

RESEARCH ARTICLE

Attitudes Toward Hypothetical Uses of Gene-Editing Technologies in Parents of People with Autosomal Aneuploidies

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Abstract

Researchers are exploring the use of gene-editing technologies to prevent and/or treat genetic conditions in humans. Stakeholder views, including those of patient and family populations, are important in the ongoing bioethical discussion. We conducted 27 semi-structured interviews with parents of people with trisomy 21 (T21; $N=10$), trisomy 18 (T18; $N=8$), and trisomy 13 (T13; $N=9$)—conditions not previously studied in regard to attitudes toward hypothetical gene editing. While many discussions focus on the morality of gene editing, parents in our study focused on quality of life and concerns about changing their children's identity. All participants prioritized ameliorating life-threatening health issues when those were present; many also emphasized increasing their children's communication and cognitive ability. These results suggest that patient populations with the lived experience of genetic conditions have unique concerns that may differ from broader discourse.

Introduction

Technologies such as CRISPR-Cas9 have been used to modify genes in humans and animals successfully, both somatically and in the germline.^{1–5} However, technological advances, increased interest, and broader funding⁶ have triggered heated bioethical debate. Most scientists and bioethicists have expressed support for research on human somatic gene editing,⁷ but the majority agree that germline editing for reproductive purposes is ethically inappropriate.^{8–11} Nevertheless, in November 2018, a Chinese scientist announced the birth of twin girls from embryos with a genetically edited *CCR5* gene, sparking an international ethical outcry and emphasizing the need for increased discussion around regulation.¹²

Increased stakeholder engagement surrounding development of gene-editing technologies is vital to this discussion.¹³ Some stakeholder views have been represented, including those of genetics providers and the general public.^{14–16} Recent studies have illuminated the perspectives of some patient and family groups, including sickle cell disease,¹⁷ congenital and acquired hereditary blindness,¹⁸ and Down syndrome.^{19,20} Each population raised unique concerns. For example, some people with sickle cell dis-

ease expressed mistrust of a gene-editing cure, citing the historical context of marginalization of people with the condition.¹⁷ People who were more troubled by their blindness were more excited about the potential of gene editing.¹⁸ Parents of individuals with Down syndrome had ambiguous feelings toward gene editing. Many considered the impact the condition had on their child's quality of life (QoL) and need for long-term care, but were wary of the potential impact on personality.^{19,20} However, common themes also arose among groups, including qualified optimism around the technology, willingness to weigh risks and benefits, and societal implications.^{17–19,21} Further research is needed to build on these studies, identifying ethical questions and perspectives from a range of stakeholders.²¹

We utilized Rolland's Family System Genetic Illness (FSGI) model to identify different typologies from those studied previously.²² The FSGI model posits that a combination of personal and family experiences, cultural beliefs, values, and typology of genomic illness shape how one views their genetic condition. Trisomy 21 (T21) or Down syndrome, trisomy 18 (T18) or Edwards syndrome, and trisomy 13 (T13) or Patau

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syndrome are the three most common aneuploidies with a range of phenotypes.²³ Different genetic forms of these conditions include mosaicism and translocations. However, for ease, we will use T21/T18/T13 to encompass all forms. Based on their congenital nature, cognitive impact, lack of treatment, and moderate to severe presentation, they offer a valuable model to study attitudes toward gene editing.²²

Families of individuals with T21 and other genetic conditions have previously expressed ambiguous feelings toward new genetic technologies such as prenatal diagnosis, gene therapy, and hypothetical cures.^{24–26} Studies have found most parents of children and adults with T21 reported they were happy with their decision to have their child and that adolescents and adults with T21 overwhelmingly have a good QoL, although these findings are limited by self-selection bias.^{27,28} Less research has been done on attitudes of families of children with T18/13. Many parents of living and deceased children with T18/13 described the experience of their child's life as being positive and having value, but the question of a possible cure has not been addressed.^{29,30} Given the more severe course of T18/13, which are frequently lethal within the first year of life and have profound cognitive and physical impairments in those who survive, we hypothesized these families would show more interest in potential gene editing than families who have people with T21. However, the strong sense of community and disability identity in T21/18/13 patient/family populations might suggest an aversion to the hypothetical use of gene editing as a treatment or potential cure. We sought to investigate the attitudes of parents of children with T21/18/13 toward hypothetical uses of gene-editing technologies for their children and others.

Methods

Stanford University's Institutional Review Board approved all aspects of the protocol.

