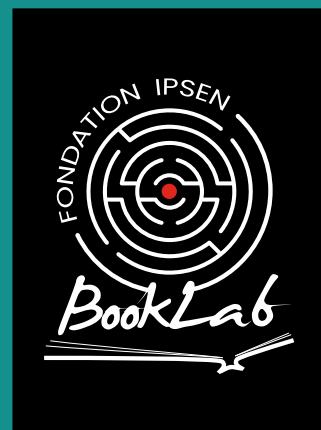


***RARE BUT* NOT ALONE**

Living with a  
**RARE**  
disease  
worldwide

volume 2





# Rare Disease Reporting Given New Depth

In many ways, the term “rare diseases” is a misnomer. Roughly 10% of the population has one of approximately 7,000 of these elusive ailments. Taken together, the number of rare disease patients and those who love and care for them may easily number half a billion people – and the advances being made in diagnosis and treatment may benefit far more.

Yet investment in rare disease – not only by governments and drugmakers but by the news media – often falls short.

That is why the National Press Foundation works tirelessly to create the Rare Disease Reporting Fellowship, with the support of Fondation Ipsen, to give reporters access to experts in genetics, targeted testing and drug development and patient advocacy. Over the course of a three-day virtual training, fellows heard from nearly two dozen speakers. NPF produced more than a dozen resources and videos from every session of the workshop, which are available for free on [nationalpress.org](http://nationalpress.org) to encourage journalists who were not selected as fellows this year to cover this vital topic.

From what they learned, the 25 reporters of the second annual cohort produced in-depth journalism that told impactful, devastating, hopeful, and ultimately human stories. Reporting in print, online and broadcast was conducted from five continents, resulting in 48 pieces in the first 90 days after the convening. This volume includes much of that exemplary work:

Journalist-fellow Hawken Miller, who lives with Duchenne muscular dystrophy, completed seven stories for BioNews, several of which outlined his personal challenges and triumphs. Chimwemwe Padatha, a radio journalist in Malawi, produced a broadcast feature for Zodiak Online about two families caring for children with Duchenne muscular dystrophy. The head of Malawi’s Ministry of Gender, Community Development and Social Welfare heard that report and contacted one of the families interviewed to help them apply for disability support from the government.

In National Geographic, Bijal Trivedi highlighted the racial inequity in diagnosis and treatment for cystic fibrosis. Vincent Kaguta examined a mysterious epileptic disorder in Uganda known as “nodding syndrome” which doctors have yet to determine an origin or treatment for. In The Star in Malaysia, Tan Shioh Chin told the story of a teen with hydrocephalus – a disease so rare that he is the only person in Malaysia known to be diagnosed with it.

We hope that this selection of gripping and diverse journalism will offer patients and their families comfort in knowing that audiences worldwide now know and care about their struggle and their resilience.

Portia Gabor created a moving 27-minute documentary-style video on sickle cell disease for TV3 Ghana. Amit Mandal of India wrote of children in her country who must rely on donations to get care. Michele Calamaio created an in-depth piece on Tmau disease published with the wide reach of Reuters. Ernesto Cabral produced stories about rare disease patients with six different diagnoses cystic fibrosis, ankylosing spondylitis, pulmonary arterial hypertension, multiple sclerosis and Williams syndrome – even as political turmoil in Peru almost fueled a governmental coup d’état. And Kristina Fiore looked at rare diseases through a new lens with “COVID Vaccines Made mRNA a Household Name. How Can It Help in Rare Diseases?”

The National Press Foundation thanks the Fondation Ipsen for their unfailing support on this crucial topic and at this crucial time.

**Anne Godlasky**

*President, National Press Foundation, Washington D.C.*

## Because we can’t wait longer

One of the great challenges faced by people living with rare diseases is that the public knows so little of their struggles, challenges, and the need for unrelenting resilience in a world that doesn’t understand. Coupled to the 300 million people living with rare diseases are hundreds of millions of caregivers who sacrifice time, work and money in the name of love. Working with the National Press Foundation, top world journalists highlight in these writings the plights of patients living with rare diseases and those who care for them. The stories are informative, dramatic, and heart-rending. I thank most the patients living with rare diseases and the people who love them for sharing their stories with these gifted journalists.

**James A. Levine, MD, PhD, Professor**

*President, Fondation Ipsen, Paris.*



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# Undral AMARSAIKHAN

*Mongolia*



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# Lana BUNJEVAC

*Croatia*



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# GENE BIOBANKS - THE FUTURE OF PERSONALIZED MEDICINE

## PART 1: How Andres Metspalu brought Estonia world primacy



Tartu is the second largest Estonian city and is called the “intellectual capital”, because it is famous for the oldest and best Estonian university. However, its history was quite turbulent. The river Emajõgi that flows through the city during World War II was the border of the front between the Red Army and the Wehrmacht, so the city was bombed twice and suffered a lot, about a third of the city was completely destroyed. After the war, Raadi Airport became the main Soviet military airbase in the Baltics, hosting dozens of nuclear-armed bombers. Because of this, Tartu was closed to foreigners until 1989, and access to the airport was impossible for all other citizens, and there was barbed wire separating the city from the military area.

When the human genome sequencing project began in America in 1990, few could have thought that within 20 years, a small European country would take the lead in genome research. Estonia is rightly considered a pioneer in this area, as shown by the ambitious gene biobank project, but this is not accidental: they are extremely open to new technologies, and the relatively small population of only 1.3 million favors the implementation of the project at the national level. Estonia is the country with the most startups per capita (five and a half times more than the European average), there are as many as ten unicorns (the most famous are Skype and Bolt), and one of the reasons why they are so successful is the Estonian education system, which is the world’s top, which is also confirmed by the excellent results achieved by Estonian students on the PISA tests. Another reason is the ease of doing business in Estonia - Estonia is the first country in the world to offer e-Residency, a government-issued digital identity and status that allows access to the country’s transparent business environment.

Biobanks function as a kind of genetic “archive” of the population, where blood samples of patients are stored together with their personal information about the disease and lifestyle. Genome analysis provides key information for disease prevention, early diagnosis and optimal treatment selection. The Estonian biobank is located in the city of Tartu, and it is specific in that over 200,000 people have volunteered their data so far, which is roughly 20 percent of the adult population.



*The building of the Estonian Biobank in Tartu (Photo by Argo Ingver)*

The head of the Estonian biobank and the visionary behind the idea of collecting population genetic data is 71-year-old professor Andres Metspalu, who received me in his office in Tartu. His office is on the first floor of an inconspicuous building located within the University, but it is also one of the most secure buildings in the city, since valuable genetic material is stored in its basements.

Metspalu became interested in genetics in high school in the late 1960s. He entered the University of Tartu in 1969, graduated in medicine in 1976, and received his doctorate in molecular biology, but not in Tartu, but in Kyiv.

- It is more accurate to say that I only defended my doctoral dissertation in Kiev - I actually completed my doctoral studies here in Tartu, but since there was only a biochemistry department here, I could only get the title of doctor of biochemistry. But I really wanted to specialize in molecular biology, which was a new discipline at the time, and that could only be done in Moscow or Kiev. Moscow is a huge city with many students and the waiting list for dissertation defense was two years, while in Kiev it was much shorter - six months, so I decided on Kiev. Back then, it wasn't really called a dissertation defense, but I was (pronounces it in Russian) a candidate of science - says Metspalu, today a professor of biotechnology at the University of Tartu.

### **But how did he actually start dealing with genetics?**

- Modern biology was not discussed much in the Soviet Union until sometime in the mid-1960s. Genetics was considered a bourgeois science, nobody knew anything about it, and that piqued my interest. In the late 80s, the Americans started the Human Genome Project and I believed that a lot of things would change then. But at that time we did not have sufficiently developed technology, and to study just one gene and one disease, you needed the entire period of a doctorate of four years. I wanted us to do large-scale research, and for that we needed a biobank - recalls Metspalu, who was elected a professor in 1992, but immediately took a year off and went to the USA for education, and only then, he says, started seriously dealing with genetics.



*Andres Metspalu, head of Biobanks (Photo by Karl Erik Piirimees)*

- When we entered the European Union, we could compete for money from EU funds and pre-accession funds, and our advantage was that we are a numerically small country, which is important for the biobank. I was lucky that the hospital in Tartu got a new director at that time, and he was progressive and forward-thinking, just like the Prime Minister at the time, Mart Laar. Laar, a historian by profession, is responsible for numerous reforms in Estonia, and when he became prime minister, he asked experts to give him ideas on what could be improved. The other day I brought him an A4 list with the idea of a biobank. Everything starts from politics, and in order to succeed in doing something that involves the whole country, you need to have political support - Metspalu points out.

However, at the beginning, there were heated discussions about the biobank in the public, many were skeptical, even in medical circles.

- Older doctors did not know much about genetics and it took a long time to change their way of thinking. The most common arguments were that it is too expensive, that why study healthy people when we have enough sick people... there were even some media reports that in this way people with high-quality organs, kidneys or livers will be found, which will then be sold to rich foreigners.

In December 2000, the Estonian parliament almost unanimously adopted the so-called Law on Human Gene Research. Since most people were concerned about data security, high security standards were set from the beginning to protect data from misuse. Donors have the option to withdraw their data from the database at any time, and the law prohibits access to the database by third parties such as the police, employers or insurance companies, which protects the privacy of donors and prevents possible discrimination based on knowing someone's genetic information.

Anyone over the age of 18 can give a blood sample and consent to participate in the project, and today the biobank has gene samples from more than 202,000 people, which is about 20 percent of the adult population. Estonians make up 83 percent, Russians 14 percent, and other nationalities three percent of all participants.

- There are slightly more women than men in the database, this is because women are more

responsible because they are mostly mothers, so they are interested in the future of their children, but the percentage of women in the Estonian population is higher than the percentage of men (52.54 percent versus 47.46 percent, op.a.), so that ratio is completely in line with the ratio in the population - says Metspalu.



Steven Smit, head of the laboratory biobank (Photo: Karl Erik Piirimees)

With male donors, the most common argument is that they want to support science. In general, Estonians strongly believe in science and, along with the Czechs, are the least religious nation in the European Union. The Estonian Science Barometer announced in 2020 that 90 percent of Estonians agree that scientific research is necessary, even if there is no immediate benefit, while 87 percent of residents believe that the state should support research even more.

The database includes information such as gender, age, height and weight, as well as information on dietary habits, exercise and smoking, and personal and family medical history is also recorded. Data and samples are collected from general practitioners across the country and then delivered to the central laboratory in Tartu, where they are stored in large containers filled with liquid nitrogen.

Biobanks are a relatively new phenomenon, so the knowledge gained can primarily be used for prevention, whereby prevention means discovering ways to identify at-risk individuals who can then be targeted to help them stay healthy, instead of treating the disease only when it breaks out. Has the previous research perhaps led to the recognition of some new, civilizational disease?

- I would say that obesity and diabetes type 2 is today's new disease of civilization, because we move too little and eat too much. Common diseases are also a big problem: not only cardiovascular, but also cancer, but some types of cancer can be treated very successfully today. Age is still the biggest risk factor for the development of these diseases; if by any chance we live for 120 years, most of us would surely get Alzheimer's disease - Metspalu believes.

A similar project like this one in Estonia was started in 1996 by a private Icelandic biopharmaceutical company, but cooperation with hospitals never took off there. In Estonia, they intend to advance the development of personalized medicine, and the biobank database is connected to national registries and hospital databases, so that doctors can take their genetic specificities into account when assessing patients' health risks.

- Genomics can be used most effectively in disease prevention - our goal is personal prevention, because if you have a patient you need to treat, then you are already too late; if the smoke detector goes off in your apartment, that's not good, because it means that the fire is already there. You cannot change genetics, but you can influence your lifestyle and partly the environment. The genome is a loaded gun, but the environment and lifestyle are the ones that pull the trigger - vividly explains Professor Metspalu, who a few days ago also received a prestigious award in Estonia, the award for life's work for the popularization of science. ■

*The text was published as part of the program for encouraging journalistic excellence of the Agency for Electronic Media.*

# GENE BIOBANKS – THE FUTURE OF PERSONALIZED MEDICINE

## PART 2: Biobanks in Croatia



After the Human Genome Project ended in 2001, France, Great Britain, and Japan also followed America's lead and established their own human genome programs, and many other countries followed suit later. Such national projects were coordinated by the Human Genome Organization (HUGO), which had three centers: an American one in Bethesda, Maryland, a European one in London, and one for the Pacific region in Tokyo. Researchers today have full access to a catalog of 25 to 30 thousand genes in various databases, and even after the end of this project, a whole series of new projects such as the Cancer Genome Project, HapMap and the 1000 Genomes Project are still being implemented.

In Croatia, we still do not have a national biobank modeled on the Estonian one, although there is, for example, the TransMedRi biobank in Rijeka, which collects biospecimens for the purpose of studying cancer and tumors, as well as a fecal biobank, the first of its kind in Croatia. In order for the biobank to be effective, many samples of different people are needed, and currently the closest thing we have to a national biobank is the 10,001 Dalmatians project, a population study of the inhabitants of the Dalmatian islands, which was initiated in 1999 by prof. Dr. Igor Rudan, then head of the Croatian Center for Global Health at the Faculty of Medicine in Split. The goal was to create a biobank for research into genetic, environmental and social determinants of health and disease, especially chronic diseases, which are the leading cause of death not only in Croatia but also in other developed countries. The program has

been running for more than 20 years and is one of the most successful in our science, and has resulted in the discovery of more than a thousand genes associated with a number of diseases, and more than 200 published scientific papers.

- The most important results of the project are related to the discovery of the SLC2A9 gene, which regulates the level of uric acid and causes the disease gout, then genes that cause heart rhythm disorders and traits such as body height and intellectual abilities. In one paper, we showed that height and intelligence are under strong pressure of natural selection, i.e. that in the past these two traits were very important in choosing a partner. This is why modern populations are increasingly tall and intelligent - explains Dr. Ozren Polašek, associate professor at the Faculty of Medicine of the University of Split and the current leader of the 10,001 Dalmatians project.



