



# Ambiguities faced by parents who received a genetic diagnosis for autistic offspring with intellectual disabilities

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## Abstract

Genetic testing is now routinely recommended for autism and/or intellectual disability (ID), but how parents deal with the uncertainties that may be involved has not been explored. We interviewed 28 parents who had received results identifying *de novo* genetic variants responsible for their offspring's autism. Parents faced six broad types of ambiguities concerning: cause of the *de novo* variant, likelihood of medical manifestations, children's future independence and support needs, availability of future medical benefits/treatments, potential social benefits and potential social harms. These ambiguities prompted anxiety/stress. Parents tried to manage these uncertainties in several ways: focusing on the child's immediate needs, seeking more information, seeking bases of comparison in other children, monitoring for future symptoms (and often enlisting others to do so), seeking metaphors and conceptual frameworks to understand uncertainties, making and accepting trade-offs, and participating in research. Several factors influence these uncertainties and responses, including age/life-stage of the child, psychological factors, concerns about the future of the broader healthcare and insurance systems, potential differences due to geography (e.g., local variations in medical, social and educational services available) and scientific background and literacy. Members of a couple also often perceive and respond to these issues differently. These data, the first to examine the ambiguities that arise when receiving genetic diagnoses for their autistic offspring with ID, reveal the key roles of several social factors and have important implications for future research, education of families, and training and practice of healthcare providers, teachers, social service agencies, policymakers and others.

**Keywords** Genetics · Autism · Phenotypic variation · Uncertainties · Coping · Intellectual disability

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Recently, professional guidelines in the U.S. have recommended that evaluation of people with autism and/or intellectual disabilities (ID) include genetic testing, which most parents support (Johannessen et al. 2022; Srivastava et al. 2019). Views and approaches toward genetic testing for autism vary among countries. In the UK, for instance, guidelines (e.g., National Institute for Health and Care Excellence 2017) do not currently recommend routine genetic testing for autism unless ID or dysmorphic features are also present (Thapar and Rutter 2021). Among parents of autistic children, 61.7% of those in France, but only 27.8% of those in the U.S. reported that their child had undergone diagnostic genetic testing (Amiet et al. 2014). But what types of uncertainties parents may face in receiving and making sense of these genetic results has not been explored.

Approximately 10–20% of autistic people have *de novo* variants of large effect (often a relative risk of 50–100) that are communicated to families as the cause of the person's autism, similar to other highly penetrant genetic contributors

for other conditions, and are almost all associated with ID (Appadurai et al. 2023; Chiurazzi et al. 2020; Hyman et al. 2020; Rylaarsdam and Guemez-Gamboa 2019). Humans each typically have 100–200 *de novo* genetic variants, which are largely randomly distributed (Iossifov et al. 2012). Advanced paternal age is linearly related to *de novo* sequence variants (de Kluiver et al. 2016). Whether other environmental exposures are involved remains unknown. These *de novo* variants are the focus of this paper. In autistic people without ID, single *de novo* variants of large effect size are generally not involved, but rather presumably polygenic and/or other factors.

Genetic testing can provide some information about long-term outcomes and key aspects of the lives of autistic people, although there are limitations in these tests' predictive power, as with behavioral assessments. Among the benefits to autistic people, primarily those whose autism is accompanied by ID, and to family members, is greater specificity regarding the likelihood of associated medical conditions, including seizures, psychosis and Parkinsonism (Chung et al. 2021; Craddock et al. 2019; D'Angelo et al. 2016; Kim et al. 2020; Oyama et al. 2023; Sanders et al. 2018; Webster et al. 2016), which can affect health surveillance and medical management. Genetic tests can also reduce concerns parents may have about risks of recurrence in future offspring, given the potential complexities associated with supporting children with high support needs. Families with an autistic child have a 17.4-fold increased chance of having a second child with autism (Hansen et al. 2019). But when autism results from a *de novo* variant of large effect, the chance of recurrence decreases to only 1% beyond the roughly 2% general population baseline. Genetic diagnoses can also end protracted and financially and emotionally costly “diagnostic odysseys” that families with an autistic child with ID experience (Lappé et al. 2018).

Yet genetic testing for autism has raised several controversies. Certain autism advocates have opposed such testing, concerned about potential applications aimed at eugenics. In 2021, a large British study on autism genetics of among 10,000 autistic people and their families was suspended, following criticism that the investigators had failed to appropriately consult the autism community. Concerns emerged regarding eugenics, sharing genetic data, and the potential benefits of such testing (Sanderson 2021). Many members of the autistic community value the idea of “neurodiversity,” viewing autism as a “way of being” – one of several across a spectrum of differences among people in general, none of which is innately better or worse.

Nonetheless, most autistic people have said that the cause of the condition is biological and that studying causal questions is a valid endeavor (Kapp et al. 2013). Approximately 90% of autistic people – whether diagnosed officially or not – and others without a relationship to the condition,

recruited online, believe that examining such questions about autism is valid, and 46.2% of those diagnosed with autism, 51.3% of those with autistic traits without an official diagnosis, and 28.4% of others said the cause of autism was entirely biological. People with autistic traits endorsed, more than others did, a biological rather than an environmental cause (Kapp et al. 2013). In an online study of people with several kinds of disabilities, 50% of autistic people were interested in their genetic results (Sabatello et al. 2020). In another online study (Byres et al. 2023), 27% of autistic people would have wanted genetic testing as a child, 48% would not, 24% were unsure, and 1% had already been tested as a child; 28% thought parents should make genetic testing decisions for their autistic children, 54% disagreed and 19% were neutral. Autism self-advocates opposed to genetic testing or studies regarding causes of autism may therefore not fully represent autistic people as a whole (Klitzman et al. 2024a, b, c).