Development of interview guide

A team of researchers, which included genetic counselors and bioethics researchers with experience in qualitative research (E.S., K.E.O., M.M., and M.A.) and in gene-editing stakeholder research (K.E.O., M.M., and M.A.), developed the interview questions. The questions focused around: (1) experiences having a child with T21/18/13, (2) attitudes toward somatic and germline gene editing, and (3) what factors influenced their attitudes toward these technologies. The interviewer provided education on somatic and germline editing during the interview (see Supplementary File S1).

Sample (participants): T21

We recruited parents of people with T21 from the Mayo Clinic GIFTED study,¹⁹ a recent online, mixed-methods study that addressed the attitudes of parents of people with T21 toward potential genetic interventions. T21 advocates helped recruit participants for that study through social media. Participants in the GIFTED study who had elected to be contacted for further research ($N=363$) were stratified by variables assessed in the GIFTED study³¹ to invite a broad range of participants based on: attitude toward prenatal intervention, age of child with T21, and perceived burden of T21 on the child. Once stratified, 100 parents were sent a recruitment e-mail to complete an online screening questionnaire.

Sample (participants): T18/T13

Parents of people with T18/13 (full and mosaic) were recruited via the Support Organization for Trisomy 18, 13, and Related Disorders (SOFT). We sent a recruitment e-mail to 1013 SOFT families and posted to the SOFT Facebook group. Due to the large number of respondents of parents of children with T18 ($N=42$), we further stratified participants by two variables to ensure a representative population³¹: (1) having a living or deceased child and (2) educational background of the participant. We then invited 20 potential participants for interviews. All T13 respondents who completed the questionnaire ($N=16$) were invited for an interview.

Procedures

Recruitment and interviews occurred between October 2018 and January 2019. Importantly, this period overlapped with significant media attention regarding the birth of genetically edited babies in China, which some participants referenced in their interviews.¹² A single interviewer (E.S.) performed the semi-structured interviews via Zoom—a secure conferencing application. We ceased recruitment when thematic saturation was reached based on repetition of primary themes. Participants were given a \$15 gift card after completion of the interview.

Data analysis

Interviews were recorded, transcribed, and uploaded to Dedoose v8.1.8 (SocioCultural Research Consultants, LLC, Los Angeles, CA). Four initial transcripts were inductively analyzed by three researchers (E.S., N.D., and K.E.O.) to develop preliminary and intermediate codebooks. We blindly coded two transcripts with the intermediate codebook and discussed until we reached consensus. We developed a final codebook on this basis, and two researchers (E.S. and N.D.) blindly coded nine transcripts in three rounds, adjudicating after coding each set of three

(one from each participant population). We calculated an inter-rater reliability score of 0.86, demonstrating limited bias in coding. A single researcher (E.S.) coded the remaining transcripts. After coding completion, two researchers (E.S. and N.D.) reviewed the excerpts to create a list of themes and subthemes, which were then discussed and refined by the entire research team.

Results

Sample characteristics

Twenty-eight parents of people with T21 completed the online screening questionnaire and were contacted for an interview. Of these, 10 completed an interview. The others did not respond to scheduling attempts. Sixteen parents of people with T13 were contacted, and nine completed an interview. Twenty parents of people with T18 were contacted, and eight completed an interview.

Participant and child demographic data are outlined in Supplementary Tables S1 and S2, respectively. The majority of participants were mothers (81%) who had at least some college education (100%) and an annual household income of >\$50,000 (89%). All parents of people with T21 ($N=10$) and seven parents of people with T18/13 (7/17; 41%) had living children. Interviews lasted 30–90 minutes.

General themes

Overall, parents of people with T21 and T18/13 described having mixed feelings toward somatic and germline gene editing. Several themes emerged across both population

and gene-editing types: societal implications, concerns about changing identity, and considerations about age of use. Differences in attitudes across the participant populations primarily arose around somatic editing.

Societal implications

Participants felt societal implications were important if gene editing became available (Table 1). Many participants expressed concerns about impacts on diversity and tolerance of people with disabilities. They worried that if technology could “fix” aneuploidies, it would lead to societal pressure to have a perfect child and ultimate eradication of people with T21/18/13. If gene editing became available, participants stressed that family autonomy should be preserved in decisions about its use, there should be equal access, and it should not be used for “enhancement” or superficial qualities (i.e., height or eye color).

