

IN TREATMENT: Ryace Boyer, a 14-year-old high-school student, prepares to take the female hormone estrogen as part of her gender-affirming medical care. REUTERS/Megan Jelinger

Across the United States, thousands of youths are lining up for gender-affirming care. But when families decide to take the medical route, they must make decisions about life-altering treatments that have little scientific evidence of their long-term safety and efficacy.

By CHAD TERHUNE, ROBIN RESPAUT, and MICHELLE CONLIN | Filed Oct. 6, 2022, 11 a.m. GMT

BELPRE, Ohio

n the two-hour drive back from the hospital, Danielle Boyer kept replaying the doctor's questions in her mind. Was her then-12-year-old child, Ryace, hearing voices? Was she using illegal drugs? Had she ever been hospitalized for psychiatric treatment? Had she ever harmed herself?

Danielle was still shaken when she and Ryace arrived home in this small town nestled in a bend of the Ohio River. Dinner would have to wait. She had to talk to her husband. "They were asking us these sad, terrible questions," she told Steve Boyer as the two sat in their garage that August 2020 evening. "Do you know kids have tried to kill themselves?"

"I had no idea," he said.

Ryace (pronounced RYE-us) was assigned male at birth, but by the time she was 4, it was clear to her parents that she identified as a girl. She referred to herself as a girl. She wanted to dress as a girl. But her parents feared for her safety if they let her live openly as a girl in their tightly knit rural community. So they struck an uneasy compromise. At home, Ryace could be a girl, wearing makeup and dresses. At school, around town and in family photos, Ryace would remain a boy.

Ryace chafed at the restrictions. When she started middle school, she grew increasingly anxious about what puberty would bring: facial hair, an Adam's apple, a deeper voice. That's when Danielle sought help at Akron Children's Hospital and its new gender clinic, where staff told her they could treat Ryace with puberty-blocking drugs and sex hormones to help her transition.

"This is what I've always wanted," Ryace told her mother as they left the hospital. Afterward, the pair went on a celebratory shopping trip for girl's clothes. Danielle was relieved. After years of struggling in isolation to do what they thought was best for Ryace, the Boyers were now getting expert help from people who understood their situation.



LONG-AWAITED NEWS: When clinic staff told Ryace Boyer they could help her transition, she told her mother: "This is what I've always wanted." REUTERS/Megan Jelinger

But the initial consultation brought troubling new questions. The doctor at the Akron clinic told Danielle and Ryace that puberty blockers could weaken Ryace's bones. The effects on her brain development and fertility weren't well-understood. The risk of inaction was even more alarming: Without treatment, the doctor said, Ryace would remain at increased risk of suicide.

Mention of suicide raised the stakes. "She's been asking for how many years now to be a girl?" Danielle said to her husband as they sat talking in their garage that evening. "We just keep telling her no, and we're crushing her. If they can help us, let's do this."

The United States has seen an explosion in recent years in the number of children who identify as a gender different from what they were designated at birth. Thousands of families like the Boyers are weighing profound choices in an emerging field of medicine as they pursue what is called gender-affirming care for their children.

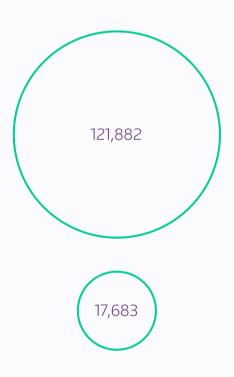
Gender-affirming care covers a spectrum of interventions. It can entail adopting a child's preferred name and pronouns and letting them dress in alignment with their gender identity – called social transitioning. It can incorporate therapy or other forms of psychological treatment. And, from around the start of adolescence, it can include medical interventions such as puberty blockers, hormones and, in some cases, surgery. In all of it, the aim is to support and affirm the child's gender identity.

But families that go the medical route venture onto uncertain ground, where science has yet to catch up with practice. While the number of gender clinics treating children in the United States has grown from zero to more than 100 in the past 15 years — and waiting lists are long — strong evidence of the efficacy and possible long-term consequences of that treatment remains scant.

Puberty blockers and sex hormones do not have U.S. Food and Drug Administration (FDA) approval for children's gender care. No clinical trials have established their safety for such off-label use. The drugs' long-term effects on fertility and sexual function remain unclear. And in 2016, the FDA ordered makers of puberty blockers to add a warning about psychiatric problems to the drugs' label after the agency received several reports of suicidal thoughts in children who were taking them.

More broadly, no large-scale studies have tracked people who received gender-related medical care as children to determine how many remained satisfied with their treatment as they aged and how many eventually regretted transitioning. The same lack of clarity holds true for the contentious issue of detransitioning, when a patient stops or reverses the transition process.

The National Institutes of Health, the U.S. government agency responsible for medical and public health research, told Reuters that "the evidence is limited on whether these treatments pose short- or long-term health risks for transgender and other gender-diverse adolescents." The NIH has funded a comprehensive study to examine mental health and other outcomes for about 400 transgender youths treated at four U.S. children's hospitals. However, long-term results are years away and may not address concerns such as fertility or cognitive development.



U.S. children ages 6 to 17 diagnosed with gender dysphoria from 2017 through 2021

U.S. children starting on puberty blockers or hormones over the five-year period

Reliable national data on how many children receive care for gender dysphoria – defined as a feeling of distress from identifying as a gender different from the one assigned at birth – have long been unavailable. <u>To get some idea</u> of the increasing prevalence of these cases, Reuters asked health technology company Komodo Health Inc to analyze its database of U.S. insurance claims and other medical records on about 330 million Americans. The analysis, the first of its kind, found that at least 121,882 children ages 6 to 17 were diagnosed with gender dysphoria in the five years to the end of 2021. More than 42,000 of those children were diagnosed just last year, up 70% from 2020.

