EVALUATING THE RISKS AND BENEFITS OF GENETIC AND PHARMACOLOGIC INTERVENTIONS FOR DOWN SYNDROME: VIEWS OF PARENTS

Kirsten A. Riggan, MA, MS[1], Christina Nyquist, BA[1], Marsha Michie, PhD,[2] and Megan Allyse, PhD[1]
[1]Biomedical Ethics Research Program, Mayo Clinic, Rochester, MN; [2]Department of Bioethics, Case Western Reserve University, Cleveland, OH

§ Corresponding Author:
Megan Allyse, PhD
Allyse.megan@mayo.edu
Mayo Clinic
Biomedical Ethics Research Program
200 First St. SW
Rochester, MN 55905 USA

Kirsten A. Riggan, MA, MS, Biomedical Ethics Research Program, Mayo Clinic, Rochester, MN, 55905, USA

Christina Nyquist, BA, Biomedical Ethics Research Program, Mayo Clinic, Rochester, MN, 55905, USA

Marsha Michie, PhD, Department of Bioethics, Case Western Reserve University, Cleveland, OH, 44106, USA

Acknowledgements

Content from this poster was presented at the American College of Medical Genetics and Genomics Annual Clinical Genetics Meeting in 2018. This work was supported by the Mayo Clinic Center for Individualized Medicine. This publication was also supported by Grant Number UL1TR002377 from the National Center for Advancing Translational Sciences (NCATS). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. The authors would like to thank the parents and family members for their time and thoughtful responses to the survey.

Disclosures

The authors have no financial conflicts of interest to disclose.

EVALUATING THE RISKS AND BENEFITS OF GENETIC AND PHARMACOLOGIC INTERVENTIONS FOR DOWN SYNDROME: VIEWS OF PARENTS

Abstract

Researchers are investigating new technologies to mitigate or prevent symptoms of Down syndrome (DS), including chromosome silencing and pharmacotherapy. We surveyed parents of individuals with DS to assess their opinions on two hypothetical scenarios describing prenatal chromosome silencing and pediatric pharmacological intervention to improve neurocognition in children with DS. While a slim majority of participants supported the availability of both therapies, respondent support was contingent on the risks presented, including the risk of miscarriage in the prenatal intervention and the impact of pharmaceuticals on their children's personality. Many parents expressed ambivalence, articulating a desire to improve their children's quality of life but requiring more safety and efficacy research before agreeing to a genetic or pharmacological intervention.

Key Words: Down syndrome; trisomy 21; chromosome silencing; gene therapy; survey

Introduction

Trisomy 21, or Down syndrome (DS), is the most common genetic cause of intellectual disability with an incidence of 1 in 792 live births (de Graaf, Buckley, & Skotko, 2015). Recent proof of principle studies have demonstrated that prenatal silencing of the extra chromosome 21 or the targeting of specific genes may change gene expression to more developmentally typical levels (Amano et al., 2015; Jiang et al., 2013; Li et al., 2012). Because neuropathological effects are

established by the beginning of the second trimester, preventative therapies would ideally occur *in utero* in the early stages of pregnancy (Bartesaghi et al., 2015). Noninvasive prenatal screening can identify DS as early as 10 weeks with high sensitivity and specificity, providing an opportunity for potential prenatal therapies to improve neurocognition as soon as DS has been diagnosed (Bartesaghi et al., 2015; Guedj & Bianchi, 2013; Guedj, Bianchi, & Delabar, 2014). The recent report of the live birth of twin girls from embryos genetically edited in an attempt to confer HIV resistance suggests that gene editing could be attempted for other genetic conditions, including DS, although its success has yet to be verified and questions remain as to how it might impact the infants' health (Marchione, 2018; Regalado, 2018).

Pre-clinical studies have also explored pediatric pharmacologic interventions to improve cognition, including short- and longer-term retention and language processing. While a number of potential therapeutic targets have been identified (including Aβ protein, gamma-aminobutyric acid (GABA), dual-specificity tyrosine phosphorylation-regulated kinase 1a (DYRK1a) protein, etc.), early stage clinical trials have detected no significant benefits and only limited improvements in cognitive performance or functioning (Hart et al., 2017; Bartesaghi et al., 2015; de la Torre & Dierssen, 2012). The majority of past clinical trials have focused on adolescent or adult populations, but it is posited that the earlier pharmacological interventions are applied, the greater impact these therapies will have on enhancing cognition (Stagni, Giacomini, Guidi, Ciani, & Bartesaghi, 2015). One Phase 2 drug trial, to improve cognition and behavior in children ages 6-11 with Down syndrome, was halted early by Roche Pharmaceuticals due to a lack of positive results, including no observed difference between experimental and placebo groups in a parallel trial with adults and adolescents. When the pediatric trial was discontinued,

many parents objected, saying that they had seen subjective improvement in their children's behavior while on the trial dose (Chevrette, 2016). At the same time, many parents report that they and their families have a very high quality of life with DS and that treatment is neither necessary nor desired (Skotko, Levine, & Goldstein, 2011).

As prenatal and pediatric interventions move forward, it is critical to understand the views of stakeholders and decision-makers in the DS community. In particular, since any such intervention would be at the discretion of either pregnant women or parents/guardians of young children, family members are an essential stakeholder group in this discussion. In 2017, we designed and implemented a mixed methods survey to assess the views of family members of people with DS. We described five hypothetical scenarios offering potential interventions and a simple yes/no response, followed by open text opportunities to describe personal responses to each scenario. Statistical analysis of quantitative responses has been reported in a separate publication (redacted for review). Here, we analyze qualitative data from two hypothetical scenarios that described prenatal chromosome silencing and a pediatric pharmacological treatment to improve cognition.