*Members of the research platform 10,001 Dalmatians*

The program is implemented by the research team of the Croatian Center for Global Health of the Faculty of Medicine in Split, which consists of health professionals and specially trained associates for field work. Given that our islands are chronically struggling with a shortage of doctors, local



communities also benefit from the project, since participation in the research includes an extensive health examination, an explanation of the results and, if necessary, advice and instructions on how to further improve health and prevent disease.

In addition to respondents from Vis, Lastovo, Mljet, Korčula, Rab and Susko, residents of the city of Split were also included in the research.

- One thousand inhabitants of the city of Split are included in the project for two reasons. The first reason is that when you are investigating a special population, as in this case isolated island communities, it is possible that some mechanisms exist only in the island population, so it is always necessary to have a replication control group to be able to test whether what you find is valid and for the general population. Second, when we took a closer look at the genetic structure of the islands, we saw that Split is actually very similar to islands; a significant proportion of the people of Split have a genetic connection with the islands, and a good part of the islanders have a genetic connection with the people of Split - stresses Polašek.

The project is not finished yet and is currently being implemented in two more financing cycles, and it is designed in such a way, says the manager, that it could last for many more years. In the biobank, therefore, biological material from research is stored, which in the future will be used for research by scientists from all over Croatia. How is the storage of sensitive data handled and who can access the database?

- Two people can access the database, it depends on which levels, but only I can access all the data. All data is protected by a password, we have two copies of the file that connects the identity and the password, one of them is located in Croatia and one in Scotland. You must protect the identities of the people who entered the research; we never had any ethical problems, we even had to not publish a couple of potentially very interesting papers because the journals asked us to give them all the genetic data. We didn't want to do that, because, theoretically, you can detect a person's identity with 99 percent certainty from 17 markers on the Y chromosome - points out Polašek.

However, this is why previous works published in eminent scientific journals such as Nature Genetics have enabled Croatia to be competitive in the scientific world as well - according to the Croatian Scientific Bibliography, this project is currently the best-ranked project in the field of biomedicine, and Professor Polašek was also on Stanford's list of the most cited scientists for 2021. ■

*The text was published as part of the program for encouraging journalistic excellence of the Agency for Electronic Media.*

# GENA BIOBANKS - THE FUTURE OF PERSONALIZED MEDICINE

## PART 3: Personalized Medicine in Croatia



Although we still do not have a national biobank, personalized medicine has already been partly implemented in the Croatian health system through genetic testing of oncology patients before prescribing the so-called smart cancer drugs and chemotherapy treatment. Today, there are courses in personalized medicine at Croatian medical faculties, the aim of which, as stated, is to acquaint students with contemporary trends in individualized medicine and pharmacotherapy based on genetics and genomics.

The sequenced human genome is the basis of the development of personalized medicine, and the cost of genome analysis, which only ten years ago was extremely high and amounted to around one million euros, has today, thanks to technological advances, dropped to approximately 800 euros. Modern medicine is already preventive, personalized, predictive and participatory, which means that we are partially responsible for our health through our lifestyle. The goal of personalized medicine is precisely to determine the predisposition to a disease and to adapt the right therapy to the right person at the right time.

In the traditional approach to treatment, patients suffering from the same disease were treated with the same drugs, and these drugs worked for some patients and not for others. Today, the approach to treatment has fundamentally changed, and personalized medicine allows us to adapt treatment more to the needs of individuals. Using the example of cancer, we can see how the results of

genetic testing can help doctors determine whether an available targeted therapy is appropriate for the unique genetic profile of a patient's tumor. Hereditary breast and ovarian cancers are most often the result of mutations in the BRCA1 and BRCA2 genes, and genetic testing can detect the risk of these diseases early and effective prevention can be undertaken. One example of targeted therapy is the identification of the HER2 protein in women with breast cancer, whose presence or absence gives the doctor an indication for specific therapy. Another example concerns the small percentage of people - about 2 percent - who metabolize drugs significantly faster or slower than the rest of the population. And this can often be seen in genes. If such a marker is found, prescriptions must be adjusted to avoid under- or overdose.



*The National Institute for Personalized Medicine will be opened at KBC Zagreb*

One of the fields of medicine that could benefit from a personalized approach is the field of mental health, where drugs are tried on a trial-and-error basis, which is often frustrating for patients because the effectiveness of drugs until optimal therapy is often very low, and some eventually and completely give up therapy. Prenatal testing and screening for genetic diseases such as Down's syndrome have long been used in clinical practice.

Such a personalized approach benefits not only doctors and patients, who have fewer unnecessary therapies and side effects, but also society as a

whole, due to a higher cure rate and more efficient use of financial resources in the healthcare system. Three years ago, it was announced that the National Institute for Personalized Medicine, i.e. a laboratory for genetic testing, would be opened at KBC Zagreb. In the second phase, the Croatian oncology database will be launched. At KBC Zagreb genetic testing is still being carried out, the cost of which is covered by the HZZO, but with the opening of the laboratory, testing will be available to a significantly larger number of patients.

And while a referral and a medical indication are required for testing at the expense of the HZZO, some genetic tests can be done today at reasonable prices in numerous private laboratories. For the purposes of this text, I myself did a test for factor V Leiden, which represents a mutation of one of the clotting factors in the blood and is the most widespread hereditary risk factor for thrombophilia, that is, for the formation of a blood clot and the development of thrombosis. I decided to get tested because my dad also had this mutation, and I did the test in a private laboratory at a price of HRK 300. It is only necessary to give a blood sample, which is then sent to a laboratory in Budapest for processing, and after about ten days the results will arrive in your mail. My result came back normal, which means that no mutation was detected, and there is no inherited risk factor for thrombosis. In the case of

heterozygous carriers (one copy of the mutated gene and one normal gene), the person would have an approximately seven-fold higher risk of thrombosis, while in the case of a homozygous carrier (inherited two copies of the mutated gene), the risk would be as much as 20 to 80 times higher. times compared to the rest of the population.

Although factor V Leiden can account for just over 50 percent of venous thromboembolisms, people who are positive can reduce their risk of developing thrombosis by, for example, using short-term thromboprophylaxis during periods of increased risk for thrombosis, such as surgery or transoceanic flight by plane. Also, knowledge of the genetic predisposition to the development of thrombosis can have an impact on a woman's decision to use oral contraception, because in the case of a positive test, the risk in homozygous women taking oral contraception is even 200 percent higher than in the rest of the population.

Of course, one should not lose sight of the fact that personalized medicine is still not cheap or accessible to everyone, and one of its limitations is ethical issues, which will be discussed more in the last part. ■

*The text was published as part of the program for encouraging journalistic excellence of the Agency for Electronic Media.*

# GENE BIOBANKS – THE FUTURE OF PERSONALIZED MEDICINE

## PART 4: Personalized Medicine and Rare Diseases



As we saw in the previous article, the implementation of genomic medicine is carried out in cancer genomics, pharmacogenomics, genomic risk prediction for common diseases and prenatal testing for chromosomal abnormalities, and in this sequel we will see how it is applied in the diagnosis and treatment of rare genetic diseases.

In Estonia, where we started this research, competence in the field of rare diseases is mainly concentrated at the University of Tartu, where doctors are also trained, using the resources of the University Hospital there. There are also two genetic centers in Estonia, one in Tallinn and the other in Tartu, which diagnose rare diseases and refer patients from all over Estonia.

Information on rare diseases and medicines for rare diseases has been available since 2004 through the public portal Orphanet. Orphanet is managed by a network of academic institutions from 40 countries, led by the Paris-based French National Institute for Health and Medical Research. The portal provides information on more than 6,100 rare diseases, and on its pages you can also see European registries of rare diseases by country. According to that list, there are two national registers for rare diseases in Croatia, namely the register of cystic fibrosis and the register of neuromuscular diseases.

- According to estimates, around 250,000 citizens in Croatia suffer from some rare disease. However, there are no accurate and comprehensive epidemiological and/or statistical data on rare

diseases in the Republic of Croatia. Only recently, due to the efforts of the Croatian Association for Rare Diseases, more systematic registration of patients with rare diseases has begun. One of the main problems patients face is late diagnosis and lack of adequate treatment - says Dr. Miranda Mrić, hematologist and member of the Croatian Association for Rare Diseases and the European Association for Rare Diseases.

About 80 percent of all rare diseases are genetic and most genetic diseases are rare diseases, although not all rare diseases are genetic. Many rare diseases manifest during early childhood, but approximately 50 percent of rare diseases usually only occur in adults, one of the most famous examples being Huntington's disease. However, only a small number of patients reach the genetic counseling center.



*Dr. Miranda Mrić, hematologist and member of the Croatian Association for Rare Diseases*

- The reason for this is the small number of organized services in which specialists trained for this form of health care are employed. Genetic tests have an important role in the process of diagnosing rare diseases, but their use is limited - some tests are only performed in certain centers in Europe/world, which requires organized cross-border

cooperation. A large number of laboratories in the Republic of Croatia carry out genetic (cytogenetic, molecular, biochemical) diagnostics of rare diseases. Prenatal diagnostics are well developed, as well as preimplantation genetic diagnostics in assisted reproduction methods, which enable couples at risk to have healthy offspring - explains Mrsić.

It is estimated that there are around 7,000 rare diseases today, but the exact number is difficult to determine. The European Union considers diseases rare if they affect less than 5 individuals per 10,000 inhabitants. Rare diseases are diseases with a particularly low prevalence, however, the number of different rare diseases is large and therefore the number of people suffering from rare diseases is relatively high.

- Presymptomatic and predictive diagnostics enable diagnosis before the appearance of symptoms and signs of the disease. In Croatia, this form of testing is possible for some neurological and psychiatric disorders (eg Huntington's disease, spinocerebellar ataxia, neurofibromatosis) and tumors (MEN, familial adenomatous polyposis, hereditary non-polyposis colon tumor). In the Republic of Croatia, a mandatory part of health care is newborn screening, which has been carried out since 1978, and in 2022 it includes phenylketonuria, conatal hypothyroidism, medium-chain acyl-CoA dehydrogenase deficiency, long-chain 3-OH-acyl-CoA dehydrogenase deficiency (isolated or as part of trifunctional protein deficiency), acyl-CoA-dehydrogenase deficiency of very long chains, carnitine carrier deficiency, isovaleric aciduria and glutaric aciduria type I. Screening for congenital hypothyroidism has been carried out since 1985 using a dry drop of blood. The aim of this screening is to identify children with reduced or non-existent thyroid function and, in the event of a diagnosis, to start therapy immediately and prevent fatal consequences - emphasizes Mrsić and adds that according to the latest media reports, Croatia will be one of the rare countries in Europe, which will begin screening school children for hereditary familial hypercholesterolemia, a genetically determined disease that leads to high cholesterol levels. Diagnosing the disease in childhood will enable early therapy and prevention of severe damage to the body.

Treatment costs for those with rare diseases are 3-5 times higher than the costs of treating common

diseases. At the same time, most genetic diseases are resistant to conventional treatment, so much effort is being invested in researching the possibility of gene therapy.

- Treatment options for rare diseases are often scarce and poorly effective. One of the most important problems in the care of people suffering from rare diseases is achieving equality in treatment, since there is a tendency for healthcare funds to be directed towards the treatment of more common diseases, and drugs for rare diseases are often expensive or non-existent. These drugs are known as "orphan drugs". The situation in this regard has improved significantly in recent years, when more and more drugs for rare diseases became available on the market due to European incentives. In 2006, the Republic of Croatia established a list of particularly expensive medicines, which also includes expensive medicines for some rare diseases. From November 15, 2010, the Agency for Medicines and Medical Products publishes on its website a list of medicines for the treatment of rare and serious diseases approved in the Republic of Croatia - adds Mrsić.

At the online conference on tracking rare diseases that I attended in October of this year, which was organized by the US National Press Foundation, one of the speakers was the well-known NBC journalist and war reporter Richard Engel, whose son Henry suffered from Rett syndrome, and he died this summer at the age of six. It is a progressive pervasive neurodevelopmental disorder that affects almost exclusively girls, and it is so rare in boys that most of them do not survive after birth. There is no effective cure for this disease, but early recognition of the symptoms and the start of therapy can slow down the development of further complications.

- Rare diseases are curable if they are treated in time, but more awareness is needed because rare diseases are not so rare - said Engel and admitted that the fact that he has a good job and that he lives near the best health centers and genetic specialists for him and his wife was a privilege, which unfortunately many parents of sick children do not have. What is the situation in Croatia, are there enough experts dealing with medical genetics, especially when it comes to children and rare diseases?

- In Croatia, medical genetics is mostly dealt with by pediatricians, subspecialists in medical genetics.

A special branch of genetics, the so-called clinical genetics already exists in all member countries of the European Union, while in Croatia it is less attractive than other specializations. Clinical genetics should not only be related to the basic specialization in pediatrics, but should also rely on other specializations, especially from the internist spectrum. Of particular concern is the fact that the number of colleagues dealing with medical genetics is unevenly distributed and most of them are located in Zagreb. The current number is insufficient and it is necessary to educate more fellow doctors to start dealing with this field of medicine, for which a stronger engagement of the health administration, especially the Ministry of Health, is needed - concludes Mrsić.

It is precisely on the example of the treatment of rare diseases that we see how in less than three decades genomics has progressed from an emerging discipline to a vital area of biomedical research. Moreover, some predictions for 2030 point out that by then genomes will be available on - our smartphones. ■

*The text was published as part of the program for encouraging journalistic excellence of the Agency for Electronic Media.*

# GENE BIOBANKS - THE FUTURE OF PERSONALIZED MEDICINE

## Part 5: Ethical issues in medical genetics



*Maja Bukovac Puvača*

In recent years, interest in medical ethics has increased with many questions and moral dilemmas arising from the rapid technological development in medicine and the discovery of new treatment options. Ethical issues arise in all branches of medicine, but medical genetics poses special challenges because genetic identity affects not only the individual but also his close and distant relatives as well as society as a whole.