Though smaller, the number of children receiving medical treatments like those the Akron clinic outlined for the Boyers is also growing fast. The number of children who started on puberty-blockers or hormones totaled 17,683 over the five-year period, rising from 2,394 in 2017 to 5,063 in 2021, according to the analysis. These numbers are probably a significant undercount since they don't include children whose records did not specify a gender dysphoria diagnosis or whose treatment wasn't covered by insurance.



FACING REALITY: Ryace identified as a girl from early childhood, and after her mother took her for her first appointment at the Akron Children's Hospital's gender clinic, she was eager to start medical treatment to transition. REUTERS/Megan Jelinger

Social acceptance

The surging numbers reflect in part the success of years of advocacy for transgender rights, which doctors say has made more children and their families comfortable about seeking help. Transgender children still live with discrimination, bullying and threats of violence. But as transgender identity has become more visible in popular culture, children with gender dysphoria have gained ready access on TV and social media to positive representations of young people who have received professional gender-affirming care.

Gender care for minors gained further legitimacy as medical groups endorsed the practice and began issuing treatment guidelines. Chief among them is the World Professional Association for Transgender Health, a 4,000-member organization that includes medical, legal, academic and other professionals from around the world. Over the past decade, its guidelines have been echoed by the likes of the American Academy of Pediatrics and the Endocrine Society, which represents specialists in hormones.

In its latest Standards of Care, released in September, WPATH notes the paucity of research supporting the long-term effectiveness of medical treatment for adolescents with gender dysphoria. As a result, the guidelines say, "a systematic review regarding outcomes of treatment in adolescents is not possible." The Endocrine Society, in its own guidelines, acknowledges the "low" or "very low" certainty of evidence supporting its recommendations.

The federal government eased the path to treatment in 2016, when the administration of President Barack Obama prohibited health insurers and medical providers from limiting care because of a person's gender identity. That prompted an expansion of public and private insurance coverage for gender-affirming care, including for children, which can cost tens of thousands of dollars a year for puberty blockers alone.

Today, more than half of states pay for gender-transition treatment through Medicaid, the government health insurance program for millions of low-income families. Nine states exclude youth gender care from Medicaid coverage. Florida, in its Medicaid prohibition, says treatments

for gender dysphoria "do not meet the definition of medical necessity."

That disparity among states is symptomatic of how gender-affirming care has become a flashpoint in the nation's highly polarized politics.

Many conservatives decry it as a form of child abuse. "You don't disfigure 10, 12, 13-year-old kids based on gender dysphoria," Florida Governor Ron DeSantis, a Republican, said at an August news conference, just days before his state banned Medicaid coverage of gender care for children. Alabama, Arkansas and Texas have enacted laws or policies to broadly limit children's access to care, all of them since blocked by courts. In more than a dozen other states, including Ohio, where the Boyers live, legislators have introduced bills that would ban care or penalize providers for treating children.

"Gender-affirming care for transgender youth is essential and can be life-saving."

Dr Rachel Levine, assistant secretary at the U.S. Department of Health and Human Services

At the same time, at least a dozen states, including New York, California and Massachusetts, have aligned with transgender advocates and many medical providers by ensuring that children are guaranteed access to care. And in July, the Biden administration proposed an expansion of the Obama-era protections.

"Gender-affirming care for transgender youth is essential and can be life-saving," Dr Rachel Levine, an assistant secretary at the U.S. Department of Health and Human Services, said in an interview with Reuters.

Levine, a pediatrician and a transgender woman, drew outcry from conservative opponents of children's gender care and some medical professionals earlier this year when she told National Public Radio: "There is no argument among medical professionals – pediatricians, pediatric endocrinologists, adolescent medicine physicians, adolescent psychiatrists, psychologists, et cetera – about the value and the importance of gender-affirming care."



NO PROBLEMS: Dr Rachel Levine, a U.S. assistant secretary for health, says fears that American children are being rushed into treatment are unfounded and that no children are receiving drugs or hormones for gender dysphoria who shouldn't. Chris Smith/U.S. Department of Health and Human Services/Handout via REUTERS

Levine was right, insofar as healthcare providers generally agree that anyone with gender dysphoria has a right to supportive care, whether that entails social transition, or counseling and therapy, or medical interventions. But her statement glossed over deep fissures that have opened within the gender-care community over the way treatment has evolved in the United States as new patients pour into clinics.

A growing number of gender-care professionals say that in the rush to meet surging demand, too many of their peers are pushing too many families to pursue treatment for their children before they undergo the comprehensive assessments recommended in professional guidelines.

Such assessments are crucial, these medical professionals say, because as the number of pediatric patients has surged, so has the number of those whose main source of distress may not be persistent gender dysphoria. Some could be gender fluid, with a gender identity that changes over time. Some may have mental health problems that complicate their cases. For these children, some practitioners say, medical treatment may pose unnecessary risks when counseling or other nonmedical interventions would be the better choice.

"I'm afraid what we're getting are false positives and we've subjected them to irreversible physical changes," said Dr Erica Anderson, a clinical psychologist who previously worked at the University of California San Francisco's gender clinic. "These errors in judgment are fodder for the naysayers – the people who want to eradicate this care." Anderson, a transgender woman who still treats children with gender dysphoria in her private practice, resigned as president of WPATH's U.S. chapter last year after her public comments about "sloppy" care prompted the organization to issue a temporary moratorium on board members speaking to the press.

In Europe, concern that too many children might be unnecessarily put at risk has prompted countries like Finland and Sweden that were early to embrace gender care for children to now limit access to care. The United Kingdom is shutting down its main clinic for children's gender care and overhauling the system after an independent review found that some staff felt "pressure to adopt an unquestioning affirmative approach."

