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ORIGINAL ARTICLE

# Parent perceptions, beliefs, and fears around genetic treatments and cures for children with Angelman syndrome

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## Abstract

Genetic therapies have shown recent promise in alleviating some of the cognitive issues associated with some genetic disorders; however, these therapies may come with significant health and socio-ethical concerns, particularly when they involve child participants. Little is known about what parents of children with genetic disorders think about genetic therapies, or about their knowledge of how genetic-based therapy might treat their child's symptoms. Forty-two parents of children with Angelman syndrome (AS) and 27 parents of a mixed etiology comparison group completed an online survey reporting on their perceptions of, and priorities for, genetic therapy. Almost all parents of children with AS (95%) and the comparison group (89%) agreed that treatments aiming to reduce symptoms associated with their child's syndrome were positive. However, significantly more parents of children with AS (95%) than the comparison group (56%) felt that genetic treatment trials aiming to "cure" their child should be a research priority. AS parent priorities for the focus of clinical trials were neurology/seizures, communication skills, and motor skills/mobility. For the comparison group, the priorities were IQ, immune response, and expressive speech. Parents of both groups did not want treatments to change their child's personality or their happiness. Global assumptions cannot be made about targets for therapy between syndromes, about parental understanding of genetics, or about research evidence across syndromes. This study highlights the need for true family and patient engagement in all stages of the research design and treatment evaluation.

KEYWORDS

genetic, intervention, parent, priorities, syndrome, treatment

## 1 | INTRODUCTION

Angelman syndrome (AS) is a genetic disorder with an estimated prevalence of 1/12,000–24,000 live births. It is caused by a loss of function of the maternal copy of the *UBE3A* gene (Knoll et al., 1989; Mertz et al., 2013) which can occur through several genetic mechanisms including deletion, *UBE3A* gene mutation, imprinting defects, or uniparental disomy (Williams et al., 2006). AS is characterized by physical, cognitive, and behavioral phenotypes, with suggestions that some of these may change with age (Adams, Horsler, & Oliver, 2011; Adams, Horsler, Mount, & Oliver, 2015). Key characteristics of these phenotypes include severe to profound intellectual disability, significant impairment in expressive language skills compared to receptive communication skills, epilepsy, ataxic "puppet like" gait, and a happy demeanor with frequent smiling and laughter (Horsler & Oliver, 2006).

The rapid growth in genomic medicine has led to advances in potential treatments for several rare syndromes associated with intellectual and developmental disabilities. The advancement of genetic therapy specifically for AS has progressed to the point where, in one mouse-based trial, the normally silenced paternal copy of the *UBE3A* gene was unsilenced using anti-sense oligonucleotides, resulting in the amelioration of some of the cognitive deficits associated with AS

  

in the mice (Meng et al., 2015). Research using mice models of AS have identified time frames where specific skills can be rescued (Rotaru, van Wooerden, Wallaard, & Elgersma, 2018; Silva-Santos et al., 2015). At the time of writing, it is not possible to definitively answer the question of when in a person's life treatment should be instigated for maximum benefit. It might be assumed that it should occur during childhood; however, this of course brings additional ethical issues.

There is very little literature documenting family members' thoughts and feelings about the option of genetic therapeutic options for their child with a rare genetic syndrome, and at present, there are no papers relating to parents of children with AS. This is surprising as the beliefs and attitudes towards genetic therapies for children with rare genetic syndromes, particularly socio-ethical concerns and specific outcome goals of parents for their children, should ideally be considered as one critical part of the advancement of such technologies. The majority of literature focusing upon parental beliefs regarding genetics in intellectual and developmental disabilities tends to focus upon the impact of the diagnosis itself (e.g., Goodwin et al., 2015), upon genetic screening (Skinner, Sparkman, & Bailey, 2003), or upon parents' beliefs and attitudes in other neurodevelopmental disorders, such as autism spectrum disorders (ASD; see review by Xu, Talwar, Richman, & Forster, 2015). Fewer studies evaluating families' thoughts and feelings about genetic therapeutic options for their children with rare genetic syndromes are available and those that are have focused upon two of the more common syndromes—Down syndrome (DS) and Fragile-X syndrome (FXS)—with few comparison studies conducted across genetic syndromes. Comparisons between syndromes, or at least to a mixed comparison group, are important when considering whether the reported beliefs and priorities are syndrome specific, or related to treatments for any syndrome with a genetic cause.

