



Benita Arren was the third person to join an innovative study of transgender individuals in Belgium.

Science in transition

The largest study of its kind is starting to provide long-sought insights into the health and well-being of transgender people.

BY SARA REARDON

Benita Arren wishes that the human body came with instructions. “We have a manual with every little thing we buy, in eight languages, but not for myself,” she says. About a decade ago, Arren was struggling with inner conflict. Designated male at birth, she had secretly dressed up in her mother’s clothes as a child, but she suppressed her feelings for decades. Then in her forties, married with two children and busy with a job in Antwerp, Belgium, she found them resurfacing. The masculine persona in her head — how she had long known herself to be — was falling away, leaving her feeling as though she had no personality at all. “Your consciousness is not fast enough to understand all those emotions,” she says.

Hoping that she was experiencing a temporary condition, Arren sought out the closest

thing she could find to a handbook for the human experience: the *Diagnostic and Statistical Manual of Mental Disorders*, a compendium of mental illness and neurological diversity used by psychiatrists. It described what she was going through, but to her dismay, it indicated that these feelings were not going to change. “You panic because you know everything, you know there is no way out, there is no way back,” says Arren. “There are people that think it’s something we want. I didn’t want it at all.”

In 2010, Arren sought help at the gender clinic of Ghent University Hospital in Belgium. By the time she walked in the door, she had learnt everything she could about the counselling she was required to take and the treatments she might anticipate if she decided to make the transition to live as a woman.

But she didn’t expect an unusual request from an endocrinologist at the university named Guy T’Sjoen. He had just launched a study — the

first of its kind — that would follow people such as Arren through their transition and for years afterwards. She agreed to join the study immediately, grateful to the physicians who helped her and curious about why she didn’t identify with the gender she was assigned at birth. Arren would be the third person to enrol.

On a snowy day earlier this year, she returned to the hospital, as she does annually, to give blood and answer surveys. On her way out of the clinic, she bumped into T’Sjoen. They embraced like old friends and chatted for a minute before T’Sjoen had to see his next patient. He is busy these days: the study has now reached 2,600 participants across 4 clinics in Europe.

The European Network for the Investigation of Gender Incongruence (ENIGI) is the largest study of transgender people in the world, and it’s unique: most studies are small and look at the outcomes of people who have already undergone hormone treatment and surgery.

PHOTOGRAPHY BY BEA UHART

That has left scientists and physicians with little data about the long-term effects of such treatment on health, such as cancer susceptibility, or how the brain and body change as people transition both socially and medically. Joshua Safer, an endocrinologist at Mount Sinai Hospital in New York City, says that ENIGI is a major contribution to his field, and praises T'Sjoen for the scale of its ambition. "He's doing this on his own without tons of resources. It's very impressive," Safer says.

ENIGI and a handful of other emerging studies could provide invaluable information. Media attention on transgender issues and a general shift in public opinion over the past decade has allowed more people than ever to open up about how they identify and to seek treatment. But even though scientific societies have produced medical guidelines, each person's treatment is still generally a matter of an individual physician's judgement.

ENIGI and a few other studies hope to change that by providing data on the best treatments and outcomes. The research could also reveal some of the basic biology underlying differences among sexes. Tantalizing hints are already beginning to emerge about the respective roles of hormones and genetics in gender identity. And findings are beginning to clarify the medical and psychological impacts of transitioning. T'Sjoen thinks that the rapidly growing field already has the potential to improve the care that people receive. "Saying you're not informed about this topic is not really valid any more," he says. "It's just that you're lazy."

PIONEERING PROJECT

T'Sjoen's interest in the field was sparked by the films of Spanish director Pedro Almodóvar, whose work frequently features transgender characters. But he says it was cemented by his first meeting with a transgender person seeking treatment while T'Sjoen was a resident physician. At the time, Belgium had no legal protection for transgender people, and those who didn't conform to societal norms around gender were frequently shunned by their families. The topic was not discussed. "Still, she was sitting there in front of me as a very proud woman," he says. "I was very inspired by her courage."

Searching through scientific literature, T'Sjoen noticed that transgender endocrinology wasn't discussed either. "There was a lot to be found about surgical techniques, and about psychological reports about the relationship with their mother or the absent father — things we don't think are relevant anymore," he says.

