted that there are a number of confounding

factors that influence disease severity e.g. Plastin 3 [Opera et al., 2008].Therefore, while typing is able to differentiate between the extremes of the clinical spectrum, additional work is needed to produce a stratification system that accurately classifies at the type I / type II and type II / type III boundaries.

Internationally, approaches to SMA screening vary significantly, with some countries implementing compulsory pre-marital carrier screening for SMA (Qatar), with others offering screening through state-subsidised health care plans (Israel, Australia). Within the UK, SMA screening may be purchased privately through direct-to-consumer genetic testing companies, but when set against UK National Screening Committee criteria (the advisory body to government on issues related to screening) the potential for mis-typing was judged to be a major obstacle to screening implementation in the last policy review [Cartwright, 2012].

As well as technological concerns, there is also limited evidence within the literature on attitudes towards SMA screening amongst both the general public (with a few notable exceptions [Prior et al., 2010; Rothwell et al., 2013; Norton et al., 2014]) and families living with SMA. Where families living with SMA have been included in screening studies, numbers have typically been low- only 5 parents of a child with SMA were included in Wood et al.'s [2014] US-based comparative study, and 28 in Lawton et al.'s [2015] Australian study. Furthermore, neither of these studies included individuals with SMA themselves. No previous study, therefore, has explored the views of families and adults currently living with SMA towards population level genetic screening for the condition. This research fills this gap in the literature by presenting the views of people currently living with SMA (either through having it themselves or having an affected family

member) in the UK on two different types of screening programme; 1) a pre-conception genetic screening programme (whereby would-be parents are screened *prior* to conception to identify whether they are SMA carriers) and 2) a prenatal genetic screening programme (whereby the parents are screened for their SMA carrier status *after* a pregnancy is established, including genetic testing of the foetus where indicated). Whilst data were also collected within this study on attitudes towards newborn screening, as newborn screening for SMA raises unique issues distinct to those associated with carrier screening [Swoboda, 2010], these data will be presented separately.

METHODS AND MATERIALS

An exploratory sequential mixed methods research design was adopted to address the complex and multi-faceted question of screening for SMA. The research took place in three distinct phases which are outlined below.

Qualitative interviews: Phase I

In-depth qualitative interviews were conducted with 36 people who either have SMA themselves, or have SMA in their family, recruited through the main support group for families living with SMA, SMA Support UK (see Table 2 for a breakdown of interview participants). A sub-set (n=17) of these interviews were conducted as follow-up interviews to a previous study around uses of prenatal testing and selective termination in families affected by SMA [Boardman, 2010]. Advertisements were placed in SMA Support UK's quarterly newsletter and electronic newsletters to call for participants. Interviews were designed to explore experiences with SMA, views around, and experiences of, genetic testing technologies and selective termination, as well as perceptions

of population screening for SMA. Respondents were eligible for interview if they were aged 18 or over, English speaking and either had SMA themselves, or had at least one diagnosis of SMA in their family.

The various calls for participants led to responses from 41 individuals (5 individuals were excluded; 4 because the diagnosis in their family was of Muscular Dystrophy and 1 because they were under 18). Out of the 36 audio-recorded interviews that were carried out, 31 were completed over the telephone and five face-to-face. 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. Initially, 'open coding' of the data was carried out which was largely descriptive, before hierarchical coding. 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 and Strauss, 1967].

The qualitative data revealed a complex picture of attitudes towards screening, and seven key overarching themes emerged, as set out in Table III. These overarching themes were not identified by the number of times they appeared in participants' responses (indeed, some themes appeared far more frequently than others), but rather they comprise an exhaustive list of all the overarching themes under which all participants' accounts could be coded. These seven themes were subsequently used to delineate the key domains of the SMA Screening Survey (UK).

SMA Screening Survey (UK): Phase II

Having identified the broad domains of the survey directly from the qualitative themes, the domains were next transformed into single sentence 'attitude/belief' statements, which were in turn developed into quantitative survey questions through the use of a Lickert scale. Where possible, verbatim text from participants' interviews was used to create these attitude statements. Through this process, the qualitative analysis directly informed the content of the survey. 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 from the 2011 UK Census survey.