Yet these studies of genetic testing in autism have asked questions about testing as *hypothetical* scenarios, and none reported how people or their families who have actually undergone testing view these domains. Key questions therefore remain about how parents of autistic offspring who actually undergo such testing view and respond to test results, and what challenges, if any, they may then face.

People receiving a genetic test result, in general, often confront challenges in understanding it and its implications and may manifest various types of misunderstandings, often related to uncertainties (Klitzman 2009). In genetic testing, along with possible misinterpretations of such tests, have received attention, regarding several medical conditions (Clift et al. 2020). As WGS (Whole Genome Sequencing)/WES (Whole Exome Sequencing) continue to spread and more results of large effect are returned to patients and families, questions regarding uncertainties that may emerge regarding such results, in general, become increasingly crucial.

Uncertainties faced by parents who receive *de novo* results may face are critical because ambiguities, in general, can cause stress. Tolerance of uncertainty has been associated with emotional well-being; and conversely, low tolerance of ambiguity can produce stress (Strout et al. 2018). Han et al. (2011) have suggested a conceptual taxonomy for varieties of uncertainty in healthcare, related, for example, to lack of information, indeterminacy of future probabilities, imprecision in epidemiological estimates, conflicting professional opinions, and multiple factors involved in prognostic estimates. Perceived ambiguities are important since they have been found to be obstacles to patients' willingness to learn their genetic results. Specifically, patients who see results as more ambiguous have less favorable views and beliefs about results and fewer intentions to obtain and share such results, partly due to concerns that results may

be inaccurate or untrustworthy (Taber et al. 2015). The theory of stress and coping suggests that people seek to manage stresses, such as those caused by ambiguity, in several ways, depending on associated factors (Folkman 1984, 2009; Thomsen et al. 2010).

## Methods

### Study aims and rationale

This study aimed to understand what types of ambiguities parents who had received results identifying *de novo* genetic variants responsible for their offspring's autism faced in receiving this information and how they responded to these. These topics are important to shed light on whether parents face stresses due to receiving these results, and if so, what kind, and how they respond. This knowledge can inform the provision of psychosocial and other support from which they might benefit.

### Participants

To explore these issues regarding genetic testing for autism, we surveyed and interviewed parents in the Simons Foundation-funded SPARK (Simons Powering Autism Research 2025) study, which includes over 135,000 autistic people and 250,000 of their family members. As we have described elsewhere (Wynn et al. 2024), 3,597 parents of autistic children, who participated in SPARK and had whole exome/genome sequencing completed between 2017 to 2020, were contacted by email before receiving their genetic test results to see if they would be interested in participating in a survey study; 847 (23.5%) agreed and completed both baseline and follow-up surveys, of whom 148 received a genetic diagnosis for their offspring (Wynn et al. 2024). Among offspring, 76% who received genetic diagnoses and 61% who did not have cognitive impairment.

We also conducted in-depth, semi-structured interviews with a subset of the parents. We have previously examined other, distinct themes that emerged in the interviews regarding the impact of genetic tests on parents' views of their autistic offspring (Klitzman et al. 2025), of reproductive decisions (Klitzman et al. 2024a), and of perceived benefits and limitations of testing (Klitzman et al. 2024b). In addition, we have interviewed autism self-advocates concerning their views of genetic testing (Klitzman et al. 2024a, b, c). Critical questions also arose about whether these parents faced uncertainties in receiving, understanding and responding to these genetic diagnoses, and if so, what kind, how they responded, and what factors might be involved. Hence, we examined these domains as well and present these data here.

We drew on COnsolidated criteria for REporting Qualitative research (COREQ) guidelines (Tong et al. 2007) for conducting qualitative research. The Principal Investigator (PI) has extensive experience conducting and analyzing qualitative interviews (Klitzman 2012; 2015; 2019; Klitzman and Bayer 2003). At the end of the one-month post-disclosure survey, the 148 parents were asked if they would be willing to be contacted for an interview, and 62% (92 of 148) agreed, at which point their contact information was forwarded to one of us (the PI), who then contacted them to arrange a time for the interview. We conducted in-depth qualitative interviews with 28 parents who received *de novo* results, until "saturation" was reached – described as "the point in the research when all concepts are well-defined and explained" (Corbin and Strauss 2014), and "the point at which no new information or themes are observed in the data" (Guest et al. 2006). The interviews each lasted one hour and were conducted by phone from April 2019 through June 2021. Participants were compensated with a \$50 gift card. The Institutional Review Board of the New York State Psychiatric Institute reviewed and approved the study, and all participants gave informed consent. We did not return transcripts to interviewees for checking, but future studies could do so. Inclusion criteria were being a parent who had participated in the SPARK study and had an autistic child or offspring who had received a *de novo* genetic result of large effect.

In all, we interviewed 32 parents (17 mothers and 15 fathers) who had received a genetic diagnosis for their offspring, of whom 28 (15 mothers and 13 fathers) received genetic diagnoses indicating a *de novo* variant and are therefore included in the present analysis. Interviews were all conducted within several months of genetic testing. Of these 28 parents, 96% identified as White and 4% as Latino. The mean age of the parents at the time of the interview was 47.8 years (S.D. = 9, range 32–70); the mean age of the parents at birth of the autistic offspring was 33.7 years (S.D. = 4.5, range: 25–46). They resided throughout the U.S. We interviewed both the mother and the father in six couples; these 28 parents thus had a total of 22 autistic offspring.