Ranged against those advising caution in the United States are members of the gender-care community who say that denying treatment to any child with gender dysphoria is unethical and dangerous. "You shouldn't have to jump through hoops to prove your own trans-ness," said Dallas Ducar, a psychiatric nurse practitioner and trans health provider in Massachusetts.

Ducar and officials at other clinics said the waiting lists at many facilities show that children already face significant barriers to treatment due to a shortage of providers and a persistent stigma in healthcare attached to transgender patients. "If you put unnecessary roadblocks in the way, we know the kid will still be trans and they will continue to experience deep psychological stress that increases the risk of suicide attempts or suicide itself," Ducar said.

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Dr Marci Bowers, a surgeon specializing in transgender procedures who became WPATH's president in September, said in an interview that the organization is trying to find a middle ground between "those who basically would have hormones and surgeries available at a vending machine, let's say, versus others who think that you need to go through all sorts of hoops and hurdles."

In its new Standards of Care, WPATH retained its longstanding recommendation of comprehensive assessments to determine that adolescents are suitable for medical treatment. "There are no studies of the long-term outcomes of gender-related medical treatments for youth who have not undergone a comprehensive assessment," the guidelines note. Without such evidence, the document adds, "the decision to start gender-affirming medical interventions may not be in the long-term best interest of the young person at that time."

Levine, the U.S. assistant secretary for health, said that clinics are proceeding carefully and that no American children are receiving drugs or hormones for gender dysphoria who shouldn't. "It's not like anyone who arrives automatically gets medical treatment," she said.



EYES OPENED: Ryace says young transgender people she saw on television and online helped her realize she could transition. REUTERS/Megan Jelinger

A good candidate

Belpre, Ohio, is in Washington County, a rural community of farmhouses, trailer homes and churches set among lush green hills. The area has been home to generations of Boyers. Danielle, 37, works in education. Steve Boyer, a 36-year-old plumber and pipefitter, has served on the board of a local fair, where Ryace and her older brother, Aiden, have shown ducks and lambs they tended. Weekends are spent camping or attending horse shows where Ryace, an accomplished equestrian, competes in barrel races and roping events. "Everybody knows the Boyers," Steve said.

Steve and Danielle had no direct experience with transgender people when Ryace was born. By around age 4, she referred to herself as a girl, played with girls at friends' houses and became fascinated with women's clothing and jewelry. On Christmas morning 2011, shortly before her 4th birthday, Ryace was thrilled when she got much of what she had wanted from Santa: Barbie dolls, a dollhouse, and toys in pink and purple.

But Danielle feared Ryace wouldn't be accepted as a transgender girl in their conservative community, and she wanted to protect her child from the stares, hateful comments and broken relationships that would inevitably come. "The agreement was, house only," Danielle said.

Ryace constantly pushed back. From early on, when friends and neighbors complimented her as a cute little boy, she would correct them: She was a girl. Danielle then felt compelled to correct Ryace.

Danielle sought compromises. In elementary school, they often settled on outfits for Ryace of neutral black leggings and brightly colored T-shirts. She picked up dresses and hair pins at yard sales and let Ryace wear them at home. On trips into town, Danielle had Ryace take off the dresses she wore over her boy's clothes and leave them in the car.

As middle school – and puberty – loomed, Ryace started sneaking bras and mascara to school. She repeatedly texted her mom, "Will you start calling me a girl?"

Television and the internet had opened Ryace's eyes to new possibilities. She watched "I Am Jazz," the reality TV show about Jazz Jennings, a transgender girl who socially transitioned at an early age and went on to take puberty blockers and hormones and have surgery. She watched young people on YouTube discuss gender dysphoria and their transitions and saw the beforeand-after images they shared. On Instagram, she followed Nikita Dragun, a makeup artist and model who came out as transgender as a teenager and now has 9 million followers.

"This is actually a thing," Ryace recalled thinking at the time. "I can actually do this."



FAVORITE PASTIME: Ryace is a passionate equestrian and regularly competes in local horse shows. REUTERS/Megan Jelinger



 $A \ PAINFUL \ VICTORY: When \ Ryace \ was \ crowned \ Horse \ Princess \ at \ a \ local \ fair, some \ members \ of the \ crowd \ grumbled. \ REUTERS/Megan \ Jelinger$



ACCOLADES: Ryace has adorned a wall in her bedroom with awards from sports and horse competitions. REUTERS/Megan Jelinger

Ryace is the type of child that doctors in the Netherlands focused on in their pioneering work in the early 2000s on medical treatment for adolescents with gender dysphoria. Researchers at the Amsterdam University Medical Center methodically screened their subjects to ensure they met certain criteria before receiving treatment. Like Ryace, these adolescents exhibited persistent gender dysphoria from a very early age, lived in supportive environments, and had no serious psychiatric issues that could interfere with a diagnosis or treatment.

The assessments generally lasted about six months before treatment could start. The children filled out a series of questionnaires, and clinicians talked to them frequently to confirm that their gender dysphoria was persistent and to ensure that they understood the long-term implications of treatment. For patients who had psychiatric problems, the researchers extended the assessment phase to more than 18 months before considering medical treatment.

In 2011, the Dutch published detailed results of their work. In one study involving 70 adolescents, the group showed fewer behavioral and emotional problems and fewer symptoms of depression after nearly two years on puberty blockers. Feelings of anxiety and anger were relatively unchanged. All of the patients went on to take hormones.

European countries and the United States adopted the Dutch model for the newly emerging field of gender-affirming care for minors. WPATH and other professional groups issued guidelines recommending comprehensive psychological evaluations before referring any child for medical treatment.