Conflict, identity, and “fixing”

Several themes were common across all participant cohorts, independent of gene-editing type (Table 2). Regardless of whether participants generally supported gene editing, they expressed internal conflict about hypothetically using it for their own children. This conflict centered on how much they perceived that trisomy impacted their children’s personality and identity, and not wanting those aspects to change. Some rejected gene editing altogether because they felt their children’s

Table 1. Societal implications raised by participants

<i>Societal implication</i>	<i>Representative quotes</i>
Less tolerant of diversity and disability	“I have concerns that if we are ultimately in a world without people with disabilities, that we may be less tolerant of people who are born with disabilities. I think there will always be a certain level of disabilities through accidents, or things that happen after birth. I just think we’ll be less tolerant, less understanding of people with differences, less compassionate.” Mother of living child with T18
Pressure for “the perfect child”	“It makes me concerned that if we are working toward this perfect society or society of perfect people it feels like it’s ... it doesn’t sit well with me in a way. It makes me sad for [CHILD WITH T13].” Mother of living child with T13
Eradication of people with T21/18/13	“It’s [gene editing] gonna eradicate it [T21] ... you don’t need gene editing for that to be a fact. If you look at what’s happening in Denmark and Iceland, they’re already seeing termination rates in the nineties ... I think it’s evil. I think it’s sick, I think it’s wrong, I think it’s eugenics and yeah, it’s going to eliminate children with Down syndrome.” Mother of living child with T21
Preservation of patient/family autonomy (not being forced on people)	“...if we eliminated people’s disabilities like that, would there be a stigma or a judgment passed upon someone who had a child with a disability? ... I would hope that it wouldn’t result in people with disabilities being looked upon worse than they are now. I wouldn’t want a parent to be accused of child abuse because they didn’t prevent a child’s disability.” Mother of deceased child with T18
Need for equal access to the technology	“There’s perhaps a negative societal impact in the fact that if this kind of technology is only provided to the wealthy, then it puts those who are poor on yet another level downwards with their inability to have access to that. It further emphasizes the un-leveling of the playing field between people.” Father of deceased child with T13
Use for enhancement	“I do not support gene editing to make your child’s eyes a different color, their hair a different color, or make them taller, or less prone to being obese. Those things are ridiculous and superficial. I would only be in support of this technology if it’s to help a child live if they’ve been given a fatal diagnosis, to help them not be in pain if their body is broken.” Mother of deceased child with T18

Table 2. Themes consistent across participant cohorts and types of gene editing

<i>Theme</i>	<i>Representative quotes</i>
<i>Internal conflict</i>	
Internal conflict over how much condition shapes identity	“...part of that is my own indecision on how much having Down syndrome has formed his little personality because I wouldn’t want to change those pieces of him. He just lives life in the fullest. He truly doesn’t really care what other people think about what he’s doing so his emotional reactions to things are big whether that’s happiness or being irritated with something. So those pieces I wouldn’t want to change for sure and his total ability to be himself.” Mother of living child with T21
Would not want to change child’s personality/identity	“Maybe I hesitate in wanting to change him if this is how he was truly intended and created to be ... It’s sort of like the notion of playing God I guess and changing him.” Mother of living child with T13
Condition does not need to be “cured”	“In some ways, it [somatic gene editing] turns my stomach. Just a couple seconds ago you used the word ‘cured’ and I wholeheartedly reject that my son’s genetic condition is a disease that needs a cure.” Mother of living child with T21
Conflict between accepting their child and wanting to improve their QoL	“You want people to accept your child and those with disabilities because they do add so much to our lives, but you also want to make their lives easier and in turn your life easier in some aspects so that’s pretty much where I’m at. Would I do it? Yeah. Would there be a part of me that always thought that it might be ableist? Yeah.” Mother of living child with T21
<i>Societal use and other diseases</i>	
Would not personally use, but okay with gene editing being available for society	“It would be okay for me if it’s [somatic gene editing] available. I would not go for it. It’s really the choice of the parent but for me, as a parent, I wouldn’t choose it.” Mother of deceased child with T13
Participants overwhelmingly accepting of gene editing for other diseases	“When it comes to [other] diseases and ailments ... If there’s a way to make people’s lives better and easier, my inclination is to say go for it ... It’s as if the other diseases are things that happen to people versus it being who they are...” Mother of living child with T13
Comparison to existing technologies	“I guess to me gene editing seems like a better option [than prenatal diagnosis and termination] because it isn’t ‘life or not life.’ I mean there is definitely a lot of ethics involved as far as decision of whether you change the life that you already have, but at least the life is there.” Mother of living child with T21
<i>Age considerations</i>	
“Fixing” earlier in life	“I would think the earlier the better would be the way to go ... if you have a full grown person, not that it would maybe necessarily hurt them, but the benefits probably just wouldn’t be as great.” Mother of deceased adult with T13
Parents of adults would want to consider child’s wishes	“...if the patient, or my daughter, is happy where she is, I don’t know if I want to make any changes just because I feel like it.” Mother of living child with T18 “...depending on age, if it was to the point where he was old enough to be part of a decision, I think it’d have to be kind of have to be up to him.” Mother of living child with T21