As seen in Table 1, 59% of these autistic offspring were male and 41% were female. The mean age of the offspring was 13.6 years (standard deviation = 6; range: 5–38 years), with 14% over 18 years old. Hence, we refer to them here as "offspring" since not all were "children" per se. Seventy-seven percent were diagnosed with intellectual disability or developmental delays. The mean Vineland score, assessing adaptive behavior (Sparrow et al. 2016), was 58 (population mean is 100 with standard deviation of 15), and based on the data, 21/22 (95%) had a "cognitive impairment likely" determination (Shu et al. 2022). Hence, the majority of the offspring of interviewed parents were likely to have had both autism and ID. Two children each had *CUL3* or *POGZ*

**Table 1** Characteristics of Offspring with Genetic Diagnosis of de novo Variants

| Variable  | Number | Percent |
|---|--------|---------|
| <i>Gender:</i>  |        |         |
| Male  | 13     | 59%     |
| Female  | 9      | 41%     |
| <i>Age:</i>   |        |         |
| 0–5 years   | 2      | 9%      |
| 6–12 years  | 8      | 36%     |
| 13–18 years   | 9      | 41%     |
| > 18 years  | 3      | 14%     |
| <i>Vineland 3 Adaptive Behavior: Composite Scores and Levels:</i>   |        |         |
| Range   | 20–79  |         |
| Mean  | 58     |         |
| Median  | 64     |         |
| Adaptive Behavior Level:  | 4      | 18%     |
| Moderately Low (71–85)  |        |         |
| Low (20–70)   | 14     | 64%     |
| Unavailable   | 4      | 18%     |
| <i>Medical Conditions: Major Categories:</i>  |        |         |
| Diagnosed speech and language, Intellectual Disability (ID)/cognitive impairment, Learning Disability (LD) or other developmental delay or developmental disability | 17     | 77%     |
| Birth or pregnancy complications: E.g., Premature birth, Oxygen deprivation at birth, Serious prenatal infection (e.g., Rubella)                                    | 12     | 55%     |
| Attention or behavioral disorders   | 10     | 45%     |
| Mood, anxiety or Obsessive–Compulsive Disorder (OCD)  | 7      | 32%     |
| Sleeping, feeding/eating or toileting problems  | 6      | 27%     |
| Neurological conditions   | 6      | 27%     |

variants, and one each had variants in other autism-related genes (*ADNP*, *CASK*, *CTCF*, *EP300*, *GIGYF1*, *GRIN2B*, *KCNQ5*, *KMT2A*, *KMT2C*, *MED13*, *NRXN1*, *SCN2A*, *SHANK3*, *SYNGAP1*, *TAOK1*, *TBR1*, *TCF20*, *WDFY3*).

## Instruments

The semi-structured interview questionnaire was drafted, drawing on the prior literature (LS Chen et al. 2013; WJ Chen et al. 2020; Hens et al. 2016; Tabor et al. 2011). Questions explored participants' views and experiences regarding autism, focusing on questions of ambiguity, responsibility and identity. The Principal Investigator (PI) for the qualitative study conducted all the interviews. Sample questions, asked of all participants, include those below. (The Supplemental Material contains additional questions from the Semi-structured Interview Guide used in the larger project as a whole.)

- How have you viewed the genetic test results that you received?

- Are there uncertainties that you have faced regarding the genetic test result? If so, what?
- How have you responded to these?

## Data analysis

The methods for the present study adapted key elements from “grounded theory” (Corbin and Strauss 2014), which was used because few empirical data have been published on the subject. Our methods were thus informed by techniques of “constant comparison,” with data from different contexts compared for similarities and differences, to see if they suggest hypotheses. This technique generates new analytic categories and questions and checks them for reasonableness. We engaged in line-by-line coding and data comparison and in iterative analysis, analyzing data during the collection process, reviewing data from each interview after it was conducted, and seeking to develop theory.

Interviews were audio-recorded. Transcriptions and initial analyses of interviews occurred during the period in which the interviews were being conducted, helping to shape subsequent interviews. The PI and two trained research

assistants (RAs) kept and analyzed extensive field notes after each interview, including reactions and potential effects on the interviews, probing issues concerning position and helping to inform analysis. Once the full set of interviews was completed, subsequent analyses were conducted in two phases by RAs and the PI. In phase I, each of these coders independently examined a subset of interviews to assess factors that shaped participants' experiences, identifying categories of recurrent themes and issues that were subsequently given codes. The PI and RAs read each interview, systematically coding blocks of text to assign "core" codes or categories (e.g., sources and types of ambiguities, feelings about ambiguities, ways of managing ambiguities and factors involved, specific types of ambiguities, related to causes of variants, or future symptoms, treatments or support needs, and specific types of ways of managing ambiguities, such as focusing on the present or monitoring of symptoms).

While reading the interviews, a topic name (or sub-code) was inserted beside each excerpt of the interview to indicate the themes being discussed. The PI and RAs then worked together to reconcile these independently developed coding schemes into a single scheme. A coding manual was prepared, defining each code and examining areas of disagreement until reaching consensus. New themes that did not fit into the original coding framework were discussed, and modifications made in the manual, adding these themes, or sub-dividing existing codes, as deemed appropriate.