As well as the underpinning qualitative work, the survey was also passed through three expert panels. The first of these panels comprised six staff members from SMA Support UK. The second group consisted of four members of SMA Patient Registry staff. These two professional panels reviewed the survey once it had been completed in first draft form and offered feedback on the questions as well as advice on the implementation strategy. A separate expert review panel was also established that was made up of people living with SMA. Nine individuals sat on this panel, three of whom had SMA themselves and six of whom had a relative with SMA. This panel met to discuss the qualitative analysis and early design of the survey. Once the SMA Screening Survey (UK) had been drafted, they were contacted once again to undertake a cognitive interview. 'Cognitive interviewing' is a widely used technique that uses in-depth interviewing techniques in order to explore the mental processes that participants use to answer survey questions [Willis, 2005]. Six members of the expert review panel undertook such an interview. Ethical approval for

the SMA Screening Survey (UK) was granted by the Biomedical and Scientific Research Ethics Committee in July 2014.

Quantitative data collection was carried out over a period of ten months, from 1st September 2014 to 30th 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 distributed to families living with SMA through a variety of channels. Firstly, all members of SMA Support UK (1,500 households) received a paper copy of the survey (and a pre-paid returns envelope) in September 2014 together with their quarterly newsletter which included an article on the project. Participants were encouraged to distribute the survey to interested family members/friends affected by SMA. A reminder to complete and return the survey was sent out in December 2014. Postal returns were all processed using data scanning technology to reduce human error.

A link to the online survey was additionally included on SMA Support UK's webpage with a link to it distributed through their social networking pages (Facebook and Twitter). The link was also emailed to all members of the SMA Patient Registry, which holds the details of 538 people diagnosed with SMA and their families, as part of their quarterly newsletter. A reminder was sent out to Patient Registry members in April 2015.

Finally, the survey was advertised through the research project's webpage and through its associated social networking accounts (Facebook and Twitter), and a link was placed on two private Facebook group pages dedicated to supporting people with SMA. This was done in

order to reach people with SMA who might not be affiliates of the support group or Patient Registry.

People were invited to complete the survey if they were over 18 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 (see Table 1 for descriptions). No restrictions were placed on the nature of the familial relationship: step, adopted and fostered family members were included. The definition of 'family member' was kept broad and included non-biological relatives as the social relationship to the person with SMA was considered as important than the biological relatedness of the person in dictating reproductive attitudes [Boardman, 2010]. Furthermore, it was considered important for the analysis to include people with varying degrees of proximity to SMA.

Survey Data Stratification and Statistical Analysis

Responses to each question were stratified as follows: gender (Male 1 v Female 0); age (35-45 1 v other 0); qualifications (degree or above (1) v other (0)); religious (yes (1) v no (0)); do you have children (yes (1) v no (0)); relationship to SMA (patient (1) v family (0)); type of SMA associated with your family (type 0 or type 1(1) v other (0)); living or lived with an SMA patient (yes (1) v no (0)); current health (good or very good (1) v other (0)); current pregnant or trying to get pregnant (yes (1) v no (0)). For all questions regarding screening answers were stratified as either agree/strongly agree (1) or other (0). This was done because it allowed the simplest way of assessing the positive views of respondents.

The attitudes of families and adults with SMA towards pre-conception genetic screening (PCGS) were compared to determine if there were any statistical differences. The following sub-group analyses were performed: All responders were analysed collectively to identify any overriding trends (all responders). Responses from families (all) and adults with SMA (all) were compared to determine if living the disease altered views (NB this analysis included all responders, including the adult living with type IV SMA and the rarer severe forms (SMARD)). Sub-analyses on responders 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 responders; 2) type III-associated responders 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 form 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 Q19g (I would support a pre-conception genetic screen for SMA), Q20i (I would support a prenatal screening programme for SMA). Logistic regression was performed using SPSS v22 (IBM).

Re-interrogation of Qualitative Data: Phase III

After statistical analysis of the survey was completed, the qualitative data was returned to. Data that was coded for the key themes and idea that emerged as significant from the quantitative analysis were explored further within the qualitative data. This technique of returning to qualitative data in an exploratory sequential mixed methods research design is particularly useful in drawing out the nuances, complexities and contradictions in participants' views that might otherwise be missed by use of statistical analysis alone, whilst retaining the generalisability of findings achieved through quantitative methods. For a topic area as complex as screening, this technique proved particularly useful in illuminating and clarifying the key findings of the study. Excerpts from the qualitative data were selected for inclusion in this paper if they particularly eloquently reflected or clarified a key finding.