More recently, though, many of the patients flooding into clinics wouldn't meet Dutch researchers' criteria. Some have significant psychiatric problems, including depression, anxiety and eating disorders. Some have expressed feelings of gender dysphoria relatively late, around the onset of puberty or after, according to published studies, gender specialists and clinic directors. Such cases require more extensive evaluation to rule out other possible causes of the patient's distress.

And for reasons not understood, a disproportionate number are patients assigned female at birth. In the NIH study of children's treatment outcomes now under way, minors designated female at birth made up 61% of enrollees. The gender clinic at Children's Wisconsin hospital in Milwaukee said 65% of its patients were assigned female at birth. Some researchers and clinics say transgender females are less likely to seek treatment because they face greater social stigma for doing so. Critics of children's gender care blame peer pressure, reinforced by social media, for boosting the number of transgender males seeking care.

Dr Annelou de Vries, a specialist in child and adolescent psychiatry, is one of the Dutch researchers whose early work established the importance of rigorous patient assessments before starting medical treatment. She said that while she worries about the growing number of children awaiting treatment, the graver sin is to move too fast when puberty blockers and hormones may not be appropriate.

"The existential ethical dilemma in transgender care is between on one hand the (child's) right for self-determination," de Vries said. "On the other hand, the do-not-harm principle of medical intervention. Aren't we intervening medically in a developing body where we don't know the results of those interventions?" In the United States, in particular, she said, "the transgender right or child's right seems to be put forward more strongly." De Vries helped write the section on adolescents in WPATH's updated Standards of Care. She said she was gratified that language stressing the importance of rigorous patient assessments remained.

In interviews with Reuters, doctors and other staff at 18 gender clinics across the country described their processes for evaluating patients. None described anything like the months-long assessments de Vries and her colleagues adopted in their research.

At most of the clinics, a team of professionals – typically a social worker, a psychologist and a doctor specializing in adolescent medicine or endocrinology – initially meets with the parents and child for two hours or more to get to know the family, their medical history and their goals for treatment. They also discuss the benefits and risks of treatment options. Seven of the clinics said that if they don't see any red flags and the child and parents are in agreement, they are comfortable prescribing puberty blockers or hormones based on the first visit, depending on the age of the child.

"For those kids, there's not a value of stretching it out for six months to do assessments," said Dr Eric Meininger, senior physician for the gender health program at Riley Hospital for Children in Indianapolis. "They've done their research, and they truly understand the risk."

"We do not have enough therapists and psychologists who have had adequate training in this area to keep up with the pace of more gender-diverse patients who have come out recently."

Dr Michael Irwig, director of transgender medicine, Beth Israel Deaconess Medical Center

Many clinicians bristle at suggestions they may be moving too fast, treating children before adequately vetting them. Months-long assessments and counseling in lieu of medical treatment puts children at risk, pathologizes them and denies them their fundamental identity, they say. For minors with psychiatric problems, they say, medical treatment often alleviates the distress of gender dysphoria and allows professionals to then address those other conditions.

"Being trans is an identity, not a diagnosis, and transgender people just want the care that affirms who they are," said Ducar, the trans health provider in Massachusetts.

Ducar and others were disappointed that in its updated Standards of Care, WPATH noted that "social influence" may impact some adolescents' gender identity. They said the idea of a "social contagion" infecting children perpetuates an offensive misconception that being transgender is a fad spread among impressionable adolescents by friends and social media and fails to recognize the stigma, bullying and discrimination transgender people experience.

Dr Eli Coleman, director of the University of Minnesota Medical School's Institute for Sexual and Gender Health who oversaw the update of WPATH's Standards of Care, said: "A knowledgeable and competent clinician can discern between a person's gender identity that is marked and sustained and an identity that might be socially influenced."

The issue of assessments is complicated by a chronic shortage of mental-health professionals for children that has only worsened amid soaring rates of depression, anxiety, mood disorders and self harm nationwide.

"We do not have enough therapists and psychologists who have had adequate training in this area to keep up with the pace of more gender-diverse patients who have come out recently," said Dr Michael Irwig, an associate professor at Harvard Medical School and director of transgender medicine at Beth Israel Deaconess Medical Center. "We are going to miss some people who haven't been vetted appropriately or who haven't gotten the mental health care that they need." That, he said, may increase the number of people who later detransition.

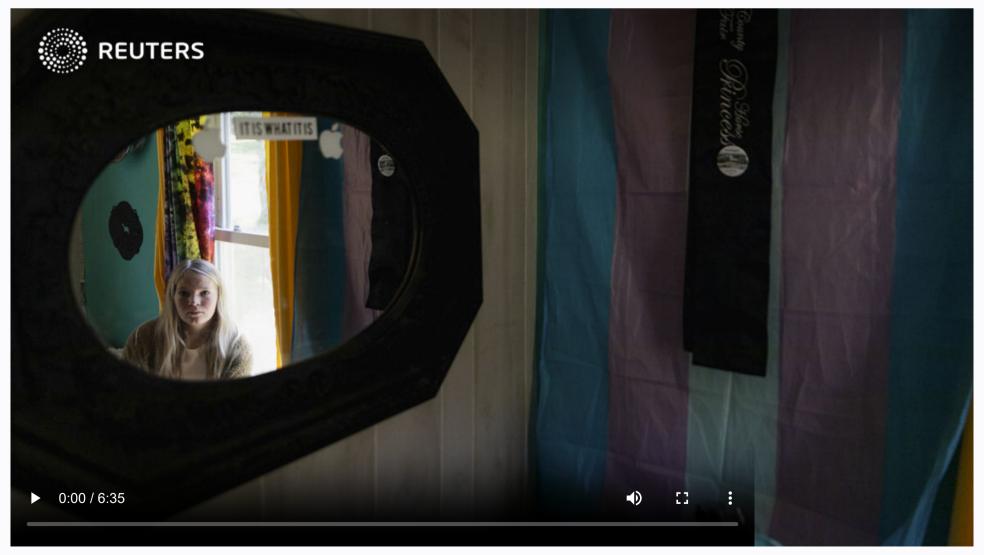
Reuters interviewed parents of 39 minors who had sought gender-affirming care. Parents of 28 of those children said they felt pressured or rushed to proceed with treatment.