Methods

Survey Design

The therapies described in the hypothetical scenarios were based on previously published and ongoing pre-clinical and early stage clinical research into therapeutic targets to rescue the neurocognitive phenotype of DS (de la Torre & Dierssen, 2012; Hart et al., 2017). The risks and

benefits postulated in the hypothetical scenarios were extrapolated from this research. The survey was reviewed for accuracy and sensitivity to the concerns of the DS community by parents of children with DS, a clinician/researcher specializing in DS, and bioethicists. The prenatal scenario involved a genetic intervention in a 10-week-old fetus to silence the extra copy of chromosome 21. The risks presented included treatment failure, a small risk of miscarriage, a lack of long-term data, and possible maternal infection from the invasive intervention. The benefits included fewer physical symptoms of DS and the potential for typical IQ at birth. The pediatric intervention involved a theoretical drug that would improve memory and attention in an 11-year-old girl with DS. The child would have to take the drug every day, with no known side effects. The risks presented included unknown long-term health risks of taking the drug, treatment failure, and a reduction in personality aspects most often associated with the DS phenotype, including high levels of outward affection and a general lack of social self-consciousness (Cunningham, 2006; Fidler, 2006; Sigman et al., 1999). Benefits included improved learning ability and an increased likelihood of living independently as an adult. The text of both scenarios is included in Appendix A; text of the full survey is available elsewhere (redacted for review).

Data Collection

The study recruited family members of individuals with Down syndrome in order to gather their perspectives on genetic interventions in utero or after birth. The survey was open to all relatives of an individual with DS. An anonymous, 20-item survey containing both quantitative and qualitative questions was fielded through RedCap and a web link was disseminated through the researchers' social media accounts (Twitter and Facebook). Selected DS advocates employed by

academic institutions, and known to the researchers from prior outreach to the DS community, also disseminated the survey link to their social media followers. The strategy to recruit via social media was employed to engage with a diverse population of the DS community in terms of severity of DS, distance from medical care, and involvement with DS advocacy. The survey remained open for 7 days during July 2017. A brief consent statement was appended to the top of the survey to inform participants that by continuing with the survey they affirmed their consent. This study was declared exempt by the Institutional Review Board of [Institution Redacted for Review]. Due to its dissemination via social media and anonymous design, response rate and geographical distribution of participants cannot be determined. Due to the very small number of responses from other relatives, only those surveys completed by a self-identified parent were included for analysis. This analysis includes all completed surveys; however, the number of qualitative responses varies by individual question.

Participants responded to background questions about their family members with DS and were asked whether they would choose, or encourage a family member to consider, the interventions proposed in five hypothetical scenarios. For each of these binary "yes/no" responses to the scenarios, respondents were asked in open-ended responses to explain their reasoning, what risks or benefits they saw, and any other thoughts. Using methods described below, we analyzed qualitative responses to two of the five scenarios; these two scenarios describe genetic and pharmacological interventions for the improvement of neurocognition in DS, and were our primary targets of interest when designing the survey. Our prior quantitative analysis (redacted for review) found that responses to these two scenarios, unlike the other three, garnered responses that were significantly influenced by respondents' own perceptions of the positive and

115 negative effects of DS. Two of the other three hypothetical scenarios (centering on existing
116 prenatal and pediatric interventions for structural abnormalities) were included largely as
117 quantitative controls; the third described a treatment to reduce Alzheimer risk in DS individuals.
118
119 Data Analysis
120 A qualitative codebook was developed between two researchers, using an iterative parsing
121 mechanism that grouped concurrent themes by thematic content (Donovan, 1995). The codebook
122 underwent edits throughout the coding process, with the two researchers negotiating consensus
123 on changes and use of codes. One researcher coded all open-ended responses using the final
124 codebook. Trends and coded material were reviewed between the two researchers once a week in
125 order to maintain research rigor and achieve coding consensus, according to standard qualitative
126 methodology. Additionally, the coded material was spot checked by two researchers for
127 accuracy. We report here on the codes ‘yes to scenario,’ ‘no to scenario,’ and ‘ambivalence.’
128
129 Codes were analyzed by scenario and categorized into those who overall agreed to the scenario
130 and those who overall disagreed, based upon whether they selected ‘yes to scenario’ or ‘no to
131 scenario’ for the quantitative question and their reasons why they supported or rejected the
132 intervention in the open response. Reponses coded ‘ambivalent’ were those who selected ‘yes to
133 scenario’ or ‘no to scenario,’ but then provided contradictory answers or expressed uncertainty in
134 the open response. These responses were co-coded with ‘yes to scenario’ or ‘no to scenario’
135 based upon their quantitative response. For example, if a participant selected ‘no,’ but then stated
136 the circumstances in which they would be willing to consider the therapy, their response was
137 coded as ‘no to scenario’ and ‘ambivalent.’ Respondents who declined to answer the qualitative

question were also coded as 'ambivalent.' Appendix B contains a fuller description of the coding schema. The software package NVivo Version 11 was used to facilitate data analysis. Risk and benefit analysis and thematic analysis (Donovan, 1995; Corbin & Strauss, 1990) were undertaken for parents' explanations of their choices in the prenatal and pediatric cognitive intervention scenarios.

Results

Participant Demographics

532 individuals identifying as parents of individuals with DS completed the survey. While our recruitment mechanism prevents us from calculating a response rate, 1093 individuals initiated the survey by answering at least one question, for a completion rate of 48.7%. The median respondent age was 41 years old (range 17-74) (Table 1). Median reported age of the person with DS was 5 years (range <1-44). For 39% of respondents, their children's DS had been diagnosed prenatally, while 61% said their children were diagnosed after birth. 17% said their children were "very affected" by DS, 55% said they were "moderately affected," and 28% said they were "mildly affected." Scenario responses are summarized in Table 2. A full quantitative analysis of "yes/no" responses to scenarios and statistical interaction with demographic variables is published separately (redacted for review). The majority of respondents (93% for the prenatal scenario; 91% for the pediatric scenario) wrote open-ended comments discussing their response to the scenarios. Quotes have been minimally edited for readability.

Table 1. Self-Reported Demographics of Respondents and their Child with Down syndrome

Perceived Benefits of Intervention as Identified by Parents

Prenatal Genetic Intervention

Participants were divided over whether they would elect to undergo a prenatal intervention to silence chromosome 21, with roughly half of parents (50.9%) supporting the intervention. Parents who were supportive of the intervention frequently expressed a desire to improve their child's quality of life. Some parents expressed a parental responsibility to try an intervention that could benefit their children.