Inglis, Lohn, Austin, and Hippman (2014) evaluated the views of 101 Canadian parents of children with DS. Results showed the majority (61%) viewed the possibility of reversing the intellectual disability in DS positively, but only 41% said that they would "cure" their child of DS if it were possible. The most commonly cited motivation for opting for a "cure" was to increase their child's independence. However, parental attitudes towards a "cure" for DS were complex, affected by ethical issues, perceived societal values, and pragmatic factors such as the age of the individual and long-term care-giving burden. This complex relationship highlights the importance of future explorations using approaches that both collate basic data as well as allow for open responses to explore the beliefs, hopes, and fears of parents in more depth.

D'Amanda, Peay, Wheeler, Turbitt, and Biesecker (2019) interviewed parents of children with FXS ($n$ = 16) who had given or declined consent for their child to be in a therapeutic drug trial ($n$ = 15). Parents who included their children within drug trials felt that the trial would have a positive impact upon the disease mechanism of FXS, would directly target and benefit specific characteristics of their child, and was positive for the FXS community. Decliners reported that drug trials had to specifically target the behavioral priority for their child and be convenient for them to attend. Overall, this study indicated that parents of children with FXS were more likely to decline drug trial participation due to adverse drug side-effects that might compromise the physical health of their child.

Reines et al. (2017) compared interview findings of parents of children with FXS ($n$ = 9) and DS ($n$ = 15) to identify factors when deciding to enroll their child in a clinical drug trial, drawing on the parents' perceptions, knowledge, and experiences of drug trials. All the parents of children with FXS held positive beliefs about drug trials, with many identifying a positive in that these trials were targeting the core genetic mechanism of FXS, not just the symptoms. Overall, parents wanted to see an improvement in their child's health ($n$ = 13) or held an altruistic motive to see the improvement in knowledge and health for all affected by FXS ($n$ = 5), with four parents motivated by both. Of 18 parents who held concerns about drug trial participation, 15 were concerned by long-term use and adverse side effects. Parents of children with DS reported mixed results in their beliefs of drug trials, with the change in their child's personality being a common concern. Overall, there was an expressed need for parents to obtain further knowledge about clinical trials, with many participants demonstrating a misunderstanding of the way placebo-controlled trials are run and what the expected outcomes might involve (Reines et al., 2017). The notable differences between the FXS and DS cohorts highlight the need for syndrome-specific exploration of parents' thoughts and beliefs towards genetic treatment trials.

A consistent finding across these three qualitative studies is that parents want to make carefully considered decisions around treatment options for their children. For this to occur, the process, treatments, procedures, and outcomes must be carefully described and explored with parents (D'Amanda et al., 2019; Inglis et al., 2014; Wagner et al., 2019). Positive attitudes towards treatments were associated with parents wanting to cure the perceived difficulties associated with their child's syndrome (such as intellectual disability, health conditions, or anxiety) and to improve the health and quality of life for their child (Inglis et al., 2014) and with being willing to participate in clinical trials (D'Amanda et al., 2019; Reines et al., 2017). Although parents were motivated to reduce their child's difficulties, parents did not want to risk changing their child's personality or strengths (Inglis et al., 2014; Reines et al., 2017).

Based upon the previous findings of syndrome-specific beliefs and attitudes towards genetic treatments, this study will begin to explore AS-specific and more broadly held beliefs around genetic treatments and cures for syndromes. Responses from parents of children with AS will be contrasted against a mixed etiology comparison group in order to identify syndrome-specific perspectives for AS, as well as perspectives which are more broadly held by parents of children with rare genetic syndromes. Comparison groups involving participants with mixed aetiologies are commonplace in syndrome research (e.g., Arron, Oliver, Moss, Berg, & Burbridge, 2011; Didden, Korzilius, Ducker, & Curfs, 2004; Most, Fidler, Laforce-Booth, & Kelly, 2006).

This study aimed to (a) explore the perceptions of parents of children with AS and a mixed etiology comparison group around genetic therapies that could treat or potentially "cure" their child of their syndrome; (b) explore possible factors that may influence these views, including child, social, and parental factors; and (c) explore the

perceptions, hopes, and fears of parents of children with AS and a mixed etiology comparison group towards genetic treatments, and the views across the groups on the process of engaging in trials and documenting outcomes.