RESULTS

Cohort Descriptive Characteristics

In total, there were 146 online completions of the survey, and 191 postal returns. Of the 337 participants, 255 were family members of people with SMA (75.7%) and 82 had SMA

themselves (24.3%; ***table III***). Basic descriptive analysis highlighted most participants were female (74.4%); aged between 35-55 years (52%); were not educated to degree level (63.8%); were religious (55%); parents (82%); had lived/were living with someone with SMA (82%) and had experience with SMA types 0, I or II (69.4%) (***table III***). The remainder of the sample (31.6%) were affected by rarer forms of SMA (type IV, Spinal Bulbar Muscular Atrophy, Spinal Muscular Atrophy and Respiratory Distress.) A small sub-set of participants were either pregnant or trying to get pregnant (7.4%) (***table III***).

Pre-Conception Genetic Screening (PCGS)

Overall**,** 77.2% of survey participants were in favour of PCGS, with no statistical differences between families and adults with SMA (SMA families 79.6% v adults with SMA 69.5%; p=0.16) or families and adults associated with type II/III SMA (type II/III families 72% v type II/III adults with SMA 76%, p=0.71; ***table IV***). However, there was statistically more support for PCGS in type I SMA families (88%) compared with type II/III SMA families (72%; p=0.002) and type II families alone (72%; p=0.005) (***table IV***). The lowest level of support was reported amongst adults with type II SMA (63%), which was significantly lower than support amongst adults with type III SMA (94%; p=0.008; ***table IV***).

Interestingly, while the majority of participants agreed that PCGS was important because it would reduce the number of SMA-associated terminations and would raise awareness of SMA in the general population, there were significant differences in the type II associated participants when compared with other sub-groups (***table IV***). For example, fewer type II adults thought PCGS would reduce the number of terminations, when compared to type III adults with

SMA (56% v 80%, respectively; p=0.05; ***table IV***). There was also a significant difference between type I and type II families when assessing if a carrier screen would raise general awareness of the disease (96 % v 80%, respectively; p=0.0005; ***table IV***). Interestingly, no similar disagreements were observed between type I and type III families, suggesting that participants associated with type II have distinct views on screening and the disease, while participants associated with the severe (type 0/I) and mild (types III/IV) ends of the spectrum appear to be in closer agreement.

Comparing families and adults with SMA highlighted that a higher proportion of adults thought carrier screening would result in carrier stigmatisation (42%) compared to family members (17%; p<0.0001; ***table IV***); this difference was seen in all patient v family sub-group analyses performed. In addition, within the families, it was clear that the type II and III family members saw the issue of stigmatisation as a larger problem than the type I families (***table IV***). However, this difference could be explained by the potential long-term exposure to stigmatisation experienced by type II/III families when compared to type I families, whose experience with SMA is comparatively shorter.

A higher proportion of adults with SMA also thought PCGS was a form of social engineering (44%) compared with families (20%; p<0.0001; ***table IV***). This difference was predominantly driven by adults with type II SMA, 56% of whom agreed that PCGS is a form of social engineering (***table IV***). However, it should be noted that in each of the other sub-groups, the majority of participants did not agree that screening will stigmatise or that it is a form of social engineering.

PCGS Drivers: *Why do participants want PCGS?*

Univariate logistic regression analysis confirmed the direct comparison analysis, with all participants and sub-groups in favour of PCGS believing it will reduce the number of SMA-related terminations and increase the awareness of SMA in the general population (***Table VI***). Participants in favour of PCGS, in general, did not agree it will result in stigmatisation or that it is a form of social engineering (***table V***). This is also the case for type II/III associated participants, again highlighting that although there is an increased proportion of these participants who did not overtly support PCGS, the majority do.

Prenatal Genetic Screening

The attitudes of family members and adults with SMA towards prenatal genetic screening (PGS) were compared to determine if there were any statistical differences using the same four sub-group analyses used for PCGS (***table VI***). Overall, 76.3% of participants were in favour of PGS, with no statistical difference between families and adults with SMA (SMA families 78.4% v SMA adults with SMA 69.5%; p=0.25; ***table VI***), or families and adults associated with type II/III SMA (type II/III families 71% v type II/III adults with SMA 67%, p=0.72; ***table VI***). However, as with PCGS, there was a significant differences within family and patient sub-groups: 1) type I families showed a greater level of support (88%) compared to type II (72%) and type III (68%) families; and 2) type II adults with SMA showed lower levels of support (52%) compared to type III adults with SMA (81%), again highlighting the divergent views of the intermediate adults with SMA (***table VI***).