Codes and sub-codes were then used in analysis of a subset of the interviews, which, to ensure coding reliability, was performed by two coders, who analyzed all interviews. Where necessary, multiple codes were used. Similarities and differences were assessed among participants, examining categories that emerged, ranges of variation within categories, and variables that may be involved. Areas of disagreement were examined through closer analysis until consensus was reached. All interviews were then coded by one of the RAs and the PI. Consistency and accuracy in ratings were checked regularly by comparing earlier and later coded excerpts. To enhance trustworthiness, we triangulated the data with existing literature. During these processes, the researchers continually engaged in reflexivity, exploring their own views, prior understandings and potential biases to check that these did not affect the data collection, analysis or presentation, drawing on extensive field notes and close interactions with autistic people through our Advisory Board and interviews. We discussed the research at all stages with our Advisory Board, which included autistic people and parents who are members of the autistic community, who provided crucial input and feedback on the study aims, design, methods, results, data analysis and implications, and whom we compensated. The researchers also have autistic family members, adding to our sensitivity concerning the perspectives and needs of autistic people, and have worked closely

with autistic patients. We have also previously interviewed autism self-advocates, whom, we found, generally felt that genetic testing was neither wholly good or bad in itself but rather may be acceptable depending on how it is used, and should be employed in beneficial ways (e.g., to make services more available), rather than for harmful purposes) (Klitzman et al. 2024a, b, c). These autism self-advocates have not undergone genetic testing themselves; however, of note, there have been no published articles of autistic people's experiences of undergoing genetic testing themselves. The themes that appeared in the data are illustrated below by excerpts from the interviews. To provide all of the extensive quotes from all of the parents regarding all of these issues is beyond the scope of a scientific journal article, and we have instead included quotes that are representative of the themes that emerged. We have quoted most of the sample (18/28 participants).

## Results

In brief, as outlined in Fig. 1 and described more fully below, parents of offspring undergoing genetic testing for autism confront several types of uncertainties regarding genetics, symptoms, and potential institutional and social benefits and harms, which they responded to in various ways, often shaped by social factors.

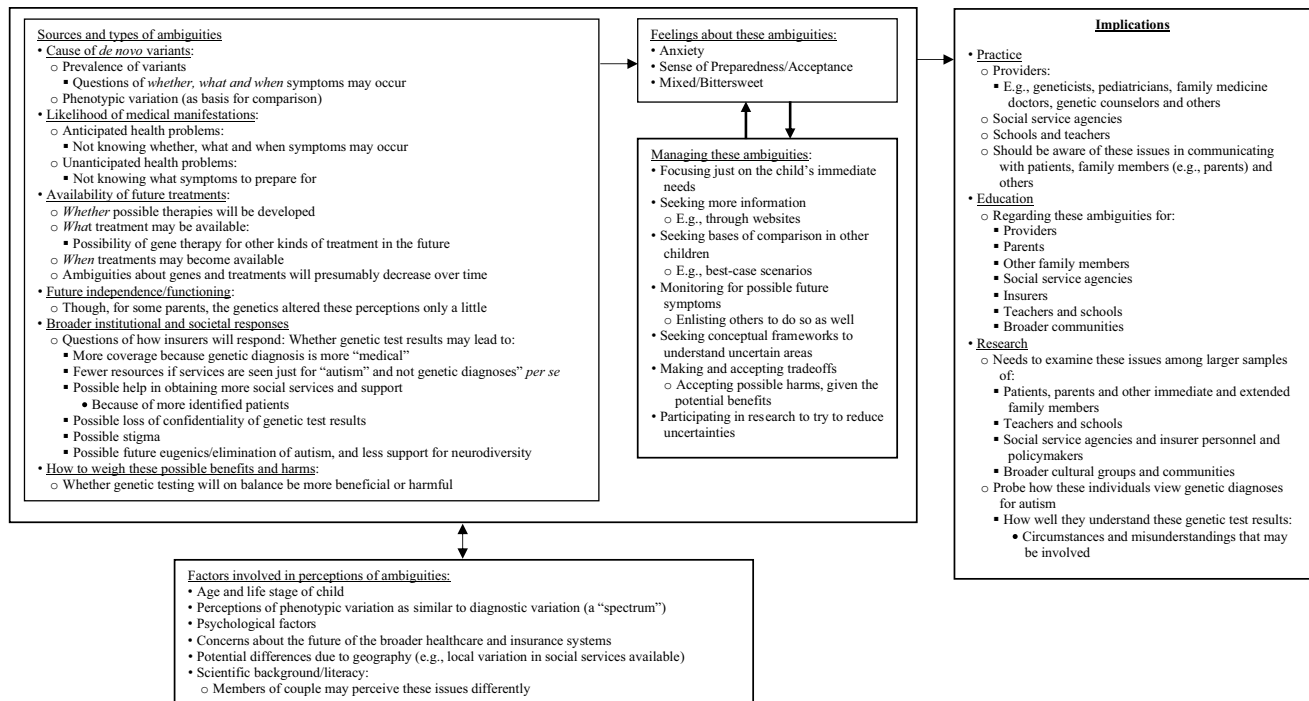
### Types of ambiguities

#### Ambiguities about the cause of *de novo* genetic variants

Parents face uncertainties due to limitations and ambiguities in the current state of genetic knowledge, such as the cause and prevalence of the genetic variant identified for their offspring. Clearly, uncertainties existed beforehand regarding autism as well, but the relatively brief time since the scientific discovery of most of the variants, the small number of people identified with each genetic diagnosis and the offsprings' relatively young ages result in new sources of ambiguity. Only a few dozen cases of some genetic diagnoses have been identified world-wide, and the prevalence and natural history remain unknown. Parents recognized that knowledge is advancing, but takes time. "I'm sure there's lots of people out there who just haven't done the genetic testing, and they'll find more eventually." [Father 3].

Parents can face ambiguities, too, about what caused the variant to occur, and whether they themselves may have inadvertently contributed to it.