Therefore, it is not surprising that five percent of the original budget of the Human Genome Project, the largest project in the history of science so far, was intended to finance the study of the ethical, legal and social consequences that could arise from knowing the genetic information of a person. On the example of Facebook and other social networks, we see how profitable personal data can be, so imagine how profitable data about the genes of individuals can be. There are, namely, many institutions that would like to have insight into the genes of the population, so the question arises, can this information be available to your employer, school or health insurance?

In the first text of this series, we saw how the Law on Human Gene Research was passed in Estonia in 2000, which prohibits access to the biobank database to third parties such as the police, employers or insurance companies, thus protecting the privacy of donors and preventing possible discrimination based on familiarity one's genetic information.

In Croatia, such a law does not (yet) exist. As Maja Bukovac Puvača and Loris Belanić from the Faculty of Law of the University of Rijeka point out in their exemplary scientific paper from 2021, there are several regulations in Croatian law that partly refer to the (im)possibility of using genetic tests for insurance purposes. These are the Act on the Protection of Patients' Rights and the Act on Suppression of Discrimination, while the express prohibition of genetic data processing for insurance purposes can be found in Art. 20 of the Act on the Implementation of the General Regulation on the Protection of Personal Data. In principle, according to the authors, it is prescribed that genetic tests that indicate diseases or serve to identify patients can only be performed for health purposes or for scientific research related to health purposes, and discrimination of individuals on the basis of genetic inheritance is prohibited.

Another point of contention from an ethical point of view is dealing with hereditary diseases - participants in scientific research or genetic testing have given their consent, but what about their close relatives? In the case of scientific research, may the doctor inform the subject and/or his relatives about a possible genetic risk? Genetic testing brings with it a kind of fear of stigmatization, as well

as psychological and social implications for the parents, siblings and children of the test participants. Also, it is not a rare case that when performing genetic testing, an unexpected discovery of false paternity occurs or a person learns that he was adopted.

One of the most common ethical issues in medical genetics is the issue of misuse of gene therapy to ensure some desirable features. With gene therapy today we can successfully treat some inherited genetic diseases, which is not controversial from an ethical point of view, but it is ethically doubtful that the technologies we are developing can enable healthy people to change their own genome in order to become taller, stronger or more intelligent. Are we allowed to allow such genetic modification of people? That is a much more difficult question. It does not only apply to living individuals, but also to their future children. Today, the prevailing consensus is that this is morally and ethically completely unacceptable, but in the future couples could pay for genetic modifications of their fertilized eggs in order to have offspring with certain characteristics.

And finally, there is the question of fair distribution of medicines. Although personalized medicine leads to savings in public health, it is certainly not cheap. Medicines for the treatment of rare diseases are extremely expensive, even those that already

exist, and the case of the girl Mila Makovec from Colorado, for whom a special medicine called Milasen, is known from the media. Mila suffered from the fatal and incurable Batten disease, and a team of Boston doctors developed a customized drug that allowed her to slow the progression of the disease. It was the first drug in the world developed specifically for one patient, which pushed the boundaries of personalized medicine, but also opened up numerous ethical questions. Namely, the development of such a drug is extremely expensive, which means that customized drugs would be an option only for the very rich or for those who receive support from foundations, as was the case with Milo.

These and numerous other ethical issues in medical genetics represent a separate area worthy of future research. ■

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## Ermesto CABRAL

*Peru*



**Ermesto Cabral** is a journalist, member of the Peruvian team which published the Panama Papers and Paradise Papers investigations. He is finalist of the Inter American Press Association's Excellence in Journalism Awards due to his coverage of drug trafficking and money laundering in Peru (2018), and the publication of a major leak of financial intelligence documents, which revealed the introduction of organized crime assets into the

Peruvian banking system. Both his work on 'Fondos de Papel' (2018), a data journalism project about the electoral process in Peru, and his publications of the Lava Jato case (2016) were listed as one of the best journalistic coverages in Latin America by The Gabo Foundation. He was a member of the team which published 'Funes', an award-winning investigation of the Sigma Awards (2020) and one of the finalists of The Gabo Foundation Awards (2021).

## A patient's odyssey: the challenges of living with a rare disease in Peru



*Valentino, a seven-year-old boy, is a cystic fibrosis patient in the heights of Huancayo, in Junín, where he must be nebulized and receive other medications daily. Photo by Leslie Moreno Custodio*

Diagnoses that arrive after years of no answers, a drastic impact on work and economy, and the obligation of migrating to Lima to survive illness. These are some of the main difficulties that people living with rare diseases in Peru must endure. Part of the crew of La Encerrona, in coordination with Somos Periodismo and the collective Los Pacientes Importan, along with the support of the NPF travelled across the country to collect the stories of these citizens demanding better care from the Peruvian government.

When she first heard the preliminary diagnosis from the doctor, Marki's world fell apart. It was mid 2012 and Sofie, her daughter, had spent the first months of her life with frequent coughing and difficulty to gain weight. The absence of specialists in Chepén, a city located in the northern region of La Libertad where both lived, had forced Marki to travel for over 45 miles with her baby to receive medical attention at Almanzor Hospital, in the neighboring region of Lambayeque. Based on his experience with other patients, the pediatrician of that health center had a suspicion Sofie suffered from cystic fibrosis.

The first sign of this disease showed up hours after Sofie's birth. As Marki recovered from her C-section, her sister noticed how the baby's face turned purple and ran for the doctors. Sofie was born on May 13th, 2012, a month prior to the Peruvian Congress declaring the screening of cystic fibrosis in newborns a matter of national interest, although the first diagnoses were not conducted until eight years later. The 169 cases of this disease in babies which, up until now, have been identified by the Peruvian government were not detected until 2020.

Cystic fibrosis is classified as a rare disease due to its low prevalence, meaning the number of cases in the population is low. Although its incidence in Peru is still unknown, in Europe there is a case for every ten thousand people. This condition affects multiple organs, as body discharge becomes abnormally thick, which causes inflammation, obstruction and infections in vital areas of the body, such as the pancreas and lungs, according to the National Rare Disease Organization of the United States of America. The National Health Institute of that country adds that cystic fibrosis causes symptoms such as salty perspiration, a persistent cough and difficulty to breathe, growth deficit and malnourishment.



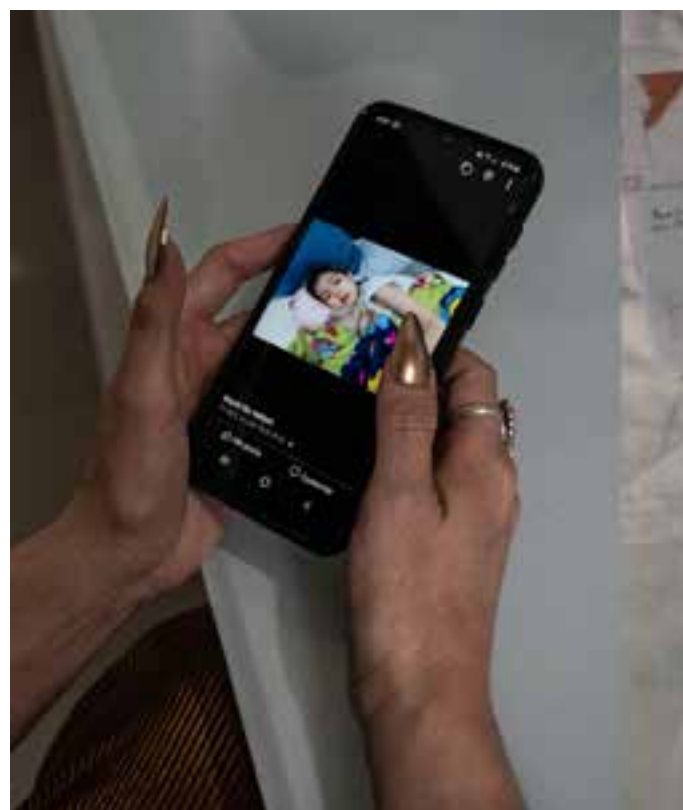
*Marki lives in Chepén, La Libertad, and has decided to donate the medication that Sofie used to the association of cystic fibrosis patients in Perú.*

*Photo by Leslie Moreno Custodio*

Sofie received her official diagnosis when she was fifteen months old. From that moment on, Marki and her daughter travelled by land on a regular basis to Almanzor Hospital in Lambayeque. Nevertheless, since she was four and due to the scarcity of dornase alfa, a medication used in nebulization, Sofie’s care was derived to Rebagliati Hospital, in Lima. Since Chepén doesn’t have an airport, they both travelled to Lambayeque by bus quarterly. Here, they would take a one-hour flight with their airfare covered by Health Social Insurance (EsSalud). As time went by, trips to the capital became more frequent.

At Rebagliati Hospital, Marki installed an inflatable mattress to sleep next to her daughter, who she used to gift with balloons. Sometimes, she would even sneak in some fried chicken from KFC. Before every meal, Sofie had to take pancreatin, a supplement that made up for the pancreatic failure derived from cystic fibrosis. Her treatment also consisted of daily nebulization, around seven punctures a day to check her insulin levels and, during the last stage of her disease, the insertion of a chest tube to drain her lungs. Sofie’s hospitalisations were over a month long, as told by her mother.

Sofie and her mom’s hopes were deposited in the “triple therapy”: a combination of drugs sold by Vertex, an American lab, under the name of Trikafta and has been approved approved for the treatment of cystic fibrosis in countries like The United States and Canada. In Latin America, the Argentinian lab Gador manufactures this treatment under the name of Trixacar. The application of this triple therapy for cystic fibrosis in other countries has resulted in drastic improvements in patients. However, as of yet, patients of the national public health system in Peru have not received this medication. “Sofie used to say ‘Mommy, I think God can’t hear me’ because she was not being administered the triple therapy,” Marki recalls.



*Marki keeps as a memento the letters Sofie wrote to her during her 10 years of life, thanking her for taking care of her while she was a cystic fibrosis patient. Photos: Leslie Moreno Custodio*

Sofie’s condition worsened little by little and hospitalizations became more frequent. Both mother and daughter talked about saying goodbye. Marki remembers Sofie approached her one day and asked her to never forget she would always love her. “I feel that was my daughter’s way of saying goodbye.” Sofie passed away at ten years old on September 28th, 2022, in the Intensive Care Unit (ICU) at Almanzor Hospital. Her body was buried in Chepén. “I was afraid this would happen. Seeing how my daughter’s life went out like a candle, little by little,” Marki admits.

Sofie’s case is representative of the thousands of patients in Peru living with cystic fibrosis or any other of the 500+ rare diseases recognized by the Peruvian government. Part of the crew of La Encerrona, with the support of The National Press Foundation (NPF) and the website Somos Periodismo, travelled to the coastal regions of La Libertad and Lambayeque in the northside of the country, as well as Ica in the south and the highland area of Junín to talk with people who suffer from different rare diseases, all teamed up in the collective Los Pacientes Importan. Their stories reflect the crisis these citizens must face.

## A diagnosis odyssey

Across from Valentino’s house, little more than three feet away from the entrance, the Peruvian government is building the first hospital in Chupaca, a city located 9842 feet above sea level in Junín, a region of the Peruvian highlands. His parents, Patricia and Gerardo, explain that, unfortunately, Valentino won’t be able to receive medical attention in this health center due to a lack of specialists in cystic fibrosis in their city. Instead of crossing the street, his family will have to keep getting on buses to Lima every two months, for an eight-hour trip through 265 miles of road to treat his rare disease.

Arriving at Valentino’s diagnosis was not easy. With early symptoms, which showed up shortly after his birth, Patricia and Gerardo sought help from different doctors in Junín, not one of them being able to explain the respiratory complications and low weight of their child. Once, a nurse even shouted and accused Patricia of neglecting Valentino, she recalls. With no answers in sight, both parents resorted to alternative methods: on three consecutive Saturdays, for example, they covered their six-month-old baby in black ram’s blood that they got in the animal fair of Chupaca.

“We were told he had ‘chacho’, ‘malaire’ (bad breeze), that a tree had sucked out his energy,” Gerardo remembers. On a different occasion, they took Valentino to “Los Angelitos Sanadores” (Healing Little Angels), a dark room where you can only hear the sound of wings flapping. The family also tried a magnet treatment that allegedly stabilizes body energy. “We’ve done everything in the search for answers,” Patricia explains. It was not until May 2017, a year after his birth, that Valentino was diagnosed in Lima. “The doctor said ‘your child

has fibrosis and there is no solution. He’s going to die.”



*Valentino, as well as other cystic fibrosis patients, is waiting for the Peruvian State to provide him with triple therapy. Her parents are considering migrating abroad so that their son can access said treatment. Photos: Leslie Moreno Custodio*

The “diagnosis odyssey” is a term that describes how hard it is to identify a rare disease due to a lack of specialists and a scarcity of public resources. On average, a patient has to go through seventeen doctors and wait for ten years before reaching a diagnosis in Latin America, as explained by Claudia Gonzaga, researcher at the Mexican Network for Rare Diseases, at an NPF event in October of last year. In its Universal Screening Law, the Peruvian government acknowledges these difficulties. However, this norm only contemplates screening for six out of thousands of rare diseases.

Cystic fibrosis is, precisely, one of the six rare diseases included in the Universal Screening Law, which has had regulations for its implementation since 2013. Although Valentino was born in September 2015, this screening wasn’t applied to him. His cystic fibrosis was detected by a private practice through a sweat test, which measures the amount of chloride in the body and was worth S/250 (two hundred and fifty soles, around seventy-eight dollars). Today, his family is part of the FIQUI, a collective of patients with cystic fibrosis in Peru that protects the rights of and that, by September of

last year, counted 93 members in total. During the making of this report, however, Sofie, a four-year-old child and an eighteen-year-old woman passed away.