## 2 | METHODS

### 2.1 | Participants

Parents of children with AS and those with other rare genetic syndromes (that formed the mixed etiology group) were invited to take part in an online survey via advertisements shared on parent support group social media pages and networks. For reasons of confidendiality and practicality, this study is able to report only on those who saw the advertisement and completed the survey and cannot comment on or compare to parents who may have seen the advertisement and not completed the survey. In order to include a diverse group of participants, there were no limitations on the age or ability of the child.

A total of 69 parents completed the survey; these included 42 parents of children with AS and 27 parents (including nine parents of individuals with Cri-du-chat syndrome, two with Cornelia de Lange syndrome, one parent each with a child with Prader-Willi syndrome, Sotos syndrome, Tuberous sclerosis complex, Kleefstra syndrome, Williams syndrome, Pitt-Hopkins syndrome, Noonan syndrome, and Jacobsen syndrome, and eight parents noting other specific genetic mutations, deletions, or duplications) who formed the mixed etiology comparison group (hereafter to be referred to as the comparison group). Participant and child demographics are presented in Table 1. The sample was predominantly parents of younger children (total sample 39% under the age of 5), but the groups did not significantly differ in their age ($t[67] = 1.25$, $p = .22$).

**TABLE 1** Demographics of caregivers and children in the AS and mixed etiology comparison group

| Parents | AS *N* = 42 | Comparison group *N* = 27 |
|---|---|---|
| Gender | | |
| Female | 36 (86%) | 26 (96%) |
| Male | 6 (14%) | 1 (4%) |
| Relationship | | |
| Mother | 35 (83%) | 26 (96%) |
| Father | 5 (12%) | 1 (4%) |
| Other | 2 (5%) | 0 |
| Country of residence | | |
| Australia | 18 (43%) | 25 (93%) |
| Other | 24 (57%) | 2 (7%) |
| Education level | | |
| Primary school | 1 (2%) | 0 |
| Secondary school | 4 (9%) | 2 (7%) |
| Post-secondary school | 12 (29%) | 11 (41%) |
| University | 25 (60%) | 14 (52%) |
| Salary (AU$) | | |
| <$20,000 | 5 (12%) | 2 (7%) |
| $20,001–60,000 | 9 (21%) | 5 (18%) |
| $60,001–110,000 | 12 (29%) | 9 (33%) |
| $110,000+ | 12 (29%) | 10 (37%) |
| Did not disclose | 4 (9%) | 1 (3%) |
| **Children** | **AS *N* = 42** | **Comparison group *N* = 27** |
| Gender | | |
| Female | 20 (48%) | 12 (44%) |
| Male | 22 (52%) | 15 (56%) |
| Current age | | |
| Under 5 years | 13 (31%) | 14 (52%) |
| 5–10 years | 12 (29%) | 4 (15%) |
| 10–15 years | 6 (14%) | 4 (15%) |
| 15 years + | 11 (26%) | 5 (18%) |

### 2.2 | Procedure

This study was approved by Children's Health Queensland Human Research Ethics Committee. Once the parents clicked the link to get through to the survey, they were presented with the information sheet and consent form. Once consent was provided, parents began the questionnaire, which they could pause and restart at any point.

### 2.3 | Survey

The online survey comprised a multiple choice with Likert scale ratings, and short-answer questions covering three general topics: (a) demographic information about the child and the family (including the age, gender, and diagnosis of child, relationship to child in care, the type of genetic mutation involved in their child's syndrome, level of schooling, and salary information); (b) views on clinical trials (including beliefs about the importance of clinical trials, perspectives on reducing their child's symptoms and finding a cure, the trial stage at which they would consent for their child to participate and their confidence in their knowledge of their child's syndrome, the genetic causes associated with their child's syndrome, the ways that genetic therapy aims to treat their child's syndrome, the way that medications acting on gene pathways aim to treat their child's syndrome, the way that clinical trials of new medicines are conducted, the ways in which they can find out about new treatments or genetic therapies, and the ways in which they are able to access the evidence about new treatments or genetic therapies); and (c) open questions asking parents to identify their top three priorities for the focus of genetic treatments as well as the three things they would not want genetic treatments to change.