...all of those things [mother's actions during pregnancy] are still an issue because something went wrong, but we don't know why. So, while I felt initially



**Fig. 1** Ambiguities Concerning Diagnoses of de novo Genetic Variants for Autism

relieved that it wasn't me, it still could have been... [Mother 12]

Parents wonder about multiple possible environmental exposures that may have played a role.

I've always felt guilty about taking an antibiotic early in my pregnancy, before I knew I was pregnant. Just those niggling fears: 'Did *that* cause it?' I might have had a glass of wine before I knew I was pregnant. 'Could *that* have caused it?' I refinished an old piece of furniture that had been painted: 'Was there lead in that paint? Did I inhale that? Did *that* cause it?' Those are my fears. My husband is older: 'Was his sperm defective?' He's a machinist, exposed to a lot of different chemicals: 'Was it that?' Any of those, I suppose, is still possible. [Mother 1]

### Ambiguities about likelihood of medical manifestations

Parents faced uncertainties, too, regarding both anticipated and unanticipated health problems – not fully knowing *whether, what and when* symptoms may occur. "The second thing [of concern] is that there are a whole host of other potential things that kind of go with this...like schizophrenia." [Father 12] Uncertainties persist about potential variation in phenotypic expression. "I'm sure not every person

has that [bad outcome]...it's prevalent among *some*." [Father 3].

Since clinical knowledge about the likelihood of developing various symptoms is still evolving, parents may be unsure what symptoms to realistically prepare for.

It would be nice, looking at a bigger group of these children, knowing if there were any particularly identified comorbidities/coexisting conditions that we could expect down the road, things we should be looking for, screening for in her life. [Mother 12]

Due to phenotypic variation, certain symptoms may have been reported, but the *likelihood* of these occurring in any particular person may remain unclear, generating anxiety.

The information we received says that the gene typically might present seizures or epileptic issues...Will that be a future problem? We haven't seen it yet...It *could* happen. So, we wonder and worry about that. Is she more likely to have that? Is that going to be an adult issue for her? I don't know. [Father 7]

### Ambiguities about future independence and support needs

Parents confront ambiguities, too, about their child's future developmental progress and potential *independence* and social and other *needs*.

How far will she develop before she stops? What are we going to end up with for the rest of our lives?... What does [our daughter] end up achieving? *That's* the uncertainty. [Father 6]

Parents faced uncertainties prior to undergoing genetic testing as well, but now have further questions of what, if anything, the results may change. The test results might alter these ambiguities only a little, if at all.

The harder thing for me is not knowing whether he will be able to be independent. Is he going to be ok on his own? Or at least semi-independent... And does having the genetic test result change that? It's a tough one. I don't know. It's hard to say. Maybe a little bit – I wouldn't say a lot. Everything's still up in the air. [Mother 1]

A person's alignment with the medical/social/psychological model of disability may influence their perception of autism genetics research, genetic testing and treatments, but did not appear to be strongly associated with their perceptions of the *ambiguities* per se of genetic test results. Parents generally supported a neurodiverse perspective.

I would probably just describe autism as a 'condition'... It's just like having brown eyes or blue eyes, or red hair, which is very rare... It's different than a lot of other people, but obviously not a disease... [Mother 3]

But parents still saw their offspring as having support needs, and felt it was unclear whether such test results would change these needs, and if so, to what degree. At times, parents grappled to bring together a neurodiversity perspective with their child's needs for high levels of support and inability to live independently.

I absolutely agree that there is a neurodivergence, and that's good and needs to be respected... But that doesn't always help – I don't find that overly helpful to parents who are just trying to swim through oceans of information to try and help how to best support their kids. [Father 12]

### Ambiguities about medical benefits/possible treatments

Uncertainties emerged, too, about possible future interventions or treatments – e.g., whether therapies will be developed based on the genetic diagnosis, and if so, when. Uncertainties also arose, for instance, about *what types* of treatment might be available in the future:

There's always some glimmer of hope as we figure out more and more about genetic treatments. There's

always that glimmer about CRISPR-Cas9 and all this other stuff. [Father 6]

Parents with a scientific background might imagine or envision various potential future interventions, based on recent advances in science more broadly.

The chances of any kind of genetic treatment are pretty low. But a gene product treatment – if you could replace...the protein the gene codes for – offers hope. Or, some medicines look like they might upregulate ADNP [Activity-Dependent Neuroprotective Protein] expression. [Father 4]

Yet, *when*, if ever, such treatments might become available remained unclear. "If I'm guessing, treatments probably won't be in [my son's] lifetime – but I don't know that." [Mother 1].

Parents commonly recognize that ambiguities about genes and treatments will presumably decrease over time, but not for several years.

We would like to be in this situation maybe 10-15 years down the road, when we know a lot more about other people with this mutation and how it will change interventions... [Father 5]

### Ambiguities about social benefits

Parents encountered uncertainties, too, regarding benefits and risks concerning future institutional and societal responses, related to stigma, institutional and structural factors, future insurance coverage and social services.

Testing could provide a sense of preparedness and enhanced acceptance of possible future symptoms.

It may give you worries... It made us think: consider things that may be an issue that we had never thought about, but at least we now know! At least, going forward, we will *be better prepared* to deal with that... The fact that we have this information gives us a head start on being able to identify any issue. There is some uncertainty there, but again, having the information gives us sort of a *jumpstart* on the symptoms that might start to show up. [Father 1]

Discovery that a child has a genetic diagnosis might prompt more insurance coverage and social services than does a non-specific autism diagnosis alone.