Across the sub-groups, there was agreement that PGS will allow families to make informed decisions and will raise awareness of SMA in the general population. There was a noticeable difference in the sub-group analysis on whether PGS will prevent unnecessary suffering: 1) fewer adults with SMA (43%) agreed with this statement compared with family members (65%; p=0.001; ***table VI***), with type II adults displaying the lowest amount of agreement (22%); and 2) fewer type II and type III families (52% and 59%, respectively) agreed with this statement compared to type I families (79%; ***table VI***).

The SMA Screening Survey (UK) contained two core 'negative' statements: 1) identifying SMA in pregnancy will inevitably lead to less people with SMA coming into the world who could have lived fulfilling lives; and 2) it would be a loss to society to have less people with SMA coming into the world. Comparing responses for the first of these questions, there was no statistical difference between families (51%) and adults with SMA (62%; p=0.18) when analysed collectively (***table VI***). However, there was a difference between type II families (66%) and type I (41%; p=0.0007; ***table VI***), but not type I and type III families (p=0.81; ***table VI***). Conversely, there was a difference between type II and III families (66% v 45%), but this was only approaching significance (p=0.09; ***table VI***). Collectively, this may suggest that type II families have a more positive view on the standard of life that can be achieved by people with SMA, which may account for their comparatively lower support for screening.

When the second question was analysed (it would be a loss to society to have less people SMA coming into the world), there was a clear difference between adults with SMA (39% agreement) and families (24% agreement; p=0.02; ***table VI***). This difference was the only

significant difference identified between the type II/III families (28%) and type II/III adults (45%; p=0.04; ***table VI***), highlighting an interesting dichotomy between how adults with SMA and families see the disease. Interestingly, significantly fewer adults with type III SMA thought this would have a negative impact on society, when compared to type II adults with SMA (26% v 67%; p=0.003; ***table VI***), suggesting type III adults with SMA have a more negative view of the disease and the wider value of people with SMA to society.

Prenatal Genetic Screening: Ability to Type

A lack of clinical evidence that SMA can be typed at diagnosis was identified as a substantial obstacle to SMA screening when set against UK National Screening Committee criteria [Cartwright, 2012]. Therefore, a central question for PGS is whether families and adults with SMA want screening, even if the screen cannot determine the type of SMA. When analysed collectively, there was no significant difference between families (69%) and adults with SMA (63%) who think screening is useful even if type cannot be determined (p=0.64; ***table VI***). However, there was a significant difference between the type II families (60%) and type I SMA families (77%; p=0.01; ***table VI***); this lower level of support for screening without typing was also seen in type II adults with SMA (44%; ***table VI***); suggests that typing is more of an issue for the families and adults associated with type II SMA (***table VI***).

Prenatal Genetic Screening Drivers: W*hy do participants want prenatal screening?*

Univariate logistic regression analysis confirmed the direct comparison analysis, with participants and sub-groups in favour of PGS in generally believing that it will allow informed decisions, will prevent unnecessary suffering and raise awareness of SMA in the general

population (***table VIII***). In addition, all participants in favour of also generally agreed that screening was important, even if the type could not be determined (***table VII***).

Participants in favour of PGS, with the exception of type II/III participants, generally did not agree it will result in fewer adults with SMA being born who could live fulfilling lives, or that this would be a loss to society (***table VII***). It is interesting to note that this highlighted a statistical difference between type II/III families and adults with type II/III SMA (***table VII***) and confirms the difference in how the two groups view the impact on society (***table VI***).

Views on SMA: *Families v Adults with SMA*

Our data suggests interesting differences between adults with SMA and families, as well as between families associated with different SMA types. To analyse this further, we analysed responses to questions designed to tests general views of SMA (***table VIII***). All participants, irrespective of their sub-group, agreed that quality of life varies between SMA types (***table VIII***). However, this was the only question with standardised agreement.

Compared with adults with SMA, more family members thought: 1) SMA causes people to suffer (families 80% v adults with SMA 53%, $p<0.0001$); 2) people with SMA have heightened intelligence (families 61% v adults with SMA 40%, $p<0.0001$); and 3) SMA families and adults are well supported by society (families 29% v adults with SMA 15%, $p=0.02$) (***Table VIII***). Sub-analysis shows the difference in views on whether SMA causes people to suffer between families and adults with SMA was maintained when type II/III families (74%) and type II/III adults with SMA (47%) were compared ($p<0.0001$; ***table VIII***). Interestingly, the analysis confirmed that

type III adults with SMA had a more negative view of the disease than type II adults with SMA: 1) comparatively more adults with type III SMA thought SMA causes people to suffer (65% v 26%; p=0.004; ***table VIII***); and 2) comparatively fewer adults with type III SMA thought people with SMA have heightened intelligence (35% v 74%; 0.004; ***table VIII***).