The same diagnosis odyssey is endured by Harold, although with a different rare disease. Raised in Lambayeque since he was six, and with a family dedicated to tourism, Harold was passionate about travelling. Four years ago, however, he started experiencing pain in his joints and lumps started appearing in his knuckles and hips. One of the first doctors that saw him at Almanzor Hospital said he was crazy and told him to go to a psychiatrist, as he would complain about everything. “My joints hurt even when I tried to move my neck. You have no idea of how hard it’s been to receive a diagnosis,” he explains.

In his odyssey to find answers, Harold claims to have visited up to eight different doctors in public and private health centers, among neurosurgeons, rheumatologists and internists. “They would all blame each other. That’s what it was,” he shares. At one point, doctors thought he had multiple sclerosis or a bacterial infection in his spinal cord, but both suspicions were eventually discarded. “There is a lot of ignorance around rare diseases when it comes to providing [patients] with an accurate, suitable diagnosis and treating them in a timely manner instead of waiting for such a long time, the way I did,” Harold thinks.



*Harold fondly remembers the trips he took before suffering from ankylosing spondylitis, a disease that now requires him to use a cane to get around. Photos: Leslie Moreno Custodio*

Finally, in 2019, a different doctor at Almanzor Hospital diagnosed Harold with ankylosing spondylitis. “They gave me a diagnosis...but a hesitant one,” Harold admits. To identify ankylosing spondylitis, different clinical manifestations that cause this disease are evaluated. The criteria established by the International Society of Spondyloarthritis are the most commonly used and include MRIs, as well as X-ray tests. Through EsSalud, the insurance to which Harold is affiliated independently, Harold went through several of these tests with no answers being found promptly.

According to the Spondylitis Association of America, this disease is a form of arthritis that appears before the age of forty-five and causes inflammation, as well as pain in the column and hips. In some cases, it can be the cause for spinal fusion, reducing mobility and leaving patients with a disability. Now forty, Harold relies on a cane to walk. “I used to love dancing to electronic music, jogging and cycling, but I can’t do that anymore,” he acknowledges. Over time, loss of feeling and involuntary leg spasms, as well as urinary incontinence were added to his initial symptoms.

In October 2022, when Harold shared his testimony for this report, he was hospitalized at Almanzor Hospital due to his symptoms. His stay at the hospital was about a month long and different tests were performed on him. “They punctured me every single day to draw blood, inserted catheters through my nose to drain gastric fluid and performed a spinal tap to take a sample of spinal fluid.” By November, he was back home, where he lives with his mother and stepfather. He hopes his disease doesn’t worsen, as he would like to avoid using a wheelchair and is currently in the search for a job adapted to his condition.

## Working while having a rare disease

What’s the life of a person with a rare disease like? Pretty hard, since not only do you have to deal with physical pain, but even bullying when looking for a job,” Harold explains from his home in Chiclayo, the capital of Lambayeque. His first attempt at finding a job since receiving his diagnosis was an in-person position at a call center. Although they had already confirmed he would be hired, the company stopped returning his messages and calls after letting them know he used a cane due to his ankylosing spondylitis. “It’s really hard to get a job as a person living with a disability,” he adds.

Over 920 miles away from Harold, in the Ica region, a city built in the middle of the desert of the southern Peruvian coast, lives José, a fifty-one-year-old man who also lives at his parents' house.

On top of a piece of furniture lies a framed picture, discolored by the pass of time, where a very young José appears wearing the uniform of Alianza Lima, a Peruvian soccer team, and a ball right next to his foot. The ball is so big and José so little that it reaches his knee. Five decades later, José needs a walking frame to move around and, even so, with difficulty.



*At 51 years old, José maintains a passion for Alianza Lima and work. He hopes that this year he will get a job according to his needs and, with that income, cover part of his treatment. Photo: Leslie Moreno Custodio*

Up until a few years ago, his life was completely different. As an engineer for an important electricity company, José's salary was enough for him to move out of Ica and relocate to San Borja, an affluent district in the city of Lima. By late 2014, however, he started feeling "a tingling" in his body that, little by little, weakened his legs. It wasn't until 2019 that the National Institute for Neurological Diseases diagnosed him with multiple sclerosis, a rare disease with no known origin, that causes vision problems and difficulties to walk and talk.

Multiple sclerosis forced José to abandon Lima and return to his parents' house. He also had to quit his

job. "I let my boss know that I had had an accident, but did not insist. Besides, I didn't want for anyone to see me like this," he explains. Since receiving his diagnosis, José got a job at a government entity three different times; however, once again, the disease pushed him to leave work: "I had to quit all three times because I can't walk." In 2019, for instance, he worked at an office in Arequipa for the same public entity, but had to vacate his position as the muscles in his legs became inflamed.

Difficulties to get or keep a job are common among patients with rare diseases, a situation that is aggravated by the high costs of many required treatments, which the public health system does not always cover. In 2020, the plan to care for rare diseases of the MINSA (Ministry of Health) Plan para atender las enfermedades raras del Minsa acknowledged that "there are still difficulties in the assistance for treatments that are considered to be of high cost" since, amongst other reasons, government entities lack budget availability. This problem does not only have an impact on the patient, but on their caregivers as well.



*Due to multiple sclerosis, José has had to move his bed to the first floor of his parents' house, where he performs a series of daily exercises as part of his therapy. Photo: Leslie Moreno Custodio*

For example, Mathews's parents, Almendra and Augusto, both had to quit their jobs at different points in time. This family also lives in Ica, in

the so-called Orongo village, located twenty minutes away from the main square of the city by car. Mathews is four years old, although “he had a difficult story since he was born,” his parents explain. Two hours after his birth, on August 17th, 2018, Mathews had to be taken to the ICU due to a respiratory complication. A week and a half later, the baby choked while being fed.

On top of this, an uncontrollable cry came as Mathew’s response to a gastric issue with no apparent cause. At night, Almendra and Augusto’s child would only sleep sitting up due to a sleep disorder and, by the time he was four months old, his muscle tone was affected. Being faced with this situation, Almendra had to quit her job as an economist in a telecommunications company to look after her son. “I can’t work. It’s impossible for me,” Almendra says, who tried working from home using a laptop only once, a task she abandoned after Mathews had a domestic accident.

In the beginning, Augusto’s insurance as an electronic technician for a private company covered Mathews care at Rebagliati Hospital, located in Lima, a six-hour drive away from their home. Given the difficulties to receive a diagnosis, the family went to Hospital del Niño, where care is covered by the Integral Health Insurance (SIS), a different public insurance system. Mathews’s father had to vacate his position so as to have his EsSalud insurance cancelled and be able to register in the SIS. This way, in July 2021, Hospital del Niño was able to diagnose Mathews with Williams Syndrome through a test that would have cost around S/4000 (four thousand soles, approximately a thousand dollars) without SIS coverage.



*Mathews’ parents must measure their son’s blood glucose level daily and, every two months, go to the capital to pick up his medicines. Photos: Leslie Moreno Custodio*

Williams Syndrome is a genetic condition that affects different parts of the body. In Mathews’s case, cardiovascular problems and chronic constipation have been detected in addition to complications in his kidneys, hypothyroidism and speech difficulties. Since he was diagnosed, Mathews had had to travel to Lima on a regular basis for his treatment. “The trip involves a lot of expenses, among stay, food, and, at times, tests the insurance does not cover,” Almendra says. Moreover, half of Augusto’s salary is used to pay off debts they have accrued in order to finance Mathews’s treatment.

### Forced migration as a condition to live

Due to a lack of specialized pediatricians in Ica, Almendra and her child had to keep travelling to Lima even during the COVID-19 pandemic, when moving across regions was prohibited. At dawn, they would both get inside informal cabs to travel 186 miles to Lima through a dark road so as not to miss Mathews’s appointments. “We would like for everything not to be in Lima, that health is decentralized,” Almendra says. Augusto admits that, in the event that his son’s condition worsens, they will have to relocate to the capital city permanently.

Almendra directs the Peruvian Association for Williams Syndrome, which hosts thirty-three families. Out of these, eighteen do not reside in Lima. This situation repeats itself among different collectives of patients with rare diseases. According to official information provided by the Ministry of Health (MINSA) for this report, 54% of cases of rare diseases in Peru are located in regions different from the capital. “If my son were to have a renal or cardiac emergency, which can be fulminating, we won’t have enough time to make it to Lima,” Mathews’s mother explains. She adds that “we need to have specialists in every single region [of the country].”

John’s case is similar, a young 21-year-old man, from the high-Andean area of Junín, who spent last Christmas away from his family as he was hospitalized at Rebagliati Hospital in Lima. When he was twelve, John received his cystic fibrosis diagnosis, after living his early years with respiratory difficulties and having had incorrect diagnoses, such as asthma, pneumonia and even tuberculosis. His disease and a lack of specialized doctors in Junín forced him to be hospitalized in

this health center in the capital of the country three times a year. “I failed my senior year of high school because I was hospitalized in Lima,” he recalls.



*During the pandemic, John lost his father. Today he lives with his mother and his brothers in Huancayo, Junín. The doctors have already recommended that he move to Lima as a result of his illness. Photos: Leslie Moreno Custodio*

John lives with his mother and two siblings in the city of Huancayo, Junín, 10498 feet above sea level. When he has to be hospitalized or receive medical attention in Lima, John has to get on a bus that travels 264 miles and reaches the heights of Ticlio, a mountain range in the Peruvian highlands located 16404 feet above sea level, prior to descending to the capital of the country. Starting a few years ago, however, his disease has reduced his lung capacity to 30%, which means the height and little oxygen of Ticlio may put his life at risk. A two-way ticket between Huancayo and Lima can reach the cost of fifty dollars, which exceeds his family’s budget.

“Lima’s weather and oxygen levels improve his quality of life. His nails are no longer purple,” his mom says. Due to his disease and the lack of oxygen derived from Junín’s altitude, doctors have already told John he must relocate to the capital. “We don’t have the economic means to rent a room,” she adds. In January, John went back to Huancayo from Lima after being hospitalized, although a snowfall had his bus stop for four hours in Ticlio and made it back

home decompensated due to the lack of oxygen in the area.

For her part, Alicia is one of the few patients that has managed to migrate to Lima permanently, although not without making sacrifices. She is a native of Ayacucho, a region that is also located in the Peruvian highlands, over 8858 feet above sea level. In February 2012, her symptoms started showing up: “I would walk for two blocks and felt my heart was about to come out of my mouth,” she recalls. Sudden fatigue was followed by fainting spells and an accelerated heart rate when performing simple tasks, such as going up stairs. In Lima, Alicia received her definite diagnosis in October 2014: pulmonary arterial hypertension.



*For a few years, Alicia has lived in Lima due to the indication of her doctors. Her illness and her lack of access to quality health services do not allow her to reside in her native Ayacucho. Photos: Leslie Moreno Custodio*

Due to high tension in her pulmonary artery, this disease causes trouble breathing, dizziness, edemas in the legs, chest pain and tachycardia. In 2014, doctors performed a catheterization in Alicia, which kept her in the ICU for three days. Following her procedure, the health staff told her she could not go back to Ayacucho due to the risk of suffering from pulmonary hypertension and living in the highlands. “I had to come with my family. My husband quit



his job and our children had to change schools,” Alicia shares. She also had to leave her position as an accountant and now receives a pension for being incapacitated to work.

Her mornings in Lima alternate between getting her children ready for school and taking her medications. One of these is Iloprost. As she explains it, each box of this drug is 700 dollars and the government does not supply it as part of patient care. She, alongside other patients with the same disease, all teamed up in the collective called Llapan Kallpa, have access to this medication as a donation from abroad. “Sometimes we have to smuggle this medication, since Customs agents tend to seize it and we have brought up this issue in meetings with authorities: “You do not provide us with this medication and won’t allow us to import it either,” she explains.

Moving has allowed Alicia to breathe better, although her family has yet to get used to living in the capital. Last time she visited Ayacucho was before the COVID-19 outbreak. On November 8th 2022 the National Cardiovascular Institute confirmed her disease is at an advanced stage and have proposed her a new, very invasive course of treatment. “I am privileged for having a supportive family and friends, but that is not the case for most patients. Most of their lives are quite different,” Alicia claims as she leaves her home to face, as she has done every day for the past seven years, the capital of her country. ■

*Translation: Ana Paola Yamada*



# Michele CALAMAIO

*Italy*



**Michele Calamaio** is a multidimensional journalist, a hybrid professional with expertise in visual communication and journalism, who has had the chance to work in all kinds of communications fields.

He is currently working as Google News Initiative fellow reporter at Italy's La Repubblica, in Rome, covering both multimedia news coverage of national and foreign affairs. In the recent past, he has worked as Multimedia producer,

Social Media content creator, Filmmaker and Freelance multimedia reporter.

In all of his working experiences, he has writing news and making audiovisual stories about cultural and political dynamics. At the same time, he was producing stories for broadcasting across TV, radio, and digital platforms and, finally, carrying out continuous monitoring of political Social media communication.

## Living with TMAU, the rare disease of “rotten fishy smell”



There was a time when syndromes such as tuberculosis, chickenpox or the Black Death were considered rare diseases. That was until, thanks to scientific advances, treatments were found to ‘normalize’ them and turn the consequences they entailed into distant memories. Today, while there is no shortage of researchers and scientists, there are still some diseases that await a definitive cure, so-called rare diseases that affect a very small population and for which, in some cases, treatments and cures are limited due to less research being done. Every year, Rare Disease Day is celebrated on Feb. 28 to spread awareness and initiate change for those who suffer from them. According to [rarediseaseday.org](http://rarediseaseday.org), 300 million people suffer from rare diseases, with more than 106 countries around the world involved in the battle to find adequate medical treatment. In Italy, there is the National Rare Disease Registry (RNMR), established at the Istituto Superiore di Sanità in order to carry out surveillance of rare diseases and to support national and regional planning of interventions for individuals with rare diseases (MR). Given their nature, within it are diseases such as Gardner Syndrome, a genetic disorder characterized by abnormal tissue formation in the colon, or Wilms’ Nephroblastoma, a tumor that arises from the primitive renal outgrowth. But not Trimethylaminuria (TMAU): also known as ‘fishy smell syndrome,’ this is a metabolic disorder due to the human body’s inability to produce an enzyme specialized for the breakdown

of a substance, trimethylamine (TMA). Patients suffering from this inherited genetic defect, due to mutations in the FMO3 gene, accumulate the substance through diet, as it is present in various foods (including eggs, fish and shellfish), and release it through sweat, urine and breath. These, therefore, acquire a peculiar rotten fish or egg odor, not at all risky medically but highly disabling socially.