Insurance may actually end up covering more of the services that [my son] needs because there is a *genetic* component that you can point to, whereas now they don't cover a lot of things because autism is just a very broad term. Genetic testing might actually

be a benefit to [getting] service[s], because there's something that you can actually point to as a *medical* cause. [Father 1]

The genetic diagnosis could therefore potentially help in obtaining resources and support, at least if and when more patients are identified:

This mutation has only been seen since 2010. I just think of all the people who haven't been tested who could have this diagnosis. More people who are older who have it will create a larger group, which can help in figuring out what to do when people with this diagnosis get older – maybe find funding to create some living places for them. [Mother 7]

### Ambiguities about potential social harms

Alternatively, changing diagnoses due to genetic testing could lead to reevaluation and *decreases*, rather than increases in services provided.

We talked to his pediatrician about it and shared the information. She said that from a services standpoint, as far as the state is concerned, we want to continue to list it as 'autism,' because autism has all kinds of the different services and funding packages that go along with the autism diagnosis. If you change that and say, 'It's a genetic disorder with autism-like symptoms,' there might actually be a loss of services. [Mother 11]

Parents may therefore feel uncertain and uneasy about whether and how to approach the topic with insurance companies. "I'm unsure how I would explain it as a diagnosis [to the insurance company]." [Mother 6].

The presence of stigma and discrimination fuel these uncertainties, and parents vary in their levels of confidence and concern regarding the future of the broader healthcare and insurance system.

The status of our healthcare system in general, the fact that they can later charge us for something or take away rules or laws is scary. It's a scary environment out there... We participate in a lot of studies to try to get the edge on his treatment, but also wonder about how is [the genetic diagnosis] going to affect his ability to find a job or have health insurance later on? I don't know what that world is going to look like ten or 20 years from now... My faith in the political system has not been very good in the past few years. [Mother 8]

Interviewees described uncertainties, too, about broader possible future loss of confidentiality and increased or decreased stigma as a result of genetic testing.

I don't know how much somebody can guarantee me that what we've done with our saliva isn't [shared inappropriately after being used for genetic testing]. I don't know how 100% sure they can be of that. Once your information is out there, it's out there. [Mother 5]

Given stigma, parents also wondered if genetic etiologies will lead to elimination of autism or decreased support for neurodiversity. Parents were concerned that their autistic offspring might face or fear heightened stigma and discrimination – potential worries that an autistic person might think, "Now that they've labeled me, I'll be easier to be pointed out, or maybe genetic testing in the future will eliminate people like me." [Mother 8].

### Anxieties and stresses due to uncertainties

These uncertainties triggered, in turn, a range of emotional reactions, including anxiety and stress. Parents felt ambiguities about how to weigh possible benefits and harms, and whether genetic testing will on balance be more beneficial or harmful. Not surprisingly, parents may also feel mixed and bittersweet emotions, glad to receive the information, but wishing that there were fewer uncertainties and more medical actionability.

It's bittersweet, because I feel we're on the front edge of everything. It would be nice to get this information, and have the time be 10 years from now, not today, when we're finding out, 'Oh, you're one of 12, and we know nothing about it. But keep in touch, and maybe someday we'll get information.' So, it's a little bit of a mixed bag. [Mother 5]

### Managing these ambiguities

Parents sought to manage these uncertainties in several ways – trying to focus on the child's present needs by comparing one's child to others with the same genetic diagnosis, seeking to obtain more information online or from other sources, joining support groups or disease advocacy organizations, or being proactive in other ways.

In the face of these varied uncertainties, many parents concentrate just on their child's short-term needs:

It's maybe just that glimmer of hope that maybe someday there's going to be something out there that will help us, but in the meantime you still have to plan for what his *current* path is right now. [Mother 11]

Parents also sought bases for comparison, trying to look at other children with the same genetic diagnosis as their child to gauge best- or worst-case scenarios. "We look at some of these other kids, and some of them are clearly

disabled, but they can even order from Starbucks with help and stuff like that.” [Father 6].

Parents sought, too, to be as prepared as possible, by monitoring for potential symptoms. They may feel that they must accept such challenges, if and when these arise in the future, and that they can’t anticipate specifics too much, but rather must just watch and be ready for the development of these new challenges. “We started to get more frightened about, ‘Ok, yes, we definitely want to make sure that we’re keeping our eyes open for all these things.’” [Father 12].

Parents can also enlist others to monitor for new symptoms.

Our daughter has never experienced a seizure that we’ve noticed or seen or caught. So, that’s definitely something to keep an eye on. We did let the school-teachers and the school know that. Just be aware: if she ever does have a seizure. It could happen. [Father 7]

Parents also sought conceptual frameworks and metaphors for grasping these vagaries. Autism is commonly seen as constituting a “spectrum,” and this conceptualization can serve as a model for understanding the wide possible variations for a genetic diagnosis as well.

Even just having the autism diagnosis...there’s such a huge spectrum of who can manage to function independently, and deal with things. To me, what I’m seeing, it’s kind of the same with [name of genetic variant]. [Mother 1]

Parents also balanced and accepted trade-offs regarding these uncertainties, seeing the value of having the genetic diagnosis as outweighing the challenges posed by these ambiguities. They thus accepted possible harms, such as impingements on privacy, given the potential benefits.

I’m just not putting my time into concerning myself with [threats to confidentiality]. I’d rather have the knowledge and contribute to this pool of genetic information they’re trying to gather on these kids. I’m happy to do that. So, maybe the sacrifice of whatever is to come is, for me, I guess worth it. [Mother 5]

Parents also seek online information and groups to help reduce or cope with uncertainties.