Qualitative Data

That screening is a complex issue for families that can elucidate variant views amongst affected families was not only reflected in the quantitative data, but also in the 36 qualitative interviews. Upon completion of the quantitative analysis, the qualitative data was returned to in order to better understand the key statistical findings.

Many participants confirmed that the nature of their experience with SMA was critical to determining their attitudes. One participant, Sarah, a parent of an adolescent child with type III SMA commented on this diversity in the following way:

You're always going to get mixed views if you ask families about screening, because it cuts close to the bone really, doesn't it? You won't just hear what people think about screening, what you're also hearing about is how people cope with their SMA, what they've experienced….and of course their views on abortion which is a moral quagmire at the best of times! I think this is particularly true for a condition like SMA, you're always going to get differences of opinion because the condition is so different. We've all got the same condition, but we're fighting our own personal battles a lot of the time.

As Sarah eloquently expressed, views towards screening were inextricably bound up with participants' personal experiences of the condition itself. *'Personal battles'* came to be translated into reproductive attitudes; they formed the basis of how the condition was conceptualised, and consequently views towards screening for it. A key way in which this divergence in the conceptualisation of SMA emerged in the data was within the responses of adults living with Type II SMA. This group emerged from the quantitative analysis as the group least likely to support any form of screening at all, and most likely to actively raise objections to screening, on the grounds of their relatively positive view of the condition. Charlotte is an adult with type II SMA, as well as a parent to a young son. Her views on the condition were typical of other adults with Type II in the sample:

Charlotte: Well, you see, I don't think I support it [screening for SMA] because I don't necessarily view SMA as a bad thing. You know, I keep going back to…you know, I think that variety and diversity is really important in life and […]…it's more important to me, personally, to educate society to remove the barriers that are in place for lots of disabled people because even if SMA wasn't there, there are so many other things that cause disability. And when I was thinking about my own child, yes I didn't want him to have SMA, but not enough to test and [selectively] terminate [an affected foetus], and not enough to not have him because of it.
Interviewer: And why is that?
Charlotte: [pause] Because… I wouldn't change my own condition.

For many adults living with SMA, such as Charlotte, who feel comfortable with their condition and are living full and satisfying lives with access to independent living work and parenthood,

'eradicating' SMA through a screening programme was simply not a priority when set alongside other goals, such as improving support and care for those currently living with SMA. However, this view contrasted with adults affected by Type III SMA, many of whom had different experiences with the condition. Rory is in his early 40s and has Type III SMA. He described his views in the following way:

I support screening really. At the end of the day, SMA is a disease and it robs people of life…and life experiences that they could have had, so if that's preventable for someone, shouldn't that be the case? In my case, I was able to walk at one point- I know how that feels- and now I can't and that's just had massive repercussions in my life, massive, and also in the lives of those around me. I have to rely on others now, whereas I didn't before, and that's massively hard to accept…[…]… It's a bit like a bereavement in some ways, you know? You mourn your old life and everything in it…. So yeah, it's just common sense to me that you would want to stop that happening. I can't understand anyone who would think otherwise.

Whilst Rory's SMA would be medically defined as less severe than Charlotte's (who had been unable to walk since birth), the contrast between their two perspectives on the condition were stark, and this contrast between the views of adults with Type II SMA and Type III was underpinned by the quantitative evidence.

DISCUSSION

This research is the first to systematically report the views of families living with SMA towards population level genetic screening in the UK. Our sample includes a range of severities and sub-types of SMA, as well as affected adults, who have previously been omitted from studies of attitudes towards screening [Wood et al., 2014; Lawton et al., 2015]. The study has demonstrated that the majority of participants (75%) with experience of SMA were in favour of some form of screening programme for the condition, irrespective of the form (pre-conception/prenatal) and irrespective of the potential for mis-typing, in spite of this being a major stumbling block to the implementation a screening programme in the UK in the 2013 review [Cartwright, 2012]. Pre-conception genetic screening fostered slightly more support (77%) than prenatal screening (76%), which echoes the findings of Lawton's Australian study [2015]. Moreover, attitudes to screening were highly correlated with perceptions of quality of life, with those perceiving the lowest SMA-related quality of life most likely to support the introduction of population level genetic screening for the condition than those who perceived high quality of life.