To ensure that parents were aware of what was meant by terminology in the questionnaire (clinical trials of gene therapy), they were told that these terms were used to describe “interventions involving

gene therapy (which changes the gene function, for example, switching the gene on or off) and also specific medications which interact with the pathway associated with the gene involved with your child's syndrome or condition". Example questions are provided in Table S1 of the supplementary appendix material and a copy of the online survey is available by emailing the lead author.

### 2.4 | Data analysis

Closed questions resulting in quantitative data were analyzed using SPSS. As these data were nominal or ordinal, non-parametric analyses (Chi-square for nominal data and Mann–Whitney *U* for ordinal data) were used to compare responses from the AS group to the comparison group.

Open-ended questions resulting in qualitative data were coded by the lead author using content analysis. The steps of Dey (1993) were followed, which were (a) divide the data into manageable parts, (b) collect responses together that relate to the areas or questions of interest, (c) create categories that describe similar responses within these general groupings, and (d) combine or split categories where data can best be described in a rearranged structure. As per previous research using this approach with parent data (e.g., Adams, Young, Simpson & Keen, 2019), categories which had <5% responses within them were subsumed into a new combined category, where possible and logical (e.g., if anxiety had 10% and depression had 4%, a new category of "mental health" could be made from the combined responses). Due to having fewer than 50 participants per group, percentages in the text and tables are presented as integers.

## 3 | RESULTS

### 3.1 | Parent's perceptions of genetic treatment trials for their child's syndrome

Almost all parents of children with AS (95%) and the mixed comparison group (89%) reported that clinical trials aiming to reduce symptoms associated with their child's syndrome were positive. However, significantly more parents of children with AS (95%) compared to the mixed comparison group (56%) felt that genetic treatment trials aiming to find a "cure" should be a priority within their child's syndromes ($\chi^2(2) = 17.2$, $p < .001$) and that they would want to "cure" their child's syndrome if possible ($\chi^2(2) = 16.3$, $p < .001$).

### 3.2 | Knowledge about genetics mechanisms associated with their child's syndromes and genetic therapies

Parents rated how confident they are in their understanding for each area on a Likert scale ranging from *Not at all* to *To a very great extent*. The results are shown in Figure 1. Although there was no significant