Kate, a 53-year-old mother in New Jersey, said she and her husband were shocked in November 2020 when their 13-year-old told them he was transgender. The child, assigned female at birth, had always played with other girls and had never expressly identified as a boy. They just thought their child was a "tomboy." Now, they learned, he had chosen a male name and wanted to start puberty blockers and get breast-removal surgery.

After an initial one-on-one consultation of little more than an hour with the teen, a psychiatrist said he was a good candidate for puberty blockers, Kate said. An endocrinologist recommended the same after talking with the family for 15 minutes. Kate and her husband also attended a parents' support group organized by a local gender therapist. Through it all, Kate said, "the message was, let your kid drive the bus. Wherever they lead you, that's what you should do."

Kate, who asked that only her first name be used to protect her child's identity, had read up on puberty blockers. Concerned about their off-label use and possible side effects, she wouldn't agree to treatment. She supports her son's social transition, using his preferred pronouns and buying the tape he uses to bind his breasts. But she thinks he is too young to make decisions about life-altering medical treatments.

"Children, when they are 13 or 14, are sometimes totally different people from when they are 18 or 19," she said. As a result of her decision, her relationship with her son has been "fractured," Kate said. If he chooses to pursue medical transition after he turns 18, she said, she and her husband won't be happy, but they won't stand in the way, either.



■ VIDEO: Ryace Boyer and her family's journey through gender-affirming medical treatment.

Suicide Watch

The fragile truce between Ryace and her parents – girl at home, boy everywhere else – collapsed after Ryace started middle school.

In December 2019, Danielle let Ryace, 11 at the time, wear makeup and black bell-bottom pants to a basketball game at a nearby school. Danielle's mother, Ruth Alden, was at the game, and afterward, she scolded Danielle. It was embarrassing to the family, Alden said, and other kids are "gonna beat the crap out of her." Her granddaughter could be driven to suicide, she warned.

Danielle was incensed – and despondent. She felt trapped. She had long worried that she was pushing Ryace toward suicide by insisting that her identity remain a secret. That night, Danielle yelled at her own mother: "What do I do, Mom? Regardless of my decision, I could have a dead child."

Early in the new year, Danielle, desperate for guidance, joined a Facebook group for Ohio parents of transgender children. That eventually led her to the children's hospital a two-hour drive away in Akron, for the Aug. 6, 2020, meeting with Dr Crystal Cole and her team.

Dr Cole, an Akron native and specialist in adolescent medicine, founded the hospital's Center for Gender Affirming Medicine in 2019. The clinic saw 25 patients that year. It now is treating more than 350 young people.



THE PROVIDER: Dr Crystal Cole, founder of the Akron Children's Hospital's Center for Gender Affirming Medicine, has been treating Ryace in her transition for two years. Akron Children's Hospital/Handout via REUTERS

In their two-hour meeting, Cole started with general questions about Ryace, her family and their medical history. Then she sharpened the focus on Ryace's mental health and readiness for treatment. Danielle exhaled with relief after Ryace responded that she wasn't hearing voices, wasn't using illegal drugs and had never tried to harm herself.

The doctor then laid out the treatment options. Ryace could socially transition. She could also opt to receive counseling and therapy to support her through transition. And she could receive treatment to medically transition. At age 12, Ryace was a candidate for puberty suppression to spare her the masculinizing features she feared, with known and unknown risks.

"Ryace is a very vibrant, well-adjusted young lady that just happened to be assigned male sex at birth."

Dr Crystal Cole, Akron Children's Hospital's Center for Gender Affirming Medicine

Cole then moved on to the danger of inaction. "The risk of people in the transgender population attempting suicide is over 40%," she told Ryace and Danielle. "One of the things shown to lower that is affirming care and an affirming environment."

The statistic Cole referred to came from the 2015 U.S. Transgender Survey, an anonymous online survey of nearly 28,000 transgender adults conducted by the National Center for Transgender Equality, a nonprofit advocacy group. Compared to the 40% of respondents who reported attempting suicide at some point their lives, the rate for the general U.S. population at the time was 4.6%, the authors of the 2015 survey said.

It's one of several surveys that healthcare professionals cite when advising families with children seeking gender-affirming care. Another was by the Trevor Project, a nonprofit group that focuses on suicide prevention for LGBTQ youth. In that 2021 anonymous survey, 52% of transgender and nonbinary respondents ages 13 to 24 said they had seriously contemplated killing themselves. More than 13,000 survey respondents, or 38% of the overall sample, identified as transgender or nonbinary.

Dr Jonah DeChants, a Trevor Project research scientist, said the group's survey data "tell a really important story about the mental health impact of being an LGBTQ person and living in a world that tells you that you're wrong, that you're an abomination and that you are not safe to be around other children."

Such online surveys have become common in science, but researchers say they may not be fully representative of the larger population being studied. The authors of the 2015 U.S. Transgender Survey said: "It is not appropriate to generalize the findings in this study to all transgender people."

Experts in gender care say more specific research is needed to determine whether medically transitioning as a minor reduces suicidal thoughts and suicides compared with those who socially transition or wait before starting treatment.

Some gender-care professionals complain that suicide risk is too often used to pressure and even frighten parents into consenting to treatment. "I think it's irresponsible for clinicians to do that," said Anderson, the former president of WPATH's U.S. chapter. "As a clinical psychologist, I don't do a suicide assessment by membership in a class. The level of risk varies tremendously across individuals."