T'Sjoen decided that this could be a good niche for an aspiring endocrinologist, and could find only one researcher, Louis Gooren at the Free University of Amsterdam, who was studying the topic. T'Sjoen worked briefly with Gooren and quickly saw the challenges in maintaining funding for such a controversial area of work. "If you work in this field, you have a thick skin," T'Sjoen says.

Nevertheless, he moved on to launch the

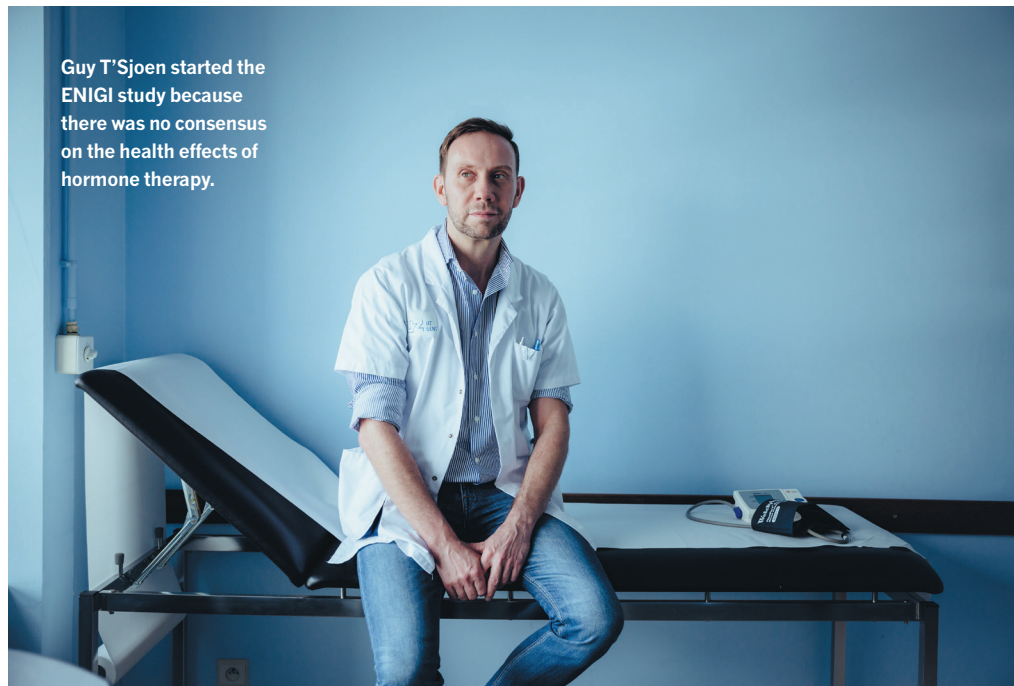
ENIGI consortium in 2010, at a time when things were starting to improve for transgender people in Europe. Ghent University Hospital was a pioneering centre for gender-affirming surgeries, providing T'Sjoen easy access to a patient population. But patients at the hospital had all received different courses of treatment: physicians generally use their own judgement in choosing a hormone and dosage for each person. Working with endocrinologists from universities in Amsterdam, Oslo and Hamburg, T'Sjoen developed a standard pro-

transgender started to recede in Belgium. In 2018, a popular television presenter came out. The same year, a film called *Girl* about one of T'Sjoen's patients won numerous awards.

T'Sjoen suddenly found himself a celebrity. Belgian publications named him one of the nation's top doctors, leading to television appearances and his face on magazine covers. His growing visibility brought more people to the university, and to the study. Ghent University Hospital enrolled more than 450 participants in 2018, compared to 300 the year before,

"Saying you're not informed about this topic is not really valid any more. It's just that you're lazy."

Guy T'Sjoen started the ENIGI study because there was no consensus on the health effects of hormone therapy.



tol for people starting hormone treatments.

As ENIGI got off the ground, researchers worried that they wouldn't have enough participants. It can sometimes be hard to recruit transgender people to studies: a history of discrimination and exploitation has left many reluctant to trust researchers. Many have concerns about privacy, and some people question the motives of the research, fearing that some scientists might be seeking a 'cure' to being transgender.

T'Sjoen was pleasantly surprised by people's willingness to participate. Like Arren, nearly everyone he asked to be part of the study said yes. "Here, people understand almost immediately, without me explaining, that it was useful to participate in this research," he says. In fact, limited resources have occasionally forced him to turn people away.