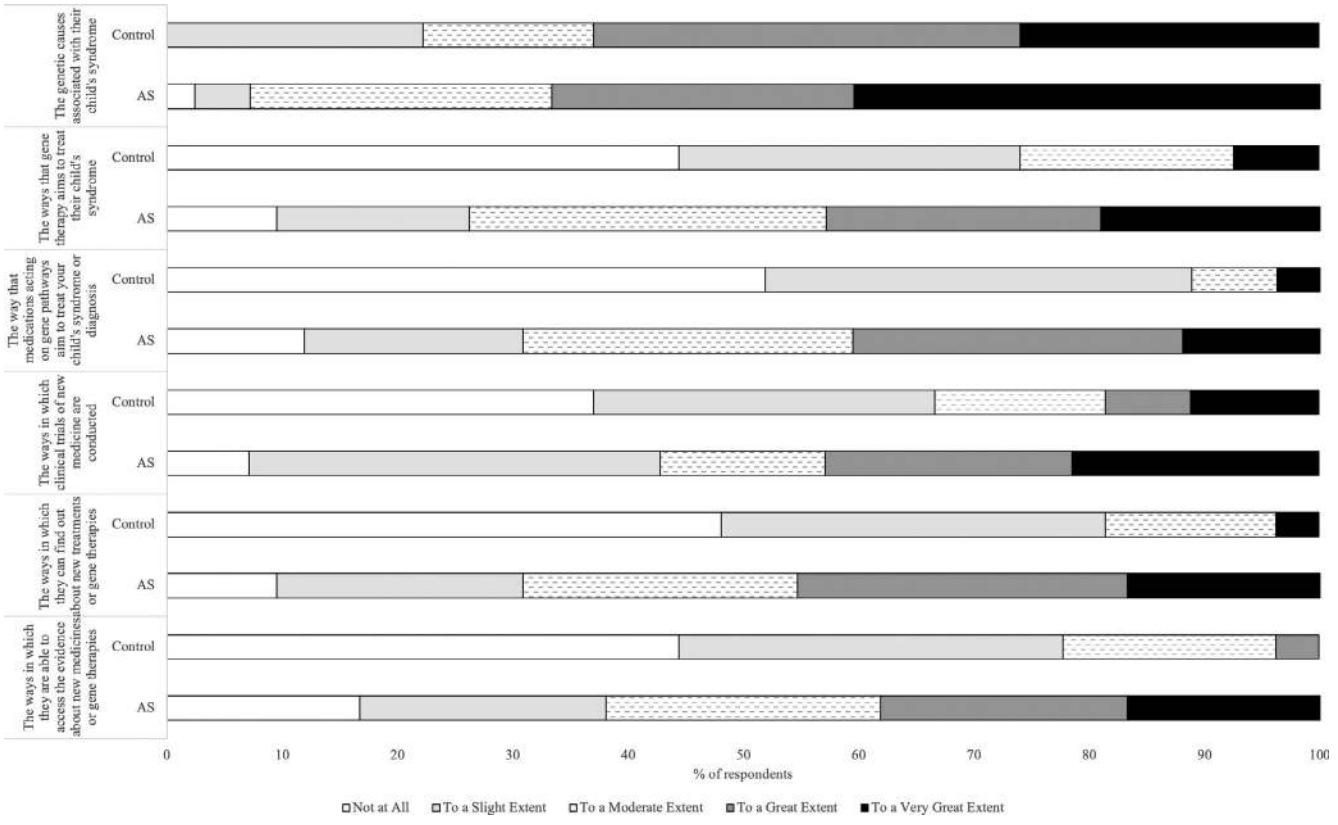


**FIGURE 1** Parent rated levels of confidence in their knowledge of areas relating to clinical trials and genetic treatments for their child's syndrome

difference between the groups on the parent ratings of confidence in their understanding of the genetic causes of their child's syndrome ($U$ = 475.5, $p$ = .24), the AS group had significantly higher confidence ratings in their understanding of the ways in which genetic therapy aims to treat their child's syndrome ($U$ = 247.5, $p$ < .001), the way in which medications acting on gene pathways aim to treat their child's syndrome ($U$ = 202.5, $p$ < .001), the way in which clinical trials of new medicines are conducted ($U$ = 352.5, $p$ < .001), the ways in which they can find out about new treatments or genetic therapies ($U$ = 213.0, $p$ < .001), and the ways in which they are able to access the evidence about new treatments or genetic therapies ($U$ = 281.0, $p$ < .001).

### 3.3 | Stage at which parents would participate in clinical trials of genetic treatments for their child's syndrome

Parents were asked at what stage they would be willing to participate in genetic treatment trials that were targeted at their child's syndrome. No significant differences were identified in the ratings between the two groups ($U$ = 501, $p$ = .389). Almost half (48%) of the parents of children with AS and 41% of the comparison group stated that they would participate in a trial if the treatment had been trialed in mice but not humans and a little over a quarter (26% of AS and 26% of the control group) would participate if the treatment had been trialed in humans but not those with their child's syndrome. Eight (19%) parents of children with AS and four (15%) of the comparison group would participate if the treatment had been trialed in humans with their child's syndrome but the treatment was still in the trial stages. A small percentage (5% of AS and 7% of the comparison group) said that they would wait until the treatment was licensed and 2% of parents of children with AS and 11% parents in the comparison group said that they would not want to consider genetic treatments for their child.

### 3.4 | Parent identified areas for focus of clinical trials

Parents were asked to identify up to three areas upon which they feel clinical trials should focus and three things that they would not want changed through treatment. Parents responded to this question with open text; multiple-choice answers were not used as the researchers did not want to predict or influence the answers. This question purposefully asked a broad question about clinical trials so as to (a) allow comments from parents who did not support or wish to consider genetic treatment trials, and (b) allow parents to identify priority treatment areas that do not necessarily require genetic treatment if these were important to them. The areas identified by parents are summarized in Tables 2 and 3. Although parents were invited to list up to three areas, not all parents provided three different responses for each question.