> *At the end of the day, the job of a parent is to give the child the best chance at a normal life and societal contribution. If this improves the child's chances to lead a better life, I'm open to it.*

> *My child is amazing, and her achievements and attitude in the face of her challenges is humbling. But as a mom, I watch her struggle to do what she wants because of physical limitations. I see her frustrated when people can't understand her speech. She talks about being a mommy when she's older. She's had open heart surgery. She is prone to pneumonia. She is at a higher risk for cancer and Alzheimer's. I know that being 'typical' is no guarantee of anything in life, but if I could safely ease the struggles and risks my child faces I think I would.*

A few parents expressed excitement about advances in gene therapy that might be used to minimize physical and cognitive symptoms of DS in their children. Some parents theorized that a prenatal intervention would lessen the family burden of caring for an infant or child with DS. For these respondents, the projected benefit of improved cognition, learning, and communication

ability appeared to outweigh concerns about miscarriage, infection, or unknown future complications.

> *Could provide better outcomes and more independence for child and family burden (worry, cost, therapy coordination, etc.) could be reduced.*

> *Small risk of miscarriage. The biggest issue with our child is behavior problems that can't seem to be changed. If different for this, I wouldn't care about him having Down syndrome. However, because it is such a huge issue for us, if there was the opportunity to 'silence' it with minimal risk, I would.*

Pediatric Pharmacological Intervention

Two-thirds of respondents (67.9%) said that they would choose, or encourage their child to choose, a hypothetical daily pill to improve memory and focus in individuals with DS, with the trade-off that it could alter certain aspects of the child's personality or increase their self-consciousness. Parents identified increased social and personal independence and safety as the primary benefits. Many parents expressed a perceived obligation to accept opportunities to improve functioning and give their children every possible chance to thrive in adolescence and adulthood.

> *Cognitive function is so important. I think sometimes people underestimate it. The ability to communicate your needs, your wants, your fears, life is much better when people understand you. I think this would be a huge benefit to the child and the family.*

> *I think we'd manage less affection and more self-consciousness given the benefits of learning faster. To be honest I'm teary-eyed as I type thinking how much I would give to*

get a drug like this to my daughter--what it could mean for her safety and independence as an adult and how much she loves to learn and read and how much she struggles at school despite working so very hard.

Many parents viewed the drug as equivalent to the medications for ADHD or hypothyroidism that were already a part of their children's daily medical regimen. Some parents mentioned their own attempts to improve their children's symptoms through herbal supplements or enrolling in clinical trials. A number of parents said they were willing to try the hypothetical therapy, provided they were able to stop the drug if the side-effects or changes to personality turned out to be undesired or detrimental.

Many parents (myself included) are using supplements and medicines for this very reason (and others) right now. Improved cognition equals independence.

Could measure the effects of the drug day to day. Could stop if effects were too serious.

Parents frequently referenced difficulties with their child's behavior and a desire for improvement in this area. Similarly, many parents made comparisons between their child's abilities and those of their more "typical" peers, often discussing the barriers DS presented to their children's social integration.

My child is 11 and is like every other 11 yr old except for her learning. I'd definitely give this a chance to help her have the best life possible.

My son wants so badly to keep up with and join in with everyone else, but I know as he gets older the extra chromosome will limit that to an extent. If I could take that barrier away I would.

Some parents disagreed with the survey scenario in its characterization of the 'risks' to the intervention; arguing that improved social boundaries and self-awareness may actually benefit their child's social acceptance.

> *The benefits completely outweigh the risks. I'm offended by the 'less outwardly affectionate and more self- conscious'. Having appropriate boundaries and self-awareness are important parts of a normal healthy life.*

> *Living independently is what every parent wants for their child … . Depending on the situation, being less affectionate and more self-conscious may not necessarily be a bad thing.*

Perceived Risks Identified by Parents

Prenatal Genetic Intervention

Approximately half of parents (48.1%) were opposed to the proposed prenatal intervention. Parents in this group expressed that they felt fetal intervention was too risky and stressed the need for more translational research before human trials. Many parents in this cohort stated that the intervention could impact fetal development in unknown ways, and some expressed concern that initiating the therapy even as early as 10 weeks would still be too late to change the phenotype of DS.

> *To me, the risks outweigh the benefits because it is such a novel treatment. Also, I know that the workings of chromosome 21 are complex and I would not trust that a technique such as this could truly 'silence' this chromosome, especially not at the 10-week mark*

when much about the baby has already developed. I would be worried about unexpected effects.

There is no way to know how suppression of a gene will affect every area of development.

Many parents expressed that the hypothesized benefits of the prenatal intervention, a near-typical IQ and physical appearance, were of significantly less concern than more severe medical complications, such as congenital heart disease, gastrointestinal atresias, and leukemias. In addition, any risk of miscarriage, however small, was sufficient to cause some parents to reject the intervention, especially since a DS diagnosis is not typically life threatening to the fetus.

If your concern is the physical traits of your child then you shouldn't even be offered this treatment. So what if they look a little different than 'typical' people, you could get hit in the fact with a baseball bat and not look 'normal' anymore too. There is too much unknown, and I couldn't risk the miscarriage for something that we have no idea how it would work.

I am wary of unproven techniques. I would rather have a child with DS than lose that child because I wanted to fix her.