### From diet to social isolation. What does it mean to have TMAU? The experts’ opinion

The literature around the disease, to date, is still very scarce. What is known, however, is mainly due to the publication of a few scientific papers, moreover only in English, which still reason in conceptual terms and not in a tangible and holistic way, in the absence of a larger case series of affected individuals and in the presence of a variety of symptoms that is still too uneven. The condition seems to be more common in women than in men, for reasons still unknown. From the 2020 research paper “Treatments of Trimethylaminuria,” in fact, the authors scientists suspect that female sex hormones, such as progesterone and estrogen, exacerbate the condition. In Italy, one of the few researchers to have been involved in the fight against TMAU is Dr Antonella Sidoti, professor of Applied Biology at the University of Messina and a researcher specializing in the study of the genetic-molecular

mechanisms underlying Trimethylaminuria. “I started studying the disease about 15 years ago, when I met one of the very first affected patients.” In Italy, at the moment, there are about 20 verified cases, but there are even more people who, finding themselves in this condition, suspect they have the disease without having yet received any kind of certain diagnosis. “The truth is that there are not only patients of TMAU in its primary form,” meaning the one linked to the genetic cause that is absolute force that causes the disease, “but also those who experience the disease through the alteration of a whole series of environmental factors that have to do with the microbiota of the intestinal flora.” In fact, according to Dr. Sidoti, in this secondary form, called TMAU2, “the deficit of reduced enzyme activity can also be caused by liver damage,” and thus patients who use drugs as a palliative to the disease end up “stressing the already compromised liver activity even more.” Although “there is not a broad finding in the literature,” which does not allow for the confluence of diverse scientific opinions regarding multiple combinations to study treatments, Sidoti confirms, however, that there are some common features in the disease: odor seems to vary depending on many known factors, including diet, hormonal changes, stress level, amount of sweat emitted, and other odors in the environment. But how do we arrive at a diagnosis? “We take advantage of two tests: the genetic test,” in which we go to analyze the gene and all the mutations it has, “and the simultaneous measurement of the concentrations of trimethylamine and trimethylamine N-oxide present in the urine,” by liquid chromatography-mass spectrometry.

Although there is currently no cure for Trimethylaminuria, Dr. Sidoti sees certain treatments as necessary to alleviate the odor: avoiding strenuous exercise, finding ways to relieve stress, washing the skin with mildly acidic soap, washing clothes frequently, and following a strict diet of specific foods. In this, Sidoti is supported by Dr. Valentina Rovelli, a pediatrician in the medical team dedicated to the care and assistance of patients with Metabolic Diseases at the San Paolo Hospital in Milan, Italy: “It is a matter of reducing or eliminating the intake of the foods richest in trimethylamine, adequately supplementing the diet with the right macro- and micronutrient supplements according to the specific needs of the individual patient.”



*Dr. Antonella Sidoti, professor of Applied Biology at the University of Messina and a researcher specializing in studying the genetic-molecular mechanisms underlying TMAU*

The foods richest in this substance include not only fish, shellfish, red meat and eggs, but also dairy products, beans and other vegetables, although, Rovelli specifies, “each patient may be different from the other in terms of the need for measures.” Despite the absence of other physical symptoms, what people with this disorder experience the most is not even the medical condition itself, but rather the severe psychological and social distress caused by the lack of awareness of the disease in society and the prejudices of people in any personal or occupational sphere. “It is precisely for this reason that it is essential to be able to identify, diagnose and treat this condition promptly, before the possible social isolation can create permanent psychological damage to the patient,” Rovelli stresses. The strong smell of fish or rotten eggs emanating from affected individuals can in fact be perceived by those around as bothersome, prompting patients to feel isolated, marginalized, concretely “at risk of developing compromising psychiatric pathologies such as depression, anxiety and mood disorders.” According to the 2020 scientific paper “Impact of Trimethylaminuria on Daily Psychological

Functioning,” symptoms such as fear, anxiety, paranoia and dysfunctional thoughts are a constant struggle of patients who report using avoidant coping mechanisms and strategic planning to cope with daily life.

In another scientific paper recently published by Sidoti himself, called “The Gut-Brain Axis Cross-Talk and Limbic Disorders as the Biological Basis of Secondary TMAU,” this is precisely what is hypothesized: how much the activity of several molecules that act as intermediaries in the metabolic reaction of the disease may underlie the psychiatric comorbidities of TMAU. In this regard, it is Professor Giovanni Addolorato, a gastroenterologist at Policlinico Gemelli in Rome who specializes in psychological research on rare diseases, who speaks of the psychological implications and the impact on mood tone that the disease can have on patients: “These people feel discouraged by the fact that they do not have a standardized disease and are stigmatized by society.” Although the odor can be clinically blocked through certain dietary accommodations, “patients develop a very important mood disorder, characterized by anxiety and distress,” not so much because of the odor itself but because of the fear of the perception of the people around them. “It’s as if they always feel judged, or feel an eternal sense of panic about their own smell, even when it doesn’t manifest.” According to Dr. Addolorato, “psychotherapy,” or for that matter all psychodynamic techniques, “can be very helpful because they undo or try to calm the feelings of guilt that patients have in an absolutely perceptive way.” This, for Dr. Addolorato, “is not tolerable”: “patients should never be left alone and,” in a pathway ranging from implementing an iron diet to reduce the production of this substance to using acid soaps for body washing, “must be accompanied toward a greater acceptance of themselves by others.”

### The watershed voice: the case of Erica Astrea

It is April 7, 2019, and, for the first time, an episode of Italian TV show ‘Le Iene’ comes out with an emblematic title, “Erica and her rotten fish stench syndrome.” The ‘Erica’ in question is Erica Astrea, a 37-year-old from Caserta who has been affected by TMAU her whole life. “If I had to describe my



*Professor Giovanni Addolorato, a gastroenterologist at Policlinico Gemelli in Rome who specializes in psychological research on rare diseases.*

life with the one word, this would be ‘renunciation,’ especially of a ‘normal’ life.”

Telling her story, especially highlighting to those very renunciations due to the disease, is one of those things she most hates to do, and talking about the effects it has had on her life even less so. She takes courage and, almost with tears in her eyes, addresses the issue that has most affected her, even before the very discovery of the disease. “From a very young age I had several friendships, but I often noticed that even the closest ones sooner or later drifted away.” Erica does not understand why everyone complained “of smelling a bad odor in my presence while I was the only one who felt nothing.” Yet she follows a normal diet, trying to diet by eating a lot of protein, not knowing how unknowingly she was feeding the issue. “There were two episodes that charted my life: the first, when a girl at dance school told me how bad my body smelled. The second, however, represented the turning point: my ex-boyfriend, during an argument, perceived a smell similar to rotten fish, and had the courage to tell me.” From there, for Erica, everything changed: “I began my research on the Internet, without results, until I arrived at the center in Messina, and consequently to Professor Sidoti, who represented the answer to all my doubts: I had the rare disease of Trimethylaminuria.” Her first reaction is of “relief,” because finally reaching the “realization” that she no longer had to blame that smell on herself but on a genetic disorder represented the watershed needed to divide the community’s ignorance about the disease and hope for a better life. “I put my face on it because, although I try to tell from the beginning about my issue every time I meet new people, discrimination is always too common: and it is

precisely for this reason that I want a wide network of information on the issue to be created, so that other people like me can feel welcomed, understood, and become an integral part of a work and social context.”



*Portrait of Erica Astrea, 37-year-old from Caserta, one of the first patients to voice the pathology of TMAU.*

Today Erica also heads "Together for TMAU," a nonprofit association whose goal is to raise awareness in Italy and avert serious consequences with early diagnosis. This is accompanied by another organization, UNIAMO Federazione per le Malattie Rare Onlus, which, with more than 170 federated entities, represents the community of people with rare diseases whose goal is to give voice to nearly 2 million people, almost 5 percent of the Italian population, who daily suffer in silence from an 'abnormal' disorder. TMAU, however, according to Erica, is not only a hindrance to her life from a medical point of view, but also and above all from an economic and psychological point of view: "Not having the support of the Government weighs on us, because this disease is disabling us both for working independence and for the stability of mental health." Hoping for a subsidy, as is the case with other diseases, would be "the least" the Government could do to facilitate a better inclusion process, "but the road to a definitive solution to the disease is still far away." If in the former case the same solution, according to Erica, lies in supporting the costs for an iron diet to be followed maniacally, in the latter is represented by psychological support: "One has to exclude those that are the precursors of the malodorous molecule, such as choline, carnitine, and

lecithin," and then eliminate all foods that contain them such as meat, fish, legumes, and whole grain products. This should be "balanced with proper use of psychological support, which is necessary to remind oneself that the answer is not depression but the courage to know how to accept one's condition." The right balance that, for the moment, is getting the desired results: "I have had a positive evolution, which has allowed me to turn a problem into an opportunity to impose myself, without shame, even in the emotional and interpersonal sphere." Erica's final appeal, as she reads the comment of a person with the disease in a private group created specifically to exchange opinions and suggestions, is clear: "Let's try to be united, we have nothing to lose. On the contrary: we have been waiting for a long time to get up in the morning and start a day full of life, leaving behind loneliness and despair."

### The 'generational line' of the disease

But how is the disease experienced when faced at different stages of life? This is the case of other patients with TMAU, who together make up the 'generational line' of the disease. Mirko is a 9-year-old boy from Bari, studying in third grade and still too young to fully understand the disease. Talking about his condition, however, is his mother, Marianna, who tackles the subject with the same courage as Erica: "Since my son's birth I had noticed a peculiar smell, almost of fresh fish, which led me each time to use very aggressive detergents to remove it but which, inevitably, altered the pH of the skin." The repeating fencing is the same: "In December 2016, after feeding him fish sticks, the smell reappeared and I wanted to give myself a definitive answer by naming TMAU after the disease from which Mirko suffered." The diagnosis came immediately: it was mid-2017 and at Sant'Orsola Hospital in Bologna Mirko, despite his tender age, discovered that that 'fishy smell' was related to Trimethylaminuria. "Fortunately, he was not bullied at school or with friends because of his condition," Marianna points out, "rather, he learned very early to live with the disease, maturing faster without really wanting to." Mirko also now follows a very strict diet as his main palliative: "He doesn't eat broccoli, meat, fish, eggs, and must never overdo milk," Marianna says. Despite such a stigmatizing abnormal disease, Marianna says she feels "lucky": "In misfortune, we can at least say we have the advantage of not facing a lethal disease. And that is why we absolutely must not hide, but be

an example for others who still live in the shadow of discrimination.”



*Medical student Giorgia Kirkham Tranchida, a 22-year-old from Messina with TMAU, at work during one of her undergraduate labs*

Giorgia and Laura also experience the same situations, but their ages change: the first, Giorgia Kirkham Tranchida, is a 22-year-old from Messina, a medical student at the University of Milan. The second is 31 years old, from Lombardy, and works in sales for an IT company. Despite being only 10 years apart, their response to the disease is very similar: “I have always accepted my genetic mutation, despite the fact that it has led me over time to feel a greater sense of disassociation from society, to distance myself from even the closest relationships because of the embarrassment I felt,” reports a sunny Giorgia, stressing that, to date, the greater awareness she has acquired “helps her on a daily basis not to feel guilty anymore, to accept herself more.” “I’ve never talked about it with my family,” Laura says on the other hand, but she reiterates that she did not do so in order not to make her parents feel guilty about the genetic mutation she carries, rather than because of personal insecurities: “I’ve always had friends, romantic relationships, and I’ve never really felt the burden of the disease on my mental health.” A second common point is the one related to the difficulty in talking openly about the condition: “The risk is to develop psychiatric conditions that affect your life,” both report,

emphasizing how, in these cases, the diagnosis can really be a safeguard against the disabling condition to which the disease often condemns. “The fact that there are 20 people with the disease or 2,000 can radically change the perspective: if we don’t spread public awareness about our condition, we will always be invisible sufferers and there will never be a cure for us,” Laura points out. The advice of Giorgia, a future doctor, follows in the same footsteps: “Talk about it, talk about it and talk about it again, so that we create awareness and not isolation.”

Luisa Fabbrini is the latest to put her face to it. 70-year-old from Pisa, she is a former professor of religion who has struggled with the stigma of the disease “for too many years now.” “Since I lost my husband, my social life is nonexistent: I live closed within the four walls of my house, I no longer go to the cinema or theater, or to events of any kind, not even to church anymore.” Luisa’s response to the disease is dramatically drastic: “I’ve gotten to weighing 43 kilograms despite constantly trying to balance my diet with healthy foods and drinking lots of water,” Luisa says. “I don’t smell myself, but I can sense it from the expressions on the faces of the people around me”; faces that, according to Luisa, speak for themselves: “The sense of frustration, depression, and the urge to cry accompany me on a daily basis, and all of this is fueled by the continuous feeling of inadequacy.” Luisa’s response is very different from all the other cases, but the final message she sends is encouraging: “Don’t be ashamed to talk about the suffering this disease inflicts on us and the help we can find in all the professionals who try, in spite of everything, to soothe the wounds of our soul.”