**TABLE 2** Parent identified priorities for clinical trials to focus upon (sorted from most to least frequent for AS parents)

| | *N* (%) of parents identifying this as priority | |
|---|---|---|
| **Priority identified** | **AS (*N* = 42)** | **Comparison group (*N* = 27)** |
| Neurology/seizures/epilepsy | 22 (52%) | 5 (19%) |
| Communication skills | 17 (41%) | 1 (4%) |
| Motor skills/mobility | 17 (41%) | 4 (15%) |
| IQ/cognitive function | 14 (33%) | 11 (41%) |
| Expressive speech | 15 (33%) | 6 (22%) |
| Sleep | 9 (21%) | 2 (7%) |
| Behavior | 8 (19%) | 5 (19%) |
| Anxiety and mental health | 3 (7%) | 1 (4%) |
| Attention/concentration/ impulsiveness | 3 (7%) | 4 (15%) |
| Physical development | 2 (5%) | 2 (7%) |
| Sensory difficulties | 1 (2%) | 2 (7%) |
| Gut health | 0 (0%) | 3 (11%) |
| Immune response | 0 (0%) | 6 (22%) |
| Social skills | 0 (0%) | 2 (7%) |

**TABLE 3** Areas that parents stated they do not want clinical trials to change in their child (sorted from most to least frequent for AS parents)

| | *N* (%) of parents identifying this as an area that should not change | |
|---|---|---|
| **Area identified** | **AS (*N* = 42)** | **Comparison group (*N* = 27)** |
| Happiness | 21 (50%) | 6 (22%) |
| Personality | 16 (38%) | 9 (33%) |
| Nothing/cannot think of anything that should not be changed | 5 (12%) | 10 (37%) |
| Physical appearance | 4 (10%) | 1 (4%) |
| Love for specific activities | 3 (7%) | 1 (4%) |
| Cognitive skills, IQ, or ability | 2 (5%) | 2 (7%) |
| Sociability or social skills | 1 (2%) | 3 (11%) |

As noted in Table 2, parents of children with AS identified priorities which were coded into 11 categories and parents of children in the comparison group identified priorities which were coded into 14 categories. The most commonly identified priorities for clinical trials in AS were neurology/seizures/epilepsy (identified by 52% of parents), communication skills (41%), and motor skills or mobility (41%). In contrast, the comparison group identified priorities in IQ/cognitive function (41%), expressive speech (22%), and immune response (22%).

When parents were asked about areas that they do not want clinical trials to change, responses were coded into seven categories across both groups. The three most identified areas for the AS participants were happiness (50%), personality (38%), and nothing (12%). For

the comparison group, the area identified by the highest number of parents was nothing (37%), followed by personality (33%) and their child's level of happiness (22%).

## 4 | DISCUSSION

This is the first study to explore parental beliefs, priorities, and concerns regarding genetic therapies and treatment trials for individuals with AS, compared to a comparison group of mixed genetic disorders. Almost all parents of children in the AS group (95%) and the mixed comparison group (89%) reported that clinical trials aiming to reduce the symptoms associated with their child's syndrome were a good thing and 95% of parents of children with AS and 56% of parents in the comparison group would "cure" their child if possible. This highlights an important finding, in that although some parents (particularly those in the comparison group) support clinical trials to reduce symptoms, they do not necessarily wish to "cure" their child's syndrome (i.e., they may just wish to reduce the symptoms associated with it). The results also show that parents report a range of levels of confidence around the genetics of syndromes and mechanisms of treatment trials, but also a range of priorities for treatments areas. In general, there were several differences in the perceptions of parents with AS compared to the mixed comparison groups, particularly in confidence in knowledge around genetic therapy mechanisms and the focus of genetic therapies. However, the two groups shared some similar features; for example, parents of children with AS and the mixed comparison group reported that genetic therapy should not change their child's personality or interfere with their levels of happiness. The reasons for the similarities and differences between the groups would benefit from being explored further with qualitative approaches and highlight the importance of considering the etiology of intellectual disability when considering and planning treatments and interventions (Oliver, Woodcock, & Adams, 2010).

Gene treatment research has been discussed for decades in other areas, including that of Cystic Fibrosis (CF). Similar to the results seen within this study, many parents of children with CF report having limited knowledge about the genetic mechanism behind their child's diagnosis and/or the genetic therapy options available (Chapman & Bilton, 2004). This is entirely understandable in CF, AS, and other rare genetic syndromes, as it is likely that the parenting focus has been on understanding what the syndrome or diagnosis means for their child in real life, rather than on trying to explain the genetic pathway for each manifestation. Genetic counseling is often offered around the time of diagnosis, but despite rapid evolvement of the knowledge around causes and genetic mechanisms of rare genetic syndromes, such services may be harder to access later in life in some (but not all) countries; for example, research highlights that professionals in the United Kingdom feel less confident in the process of referring adults than of referring children for genetic testing and/or counseling (Wolfe et al., 2018).