De Vries, the Dutch researcher, told Reuters there is no evidence that "providing care immediately leads to a decline in self harm or would prevent suicide."

DeChants of the Trevor Project said he wouldn't want the organization's data to be used to pressure people on treatment decisions. "We would never say that gender-affirming healthcare is the only way to address suicide risk, but it is an important option for youth, their doctors, and their families to be able to consider," he said.

After their two-hour evaluation of Ryace, Dr Cole and her team were confident that Ryace had gender dysphoria and was a strong candidate for medical treatment. "Ryace is a very vibrant, well-adjusted young lady that just happened to be assigned male sex at birth," Cole said. Bringing up suicide on the first visit is scary for a lot of parents, she said, but "it's a reality we have to ask about."

A few weeks after visiting Akron, Danielle announced Ryace's social transition in a Facebook message to family and friends. "I just wanted to let you know that Ryace started JH (junior high) as a female," she wrote in a Sept. 19, 2020, post. "She can finally be who she feels she is. A girl. I

wish this wasn't our life sometimes but it is and it's real and I have to let it be and be there to pick up the pieces when the world turns ugly. And it will, so we need all the love and support we can get."

Many relatives and friends were supportive, including Alden, Danielle's mother. Others stopped talking to the Boyers. Some parents complained to Ryace's school about her using the girls' bathroom. Previously, she had used a single-person bathroom. The principal backed Ryace.

Ryace was eager to begin treatment. "What are we waiting for?" she asked her mother. In November 2020, Danielle took Ryace to an appointment with the Akron clinic's pediatric endocrinologist to learn more about puberty blockers. The endocrinologist scheduled Ryace for her first injection in March 2021.



MOTHER AND DAUGHTER: Ryace says she forgives her mother, Danielle, for making her conceal her identity for so long. REUTERS/Megan Jelinger

Known unknowns

Endo International plc and AbbVie Inc dominate the U.S. market for puberty blockers. The only FDA-approved use for these drugs in children is for central precocious puberty, a condition in which children begin to sexually mature before age 8 or 9 because of pituitary gland dysfunction.

One side effect in children who take these drugs can be a decline in bone density, which is often treated with vitamin D or calcium supplements. Studies have shown that bone density can return to normal once therapy ends, but also that for some transgender girls, it may not.

In September, the FDA published a study that found "no evidence for an increased risk of fracture" for precocious puberty patients who take leuprolide, the generic name for AbbVie's Lupron and similar drugs. However, the FDA study didn't review cases of children who took the drug for gender dysphoria.

In a 2018 study published in the medical journal Clinical Pediatrics, researchers at Yale University noted a sharp increase in the off-label use of puberty blockers and said these drugs "have not been thoroughly investigated in populations with normally timed puberty."

In Texas earlier this year, bone scans indicated that a child, 15 years old at the time, had osteoporosis after 15 months on puberty blockers. The teen's mother, who asked not to be identified because she works at the hospital where her child was treated, said she thought she had done everything right when her teen came out as a transgender girl. But after the bone scan results, reviewed by Reuters, she said she regretted putting her child on puberty blockers. She stopped the Lupron injections and wouldn't agree to hormone therapy.

The child, who has socially transitioned, was at first furious with her and threatened to drop out of high school, she said. Their relationship is better now, she said, though "we don't talk about gender."

Another concern about puberty blockers emerged in 2016, when the FDA ordered drugmakers to add a warning about psychiatric problems to the drugs' label as a treatment for children with precocious puberty. On its label for Lupron, AbbVie says: "Psychiatric events have been reported in patients" taking puberty blockers. Events include emotional symptoms "such as crying, irritability, impatience, anger and aggression."

The FDA pursued the label change after receiving 10 reports through its adverse event reporting system of children who had suicidal thoughts, including one suicide attempt, according to a Dec. 5, 2016, agency report reviewed by Reuters. One of the cases involved a 14-year-old patient taking Lupron for gender dysphoria, the records show. In the report, the FDA said suicidal ideation and depression are "serious events," and there is "enough evidence to warrant informing prescribers, even in the face of uncertainty about causality."

The agency also asked drugmakers to closely monitor for these adverse events and file more detailed reports to the agency. "The FDA continues surveillance for psychiatric events associated with drugs indicated for the treatment of pediatric patients with central precocious puberty," the agency said.

Adverse event reports from medical professionals, consumers and drugmakers help the FDA detect potential safety problems with a drug that may warrant investigation. However, the agency doesn't receive reports for every adverse event, and there is no certainty that a reported event was caused by a drug. Reports may contain errors, partial data or duplicate information.

Reuters found 72 adverse event reports submitted to the FDA from 2013 through 2021 of children on puberty blockers who showed suicidal, self-injurious, or depressive behavior. The children were taking the drug for central precocious puberty or gender dysphoria or were simply identified as under 18.

A Dec. 17, 2020, adverse event report to the FDA describes a 15-year-old patient taking Lupron for gender therapy. The patient had a history of "major depressive disorder" and a family history of depression. The patient experienced "mental health deterioration" while on Lupron and attempted suicide twice. AbbVie wrote in the report to the FDA that "there is no reasonable possibility" that the adverse events were related to Lupron. The company did not elaborate.

Dr Brad Miller, division director of pediatric endocrinology at the University of Minnesota Medical School and M Health Masonic Children's Hospital, expressed surprise at the number of adverse event reports Reuters found. He said he was particularly concerned because doctors prescribe puberty blockers for transgender children, who are already at higher risk of mental health problems.