### **A (future) solution? Perhaps yes, but one must wait**

If to date the only solution to the disease seems to be the implementation of a diet capable of blocking the effects of FMO3 overproduction, on the other hand we need to have the “patience to wait for the techniques to be developed to increase,” especially in relation to an increase in the number of cases that, for the moment, “still turns out to be too modest to be studied thoroughly.” So thinks Dr. Addolorato, who addresses the need to find “comparison studies” to “standardize new medical skills.” Dr. Sidoti is of the same mind, who is even more optimistic about the possibility of finding a cure: “In the last few

months, together with a pharmaceutical company, we have been working on the testing of a drug that has given positive answers,” the University of Messina researcher lets us know. “We can’t sponsor it yet because patent delivery is evolving,” Sidoti

stresses, “but what I can confirm is that the results are encouraging.” As Neil Armstrong would say, ‘a small step’ for the discovery of a potentially definitive solution to the disease, but ‘a giant leap’ for research, with Italy proving that it deserves first place. ■





# Robi CHACHA

*Kenya*



**Robi Chacha** is a 30 year old female Kenyan journalist, whose reporting interests and passion revolve around Health, Gender, Education, Environment and general human interest, with the intention of

shifting mindsets, educate, and most importantly calling to action relevant stakeholders so as to make my community better for us and future generations.



### Rare diseases continue to be a nightmare to both patients and even doctors

[Video here](#)



### The plight of a child who lives with alagille syndrome, a condition that damages the liver

[Video here](#)



## Tan Shioh CHIN

*Malaysia*



**Tan Shioh Chin** is the deputy editor in charge of StarHealth, The Star's (Malaysia) weekly health pullout, as well as The Star Online's Health webpage. She has 17 years' experience as an award-winning journalist with The Star, beginning in the education beat with a speciality in

science, before moving to the health desk in 2005. Among the fellowships she has been awarded are the 2012 Alfred Friendly Press Fellowship, 2015 Khazanah-Wolfson Press Fellowship and 2021 APCAT Media Fellowship.

## This teen's disease is so rare that he is the only Malaysian diagnosed with it



*Lee shakes hands with Ardi, as Ardi's parents Zabidi and Maisarah look on. Prior to his treatment, Ardi was too weak to even shake hands. — S.S.KANESAN/The Star*

Ardi Izzuddin Zabidi, 16, has an ultra-rare disease that only strikes less than one in 250,000 babies.

His condition is so rare that he is the only person in Malaysia known to have it.

As his mother Maisarah Badaruddin, 46, shares, their journey started when Ardi was 16 months old.

During a regular check-up at the Klinik Kesihatan (Health Clinic), the doctor discovered that Ardi's head was much larger than expected for his age and referred him to Tengku Ampuan Afzan Hospital in Kuantan, Pahang, where the family lives.

The doctors at the Paediatric Department there initially diagnosed him as having hydrocephalus.

Hydrocephalus occurs when there is a build-up of fluids in the ventricles within the brain, resulting in an enlarged head in babies.

However, further investigations, including a CT (computed tomography) scan, showed that this wasn't the case.

"After two or three visits, they referred us to HKL (Kuala Lumpur Hospital)," says Ardi's father Zabidi Ali, 53.

"They were unable to detect the problem," Maisarah says.

It was at HKL that the doctors suspected Ardi might have a genetic condition.

A urine test known as a toluidine blue-spot test confirmed Ardi had mucopolysaccharidosis (MPS).

MPS is actually a group of inherited metabolic diseases, which are a part of a larger group of rare genetic diseases known as lysosomal storage disorders.

These disorders cause a build-up of toxic materials in the body due to the lack of certain enzymes or substances that facilitate the action of particular enzymes.

The enzymes involved in these conditions are found in the body's lysosomes, which are the main digestive units in our cells.

In MPS, there is either a lack or improper functioning of lysosomal enzymes involved in the digestion of complex carbohydrates known as mucopolysaccharides.

Because of this, the mucopolysaccharides in the body will accumulate in the body's cells, causing problems.

The excessive amounts of mucopolysaccharides, also known as glycosaminoglycans, excreted in the urine are what is picked up by the toluidine blue-spot test.

However, MPS has seven distinct types, as well as various subtypes.

Each distinct type is caused by a problem with one or more of the 11 lysosomal enzymes involved in the digestion of mucopolysaccharides.

**Types of MPS**

**Type I**  
> Subtypes are Hurler syndrome, Scheie syndrome (previously classified as Type VI) and Hunter-Scheie syndrome.  
> Caused by a deficiency of the enzyme alpha-L-iduronidase.

**Type II**  
> Also known as Hunter syndrome.  
> Caused by a deficiency of the enzyme iduronate 2-sulphatase.

**Type III**  
> Also known as Sanfilippo syndrome.  
> Caused by a deficiency of enzymes that break down heparan sulphate.  
> Subtypes are A (deficient in the enzyme heparan N-sulphatase), B (deficient in the enzyme alpha-N-acetylglucosaminidase), C (deficient in the enzyme heparan-alpha-glucosaminidase N-acetyltransferase) and D (deficient in the enzyme N-acetylglucosamine-6-sulphatase).

**Type IV**  
> Also known as Morquio syndrome.  
> Caused by a deficiency of enzymes that break down keratan sulphate.  
> Subtypes are A (deficient in the enzyme N-acetyl galactosamine-6-sulphatase) and B (deficient in the enzyme beta-galactosidase).

**Type V**  
> Also known as Maroteaux-Lamy syndrome.  
> Caused by a deficiency of the enzyme N-acetylgalactosamine-4-sulphatase.

**Type VII**  
> Also known as Sly syndrome.  
> Caused by a deficiency of the enzyme beta-glucuronidase.

**Type IX**  
> Also known as hyaluronidase deficiency.  
> Caused by a deficiency of the enzyme hyaluronidase.

**Notes:**  
1. Type VIII, also known as DiFerrante syndrome, has been shown to be a misdiagnosis, and not a valid medical disorder.  
2. All MPS types are inherited in an autosomal recessive manner, except for Type II, which is an X-linked trait.

Source: US National Organization for Rare Diseases (NORD)

Thus began a whole battery of tests to determine exactly which type of MPS Ardi had.

These included urine tests, a skin biopsy and blood tests – not only for Ardi, but also his parents –

among others.

And because Malaysia did not have the capability for detailed genetic tests at that time, the blood tests had to be sent to Australia for analysis.

It was a long process, with Maisarah sharing that Ardi was finally confirmed to have MPS VII when he was three years old.

## No cure, just support

At that time however, there was no cure for MPS VII.

“There was no medicine at all; they could only provide supportive and palliative care,” says Maisarah, adding that they would go to HKL every six months or a year for follow-up appointments to monitor Ardi’s progress.

As mucopolysaccharides are involved in the building of various tissues, including bone, cartilage, tendons, corneas, skin and connective tissue, MPS can affect multiple parts of the body.

Aside from a large head (macrocephalus), some of Ardi’s symptoms include coarse facial features, short trunk dwarfism (an unusually short trunk and growth disability), cornea cloudiness, speech and hearing impairments, bone deformities, sleep apnoea, heart and lung problems, intellectual disability, and almost-constant respiratory infections.

Maisarah says that Ardi attends 10 clinics for his various symptoms, including respiratory, cardiology, eye, rehabilitation, and ear, nose and throat (ENT) clinics.

One of the sad things about MPS is that many children with it experience a period of normal development, followed by a subsequent decline in function.

Similarly, Zabidi shares that Ardi’s ability to walk and run started to deteriorate when he was around seven years old.

Maisarah adds: “He used to be able to walk and run like other kids. “But he became slower, he was smaller (compared to children his age), his hands became stiff; then at eight to nine years of age, he couldn’t walk any more, he could only sit.”

She says that he wasn't even strong enough to push his wheelchair by himself.

However, the year that Ardi's health started to go downhill was also the year that Zabidi and Maisarah received some news that enabled them to "see a bit of light".

## Seeing the light

In August 2014, Malaysia Lysosomal Diseases Association (MLDA) president Lee Yee Seng attended the International Symposium on Mucopolysaccharidoses and Related Diseases in Bahia, Brazil.

MLDA is a non-profit organisation that raises awareness about lysosomal storage diseases, as well as advocates for patients' rights to a sustainable healthcare and support system.

At the symposium, Lee heard about a new drug for MPS VII, which had shown promising results in mice.

The drug called vestronidase alfa-vjbc, is a recombinant human lysosomal beta glucuronidase, which substitutes for the missing beta glucuronidase in MPS VII patients.

He managed to meet up with Dr Emil Kakkis, the CEO and president of Ultragenyx, the rare disease drug company that was developing the enzyme replacement therapy (ERT), at the event and shared with him about Ardi.

The following year in November, Zabidi, who is the vice-president of MLDA, shares that a representative from BioMarin Biotechnology Malaysia (the local branch of the US-based pharmaceutical company) reached out to him on behalf of a friend from Ultragenyx to say that they were looking for participants for the vestronidase alfa-vjbc clinical trial.

However, they would have to go through the hospital (HKL).

Dr Kakkis retired as BioMarin's chief medical officer in 2009 before he started Ultragenyx the following year.

While at BioMarin, he had guided the development

of treatments for MPS I and VI, and phenylketonuria.

The following month, Zabidi and Maisarah met up with HKL consultant paediatrician and clinical geneticist Dr Ngu Hock Lock, who would be Ardi's healthcare sponsor for the treatment if they decided to let Ardi start it.

"Of course, we wanted it!" says Maisarah.



*The toluidine blue-spot test, also known as the Berry spot test, for MPS; C indicates the control sample, while T indicates positive test samples. — NAVEEN K SHREEVASTAVA and ARTI S PANDEY via Researchgate*

So Dr Ngu, who is now HKL's Genetics Department head, began the process of bringing the drug in for Ardi.

As vestronidase alfa-vjbc is not registered in Malaysia, the hospital had to apply for a special import permit to bring it into the country.

According to Health Ministry Pharmaceutical Services senior director Norhaliza A Halim, the importation of an unregistered medicine can be applied for in the situation where it is not available in Malaysia, is needed for the treatment of a person suffering from a life-threatening illness, and there are no other suitable options or alternative treatments available.

In such cases, the healthcare facility treating the patient may submit an Import Permit application for the importation and use of an unregistered medicine that can be used to treat the patient.

She says: "This application for medicines of special approval or application to import products for the treatment of life-threatening illnesses provides a pathway to ensure the continuous access to medicines needed for the treatment of a patient in cases where there are no registered or suitable medicines or treatment options available locally.

Norhaliza, who oversees the National Pharmaceutical Regulatory Agency, adds: "The processing and evaluation of such applications will be expedited by the Pharmaceutical Services

Programme in order to ensure the timely access to the medicine needed for the treatment of the patient’s condition.”



*Ardi receiving his treatment at Hospital Kuala Lumpur. He is receiving the ERT through his foot as he tends to pull out the needle when it is inserted in his hand. — MAISARAH BADARUDDIN*

## A vast improvement

Despite the availability of such processes, Zabidi shares that it still took a long while before Ardi could start his treatment because the drug was still under clinical trial and needed to go through multiple layers of approval within the ministry, up to the director-general himself.

“In March 2016, Dr Ngu called us in to explain and sign the consent form.

“We waited until November 2017 before Ardi received his first dose of the medicine,” he says.

Coincidentally, vestronidase alfa-vjbc received approval from the US Food and Drug Administration (FDA) on Nov 15, 2017.

Lee shares that Ardi totally changed, “like turning into a new leaf”, after he started receiving the treatment.

“He was so weak before the ERT, but now, every time, he will shake hands with you non- stop.

“And if he wants to push the wheelchair on his own, you cannot stop him – he’s so energetic now.”

He adds that Ardi also gets sick far less than he used to; previously, “he was so sick and had runny nose all the time, macam makan cendol (like eating cendol)”.

Zabidi agrees, saying that Ardi’s health has improved tremendously after he started the treatment.

He adds that Ardi’s intellectual abilities have also improved, e.g. he knows the cues when a trip is upcoming, like when his mother packs a bag, and he will wait for Zabidi at the door when it’s time for him to come home.

Ardi is also doing well at his special education school, Sekolah Kebangsaan Pendidikan Khas Kuantan, according to Maisarah, who says that he can follow his teacher’s instructions during lessons and has mastered new skills.

As the medicine needs to be administered intravenously (i.e. via a drip into a vein) once every two weeks over four hours, Ardi and his parents need to make the trip from the East Coast to Kuala Lumpur every fortnight.

An additional challenge is that Zabidi is based in Manjung, Perak, as a contractor for Telekom Malaysia, which means that he has to travel back to Kuantan to pick up Maisarah and Ardi before making the trip back to the West Coast.

But despite the distance and thanks to understanding bosses, they have never missed a treatment, especially since it is being given to Ardi free under Ultragenyx’s compassionate use policy.

## Compassionate access

While the initial agreement was for vestronidase alfa-vjbc to be provided to Ardi as part of the drug’s clinical trial for two years (2016-2018), he is still receiving the treatment for free up to today.

At an estimated cost of about RM3.36 million a year (the dose is weight-dependent, with Ardi currently needing about 11 two-milligramme bottles each

time), the price is beyond Zabidi's and Maisarah's salaries, especially as they also have to think about Ardi's older sister who just started university this year.

Maisarah works as a nurse at Tengku Ampuan Afzan Hospital.

Says Dr Kakkis: "Rare diseases require a higher level of responsibility in how you handle them.

"The fact that in the whole world, we are the only company that has an MPS VII treatment... with the privilege of creating a drug like this, comes a responsibility to ensure access.

"But one of the biggest issues (for pharmaceutical companies) is the fear that if they have to treat someone, they have to treat the whole world.

"But I've told people that not being able to treat the whole world in some future state, is not a reason to not treat a child in front of you right now."

Although Ultragenyx is a business (and thus, needs to make a profit), he shares that their goal is to make a profit overall, but not necessarily a profit off each and every patient.

Thus, the company's compassionate use policy includes ensuring that qualified patients worldwide do not have to forego treatment due to financial reasons.

Such patients are evaluated on a case-by-case basis.

Patients (and doctors on behalf of their patients) can also gain access to the company's rare disease drugs that are still under clinical trial by requesting to participate in such trials, even if they are the only one in their country.

Dr Kakkis notes that while rare disease patients can, and do, get in touch with the company (or even himself) directly to request for access to their drugs, Ultragenyx requires that a doctor be involved in the process to be medically responsible for the patient.