Pediatric Pharmacological Intervention

Approximately one-third of parents (31.2%) were opposed to this intervention. Many parents also identified unknown side- and long-term effects as risks to the pediatric intervention. They cited the risk of increased self-consciousness and lessened affection as substantial reasons for rejecting such interventions. Some questioned the benefits of the drug for the child in the

scenario of their own children, given their individual circumstances or developmental stages. Conjecturing based on the limited information in the scenario that improved cognition at age 11 would never enable a child with DS to "catch up with her peers," this respondent questioned the balance of risks to benefits:

> *I enjoy my son just the way he is. He is a complete joy to our family and I would not take the chance of him being less affectionate.*

> *I don't like this question - it's like we're in the garden of Eden and I have to decide whether to give [the child] the apple and if I do she's going to be hiding in the bushes afraid to show herself. At 11 it's highly unlikely [she] would catch up with her peers, same as the impact of cochlear implants on language falls as recipients get older. She's missed too much development. So if she is not going to catch up but instead feel more stigmatized about her disability I'd pass.*

A strong distrust of the medical and pharmaceutical community was evident in some responses; parents stated they did not want their children to be a "guinea pig" or "science experiment." Some parents felt that there was a larger reason or purpose for their children's DS and were concerned that they might be "fixing" DS not for their children's benefit, but for their own.

> *Who gets to be the guinea pigs? I just can't see subjecting my child to drugs that could possibly have long term health risks. I could not do that to my son.*

> *My child is 10. If she could learn easier or quicker MY life (and her teacher's lives) would be easier but for her it would cheat her of the life she is meant to live.*

<u>Ambivalence Expressed by Parents</u>

Table 2: Ambivalent Responses to Interventions

Prenatal Genetic Intervention

A significant number of parents expressed views classified by the analysis team as ambivalence towards the prenatal intervention, stating views in their open-ended responses that either explicitly stated internal conflict or included statements that contradicted their overall "yes" or "no" scenario response. This includes 0.9% of respondents who did not answer the qualitative "yes/no" question. See Table 1 for an overview of "yes/no," missing, and ambivalent responses. The majority of these respondents articulated that they would need more information about safety and long-term outcomes before they could commit to a decision either way, even if they were overall more inclined to accept or reject the therapy, especially given that this therapy would alter their children's genetics.

> *It would be a benefit if it improved cognitive function, and reduced hypotonia. I would not want it to change my daughter's personality or joy in this world. --- I think a treatment like this carries significant risk, when we turn off one gene, how do we know that ONLY that gene is being turned off? What else might get damaged in the genetic structure?*

> *What is the statistical chance for miscarriage? Where do these 'genes' come from? Would gene therapy affect the biochemistry of the over expression of chromosome? Affect short-term/long-term health? Alter the slippery slope to Alzheimer's? If so, then by all means try.*

Several participants pointed out that at the time of a prenatal diagnosis their fears may have pushed them toward an intervention, but after their lived experiences of raising children with DS they would refuse the therapy.

> *When I had my prenatal diagnosis, I would have made this choice in a heartbeat. After having my daughter- it is not that simple. I would probably NOT choose a treatment like this for her- especially one without proven long term results. My answers to this question were solely based off of where I was at when I was pregnant with her. It's a very complicated thing. Now that she's here, I don't know if I would want to change her.*

> *I think this is a hindsight question… I have already had my son for 5 and a half years and would not change him. He has changed my life for the better. I have a clearer idea of priorities and what is really important in life. I have a mission now. Sure, his medical needs are a burden but they are not his fault. I do feel his quality of life suffers from his extensive medical needs.*

A few responses mentioned the possibility of misdiagnosis with DS at the 10-week mark without direct sampling of the fetal DNA at a later stage in pregnancy, and some articulated a hope that this therapy might lead to fewer women choosing abortion following a positive DS diagnosis.

Pediatric Pharmacological Intervention

This scenario generated even more ambivalence than the prenatal intervention, even though the quantitative answers were less divided than in the prenatal scenario. 0.9% of respondents left the

quantitative question unanswered. Many parents said their decision would depend upon the severity of their children's symptoms and behavioral issues.

Unsure(…) To improve his cognitive function at the expense of the characteristics that make him uniquely him? To deny him several positive qualities in order to help him fit in?(…) My son is pretty high functioning. If he were significantly impaired and unable to communicate, my answer may have been different.

It would depend on where [she] is now. She could be learning well and already have a good chance of living on her own when she grows up. If that is the case, I would not be willing to take the unknown long-term risks and possible change in personality. However, if [she] was really struggling to learn/function I may be more willing to take the risks.

Others expressed concern that increased self-awareness would make their children more aware of their disabilities or social stigma, mitigating any hypothesized benefits.

I would be somewhat concerned with the self-conscious portion of the risks, in that, perhaps my child would recognize more of how she is treated by others and be more aware of the way society in general is dismissive of people with Down syndrome/other developmental delays.

"If it changes her personality to be self-conscious about herself (appearance, disability, etc.) and possibly lead to a depressive state, I would have great concerns about that."

Participants often noted that there was not enough research or too many unknowns to justify accepting or rejecting this treatment. Many of these parents said they would need to have more

of their questions answered about the risks before initiating the treatment. Others said they would solicit their children's input or agreement in the process of making a decision.

> *This one was very hard for me to decide. I would desperately want my child to have a higher chance for independence, but I could not live with myself if I damaged my child or made them miserable by risking not knowing the long-term effects.*

> *I would want [her] to have a say in taking this medication. If she didn't like the way it made her feel and wanted to stop, I would want her to stop. If she felt that it made her happier and made life better and wanted to continue it, I would want her to continue it. Of course, if there were significant risks that came from taking it (that she cannot truly understand), I would insist she stop taking it, no matter what.*

A number of respondents expressed concerns about the ethical or societal implications for therapies to manage DS symptoms. Some parents articulated a need for the disability community to be included in the creation and implementation of any new pharmaceutical therapies, especially those targeting neurocognition.

> *My answer is actually 'maybe'. When we do any new treatment for our son, we speak to his specialist, PCP, etc. there would be 1000 more questions I'd have before we would try this.*

> *I'm not opposed to improving cognition but a comprehensive and detailed conversation on the ethics of these interventions must be had. Disability advocates, parents, family members and individuals must make up at least half of the conversation.*

Discussion

Responses to these two hypothetical scenarios indicate that the views of the DS community are not monolithic with regard to potential neurocognitive interventions for DS, or the condition itself. While a majority of participants agreed to the hypothetical interventions (just slightly over half for the prenatal scenario, and just over two-thirds for the pediatric scenario), opinions diverged regarding the perceived risks and benefits of each intervention, indicating that parents evaluated the proposed therapies through different frameworks and values. It is critical to understand the perspectives of these stakeholders, including the specific therapeutic goals they would like to see the scientific community focus their efforts on and those they would reject if they became a clinical reality. Because of this, these hypothetical scenarios were designed with current pre-clinical and early stage clinical research in mind, including chromosomal silencing and explorations into effective therapeutic targets for drug development.