The only thing [the genetic diagnosis] changed was wondering if we had made sure that health-wise, everything was ok for my son, because he still complains about a lot of different things...I don’t know if he maybe should have gone to an endocrinologist – because I belong now to a couple of the Facebook groups, and realize that a lot of the symptoms can vary quite a bit, so parents will post, ‘Does your

child have this issue?’ And then a lot of people will post about what they’re experiencing. [Mother 16] In efforts to help reduce these uncertainties, parents participated in research as well.

The genetic diagnosis is such a new finding that there’s not a lot of information out there about it. Our hope is that by doing this study, maybe [my daughter’s] grand-kids will have that information. [Mother 12]

### Factors involved in perceptions of, and responses to, ambiguities

Several factors can affect views and responses toward these uncertainties, including the age and life stage of the child. Many parents with younger children, in particular, “hope for the best” – i.e., relatively less support needs. “She has time. She does continue to develop new skills and new interests.” [Father 6].

Yet a child’s older age could make some of these uncertainties more worrisome. “As he’s getting older, we’re definitely wondering more, ‘Will he be able to be on his own? Is he going to end up living with us all of his life?’” [Mother 1].

A parent’s personal or professional characteristics can shape responses to uncertainties as well. Often one, but not the other parent had education or background in, or familiarity with, science or worked in healthcare, and hence took the lead in grappling with these genetic issues, better understanding these uncertainties and making necessary medical decisions, and was trusted by his or her spouse to do so. This phenomenon reflected a larger pattern of members of a couple frequently having a division of labor, with each focusing on different aspects of needs and issues concerning their offspring.

My husband is my researcher...He is a nurse anesthetist...He loves the knowledge, and the research...He makes me try to understand what he’s reading, and even about the testing. If he says to me, ‘I think we should do this and this,’ I look at him and say, ‘Honey, I trust you.’ Let’s try it.’ [Mother 15]

Pre-existing psychological traits may also differ among members of a couple, affecting degrees of anxiety they each experience regarding their offspring’s autism and the uncertainties involved.

My wife can be a *worrier*, and still had questions: was there something she did? [The genetic diagnosis] changed that significantly. But there might still be some *lingering*...We had a long conversation about what can cause the mutation. I told her it could be anything. It could be cosmic radiation blasting through the planet constantly. All it takes is one little dink on

a sequence chain, and you've got a mutation. So, *we don't really know what caused it*. We can relax and have some peace of mind that it wasn't necessarily drinking diet soda or a meal we had out somewhere that did something funny...*But it pops up in the back of her head... 'Could it have been this? Could it have been that?'* [Father 1]

## Discussion

These data suggest that parents receiving a genetic diagnosis about their autistic child who, in most cases, also had ID, confront and seek to manage six broad types of ambiguities and are shaped by social and community factors. These six kinds of uncertainties concern were: causes of *de novo* genetic conditions, likelihood of medical manifestations, availability of future treatments, future independence and support needs, and broader societal responses, including health and social service policies. These vagaries arise in part because scientific knowledge about these newly discovered genetic conditions is relatively sparse and rapidly evolving, and the effects of such knowledge on stigma and discrimination are unclear. In general, knowledge can help reduce anxiety, but scientific knowledge about these relatively rare genetic diagnoses and the societal implications remain relatively limited. Such uncertainties can generate fears and anxieties (Carleton 2012; Medendorp et al. 2021).

For several reasons, many parents find pure randomness, in addition to uncertainty, hard to accept emotionally, creating anxieties (Carleton 2012; Medendorp et al. 2021). Prior research has examined VUSs associated with other diagnoses; yet the current data highlight how with autism, even when the genetic finding is clearly of large effect, uncertainties can persist, regarding the six areas mentioned above. While Taber et al. (2015) suggest that perceived ambiguity of results may be associated with beliefs that these results are inaccurate or untrustworthy, the present data suggest that ambiguity can be associated not with untrustworthiness or inaccuracy, but with the fact that knowledge itself is limited and still evolving and social, not just medical, implications are unclear. In the present data, none of the parents questioned the accuracy of the results. Thus, specific types and sub-types of uncertainties may arise regarding tests for particular conditions, due to several factors, such as the current amounts of clinical, genetic and epidemiological knowledge about the specific genetic variant and the condition and broader health and social attitudes and policies. These results thus underscore needs for ongoing collection and dissemination of clinical research data to reduce some of these ambiguities.

These data indicate that parents commonly wrestle with uncertainties regarding *why de novo* variants exist, what phenotypic expression will result, and what other medical and social benefits and harms may ensue from genetic testing, including whether treatments or other interventions may become available and, if so, when and what, whether stigma and discrimination will lessen, and how to manage these quandaries. Given that, in general, people seek causes for stressful events, and assign blame for problems (Alicke 2000; Evans-Pritchard 1937), in the face of these uncertainties, parents looking for explanations may fault themselves. Even in the absence of a genetic diagnosis, parents of an autistic child express certain concerns for their offspring and his or her future (Rivard et al. 2014). Yet the current data suggest how parents receiving a genetic diagnosis, who may have assumed that the information would be definitive and concrete and lead to treatment and prognostic certainty, find that it can introduce new uncertainties.

The theory of stress and coping describes how people seek to manage stresses (Folkman 1984, 2009; Thomsen et al. 2010). The current data indicate that genetic testing produces several stresses related to types of medical and social uncertainties, which people then try to handle by, for instance, focusing just on the child's immediate, rather than longer-term potential needs, seeking more information from websites and support groups, seeking bases of comparison in other children, monitoring for possible future symptoms and seeking conceptual frameworks. Yet anxiety may still persist, albeit often lessened. Several factors influence these uncertainties and responses to them, particularly a child's age and the parent's experience with science and/or healthcare and thus inclination to be proactive in addressing and monitoring these domains. While Han et al. (2011), suggested a taxonomy of types of uncertainties in healthcare, the present data highlight, too, an additional type: uncertainty about the social implications of medical information. This research thus also suggests how families may benefit from enhanced community and psychosocial support regarding these ambiguities and the stresses that can ensue, which patients may cope with in better or worse ways, and which such support can assist in confronting.