The cohort grew as taboos around being

and the hospital now has a waiting list.

The numbers mean that the ENIGI researchers can finally draw some significant conclusions about the effects of standard care. So far, hormone treatments seem to be safe, with few side effects. The most common complaints from people are lowered sexual desire and voice changes. But the most significant change the researchers have measured is something positive — a decrease in anxiety and depression after treatment¹. "Everything seems to be very reassuring," T'Sjoen says. "But this is short term, and long term we are still collecting data."

COMPLEX IMPACTS

Justine Defreyne's examination room at Ghent University Hospital overlooks the medieval city, with a row of windmills visible in the distance. A resident physician at the hospital's endocrinology department, Defreyne is seeing

9 of the 31 ENIGI patients visiting the clinic today. Tristana Woudstra, a 23-year-old university student with waist-length curly hair, tells Defreyne that her hips hurt from the oestrogen treatment she began taking nine months ago. She doesn't mind that much though, and says she's bonding with her cisgender female friends — those who were assigned female at birth — who went through the same changes during puberty. "They say 'You're a teenager now. Welcome,'" she says. "I just roll with it."

The hospital sees participants every three months at first and eventually once per year, collecting data each time. After a consultation, participants typically have their blood taken. Researchers track biological indicators, such as stress hormones and immune markers. Later, they collate these with other data, such as psychological examinations, brain scans and DNA sequences.

Collecting all of these different data gives the ENIGI researchers a comprehensive look at how treatment affects different people. The impacts are complex, Defreyne says, and can be difficult to parse from those associated with the psychological counselling and the personal growth that many experience.

That's one of the reasons why it has been so difficult to study biological mechanisms of gender identity using animal models. Giving cross-sex hormones to rodents can alter their sexual behaviour, but no one knows whether a rat thinks of itself as male or female.

And lumping people with complex gender and sexual identities into large groups might mask subtle differences and conflate unrelated characteristics. For instance, transgender men might be attracted to men, women or all genders, and might have differences in their brain activity and response to hormones as a result.

Making matters worse, the terminology used in the literature can be confusing; uninformed authors often swap gender terms, especially in older publications. "They look at a transgender woman and call her a transgender man because they say, 'Oh, that's a man who thinks he's a woman,'" says Safer. "It's not only insulting, it's mixing us all up." Such missteps are now the outliers, he says, although they continue to raise ire in transgender communities and among scientists when they do occur.

The ENIGI researchers hope that the emerging results will help to tease apart some 'nature versus nurture' controversies about the differences among genders. People who transition early in life, for instance, might have different brain characteristics from those who transition later, owing to the way their brains are shaped by societal gender roles or biological factors, such as hormones during puberty.

Researchers debate what kind of differences — if any — exist between male and female brains, and many such studies have been poorly interpreted. But scientists who study gender issues think that the confusion could be partly the result of a simplistic view of sex and gender identity. "I don't think there is something like a

male or female brain, but it's more a continuum," says Baudewijntje Kreukels, a neuroscientist at Amsterdam University Medical Center who works with ENIGI.

Kreukels' group can test some of the differences seen on average between men and women. For instance, some studies have found that men and women use different parts of their brains to rotate objects in their minds. When Kreukels' group scanned the brains of a group of 21 transgender boys who had recently begun testosterone treatment, they found that their brains look more like those of cisgender boys².

Sven Mueller, a neuroscientist at the University of Ghent who also collaborates with ENIGI, is co-chair of the transgender working group for an international consortium called ENIGMA, which studies behaviour by linking brain scans with genomic data. His team has collected more than 800 brain scans from transgender people, many from ENIGI, as well as from other parts of the world.

Mueller, a psychologist by training, wants to know whether there are hormonal and neurological links between mental health and gender identity. Depression rates are exceedingly high in people who do not identify with the gender they were assigned at birth, and as many as 30% of transgender teenagers attempt suicide. Societal acceptance and support can improve mental health, and although depression rates drop after treatment, the levels of depression and suicide are still above normal.