Parental Evaluation of "Risk"

Parents frequently evaluated the interventions based on perceived impact upon their lives or those of their children, with particular emphasis on the safety and efficacy of the prenatal or pediatric therapy. Risk-benefit analyses for the prenatal scenario echoed some of the limited previous research on parental attitudes toward prenatal gene therapy for genetic conditions, with parents prioritizing the interests of the fetus but still weighing the potential risks to both fetus and mother (Sheppard, Spencer, Ashcroft, David, & EVERREST, 2016). In the prenatal scenario, miscarriage was frequently highlighted as the most significant risk, with many parents stating that they could not risk losing a pregnancy for an intervention "that may not even work." Risk of

infection to the fetus or mother was also of great concern. For a subset of respondents, any risk of fetal loss was sufficient to reject the genetic therapy outright.

Parents who were supportive of the prenatal genetic intervention believed it would improve quality of life for their child; many hypothesized that it could help reduce the burden and worry of raising a child with complex and lifelong needs. This finding reflects previous research in which two-thirds of parents identified improved quality of life and the increased ability to perform daily tasks as the major benefit of an undefined "cure" for DS (Inglis, Lohn, Austin, & Hippman, 2014). In general, there was less ambivalence regarding this scenario, with many parents being firmly for or against the therapy based upon its benefits and risks. However, a subset of parents expressed interest in the intervention, but indicated that it was premature to accept or reject the therapy given its experimental stage.

In the pediatric scenario, the possibility of the child becoming less affectionate and more self-conscious evoked strong responses from many respondents, who stated that their children had positively impacted their lives or their families and they would not risk a change in their children's personality. This view was compounded by the hypothesized risks, including the relatively short period of time the drug had been studied (2 years) and the unknown long-term effects. Parents frequently report the positive impact their children with DS have on their lives (Pillay, Girdler, Collins, & Leonard, 2012; Skotko et al., 2011; Povee, Roberts, Bourke, & Leonard, 2012) and have previously reported concerns that a cure for DS could negatively change their children's personality (Inglis et al., 2014), indicating that this concern may be a significant barrier to the adoption of any new pharmacotherapies in the DS community. In

contrast, parents who were supportive of the intervention discussed the possibility that it would enhance their lives by improving their children's cognition and reducing their children's immediate and long-term dependence on caregivers. Accompanying this support was a hope that this therapy would reduce parents' worries about their children's long-term well-being after their own deaths. Previous research has suggested that life-long dependence is a major concern for parents of children with DS (Inglis et al., 2014; Pillay et al., 2012), especially as the average lifespan of individuals with DS has steadily increased (Bittles & Glasson, 2004; Bittles, Bower, Hussain, & Glasson, 2007).

Perhaps for this reason, the pediatric scenario prompted more ambivalent responses. Many parents presented an 'opposing argument' in their response, stating that they could see why other parents would be support or reject the therapy, or provided circumstances which would change their mind about the intervention. Indeed, there was a significant amount of variance between the "yes/no" answer selected and the reasoning presented in their response. Many parents expressed conflicting feelings about this treatment because of its unknown long-term risks and impact to personality. Many respondents indicated they would consider this therapy only if additional research demonstrated its safety and efficacy. Others stated they would try the medication on a trial basis, discontinuing treatment if they felt the side-effects were too deleterious. It was evident that, for many parents, the risk of known or unknown side-effects or long-term complications (discussed in the scenario or hypothesized by parents themselves) swayed their opinion. This finding reflects previous research that has found significant interest in pharmacological clinical trials among parents of children with DS, though tempered by concerns about safety and long-term effects (Reines et al., 2017).

Parental Evaluation of "Benefits"

Respondents frequently evaluated the proposed therapies based on their prioritizations of their children's physical, neurocognitive, and psychosocial symptoms and limitations. In the prenatal scenario, many suggested that reducing the physical complications of DS should take priority over improving IQ or cognition. Some parents shared their children's experiences of physical complications and invasive treatments (e.g., open-heart surgery) as a way of contextualizing their response. Such responses reflect the reality that 50% of infants with DS are hospitalized before the age of three (So, Urbano, & Hodapp, 2007) due to increased risk for congenital heart disease (50%), gastrointestinal atresias (12%) and respiratory illness (Bull & Committee, 2011), and that these health challenges significantly impact parents' physical and mental health (Bourke et al., 2008). Yet many parents also expressed a desire for their children to have a "typical IQ" or improved cognition in order to more fully integrate with peers, improve academic achievement, and increase their independence.

Although many parents lamented the possibility that the hypothetical pediatric intervention could affect their children's personality or expressed fears that improved self-awareness might make their children more aware of societal stigma and discrimination, surprisingly some parents saw these side effects as potential benefits to their children, noting that a lack of personal boundaries (e.g. excessive hugging) negatively impacted their children's relationship with others. Such responses to this question may depend upon the extent to which these respondents' children have encountered academic and behavioral difficulties, reported by other parents in this study. Many parents referenced desperate home or school situations in their responses, indicating that these

experiences influenced their support of a pharmacotherapy that could improve their children's cognitive functioning. Indeed, our previously published quantitative results found a statistically significant correlation between agreement to the prenatal and pediatric cognitive interventions and views of DS as burdensome to respondents' children and/or families (redacted for review). As children's behavioral problems are frequently reported as the most significant predictor of parental stress and poor family functioning among parents of children with DS (Bourke et al., 2008; Hauser-Cram et al., 2001; Hodapp, Ricci, Ly, & Fidler, 2003; Most, Fidler, Booth-LaForce, Laforce-Booth, & Kelly, 2006; Sloper, Knussen, Turner, & Cunningham, 1991; Stores, Stores, Fellows, & Buckley, 1998; Ricci & Hodapp, 2003), parental experience and stress level may drive whether parents would be willing to try a nascent intervention.