Some scholars have wondered why assessments of impacts of genetic testing through structured questionnaires may not, overall, be more pronounced (Parens and Appelbaum 2019). The fact that these uncertainties may produce "mixed" or "bittersweet" feelings – of both relief but also challenges – may help to explain why. These ambiguities can trigger competing and conflicting responses that may effectively cancel each other out in quantitative findings that seek to assess overall impact of test results. Genetic tests results often provide some answers, but also create uncertainties, and hence may not be wholly positive or all negative.

These issues are increasingly vital as genetic testing for autism expands. Of note, currently identified genetic variants tend to be *de novo* and associated with ID. As scientific understanding of autism genetics advances, and genetic variants are discovered that are less penetrant or robustly associated with autism, the responses of autistic people with such variants who have lower-support needs may differ from the responses of parents interviewed here, who are learning of more highly-penetrant variants that are also usually associated with ID. Such differences may arise because variants that are less penetrant or strongly associated with autism will likely also be less associated with medical symptoms such as seizures and psychosis, and have fewer potential implications for future reproductive decisions.

Increasingly, autistic people will be undergoing genetic testing, and geneticists, genetic counselors, pediatricians and other providers should thus be aware and prepared to address these ambiguities that parents and autistic persons may face, reflecting in part the fact that scientific knowledge about these variants remains limited due to the relatively small number of cases identified thus far.

These findings have several critical implications for future education of providers, patients, families, insurers, social service agencies, teachers, and the public, and for practice and research. Geneticists, genetic counselors, pediatricians, family physicians, and mental health and other providers should be aware of the challenges that parents may face and of ways to help address these (e.g., by focusing on the child's immediate needs), assisting parents in recognizing that evidence does not indicate that these parents have in fact done "anything wrong." Since these uncertainties will no doubt continue, at least for the foreseeable future, providers should receive training on how best to convey and frame these in beneficial and realistic ways. Heightened awareness, among parents, providers, autistic people, policymakers, social service agencies and the wider public, of concerns about stigma can also help reduce discrimination.

Recommendations have been made for communicating medical uncertainty to patients in all aspects of medicine, including acknowledging and warning patients about inherent uncertainty, exploring patients' preferences regarding such vagaries, explaining these ambiguities in understandable, concrete and structured ways, using nonverbal as well as verbal communication, checking patients' understandings, identifying coping strategies and ways of managing the uncertainty, and emphasizing ongoing involvement with the patients' care (Medendorp et al. 2021). Pediatricians, internists, neurologists, psychiatrists, geneticists, genetic counselors, and others should receive such training regarding autism. Such training should emphasize, for instance, needs to present the likelihood of future symptoms in ways that patients and families can best understand. In conveying such statistical information to parents, the use of visuals and

absolute probabilities have been shown to be more effective than odds ratios. (Garcia-Retamero et al 2015).

These data have several potential limitations. They are based on a sample of 28 parents, which is sufficient for qualitative analysis (Guest et al. 2006; Hennink et al. 2017). Specifically, Guest et al. (2006), concluded that 12 interviews can, in general, largely reach data saturation. A systematic review examining sample sizes for saturation in qualitative research found that studies reached saturation with 9–17 interviews (Hennink and Kaiser 2022). Nonetheless, additional studies using larger samples can help elucidate these issues further. The sample was mostly white, but future studies can and should therefore include greater ethnic and racial diversity, in part given health disparities in access to genetic services. Though several interviewees spontaneously discussed how their own and their spouses' professional backgrounds shaped their views and approaches toward their offspring, we did not systematically gather data on details of all of the past and present professional and educational experiences of all interviewees and their spouses. Future research, however, should investigate whether one or both parents had had courses, training or work experiences in science and/or healthcare. Since the study participants were parents of autistic offspring who mostly also had ID, the findings' generalizability to the broader population of all parents with autistic children may be limited. However, future research can explore these issues with other groups of parents as well. We did not return transcripts to interviewees for checking, but future studies can do so.

These data suggest several additional avenues for future research: to study with larger and more diverse samples how parents and others, including providers (e.g., geneticists and other physicians), insurers, autistic people, social service agencies, teachers and the child's neurotypical siblings perceive, manage and respond to these various ambiguities, what factors are associated with having relatively more or less difficulty comprehending or managing such ambiguities, and what educational and support approaches are most effective. It is especially critical to examine perspectives on these issues among autistic people who have undergone genetic testing – including diverse autistic voices (such as people who are non-speaking, or culturally or linguistically diverse). Interviewing autistic people with ID about these issues would also be important. We had attempted to do so, using a version of our semi-structured instrument, but this approach did not appear effective, and needs became apparent to develop a different method, which future studies can and should pursue, systematically developing, revising and testing research designs.

These data, the first to examine how parents with offspring who receive *de novo* genetic findings view and

respond to the ambiguities involved, have important implications for future education, practice, policy and research.

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**Data availability** The interviewees discussed identifying details in their open-ended responses, concerning themselves, various family members and providers, and the process of de-identification would be very difficult and complicated, so that the data are not publicly available. Data used are available from the corresponding author on reasonable request.

## Declarations

**Conflict of interest** The authors declare no competing interests.

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