In February, Mueller's team launched a study examining the brain activity of 120 transgender people as they perform a psychological task designed to test their reaction to being rejected by their peers. The work could help to explain

why some people are more resilient than others, and lead to better treatment. At the very least, Mueller says, the findings could help to make mental-health professionals aware of the challenges that transgender people face. "So far, they've been kind of falling through the cracks," he says.

INCREASING EFFORT

In the examination room in Ghent, a 25-year-old transgender man named Ewan is describing how his facial hair has grown since he last visited the clinic six months ago. Defreyne asks about his chest hair.

"One hair," says Ewan's wife, Dunya, giggling.

"More than one," Ewan insists, lifting his shirt to show Defreyne, and revealing mastectomy scars.

Ewan was happy to enrol in the study, but has no personal interest in the scientific questions. "They asked, so I said yes," he says. "The more people who can study about it, the better." He and Dunya have been together for ten years and attend all of his appointments together. They live in a village near Ghent with 5 dogs, 24 chinchillas and an assortment of other animals. Dunya says she was never put off by Ewan being transgender. "I'm in love with a person," she says — anything else is just labelling.

Ewan decided not to have other surgeries apart from his mastectomy. He says he is disturbed by the surgical process to create a penis. He also opted to keep his ovaries and uterus. Defreyne cautions that he should have regular cancer screenings — no one knows whether testosterone treatments will raise the risk of ovarian or uterine cancer over time.

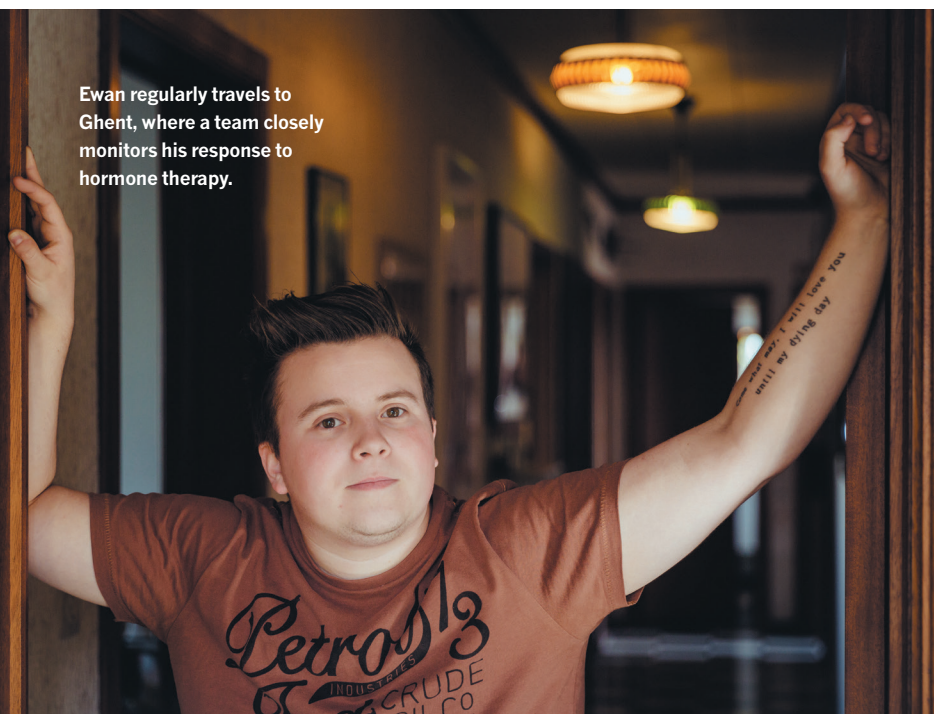
ENIGI and other studies hope to address health questions such as this, a tall order in

"So far, they've been kind of falling through the cracks."



Sven Mueller is studying the effects of gender transition on mental health and well-being.

Ewan regularly travels to Ghent, where a team closely monitors his response to hormone therapy.



a field with little research and few answers. Safer worries that, in the absence of controlled research studies, physicians are vulnerable to influence from anecdotes and single-patient case studies. Some of these will overlay the health risks, he says.

The Endocrine Society, for example, warns doctors to consider a potential link between androgen hormone treatment and reproductive tract cancer — a risk that could be important to people such as Ewan. But this link has not been proved in a controlled study.