Application of Scenario to the Parents' Child

Many respondents contextualized the proposed scenario in light of whether they would choose the intervention for their own children, recounting both the joys and challenges of raising a child with DS. This view was evident in the prenatal scenario, with many parents stating that they would not let their children be a "test subject" or a "medical experiment." A minority of respondents to the prenatal scenario noted that alterations to their children's DNA would be like "playing God" or "messing with nature," reflecting previously documented concerns of pregnant women regarding prenatal genetic screening, and public concerns regarding genomic medicine in general (Pew Research Center, 2016a; Pew Research Center, 2016b). An interesting subset of parents acknowledged that, before the birth of their own children, they might have agreed to such an intervention out of fear or uncertainty; however, many said that after the personal experience of raising a child with DS, they were less likely to make the same choice. It is worth noting that,

in our prior quantitative analysis, “yes/no” responses to these scenarios were statistically related to parents’ general views of the effects of DS on their children and families, but not to their ages or those of their children (redacted for review). This finding is reflected in our qualitative analysis, in which parents often related to the hypothetical scenario by mapping it onto the personal circumstances of their own children and families.

Many parents expressed interest in a pediatric drug therapy for DS, but were emphatic that they would not allow their children to take part in an experimental therapy without more thorough study. A small subset of parents expressed the opposite viewpoint, noting that they had either enrolled their children in a clinical trial or were utilizing herbal supplements in the hopes that they will help their children reach their full potential. This finding reflects motivations previously reported by parents using complementary and alternative medicine in their children with DS out of a desire to be a “good” parent (Prussing, Sobo, Walker, & Kurtin, 2005).

Limitations

The two hypothetical scenarios described here were based on pre-clinical research and were constructed in order to understand how parents of children with DS view potential future therapies to improve neurocognition. Hypothetical scenarios, however, cannot fully replicate the nuances of decision-making and responses to real-life situations. The risks and benefits listed for each scenario are theorized and may not reflect these therapies in practice if they are realized in the future. Due to the limitations of survey research, we are unable to control for interpretation of the scenarios and how it might affect participant responses. As this survey was distributed online through DS advocacy groups, it may have biased the sample toward younger parents, those who

were more educated and computer-literate, and those who were more involved in DS advocacy. Anonymity of the survey may have influenced responses. Finally, this study did not include individuals with DS, whose attitudes may differ significantly from those of their parents and other family members; future research is planned to understand the views of these stakeholders regarding proposed therapies for DS.

Conclusion

Fetal chromosome or gene therapy or pediatric pharmacological treatment will likely be offered to pregnant mothers or individuals with DS in the relatively near future. In this online, scenario-based survey, parents evaluated hypothetical risks and benefits of these future treatments through varying lenses. For some parents, the possibility of improved quality of life for their children and families, through improved physical health, increased cognitive ability, reduced behavior issues, and greater independence for their child, was reason enough to accept an experimental prenatal or pediatric therapy. For others, the risk of miscarriage or change in personality was too significant a risk. In both scenarios, parents regarded as problematic the chances that the treatment could be ineffective or unsafe and the lack of long-term research. Respondents' general agreement to both therapies, along with the ambivalence expressed by those who were initially inclined to reject the intervention, suggests that the majority of parents of children with DS would be interested in considering future prenatal or pediatric treatments to improve neurocognition. However, our findings suggest that much of this parental support depends upon rigorous research into safety and efficacy, and also upon the incorporation of both ethical considerations and voices from the disability community into ongoing conversations about potential interventions and how they are implemented.

References

Amano, T., Jeffries, E., Amano, M., Ko, A. C., Yu, H., & Ko, M. S. (2015). Correction of Down syndrome and Edwards syndrome aneuploidies in human cell cultures. *DNA Res*, *22*(5), 331-342. doi:10.1093/dnares/dsv016

Bartesaghi, R., Haydar, T. F., Delabar, J. M., Dierssen, M., Martínez-Cué, C., & Bianchi, D. W. (2015). New Perspectives for the Rescue of Cognitive Disability in Down Syndrome. *J Neurosci*, *35*(41), 13843-13852. doi:10.1523/JNEUROSCI.2775-15.2015

Bittles, A. H., Bower, C., Hussain, R., & Glasson, E. J. (2007). The four ages of Down syndrome. *Eur J Public Health*, *17*(2), 221-225. doi:10.1093/eurpub/ckl103

Bittles, A. H., & Glasson, E. J. (2004). Clinical, social, and ethical implications of changing life expectancy in Down syndrome. *Dev Med Child Neurol*, *46*(4), 282-286. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15077706

Bourke, J., Ricciardo, B., Bebbington, A., Aiberti, K., Jacoby, P., Dyke, P., . . . Leonard, H. (2008). Physical and mental health in mothers of children with Down syndrome. *J Pediatr*, *153*(3), 320-326. doi:10.1016/j.jpeds.2008.02.047

Bull, M. J., & Committee, O. G. (2011). Health supervision for children with Down syndrome. *Pediatrics*, *128*(2), 393-406. doi:10.1542/peds.2011-1605

Chevrette, M. (2016). Statement from LuMind Research Down Syndrome Foundation on the Roche Clinical Trials. Retrieved from https://www.lumindrds.org/statement-from-lumind-research-down-syndrome-foundation-on-the-roche-clinical-trials/

Cunningham, C. (2006). *Down Syndrome*. Souvenir Press. Retrieved from https://play.google.com/store/books/details?id=pyztCQAAQBAJ&source=gbs_api

de Graaf, G., Buckley, F., & Skotko, B. G. (2015). Estimates of the live births, natural losses, and elective terminations with Down syndrome in the United States. *Am J Med Genet A*, *167A*(4), 756-767. doi:10.1002/ajmg.a.37001

de la Torre, R., & Dierssen, M. (2012). Therapeutic approaches in the improvement of cognitive performance in Down syndrome: past, present, and future. *Prog Brain Res*, *197*, 1-14. doi:10.1016/B978-0-444-54299-1.00001-7