"While patients will request compassionate use directly from us, our response is usually to ask them to get the doctor who will be responsible for the treatment to contact us, because he is the authority we have to work through," he says.

"There's a particular team we have – the IST (Investigator Sponsored Trials) team – that is specifically designed to handle these cases.

"They are very knowledgeable about what to do and how to put a programme together for someone who needs to get treated."

The doctor is considered both an "investigator" for the clinical trial and the healthcare "sponsor" for US FDA bureaucratic purposes.

Ardi's case is the first time Ultragenyx has worked in Malaysia.

For Zabidi, Ardi's free treatment is "macam bulan jatuh ke riba (like the moon fell on your lap)" – something that was totally unexpected.

Says Lee: "At one time, I would have said this boy is just waiting for his time, but miracles can happen.

"Ardi's story teaches us to not give up on hope – he is my inspiration."

Zabidi agrees, saying: "In this world, the unexpected can happen.

"If you are patient (sabar) and strong (tabah), something good may happen." ■

*This article is part of the second package of a short series written as part of the US National Press Foundation's 2022 Covering Rare Diseases: Journalism Fellowship & Global Reporting Grant. The next one will be published this Sunday (Jan 8, 2023) in StarHealth.*



## Rare disease drugs can be costly; here are ways to ease the financial burden



Innovative treatments often come at a high cost, with many patients requiring some form of financial help to be able to afford them. — Axios

The number of rare diseases in the world is often quoted as ranging from 5,000 to 8,000.

Some people or organisations come down more firmly on the figure of 7,000, but in its *The Power of Being Counted* report, published last May (2022), US non-profit organisation Rare- X estimated that there are 10,867 rare diseases globally.

The report also states that only about 500 of these diseases have a treatment option available.

Generally speaking, a rare disease is defined as a condition that only affects a small percentage of a population.

This number varies in different countries or regions, e.g. the United States defines a rare disease as a condition that affects less than 200,000 people in the country, while the European Union considers a disease rare when it affects less than one in 2,000 citizens.

In Malaysia, the Health Ministry requires a condition to affect less than one in 4,000 citizens to be considered a rare disease.

With such small patient numbers for each rare disease, it is not difficult to see why there is not as much focus on researching and coming up with treatments for these conditions.

And for those that do have available treatments, the cost of research and development, combined with the low volume of demand due to the small patient pool, can make the price of such treatments very high.

### Volunteer for clinical trials

There are ways, however, for patients to gain access to such treatments for free – at least for a certain time period. According to Deepti, Roche runs patient assistance programmes for various of its medications, including risdiplam, where patients get free doses with their purchase of the drug. — Roche

The first, and earliest, way is to participate in clinical trials involving such treatments.

The most number of patients are often recruited for phase III of such trials, which are aimed at establishing the effectiveness and safety of such treatments.

There are two catches, however.

One is that, depending on the objectives of the trial and how it is designed, the patient might be one of those who receive a placebo, rather than the medication being tested.

Second is that the drug might be proven not to be as effective or as safe as hoped for during the course of the trial.

While many people might not relish being such a “guinea pig”, the lack of alternative treatments for life-threatening and disabling rare diseases might be incentive enough for such patients and/or their parents to agree to participate in such trials.

In addition, should the treatment prove to be effective and safe, then all trial participants will usually continue (or be started on, if they originally received a placebo) the treatment for free after the trial has ended.

This would come under the form of an expanded access or compassionate use programme.



Such programmes also provide a way for patients who didn't participate in, or weren't qualified for, the clinical trials and can't afford the drugs to gain access to these treatments.

## Removing cost barrier

For example, it is possible for Malaysian patients with spinal muscular atrophy (SMA) to obtain two of the three treatments available for this rare genetic disease through such programmes.

For the genetic therapy onasemnogene abeparvovec-xioi, there is an access programme that is open to patients worldwide.

A spokesperson from Swiss-American pharmaceutical corporation Novartis, which produces the drug, shares: "In early 2020, we launched a global Managed Access Programme (MAP) – the first for a one-time gene therapy – to make onasemnogene abeparvovec-xioi available to eligible patients with SMA, who are under the age of two, in countries where the therapy has not received regulatory approval.

"Since introducing the global MAP, we are honoured to have provided free access to this life-changing therapy to SMA families across nearly every continent – Africa, Asia, Australia, Europe, North America and South America – spanning over 25 countries to date."

Eligible SMA patients can have their names submitted to the programme through their doctor.

The patients are then selected at random to receive the treatment.

Up to 100 doses per year have been made available since the start of the programme, with six Malaysian toddlers to date being lucky enough to have been picked to receive the therapy.

The other SMA treatment available to Malaysians through such a programme is risdiplam.

Roche Malaysia general manager Deepti Saraf shares that while the Swiss healthcare company, which markets risdiplam, was going through the registration process for the drug with the National Pharmaceutical Regulatory Agency (NPRO), they first initiated a compassionate use programme.

"Early on in the journey, we realised the unmet needs and the urgency associated with some of the patients with SMA.

"So we also came up with a compassionate use programme, whereby on a first-come-first-serve basis, we were able to offer patients free treatment with the drug."

The caveat was that once risdiplam was approved, they could not continue enrolment for the programme.

Risdiplam was approved by the NPRO last June (2022).

However, Deepti assures that the 11 Malaysian children who were enrolled in the programme will continue receiving their treatment for free until a sustainable funding solution is found for them.

Although current SMA patients in Malaysia do not have a way to get risdiplam for free, Roche does have a patient assistance programme to help ease their financial burden.

"We have a programme called the Roche Patient Assistance Programme that can be accessed by any patient who is prescribed (risdiplam) by a registered, practising Malaysian physician.

"And the programme is basically designed to offer support financially, so patients who buy two bottles of our drug, get one bottle free along with it.

"So it helps to maintain the sustainability for the patient," she says.

# Treatments for SMA



Spinal muscular atrophy (SMA) is a rare, progressive, neuromuscular disease that occurs when a child inherits two defective copies of the SMN1 gene from their parents. The SMN1 gene is responsible for producing most of the body's SMN proteins, which are needed to keep motor nerve cells alive. Without motor nerve cells, the brain cannot send messages to the muscles to work. The severity of SMA depends on the number of SMN2 genes the patient has. Each SMN2 gene can produce a small amount of functional SMN protein.

## ONASEMNOGENE ABEPARVOVEC-XIOI

- A genetic therapy that replaces the defective SMN1 gene with a working copy.
- A one-time treatment given via intravenous infusion.
- Approved by the US Food and Drug Administration (FDA) in May 2019 for children less than two years old; not registered in Malaysia.
- Costs about US\$2.1 million (RM9.29 million) per shot (held the title as the world's most expensive drug until recently).

## RISDIPLAM

- A drug that boosts the production of functional SMN protein by SMN2 genes.
- A lifelong treatment given orally, with the dosage based on the patient's weight.
- Approved by the US FDA for children aged two months and older up to adults aged 60 in August 2020, and for children aged below two months in May 2022; registered in Malaysia.
- Costs a maximum of US\$340,000 (RM1.5mil) a year.

## NUSINERSEN

- A drug that boosts the production of functional SMN protein by SMN2 genes.
- A lifelong treatment given via intrathecal injection (into the spinal cord fluid via a lumbar puncture), with the dosage based on the patient's weight.
- Approved by the US FDA for both children and adults in December 2016.
- Costs between US\$625,000 (RM2.76mil) to US\$750,000 (RM3.32mil) the first year, then about US\$375,000 (RM1.66mil) annually subsequently.

*TheStar*graphics

## Third party coordinator

Unlike onasemnogene abeparvovec-xioi and risdiplam, the access programme in Malaysia for the third treatment currently available for SMA, nusinersen, is not run by the pharmaceutical company that markets it.

Instead, the programme, which just begun recently, is coordinated by healthcare access company Axios International, which is headquartered in Dublin, Ireland.

Co-founder and chief executive officer Dr Joseph Saba explains: “Expanded access programmes (by pharmaceutical companies) are usually after the clinical trial and before registration (of the drug).

“Once the product is registered, then usually, they stop the expanded access programme – this is where we come in.”

Nusinersen has already been approved by the NPRA for Malaysia.

He shares that once a doctor diagnoses a patient and decides to prescribe them the treatment, the doctor will then refer the patient to Axios.

The company will evaluate the patient, including their financial situation to see what they can afford to pay for the treatment – one key element of Axios’ programmes is that the patient or their family must pay part of the cost, although the amount depends on their financial capability.

Axios will then speak to the relevant pharmaceutical company to discuss defraying the remainder of the cost.

Dr Saba adds that the company may also coordinate with third parties like charities to help subsidise part of the cost.

Aside from the financial aspect, Axios will evaluate the patient on their willingness and ability to take the medicine as prescribed.

“For adherence, or following the treatment, we can say, ‘Ok, it is prescribed, you take it as needed’, but there is a lot of apprehension from patients.

“There are a lot of difficulties sometimes in coping with the disease that end up with the patient stopping the treatment,” he shares.

This is also why a key part of the process for the company is following the patient along their treatment journey.

“That follow-up is very important to ensure that they get proper treatment and they maximise the medical benefit,” he says.

For the nusinersen programme in Malaysia, Axios is collaborating with local SMA non-profit organisation WeCareJourney.

The NGO will help identify SMA patients who can benefit from the programme, as well as work with Axios in providing support for them.

### Sustainable solutions needed

Both Roche and Novartis acknowledge that solutions for sustainable access to rare disease drugs like the ones for SMA, need to be found. Dr Saba shares that Axios is continuing to look into various mechanisms to help subsidise patient treatment, including crowdfunding. — Axios

Deepti shares that for Roche, part of this involves supporting patient advocacy groups for SMA.

In addition, the company has been working with the Government on the establishment of the Rare Disease Trust Fund.

“It’s in its early stages, but this trust fund is an alternative way of funding the patients,” she says.

She explains that Roche’s role is a supportive one, which includes sharing best practices from other countries and highlighting the various factors and considerations that need to be taken into account while setting up and running such a fund, based on the company’s multinational experience.

Meanwhile, the Novartis spokesperson says: “The key piece that we need to solve – no matter the country – is finding sustainable access solutions for transformative gene therapies like onasemnogene abeparvovec-xioi within healthcare systems at large.”

They add: “We also believe it is imperative that the price reflects the transformative nature and benefit of our gene therapy, as well as the long-term value it provides, but also takes into account income levels, local affordability barriers and economic realities to help improve the affordability of our medicines.



“It is Novartis’ belief that it is a shared responsibility of all healthcare stakeholders to help bridge the divide between those with access to critical healthcare innovations, and those without.

“We need to play our part in that work. Our goal is to find a sustainable access solution for patients in need, agnostic of which type of system we are working in.”

For Axios, the idea is “win-win-win-win”.

According to Dr Saba, the patient wins as they are able to get treated in a sustainable way, the doctor wins as they can provide the best care for their patient, and Axios wins as everyone else wins.

As for the fourth element, the pharmaceutical company, he says: “We want the pharmaceutical company to be able to provide the drug in a financially-sustainable way.

“You know, when we started Axios, the pharmaceuticals were like, Ah, we donate; we do donations.

“That’s very nice, but it’s not sustainable – one day, it will stop, and if the patient has to take the treatment for life, it shouldn’t stop.

“So we want, from that angle, for the pharmaceutical to do it in a financially-sustainable way.” ■

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## Special exceptions for orphan medicines to treat rare diseases



Orphan medicines, which are drugs that specifically treat rare diseases, can be categorised as either emergency or lifetime therapies. — AFP

For rare diseases, time can often be of the essence when it comes to treatment. This is as many rare diseases can become fatal if not treated quickly.

The progression of symptoms can also occur quickly, resulting in increasing disability for the patient.

So what happens if a patient quickly needs a treatment that is not yet registered in Malaysia?

The National Pharmaceutical Regulatory Agency (NPRA), under the Health Ministry, is the body in charge of regulating and registering all pharmaceutical products, including traditional medicine and health supplements, as well as cosmetic products, in the country.

Health Ministry Pharmaceutical Services senior director Norhaliza A Halim, who oversees the NPRA, shares that there is indeed a mechanism to allow for such an unregistered treatment to be brought into Malaysia.

She says: “In a situation where a medicine is not available in Malaysia and is needed for the purpose of treatment of any person suffering from a life-threatening illness, whereby there are no other suitable options or alternative treatments available, the importation of an unregistered medicine can be applied for.

“In such cases, the healthcare facility treating the patient may submit an Import Permit application for the importation and use of an unregistered medicine.”

She notes that the Application for Medicines of Special Approval or Application to Import Product for the Treatment of Life-Threatening Illnesses provides a pathway to ensure continuous access to medicines needed for the treatment of patients in cases where there are no other treatment options available locally.

“The processing and evaluation of such applications will be expedited by the Pharmaceutical Services Programme in order to ensure the timely access to the medicine needed for the treatment of the patient’s condition,” she says.

Drugs for rare diseases are designated as orphan medicines.

They can be categorised as emergency treatment, which is required immediately to save the patient’s life or prevent permanent disability, or lifetime treatment, which is required for long-term or maintenance therapy for the disease.

However, just because a drug has been designated as an orphan medicine in another country, does not necessarily mean it will be automatically recognised as such in Malaysia.

Says Norhaliza: “The designation of orphan medicine is subjected to NPRA’s decision with input from the Drug Evaluation Committee (DEC).

“NPRA may seek advice from relevant experts, respective rare disease society or patient groups, or key opinion leaders, when deemed necessary.”

Another important point to note is that rare diseases also have a specific definition in Malaysia.

According to the Health Ministry, a rare disease is defined as “a life-threatening and/or chronically debilitating rare condition as listed in the Malaysian Rare Disease List”.

Inclusion in the list requires that:

There are confirmed patients with the disease in the country. The disease affects fewer than one in 4,000 people in Malaysia. The disease is a severe condition.

Approval is given by the National Rare Disease Committee.

There are over 500 diseases currently on the list, according to the Malaysian Orphan Medicines Guideline.