condition was not a disease that needed to be “cured.” Participants found it difficult to both think about changing their children while also loving them and accepting their differences. Many felt more conflicted about gene editing for their children than for general society, and many who opposed gene editing for their children supported its broader availability. Participants were less conflicted in their attitudes about using gene editing to treat other medical problems (i.e., diabetes or cancer), which they considered less integral to identity. Some participants considered gene editing in the context of prenatal testing and termination for pregnancies diagnosed with aneuploidy. They felt gene editing could reduce abortions of affected fetuses by giving families another option to lessen medical burdens. Those in favor of gene editing supported “fixing things” as early as possible, prenatally or early in life, both because earlier treatment could have a larger medical impact and because it was harder to consider changing a person after knowing them. Parents of adult children wanted to consider their children’s wishes in utilizing the technology.

Germline gene editing: Specific concerns

Participants expressed positive and negative views specific to germline gene editing (Supplementary Table S3). Major positive themes included the sense that earlier treatments would be more effective for multi-systemic conditions such as aneuploidy and that germline editing might become an alternative to abortion in some pregnancies. Negative themes included religious and moral concerns (including eugenics), concerns about unwarranted interference with nature, and difficulty in seeing the utility of germline editing for aneuploidy because (1) many people do not know in advance that their children/pregnancies are at risk for trisomy and (2) where there is a known risk, there are already technologies (i.e., preimplantation genetic screening) available to prevent the birth of children with aneuploidy. They described narrow circumstances in which germline editing would be the only option available.

Somatic gene editing: Specific concerns

Attitudes toward somatic gene editing fell on a continuum (Supplementary Table S4), although most

participants expressed positive attitudes toward using it to ameliorate significant health issues and improving QoL for their children. A few parents expressed negative views toward somatic editing, noting they would not want to change their children's identities (as described above), felt their children already had a good QoL, or had safety concerns. Given the multi-systemic nature of aneuploidy, participants expressed doubts about the effectiveness of somatic editing, recognizing that it would focus on specific aspects and would not be a full cure.

Differences in attitudes between parents of T21 and T18/13

Parents of people with T21 differed from parents of people with T13/T18 in how they envisioned gene editing impacting their child (Supplementary Tables S5 and S6).

Trisomy 21. Most parents of people with T21 reported that their children were minimally impacted by T21-associated health issues, but if their child's health issues were more significant, it would impact their willingness to use gene editing. Most parents of people with T21 prioritized improving their children's independence, including speech and communication, often citing concerns as their child aged. Additionally, participants felt that increased communication and independence would allow their children to be less stigmatized and fit in with peers. A few parents opposed somatic editing, primarily because they felt their children did not need to "be cured" and had a good QoL. Parents of people with T21 referenced their condition-specific communities more often than parents of people with T18/13, and several suspected the broader Down syndrome community would not support gene editing, even if their own opinions differed.

Trisomy 18/13. Nearly all parents of people with T18/13 supported somatic gene editing for their children. Only one mother of a deceased child with T13 shared she would not have used somatic editing for her child because of her religious beliefs and wanting her child to be loved for who they were. Parents of both living and deceased children said they would prioritize life-threatening health issues. Some parents, primarily those with living children, expressed they would prioritize improving cognitive ability over physical issues. They shared that the most emotionally challenging aspect of their children's condition was the severe developmental delay and its impact on parent-child bonding and their children's independence.

Discussion

Parents were not unanimous in their attitudes toward either somatic or germline gene editing. We hypothesized that

parents of people with T13/18 would be more supportive of gene editing than those with T21. However, we did not find striking differences between the two groups' overall support of the technology. As seen in prior studies of families affected by T21,^{19,24,32} parents in both our T21 and T18/13 cohorts expressed both positive and negative attitudes about the availability of a new intervention, both for their children and societally. Similar to previous studies among patient populations with sickle cell disease¹⁷ and hereditary eye disorders,¹⁷ our participants were cautiously optimistic about the benefits of gene editing and cited similar concerns surrounding safety, unintended consequences, and broader societal implications. They desired increased oversight and guidelines as gene-editing technologies become more clinically feasible. Parents generally had more positive attitudes toward somatic editing than germline editing, perhaps because the former's immediate impact on their families was easier to grasp. Given the multi-systemic nature, moderate to severe impact on the individual, and neurocognitive phenotype of the aneuploidies studied in this project, it is not surprising that our participants raised new considerations unique to their children's conditions.