Fidler, D. J. (2006). The emergence of a syndrome-specific personality profile in young children with Down syndrome. *Downs Syndr Res Pract*, *10*(2), 53-60. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/16869362

Guedj, F., & Bianchi, D. W. (2013). Noninvasive prenatal testing creates an opportunity for antenatal treatment of Down syndrome. *Prenat Diagn*, *33*(6), 614-618. doi:10.1002/pd.4134

Guedj, F., Bianchi, D. W., & Delabar, J. M. (2014). Prenatal treatment of Down syndrome: a reality. *Curr Opin Obstet Gynecol*, *26*(2), 92-103. doi:10.1097/GCO.0000000000000056

Hart, S. J., Visootsak, J., Tamburri, P., Phuong, P., Baumer, N., Hernandez, M. C., . . . Spiridigliozzi, G. A. (2017). Pharmacological interventions to improve cognition and adaptive functioning in Down syndrome: Strides to date. *Am J Med Genet A*, *173*(11), 3029-3041. doi:10.1002/ajmg.a.38465

Hauser-Cram, P., Warfield, M. E., Shonkoff, J. P., Krauss, M. W., Sayer, A., & Upshur, C. C. (2001). Children with disabilities: a longitudinal study of child development and parent well-being. *Monogr Soc Res Child Dev*, *66*(3), i-viii, 1. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11677873

Hodapp, R. M., Ricci, L. A., Ly, T. M., & Fidler, D. J. (2003). The effects of the child with Down syndrome on maternal stress. *British Journal of Developmental Psychology*, *21*(1), 137-151. doi:10.1348/026151003321164672

Inglis, A., Lohn, Z., Austin, J. C., & Hippman, C. (2014). A 'cure' for Down syndrome: what do parents want? *Clin Genet*, *86*(4), 310-317. doi:10.1111/cge.12364

Jiang, J., Jing, Y., Cost, G. J., Chiang, J. C., Kolpa, H. J., Cotton, A. M., . . . Lawrence, J. B. (2013). Translating dosage compensation to trisomy 21. *Nature*, *500*(7462), 296-300. doi:10.1038/nature12394

Li, L. B., Chang, K. H., Wang, P. R., Hirata, R. K., Papayannopoulou, T., & Russell, D. W. (2012). Trisomy correction in Down syndrome induced pluripotent stem cells. *Cell Stem Cell*, *11*(5), 615-619. doi:10.1016/j.stem.2012.08.004

Marchione, M. (2018). Chinese researcher claims first gene-edited babies. *AP*. Retrieved from https://www.apnews.com/4997bb7aa36c45449b488e19ac83e86d

Most, D. E., Fidler, D. J., Booth-LaForce, C., Laforce-Booth, C., & Kelly, J. (2006). Stress trajectories in mothers of young children with Down syndrome. *J Intellect Disabil Res*, *50*(Pt 7), 501-514. doi:10.1111/j.1365-2788.2006.00796.x

Pew Research Center (2016a). American voices on ways human enhancement could shape our future. Retrieved from http://assets.pewresearch.org/wp-content/uploads/sites/14/2016/07/PS_2016.07.26_Human-Enhancement-Focus_FINAL.pdf

Pew Research Center (2016b). US public wary of biomedical technologies to 'enhance'human abilities. Retrieved from http://assets.pewresearch.org/wp-content/uploads/sites/14/2016/07/02120148/PS_2016.07.26_Human-Enhancement-Survey_FINAL.pdf

Pillay, D., Girdler, S., Collins, M., & Leonard, H. (2012). "It's not what you were expecting, but it's still a beautiful journey": the experience of mothers of children with Down syndrome. *Disabil Rehabil*, *34*(18), 1501-1510. doi:10.3109/09638288.2011.650313

Povee, K., Roberts, L., Bourke, J., & Leonard, H. (2012). Family functioning in families with a child with Down syndrome: a mixed methods approach. *J Intellect Disabil Res*, *56*(10), 961-973. doi:10.1111/j.1365-2788.2012.01561.x

Prussing, E., Sobo, E. J., Walker, E., & Kurtin, P. S. (2005). Between 'desperation' and disability rights: a narrative analysis of complementary/alternative medicine use by parents for children with Down syndrome. *Soc Sci Med*, *60*(3), 587-598. doi:10.1016/j.socscimed.2004.05.020

Regalado, A. (2018). EXCLUSIVE: Chinese scientists are creating CRISPR babies. Retrieved from https://www.technologyreview.com/s/612458/exclusive-chinese-scientists-are-creating-crispr-babies/

Reines, V., Charen, K., Rosser, T., Eisen, A., Sherman, S. L., & Visootsak, J. (2017). Parental Perspectives on Pharmacological Clinical Trials: a Qualitative Study in Down Syndrome and Fragile X Syndrome. *J Genet Couns*, *26*(6), 1333-1340. doi:10.1007/s10897-017-0111-x

Ricci, L. A., & Hodapp, R. M. (2003). Fathers of children with Down's syndrome versus other types of intellectual disability: perceptions, stress and involvement. *J Intellect Disabil Res*, *47*(Pt 4-5), 273-284. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/12787159

Sheppard, M., Spencer, R. N., Ashcroft, R., David, A. L., & EVERREST, C. (2016). Ethics and social acceptability of a proposed clinical trial using maternal gene therapy to treat severe

early-onset fetal growth restriction. *Ultrasound Obstet Gynecol*, *47*(4), 484-491. doi:10.1002/uog.15880

Sigman, M., Ruskin, E., Arbeile, S., Corona, R., Dissanayake, C., Espinosa, M., . . . Zierhut, C. (1999). Continuity and change in the social competence of children with autism, Down syndrome, and developmental delays. *Monogr Soc Res Child Dev*, *64*(1), 1-114. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/10412222