The role of the Internet and specifically online parent support groups in helping parents to feel more informed about research, trials, and treatments warrants discussion, especially due to the recruitment method within this study. Parents of children with neurodevelopmental disabilities most frequently access information about treatments and research through the Internet (Nicholl, Tracey, Begley, King, & Lynch, 2017; Reichow et al., 2012) and through other parents. Parents do not report evaluating the scientific validity of information from other parents, with some parents noting that they based their ratings on the reputation or sound of the descriptive treatment title rather than their perception of actual efficacy or strength of evidence (Deyro, Simon, & Guay, 2016). This places parent support groups in a potentially powerful position to be able to inform and support parents, especially about some of the more complex issues around genetic mechanisms, syndrome-specific genetic therapies, and the genetic mechanism of treatment. The AS community has several very active online parent support groups and organizations, including the Foundation for Angelman Syndrome Therapeutics [FAST] ones which state their focus is on "*treatments that will improve the symptoms of Angelman syndrome and ultimately research that will provide a cure*" and the Angelman Syndrome Foundation [ASF] which says in their mission that they exist to give individuals with AS, their families and other concerned parties "*a reason to smile, with the ultimate goal of finding a cure*". The finding that the AS group reported significantly higher confidence ratings than the comparison group for their knowledge around genetic therapies and treatment mechanisms may therefore reflect some of the work of these parent-led organizations. However, it may also reflect the stage at which clinical trials are at in AS compared to other genetic syndromes, and/or that some genetic mechanisms targeted by specific treatments may be more complex and difficult to understand compared to others.

What is not known is whether parents in the AS group feel more confident because they have had (or perceive they have had) the opportunity to access information in the area (regardless of their level of comprehension of the area), or because they have a good comprehension of the area from the knowledge they have acquired; the drivers behind the reported confidence levels could be explored in future research. Although many parents of children with AS reported feeling confident about their knowledge of genetic therapies, it is important to be aware that a notable proportion of parents of children with AS and a large proportion of the parents in the comparison group report that they do not feel confident, or feel only slightly confident, in their knowledge. This highlights that there is still an important opportunity to provide services and/or develop resources which can help parents to understand these aspects at a time when they are ready to ask that question and understand the answer.

A notable proportion of parents reported no or only slight confidence in the ways in which they can access the evidence about new medicines or genetic therapies. Parental access to the evidence base of interventions has been extensively researched in parents of children with autism but has received less attention in other neurodevelopmental disabilities. Parents of children with autism acknowledge the importance of evidence-based treatments but rely upon professionals to identify evidence-based treatment options for them and admit to prioritizing professionals who appear to be more

engaged with their child over those who prioritize more evidence-based treatments (Trembath, Paynter, Keen, & Ecker, 2015). However, professionals report feeling challenged by the high level of misinformation around the effectiveness of interventions and research evidence suggests that health professionals themselves sometimes hold inaccurate knowledge of the evidence base around interventions and treatments and, specifically relevant to this study, generally lack confidence in their knowledge of genetics (Baars, Henneman, & ten Kate, 2005; Mikat-Stevens, Larson, & Tarini, 2015). When combined with the results of this study, this highlights the need for more work to explore the factors which impact parental treatment decision in rare genetic syndromes and whether this is similar or different for genetic therapies than for psychological and/or allied health professional focussed interventions. For trials of genetic therapies, information pertaining to the genetic mechanism and trial evidence may be complex and difficult to understand. It is therefore imperative that parents are well informed when deciding whether to have their child participate in a genetic therapy by well-informed health practitioners (D'Amanda et al., 2019; Inglis et al., 2014; Mikat-Stevens et al., 2015) and that they are provided with accurate information about the potential benefits and consequences in a way that is genuinely understandable for a lay audience (Johannessen et al., 2016).