Miller and several other doctors told Reuters they had repeatedly asked AbbVie, Endo and other makers of puberty blockers to seek FDA approval for the drugs in treating gender dysphoria in children and to conduct clinical trials to establish the drugs' safety for such use. They said the companies always declined. "They would say it would cost a lot of money to get approval," Miller said. "And they were not interested in going there because (transgender treatment) was a political hot potato."



BIG CHANGES: Since earlier this year, Ryace has been taking estrogen tablets to help her develop the secondary sexual characteristics aligned with her gender identity. They could also reduce her fertility later in life. REUTERS/Megan Jelinger

AbbVie declined to comment for this article. An Endo spokeswoman said the company has no plans to seek regulatory approval for the use of its drug for any new indications. The company did not respond to requests for further comment for this article.

As prescriptions of puberty blockers increase for off-label gender care, the drugmakers are making cheaper alternatives harder to get.

Endo's puberty blocker is an implant in the upper arm that releases medication for as long as two years. About a year ago, the company told the FDA that it had discontinued an implant called Vantas that cost about \$4,600. That left doctors and patients to use a similar Endo implant called Supprelin LA. It costs about \$45,000, according to drug pricing data analyzed by Reuters. Some families with high-deductible insurance plans might have to pay several thousand dollars out of pocket.

AbbVie sells adult and pediatric formulations of Lupron, given by injection every few months. Doctors said that there is no meaningful difference between the two, but that they prefer to use the cheaper adult version, at about \$4,700 for a three-month dose. They said insurers sometimes insist on the pediatric version, priced at more than \$10,000, when the claim specifies that the patient is a child.

Some scientists and doctors also say they wonder about possible neurological effects of puberty blockers. The question: Hormones released during puberty play a major role in brain development, so when puberty is suppressed, can that result in reduced cognitive function, such as problem solving and decision making?

Dr John Strang, research director of the gender development program at Children's National Hospital in Washington, D.C., and other researchers wrote in a 2020 paper that "pubertal suppression may prevent key aspects of development during a sensitive period of brain organization."

Strang said at the time that "we need high-quality research to understand the impacts of this treatment – impacts which may be positive in some ways and potentially negative in others." He declined to comment on whether he was pursuing such research or funding for it.

At their first meeting at the Akron clinic, Dr Cole was blunt with the Boyers about the unknowns related to puberty blockers and brain development. "We don't know the long-term effects on cognitive function. It could make it better, worse. We have no idea," Cole told them. But she said she wouldn't recommend treatment "if I didn't see the positive effect on patients."

Back at the clinic seven months later, Ryace, 13 at the time, smiled in front of a whiteboard where the date, 3-4-21, was written in green marker. It was the day of her first Lupron injection. A photograph of Ryace from that day shows a small glittery bandage on her thigh peeking through her ripped jeans.

The family's insurance is covering nearly all the cost.

As the months passed, Ryace complained of pain in her knees. She started taking vitamin D as a precaution, and her pain dissipated.



HAPPY DAY: Ryace posed for a photo to mark her first injection of a puberty blocker. Danielle Boyer/Handout via REUTERS

Questions about fertility

Early this year, the Akron clinic told the Boyers that it was time for Ryace to take the next step in her treatment: hormone therapy, to help her develop the feminine characteristics aligned with her gender identity.

Ryace was now 14. In its new guidelines, WPATH makes no age recommendation for hormones.

For decades, hormone therapy has been the central component of treatment to help adults transition – estrogen for transgender women and testosterone for transgender men.

But for children, the choice to take hormones is more complicated. As with much of transgender medicine, research on the impact of hormones on fertility consists of small observational studies or surveys of adults that have significant limitations, experts say.

Many doctors acknowledge that long-term hormone therapy may reduce fertility, and they say children who receive puberty blockers followed by hormones run the highest risk. But with no definitive science to rely on, doctors often leave the question open when talking to children and their parents.

One Tuesday earlier this year, 16-year-old Ethan S. and his mother were in an exam room in suburban Portland to talk about testosterone therapy with Dr Kara Connelly, director of Oregon Health & Science University's Doernbecher Gender Clinic. After reviewing the family's medical history, Connelly, an associate professor of pediatric endocrinology, asked Ethan what he wanted from testosterone. "My deepening of the voice definitely, and the, like, distribution of my fat and stuff. And hopefully facial hair," he said.





PATIENT EDUCATION: Dr Kara Connelly, director of the Oregon Health & Science University's Doernbecher Gender Clinic, discusses medication options with 16-year-old Ethan and his mother, Melissa. REUTERS/Lindsey Wasson

Ethan could expect those and other masculinizing changes, Connelly said. A deeper voice and hair growth would be permanent.

Connelly then turned to fertility: Nearly all patients who stop taking testosterone start to have menstrual cycles again, she told them, and they can go on to carry a pregnancy or have their eggs used by someone else. "We can't predict with 100% certainty that testosterone would not have any effect on your fertility potential," Connelly said. "All we know is generally what happens in a population, and that it does seem from that evidence that it is not as harmful to fertility potential as we once thought."

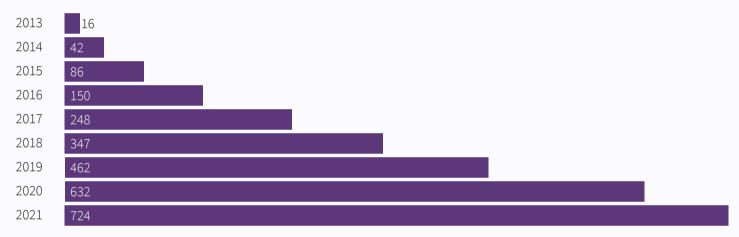
Connelly based her comments on a 2014 study published in the journal Obstetrics & Gynecology that analyzed survey responses from 41 transgender men who had a baby. Twenty-five of them reported using testosterone before becoming pregnant. However, the researchers acknowledged that the survey excluded transgender men "who attempt to get pregnant and cannot and those who do not carry to term."