Among those who might use gene editing for their children, primary motivations centered around improving QoL. The exact mechanism by which they desired to improve QoL varied among participant populations. Parents of people with T18/13 focused on ameliorating life-threatening health issues, though a few prioritized cognitive function. Some parents of people with T18/13 described negative experiences with health-care providers who were hesitant or refused to perform surgeries on their children, reflective of prior research in the T13/18 population³³⁻³⁶ and in individuals with other genetic conditions and/or neurodevelopmental delays.^{37,38} Our participants suggested that if gene editing could be used to improve their children's cognitive ability and overall QoL, health-care providers might be more willing to perform life-sustaining interventions in children with T18/13. Parents of people with T21 emphasized increasing their children's communication and cognitive ability in order to increase independence. These findings are consistent with those of a previous study on how parents of children with T21 perceived a hypothetical "cure."²⁴ However, parents in our small T21 cohort reported fewer significant health concerns than have been reported in the broader T21 population.³⁹ In both our T21 and T18/13 cohorts, parents described conflict between the desire to improve QoL and hesitation regarding changing their children's identities, including indecision around how much identity is shaped by T21/18/13.

Participants with negative reactions to gene editing voiced concerns similar to those in previous studies on interventions in children with T21.^{19,24,32} An overarching concern was that such technologies would eventually eliminate disability from society and that their children bring a unique perspective to the world that does not need to be “fixed.” This finding is reminiscent of disability critiques of other technologies and reflects well-documented arguments that selective termination for disability expresses a negative message to people living with disability.^{40–42} Some explicitly drew an interesting comparison between gene editing and currently available technologies for preimplantation and prenatal diagnosis of aneuploidies, viewing gene editing as a potential alternative to discarding affected embryos or terminating pregnancies. These participants referenced high termination rates after prenatal diagnosis of common aneuploidies, particularly T21, in European countries.⁴³ This suggests that some who are opposed to the idea of gene editing may still see it as a better option than those currently available. Gene-editing technologies have rapidly evolved over recent years and will likely continue to do so. As these technologies continue to evolve alongside their potential applications, it is important to acknowledge that stakeholder views toward them will do so as well.

There are several limitations to our study. Our population was well educated and financially secure. It was also a primarily self-selected population, recruited from condition-specific support groups, which tend to include people who are more active within the disability community and may have stronger opinions than the broader population. Additionally, our population did not include individuals who chose to terminate a pregnancy affected by T21/18/13, who may have differing opinions toward gene editing. These limitations could be addressed in future studies by recruiting participants outside of support groups, such as through hospitals or other health-care centers. Finally, gene editing for aneuploidy is not currently available, although preclinical research is ongoing into methods to silence or eliminate whole chromosomes genetically.^{44,45} In the future, it may be possible to introduce somatic gene editing during early fetal development following diagnostic confirmation. However, this is speculative, and previous studies have shown the complexities involved in these hypothetical interventions for conditions such as T21.^{46,47} Despite the hypothetical nature of using gene editing for aneuploidy, our study findings raise important considerations for its application to spectrum conditions and in the comparison of two different populations of families faced with conditions with both physical and cognitive impairments.

Conclusion

In this study, parents of people with both T21 and T18/13 expressed mixed feelings toward somatic and germline gene editing, sharing the qualified optimism other stakeholder populations have shown while maintaining some reservations. We found that their lived experience with these conditions influenced priorities in implementation, such as balancing identity values with alleviation of critical medical concerns. Improving QoL was an important goal for our participants. However, the potential broader impact that gene editing could have on their children’s identity and society introduces a hesitancy that may be difficult to overcome in the clinical translation of these technologies. Our study demonstrates the importance of including disability communities in stakeholder discussions as gene-editing technologies become more clinically feasible, given the potentially differing priorities for prevention and treatment from the scientific community.

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Author Disclosure Statement

All authors (E.S., N.D., M.M., M.A., K.R., and K.E.O.) state no competing financial interests exist.

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Supplementary Material

Supplementary Table S1
 Supplementary Table S2
 Supplementary Table S3
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 Supplementary Table S6
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