Skotko, B. G., Levine, S. P., & Goldstein, R. (2011). Having a son or daughter with Down syndrome: perspectives from mothers and fathers. *Am J Med Genet A*, *155A*(10), 2335-2347. doi:10.1002/ajmg.a.34293

Sloper, P., Knussen, C., Turner, S., & Cunningham, C. (1991). Factors related to stress and satisfaction with life in families of children with Down's syndrome. *J Child Psychol Psychiatry*, *32*(4), 655-676. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/1830885

So, S. A., Urbano, R. C., & Hodapp, R. M. (2007). Hospitalizations of infants and young children with Down syndrome: evidence from inpatient person-records from a statewide administrative database. *J Intellect Disabil Res*, *51*(Pt 12), 1030-1038. doi:10.1111/j.1365-2788.2007.01013.x

Stagni, F., Giacomini, A., Guidi, S., Ciani, E., & Bartesaghi, R. (2015). Timing of therapies for Down syndrome: the sooner, the better. *Front Behav Neurosci*, *9*, 265. doi:10.3389/fnbeh.2015.00265

Stores, R., Stores, G., Fellows, B., & Buckley, S. (1998). Daytime behaviour problems and maternal stress in children with Down's syndrome, their siblings, and non-intellectually disabled and other intellectually disabled peers. *J Intellect Disabil Res*, *42*(Pt 3), 228-237. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9678407

Appendix A

Prenatal Genetic Intervention Scenario

At 10 weeks pregnant, Jackie has a prenatal screen that finds her baby likely has Down syndrome. Jackie wants to keep the baby. Her doctor tells her that there is a new treatment that could "silence" the extra copy of chromosome 21 that causes Down syndrome. This treatment would inject the baby with genes that may block the extra chromosome. For it to work, Jackie would need to start the injections very soon.

Benefits & Risks: The baby may have fewer physical symptoms of Down syndrome. The genes may not make any difference at all. The baby may have a typical IQ. There is a small risk that the treatment could cause a miscarriage. The long-term consequences have not yet been established and there is a chance the genes might lead to unexpected infection.

If you were Jackie, would you choose to have the injections? Yes/No.

Why?

What do you think are the most important risks and benefits?

What other thoughts do you want to share about this?”

Pediatric Cognitive Intervention Scenario

Deborah is 11 years old and has Down syndrome. Deborah's doctor says that a new drug has just been approved that might help. This new drug may improve memory and attention. Deborah would need to take a pill every day. Research has found no side effects in the first 2 years that the drug was studied.

Benefits & Risks: Deborah would probably learn new things at the same speed as other children. The long-term health risks of taking the drug are unknown. Deborah would be more likely to live on her own when she grows up. The drug may not work. Deborah may be less outwardly affectionate and more self-conscious.

If you were Deborah's parent, would you choose to take the drug? Yes/No.

Why?

What do you think are the most important risks and benefits?

What other thoughts do you want to share about this?"

Appendix B

Table 2: Coding Analysis

Code	Description	Sample Quote
Yes to scenario	Benefits outweigh risks; state it would benefit their child; provides reasoning for selecting 'yes', including difficulties or burden of DS on individual or caregivers.	**Prenatal Scenario:** *At the end of the day, the job of a parent is to give the child the best chance at a normal life and societal contribution. If this improves the child's chances to lead a better life, I'm open to it.* **Pediatric Scenario:** *I would want to give my child every opportunity to succeed and cognitive improvement would be one way to do that.*
No to scenario	Risks outweigh benefits; state it would harm or negatively alter their child; provides reasoning for selecting 'no' including distrust of medicine or skepticism that the intervention would be effective.	**Prenatal:** *None of the benefits seem truly important. I don't get caught up in looks, nor is IQ an important measure of intelligence. The genes leading to unexpected infection is concerning.* **Pediatric:** *I am not willing to have my child take something that would fundamentally alter who he is, especially for some only possible short-term benefits.*

Ambivalence to scenario	Provides response conflicting with 'yes' or 'no' selection; suggests a possibility for scenario but personally disagrees; states they are unsure how to answer; would consider intervention with more research or information; states future circumstances may change their answer; did not select a response for the quantitative question.	**Prenatal:** *Very torn on this, and obviously I would need more information about initial studies. However, it sounds promising and someone has to be first.* (Yes to Scenario) *This is an exciting prospect - but long term ramifications need to be known before I could agree to it. Physical features don't matter to me - but iq does bc of link to lack of independence and increased vulnerability* (No to Scenario) **Pediatric:** *I can't say I'm all in on this one. Perhaps as I age and face the morbid reality of the child caring for itself when I'm gone I'll change my thinking. At face value I'm encouraged by the possibility of improving the child's quality of life and learning valuable skills.* (Yes to Scenario) *This is another tough one because again, if I could help my child have normal cognition, I would not hesitate. But the risks are a little higher than I am comfortable with. I would probably wait a little if that were possible to see the effect of children whose parents chose it for them.* (No to Scenario)

682

683

684

Table 1. Self-Reported Demographics of Respondents and their Child with Down syndrome

Age of parent (n=528)	
Median age (range)	41 (17-74)
Age of child with DS (n=532)	
Median age (range)	5 (<1-44)
Severity of DS (n=530)	
Minimally affected	149 (28.1%)
Moderately affected	290 (54.7%)
Very affected	91 (17.2%)

Table 2: Ambivalent Responses to Interventions

Prenatal Intervention	N (%)	Pediatric Intervention	N (%)
Yes to Scenario:	271	Yes to Scenario:	361
Ambivalent	83 (31%)	Ambivalent	117 (32%)
Not Ambivalent	187 (69%)	Not Ambivalent	244 (68%)
No to Scenario:	256	No to Scenario:	166
Ambivalent	95 (37%)	Ambivalent	66 (40%)
Not Ambivalent	161 (63%)	Not Ambivalent	100 (60%)
No Quantitative Response:	5	No Quantitative Response:	5
Ambivalent	4 (80%)	Ambivalent	3 (60%)
No Answer	1 (20%)	No Answer	2 (40%)