Ethan was unconcerned about possible side effects from taking testosterone. "When is the soonest that I can get it?" he asked.

In Oregon, teens can take hormones without parental consent starting at age 15. A social worker handed him a form, and Ethan eagerly signed it.

Busy at the clinic

Number of patients treated annually at the Doernbecher Children's Hospital gender clinic at Oregon Health & Science University in Portland



Source: Doernbecher Children's Hospital gender clinic

Ethan's mother, Melissa, was supportive. She said Ethan had already socially transitioned when he started talking about medically transitioning two years ago. Then Melissa's father, suffering from alcoholism and depression, committed suicide in February 2021. Ethan had been close with his grandfather, and with that family history, Melissa said she worried even more about her son. "There's the fear of what happens if I let him transition and then the fear of what happens if I don't," Melissa said after the appointment.

Few children choose to have their eggs or sperm preserved before gender treatment as insurance in case they decide they want to try to have children later in life. In particular, harvesting eggs can be expensive and invasive. And for both genders, it can increase the discomfort they experience with their bodies.

Dr Angela Kade Goepferd, a pediatrician and medical director of the gender health program at Children's Minnesota hospital, sometimes asks parents to write a letter to their future adult child about the decision to start medications that may affect their fertility. An adolescent's views on starting a family may change over time, so the aim is for the child to remember conversations and choices made when they were younger, Goepferd said, adding: "I don't think these are easy decisions for families."

In Akron, Dr Cole tried a similar approach with Ryace. She suggests that her patients try imagining themselves as a 35-year-old and think about what that person might want. "Kids by design don't tend to think about long-term consequences. That is not how their brains work," Cole said.

At home, Danielle asked Ryace if she was comfortable with the possibility of being unable to have her own biological children. Ryace said she would adopt. Also, a friend had already offered to have a baby for her after they became adults. "It could be sad, but I'm OK with it," Ryace told

her mother.

By April this year, Ryace was taking estrogen pills along with regular shots of Lupron. The endocrinologist started her on low-dose estrogen, gradually increasing the amount while weaning Ryace from the puberty blocker. Ryace also regularly sees a counselor. The Akron clinic, like many that Reuters spoke to, requires that most teens taking hormones receive counseling to help them through what can be a physically and emotionally challenging time.



CALMING INFLUENCE: Ethan makes use of one of the squeeze toys the Doernbecher Gender Clinic provides to patients to help ease their anxiety during consultations. REUTERS/Lindsey Wasson

'They're trying their best'

Ryace lives much of her life as any teenager. But as her transition has progressed, she has continued to confront disapproval from other relatives and the community.

At the county fair last year, members of the crowd grumbled when Ryace was crowned Horse Princess. In town, she spots people rolling their eyes and hears their snide comments. During a field trip in May, she broke down in sobs when she saw students teasing a 16-year-old boy from another school who had flirted with her and had asked to message her online.

Some patients who receive treatments like Ryace's eventually decide to undergo "bottom surgery." For transgender girls, the procedure, called vaginoplasty with penile inversion, involves the creation of a vagina and vulva from the patient's penis and scrotum. Sometimes, the testicles are removed, too. The surgery is irreversible, expensive, and can result in serious complications that require follow-up procedures.

The authors of WPATH's new standards considered advising that genital surgery generally not be performed until at least age 17, but ultimately they made no age-related recommendations. The Endocrine Society puts it at 18. In its recent policy statement, the Biden administration said gender-affirming surgeries were "typically used in adulthood or case-by-case in adolescence."

Genital surgeries performed on minors are rare, but surgeons say interest is growing. The Komodo analysis of insurance claims found 56 genital surgeries, including vaginoplasty and other procedures, among patients ages 13 to 17 with a prior gender dysphoria diagnosis from 2019 to 2021. That doesn't include surgeries not covered by insurance. In a 2017 research article that surveyed 20 WPATH-affiliated U.S. surgeons, the doctors said there had been "a definite increase in the number of minors" requesting information about vaginoplasty or being referred for surgery by their mental health providers.

Complications from genital surgeries are common. A California study found that a quarter of 869 vaginoplasty patients, with a mean age of 39, had a surgical complication so severe that they had to be hospitalized again. Among those patients, 44% needed additional surgery to address the complication, which included bleeding and bowel injuries.

For adolescents transitioning to female, puberty blockers and hormones can complicate eventual genital surgery. That's because the medications can stunt development of the male genitalia from which a vagina and vulva are constructed. In 2020, de Vries and other Dutch researchers urged clinicians to inform transgender youth and their parents about this risk when starting puberty blockers.

Bowers, the new WPATH president and a transgender woman, said she has worried that some patients who begin puberty blockers at a young age won't ever be able to have an orgasm because they never experienced one prior to pausing puberty, regardless of whether they have surgery. She said ongoing research has allayed many of her concerns, and "it seems not only probable but likely there is retention of orgasmic function." She said she has encouraged doctors to talk about this risk with adolescents before they start medication.

The Akron clinic hasn't discussed genital surgery with the Boyers yet. Akron Children's Hospital doesn't provide gender-affirming surgeries.

Overall, Ryace appears unfazed by the long-term implications of treatment. "I just go along with it pretty much," she said.

In hindsight, she forgives her mother for making her conceal her identity for so long. "Sometimes she really wasn't protecting me. She was just hurting me. And I know she didn't mean it," Ryace said. "I know a lot of parents probably do that, and they think they're trying their best."

Do you have an experience with gender-affirming care to share as a patient, family member or medical provider? <u>Share it with Reuters</u>.

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Youth in Transition

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