In an ideal world, T'Sjoen says, researchers would do a randomized controlled study comparing different hormone treatments and following patients long-term. Different countries tend to use different hormone formulations, and some physicians use progesterone in addition to oestrogen, but the approaches have never been directly compared against one another. T'Sjoen hopes, eventually, to launch such a study.

Other researchers are looking for ways to collect data on a large number of transgender individuals, such as mining health records. But because of inconsistencies in the terminology used by physicians and administrators, it can be tricky, says Vin Tangpricha, an endocrinologist at Emory University in Atlanta, Georgia.

Tangpricha's team has built an algorithm that mines anonymised medical records from Kaiser Permanente, one of the largest health-care systems in the United States, to find people who identify as transgender based on keywords. The group has found more than 6,000 such records.

Last year, Tangpricha's team published a paper³ showing that transgender women had about 13.7 times the rate of blood clots as cisgender women. But such associations might not be meaningful — one way to identify causes is to do a prospective study like ENIGI.

And such efforts are picking up. "The interest level in the research community in

transgender health has really, really grown at an incredible rate," says Karen Parker, director of the US National Institutes of Health's (NIH) Sexual and Gender Minority Research Office. In 2017, the NIH launched a prospective study of 400 transgender adolescents. It will be the first study to examine the effects of drugs that block puberty until a teenager's body and mind is mature enough to begin cross-sex hormone treatment.

Questions of how — and when — to allow transgender youth to transition medically and socially are among the stickiest in the field.

Studies such as this not only help transgender youth, but they can also provide knowledge about human diversity and the spectrum of gender identity, says Johanna Olson-Kennedy, a paediatrician at Children's Hospital Los Angeles in California who is heading part of the NIH study. "They can tell us so much about our world and dig deep into these questions."

CHANGING PRIORITIES

Although transgender issues are becoming more mainstream, the topic remains politically charged. The European groups sometimes encounter transgender activists who oppose any medical intervention — T'Sjoen says he has had talks disrupted by people arguing that transgender people should not give in to social pressure. Although that could be true for some people, he says, for others, "even if they were living somewhere on a desert island, they would still want to change their body."

The researchers must tread carefully to avoid making things more difficult for a group that is already stigmatized. This requires consultation with transgender people on their priorities, T'Sjoen says, and putting these ahead of questions that are simply scientifically interesting.

Mental health tends to rank highly among health concerns, along with HIV. According to some studies, 25% of transgender women

and 56% of African American transgender women in the United States are living with HIV, although this estimate could be high because it is based on people seeking treatment.

And yet transgender women have largely been excluded from studies on prophylactic HIV treatments, or have been erroneously lumped together with men who have sex with men. There are reasons to believe that high doses of oestrogen could affect how HIV works in the body and stymie common approaches to treating it, but no one has ever looked at the question explicitly. "If you don't ask the question in the right way, transgender people become invisible," says Sara Gianella, an infectious-disease researcher at the University of California, San Diego, who has launched a pilot study on transgender women who have HIV.

As the science picks up steam, however, some researchers worry that physicians might feel pressure to move new findings and observations into practice too quickly. "In the past, the interest wasn't there; now the interest is outstripping the science," says Madeline Deutsch, a physician at the University of California, San Francisco, who is studying how the wording of health questionnaires affects how transgender people respond. "I worry that, in the haste to get something out there, we wind up getting not-optimal methods and not-optimal science."

Even prospective studies such as ENIGI have limitations, and T'Sjoen acknowledges that the study's findings won't be the final word on the safety and efficacy of treatment. For one thing, the cohort is almost entirely white and all of the participants grew up in Europe. Their experiences might differ from those of transgender people with different backgrounds or who live in countries with more restrictive attitudes. The cohort also only includes people seeking formal medical treatment, which often excludes sex workers and people who buy hormones from the black market. And the researchers do not yet have a study for people who identify as neither male nor female.

T'Sjoen hopes to expand ENIGI to include people from some of these groups. He often takes the long view, a necessity when conducting a study that could last several lifetimes. Its value to science might still take time to emerge, but for people such as Arren, the study has already brought some comfort.

"For me, it's an extra advantage because the more tests you have, the more security you have about yourself and your body," she says. Today, she says she feels entirely female, but it took a long time to get that way. "Now this is a closed chapter for me." ■

Sara Reardon writes for *Nature* from Washington DC.

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