However, while the majority of participants supported SMA screening, a significant minority (25%) did not support either screening programme. This level of non-support appears high when compared to the findings of similar studies such as that by Maxwell et al. [2011] who reported high support for both prenatal and pre-conception genetic screening amongst family members and adults living with Cystic Fibrosis in Australia.

Ambivalence towards SMA screening in this population may in part stem from the wide spectrum of severities associated with the condition, the different ways in which participants came to know SMA (either through a family member, or having it themselves) and the diversity of experiences with the condition emerging from these standpoints. Indeed, there were marked differences between the views of adults with SMA and family members. These differences emerged in the way quality of life with the condition was perceived and rated (adults with SMA consistently rated quality of life with SMA above that of family members), but also in terms of screening support, with more family members supporting screening than affected adults. Differences in quality of life perceptions between disabled people and their family members have been widely reported elsewhere in the literature, with disabled people consistently rating their quality of life as higher than their family members' evaluations of it [Albrecht & Devlieger,1999; Young and McNicoll, 1998]. However, sub-analysis of Type II/III families v adults with SMA highlighted that the majority of these differences were determined by the severity of the disease they are associated with. While Type I associated families have wide-reaching support for screening- presumably because their experience with SMA is negative in the extreme- participants associated with milder forms of the disease have comparatively lower levels of support.

It is noteworthy that adults living with Type II SMA were the group least likely to support any form of screening and the most likely to actively oppose it. Whilst it is perhaps unsurprising that adults with SMA who are living happy and fulfilled lives would be less likely to support screening than family members living with Types 0/I SMA (who usually had experienced the death of their child at a very young age), this finding remained true even when compared to adults diagnosed with the (clinically) milder form of the disease, Type III. As highlighted by both the

quantitative and qualitative data (Rory), those affected by Type III SMA perceived more suffering around the experience of SMA, and as such were more likely to want screening for it. Shakespeare [2006] has noted that the perspectives of people who lives are affected by a static impairment (such as those with Type II SMA) are often very different to those whose impairments are degenerative (Types III and IV SMA) or associated with pain and/or premature death (Types 0/I SMA). Whilst people affected by relatively static impairments from birth are often 'well adjusted' to their condition, identify with it and organise their lives around it, people who experience periods of rapid and/or severe decline must go through continual cycles of crisis and then re-adjustment to an ever-changing reality [Shakespeare, 2006: 106-7]. As exemplified by Rory's account, many participants with late childhood or adult-onset types of SMA (Type III, SBMA) reported a sense of loss and grief as their muscle strength deteriorated over time. Similarly, for parents whose child is diagnosed with Type I SMA, this experience can be described as akin to a continual process of 'biographical disruption' [Bury,1982] followed by 'biographical repair', whereby the parents transition from that of parent to a 'healthy' child to parents of a child 'in crisis'[Young et al., 2002] . Conversely, for adults living with Type II SMA like Charlotte, the social, cultural and physical landscape of their everyday lives was often demarcated as the most significant mediator of the quality of their lives, rendering screening largely irrelevant. These contrasting experiential realities of life with the condition fed into the ways that quality of life with SMA was perceived, and ultimately how far screening for it was supported.

This study, by focusing on the views of affected families, has highlighted that while the majority of respondents generally want some form of screening for SMA (irrespective of the ability of the screen to determine type of SMA), experiences with the condition were critical in

determining attitudes. Indeed, it appeared to be the *nature* of that experience with SMA (i.e. whether it is of bereavement, deteriorating symptoms or of a fixed impairment), more so than a person's relationship to that experience (i.e. whether they have the condition, or someone else in their family does) that modifies attitudes.

This study underscores the need to include both affected adults and affected family members in debates around screening for SMA, as well as in debates around screening for similarly variable genetic disorders for which screening could soon be offered. Understanding the value and significance of prior experiences with the disease in formulating reproductive attitudes and decisions is highly relevant to anticipating the social and ethical ramifications of such genetic screening and highlights the need to interrogate patients' previous experiences with disability in the context of any population level genetic screening programmes.

Further research is indicated to explore how such attitudes might vary across families living with different types of genetic condition, particularly those with contrasting features to SMA (e.g. cognitive/behavioural symptoms, conditions associated with pain and treatable conditions), to further explore how experience with different types of condition impacts on reproductive screening attitudes.

LIMITATIONS

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.

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