A key feature of these results is that parents identified priority treatment areas for their children with AS, with the top three areas for AS (neurology/seizures/epilepsy, communication skills, and motor skills) all aligning with the behavioral phenotype (Horsler & Oliver, 2006). Interestingly, parents with AS rated neurology/seizures/epilepsy, communication skills, and motor skills/mobility as the top three priorities for genetic therapy trials to focus on; despite recent research documenting high rates of sensory difficulties (Heald, Adams, & Oliver, 2020) and anxiety problems in AS (Wheeler et al., 2019), these were not highly rated by parents. Critically, this study also highlighted the characteristics that parents did not wish to be changed. Specifically, for the AS group, their child's happiness and personality as areas they did not wish to be changed; the finding was similar from the parents of the comparison group and in line with parent reports from other syndrome groups (Inglis et al., 2014; Reines et al., 2017) who stated the importance of not changing their child's personality or their strengths. The way in which a treatment may change the personality may be difficult, if not impossible, to predict until it is trialed in humans or the individual. Personalities are influenced by a complex interaction between genetics, biology, physical, cognitive, and behavioral phenotypic expression, and the lived environment within which they reside. The complexity of the interactions of all of these levels (described in the causal model of the behavioral phenotype of AS by Oliver et al., 2013) may make it difficult to determinewhat, if any, impact a gene therapy may have on the unique elements of human personalities. It may also be very difficult for this to be understood or translatable from mouse models. Therefore, personality changes should be carefully monitored and measured within early human studies and, if present, should be carefully explained to parents considering the treatment for their child.

### 4.1 | Limitations and future directions

This study evaluated a small sample size of parents with children of AS and a smaller comparison group of mixed genetic syndromes, thus limiting the external validity of the results whereby these conclusions may not be widely representative of parents with children with a range of genetic syndromes. It is possible that responders felt more strongly about supporting genetic therapy trials than non-responders and thus biased the results. The small sample size also limited the ability to explore perspectives and priorities of parents by the age of the child, which may be particularly important given the changes noted across multiple domains with age in individuals with AS (e.g., Adams et al., 2011, 2015; Prasad, Grocott, Parkin, Larson, & Thibert, 2018; Sadhwani et al., 2019; Wheeler et al., 2019) and should therefore be included in future studies with larger samples. There is a need to ensure that priority-setting studies listen to a range of voices, even within one syndrome. This would require a larger scale priority-setting study that recruits parents from a range of sources (not just through online methods) and that therefore may recruit parents representing a more diverse group, all of whom can voice their experiences and priorities for their child. Such studies should have multiple coders to ensure inter-coder reliability, which was a limitation in the current study procedure. Parent priorities in this field are crucial for the progression of treatments and for ensuring that future trials and treatments are targeting behaviors of concern, resulting in meaningful changes in the lives of children with genetic syndromes and their families.

Further study needs to be undertaken to explore parental priorities using methodologies which allow for clarification and questions. For example, within this study, the most frequently endorsed priority for treatment trials listed by parents of children with AS (neurology/seizures/epilepsy) was identified by a little over half of parents, yet epilepsy and seizures are present in more than 80% of individuals with AS, usually involving multiple seizure types, starting in early childhood and often requiring complex and multi-pharmacological treatment regimens (Bakke et al., 2018; Thibert et al., 2009). What cannot be inferred from the priority listing is whether the (assumed) 30% of parents whose children experienced seizures but who did not list this as a priority were those whose children were responding well to epilepsy medication (therefore epilepsy was not a significant concern) or were those whose children still experienced epilepsy but whose parents felt that other areas should be priorities for treatment. As this was initial exploratory work, parents were not asked about specific types of therapies which may differ in the method and/or frequency of administration. Future study should therefore explore parent perspectives of the different therapeutic options in more detail and should fully evaluate and validate the parent questionnaires used to gather such data. To ensure that future trials and technologies are progressing in a socio-ethical way, it is imperative that those developing treatments are aware of parent priorities to ensure the drug targets are meeting the needs of those for whom they are being developed. Finally, in conducting this research we did not ascertain each parent's baseline level of genetic/medical trial education or prior knowledge, nor did

we ascertain their history of enrolling or participating in prior genetic therapy trials.

## 4.2 | Conclusions

The decision to enroll a child into a clinical trial requires serious deliberation from consenting parents. These are significant decisions that can impact upon their child's health, wellbeing, and the wellbeing of their family. Here, we show that the range of reported levels of understanding around genetics, genetic therapies, and research trials is variable across parents with children with a variety of genetic syndromes and that it highlights the importance of not assuming knowledge but allowing time to explore each parent's understanding as well as their priorities and concerns before they make important decisions. The purpose, procedures, and expected outcomes of the trials need to be clearly explained and explored with parents for future trials to adhere to socio-ethical concerns, and to develop in a socially responsible way.

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### CONFLICT OF INTEREST

The authors declare no conflicts of interest.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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