Norhaliza shares that any local, registered health- or pharmaceutical-related company or legal entity can apply for a drug to be designated as an orphan medicine through the NPRA.

“The application must be submitted before a product is registered as a New Chemical Entity or a Biologic product.

“The decision of the DEC to grant the designation of orphan medicine or otherwise will be made within 45 working days upon receipt of application.

“The Product Registration Holder (i.e. the company or legal entity making the application) is required to provide the product information, the proposed rare disease and condition, as well as the scientific rationale for the orphan medicine use when applying for the orphan medicine designation,” she says.

She adds that a drug that has been granted the designation of orphan medicine will be automatically granted priority review status for registration.

The review process will then be completed within 120 working days.

She also notes that the Product Registration Holder is responsible for post-marketing activities.

These include monitoring for any drug-related adverse effects, submitting regular safety reports and alerting the NPRA on any global safety issues relating to the drug.

Orphan medicines registered with the Drug Control Authority can be found on the NPRA website. ■

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## One couple's fight to get treatment for their son with SMA



*Yap (left) and Lim administering Branden's daily dose of risdiplam, which he is currently receiving for free under a patient access programme. — Photos: ART CHEN/The Star*

One of the most devastating things that can happen to a parent is finding out that your child has an incurable, terminal illness.

The signs that Branden Lim, 12, was not a regular healthy baby came as soon as he was born.

According to mother Yap Sook Yee, 48, her younger son had to be rushed to the neonatal intensive care unit (NICU) immediately after delivery as he couldn't really cry due to having fluid in his lungs.

After spending his first eight days of life in the hospital, Branden fortunately recovered and was able to go home.

Three months passed uneventfully, with Branden achieving the milestone of turning over by himself – but as Yap shares, that was “the first and last time he ever did it”.

From then on, he started missing more and more growth milestones, such as sitting up and crawling.

While Yap and husband Edmund Lim, 49, brought him to see a number of paediatricians and interventions like physiotherapy were prescribed, it wasn't until Branden only gained 100g between six months and one year of age that the alarm bells really started ringing in earnest.

Feeling that something was really not right, Yap did some research on her own into the possible conditions that might be affecting her child.

Armed with a few possibilities, she brought Branden to his paediatrician to discuss them.

The doctor agreed that her son might indeed have an undiagnosed condition and referred them to a paediatric geneticist for further consultation.

After doing multiple tests, it was confirmed that Branden had the rare disease known as spinal muscular atrophy (SMA).

This genetic condition occurs when a child inherits two defective copies of the recessive SMN1 gene – one from each carrier parent.



The SMN1 gene is in charge of producing a protein called survival motor neuron (SMN), which, as its name states, is crucial for the survival of motor neurons.

Motor neurons are nerve cells located within the central nervous system, which control both voluntary and involuntary muscle movement.

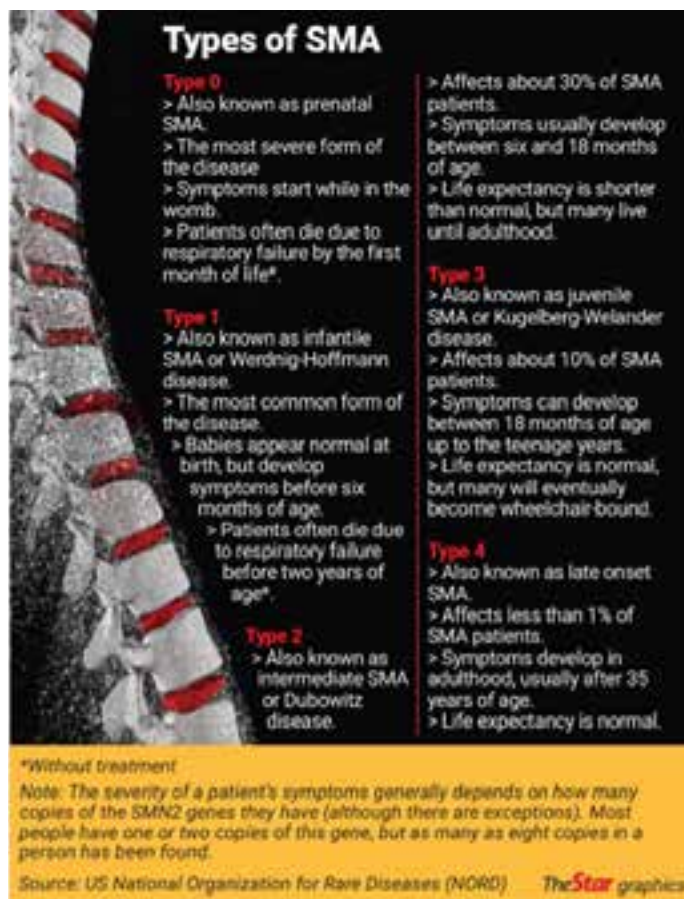
The lack of the SMN protein leads to the early death of these motor neurons.

As these cells have very limited regeneration capacities, this has a very serious impact on all the functions of the body that require muscle movement.

This not only includes movement like turning over, sitting up and crawling, but also essential functions like swallowing and breathing.

There are five types of SMA, which are classified according to when the symptoms first develop, and subsequently, how severe the disease will be (see graphic below).

Branden was diagnosed to have SMA type 1 – the most common and second most severe type.



## Striving for survival

Yap initially did not tell Lim about Branden's tests as he was working in London on an overseas assignment at that time.

However, the then-commercial manager returned in time for them to receive the test results together.

"It was like the whole house had fallen down around us; we were totally shocked by the diagnosis," he recalls.

Their shock and grief were compounded by the fact that the paediatric geneticist essentially told them there was nothing they could do for their son.

With no cure or treatment for SMA at that time, type 1 patients typically had a life expectancy of two years or less.

But neither Yap nor Lim are the types to take things lying down; they immediately started researching the condition.

They quickly discovered and signed up with Families of SMA, which sent them a care package on SMA.

This US-based non-profit was formed by parents of children with SMA, which aims to support families affected by the condition, and to fund research into treatments for it.

Their immediate focus was to manage Branden's symptoms and enable him to have the best possible quality of life.

"When Branden was diagnosed, of course at that point in time, we were mostly distracted with trying to figure out how we could care for him first, because we had so many regular issues that were often life-threatening.

"But before long, as we were looking at sources of information around the world, the research pipeline was clearly there," Lim says.

"The research pipeline is very clear to show us where drug therapies were being developed, how they were intended to work, and what stage they were at.

“So when you have that pipeline, you can see it coming through, you just don’t know when because it can fail during clinical trials.”

He shares that a couple of years after Branden’s diagnosis, they started engaging with the pharmaceutical companies that were involved in developing drugs for SMA.

That’s when they started learning more about clinical trials.

## Clinical trials abroad



Family support: (From left, seated) Yap, Branden, older son Jaden who also has the rare condition of growth hormone deficiency, paternal grandmother Chin Lin Ngook and Lim (standing behind) at their home.

“Now, clinical trials are about being a ‘guinea pig’, but I guess when you look at it from our situation, if we didn’t take the chance, we know where things would end up anyway – which would be a pretty unhappy ending sooner than we would like.

“And because SMA is progressive, you’re not at the same stage all the time, you’re continuously losing function,” Lim says.

You have to “take the bet”, as Yap says.

However, with all the trials being done overseas, the question was how to access them from Malaysia?

Lim shares: “I used LinkedIn to track down people in (the) pharma(ceutical industry) to try to figure out how things work.

“Unfortunately, we didn’t have a lot of guidance; it took us a bit of time to understand that it wasn’t pharma’s decision, it was the doctor’s decision.”

Doctors, whether in university, public or private hospitals, are the ones responsible for enrolling patients who meet the appropriate criteria into clinical trials.

The problem then arose as to how to enable Branden to become a patient of an overseas doctor involved in one of the trials, as this is a prerequisite for enrollment.

Moving to the country the clinical trial was taking place in was an option, but things never fell into place properly for it to be a real choice, according to Lim.

As SMA is a rare disease, and thus, has a smaller pool of patients willing and able to participate in clinical trials, some doctors might be willing to enrol patients based overseas.

However, there are also other issues involved.

“Even if the doctor is willing to enrol you, you have a whole host of other issues – regulatory, compliance, all these sort of things.

“But we made the effort to go through it, to fully understand the process, which is difficult, but not impossible,” Lim says.

He adds that while they have seen cases where patients have been enrolled from overseas, both the pharmaceutical company and the doctor(s) involved have to be willing to facilitate the process.

“Unfortunately, the timing never worked out for Branden,” he says.

For example, Lim got in touch with AveXis, a US-based biotechnology company that was developing a genetic therapy to treat SMA, via LinkedIn.

“One of their senior reps was willing to have a conversation with us on the phone, and Sook Yee subsequently met them at the 2016 World Orphan Drug Congress,” he says.

And while they learnt that there was a real possibility for international recruitment for SMA clinical trials, Branden, who was six years old then, was already too old to join the one for the genetic therapy named onasemnogene abeparvovec-xioi.

This drug is a one-time treatment, which was approved by the US Food and Drug Administration (FDA) in May 2019 for children less than two years old.

It replaces one of the patient's defective SMN1 genes with a new, working copy.

AveXis was bought by Swiss-American pharmaceutical corporation Novartis in 2018 and renamed Novartis Gene Therapies.

## Compassionate treatment

In June 2016, Yap and Lim founded WeCareJourney, a non-profit organisation that helps provide resources and support for Malaysian patients with SMA and their families, raises awareness about SMA, and engages with various stakeholders to help facilitate access to treatments for SMA for both Malaysian and Asean patients.

Lim resigned from his corporate job to go full-time into SMA activism, while Yap gave up her plans to eventually return to the workforce after her sons were a bit older, to do the same.

It was in his capacity as WeCareJourney president that Lim was invited by Swiss healthcare company Roche to attend the 2019 International Experience Exchange with Patient Organizations (IEEPO).

He was given the opportunity to ask Roche chief executive officer Severin Schwan a question directly on stage in front of the audience.

“So, of course, the question I had for him was around unmet needs for SMA patients in countries like Malaysia, which were, at the time, thought secondary to the developed nations.

“So my question was, how is this fair? What can we do to enable more equitable access around the world?” Lim shares.

Although he is unsure whether or not this interaction made a difference, he notes that Roche appeared

to soon start considering their SMA drug access in countries that were probably not originally on their priority list, like Malaysia, Singapore and Thailand.

Roche, through its independent subsidiary Genentech, markets the SMA drug risdiplam.

It is the first oral drug to be approved by the US FDA for SMA, and can be taken by patients from birth up to 60 years of age.

It helps the SMN2 gene make more functional versions of the SMN protein, and is a lifelong treatment.

The SMN2 genes are typically unaffected by SMA, but they produce far less functional protein compared to normal SMN1 genes.

In July 2020, Roche introduced the expanded access programme for risdiplam in Malaysia.

This programme allowed SMA patients who otherwise had no access to approved treatments or those in clinical trials, to obtain risdiplam for free under compassionate use.

Branden was one of the fortunate patients who managed to get into the programme, and is now being treated with risdiplam.

However, Lim says that the programme is no longer accepting new patients as the drug is now available commercially in Malaysia.

It was approved for children aged two months and older up to adults aged 60 by the US FDA in August 2020, and for children aged below two months last May.

Lim gives credit to the National Pharmaceutical Regulatory Agency (NPRA) for being accommodating enough to grant Import Permits for the then-unregistered drug through its Application to Import Product for the Treatment of Life-Threatening Illnesses pathway on an individual, named patient basis.

According to Health Ministry Pharmaceutical Services senior director Norhaliza A Halim, this pathway ensures continuous access to medicines needed for the treatment of a patient in cases where there are no registered or suitable medicines or treatment options available locally.

But there is an end date stipulated for the expanded access programme and its provision of free treatment.

“It is hanging over Branden’s head and the head of all these other children.

“Reassurances are given (that the free treatment will be continued), but reassurances are just that,” Lim says matter-of-factly.



Branden’s physical abilities are much improved after starting treatment for his condition. For example, he can now sit supported for much longer and speak without stuttering, which enables him to attend class and make more friends online.

## Patient access programmes

All the knowledge and connections that Yap and Lim have gained in their own journey is also being utilised for Malaysian patients with SMA through their non-profit organisation.

For example, WeCareJourney signed a Memorandum of Understanding (MoU) with healthcare access company Axios International last May (2022) to collaborate on a patient access programme for nusinersen.

Marketed by US biotechnology company Biogen, this drug was the first ever SMA treatment approved by the US FDA in December 2016.

Similar to risdiplam, nusinersen works by boosting the production of functional SMN proteins by the SMN2 gene and can be given to infants up to the elderly.

It needs to be injected into the cerebrospinal fluid of the spinal cord via an intrathecal injection.

After an initial four loading doses, the drug is administered once every four months for the rest of the patient’s life.

Through this partnership, WeCareJourney will help to identify SMA patients who could benefit from the programme, which requires some amount of co-pay by the patient.

Axios will evaluate each patient and coordinate between Biogen and the hospital for drug delivery (see this Sunday’s article in StarHealth for more information).

Lim shares: “One of the frustrations in our early days was always one party saying something’s not ready, waiting for the other party.

“So that drove a lot of the effort that we put in in the early days – to make all these connections and to have all these conversations.

“Because who else is more motivated to do it than the parents of a child who is facing a traumatic, life-limiting condition?” ■

*This article is part of the second package of a short series written as part of the US National Press Foundation’s 2022 Covering Rare Diseases: Journalism Fellowship & Global Reporting Grant. The next one will be published this Sunday (Jan 8, 2023) in StarHealth.*

## Treatments for SMA are available, but unaffordable for most Malaysians



WeCareJourney co-founder and Lim's wife Yap Sook Yee prepares the daily dose of risdiplam for their son Branden. This drug, which is based on patient weight, is estimated to cost a maximum of US\$340,000 (RM1.5mil) a year.

In the past six years or so, patients with spinal muscular atrophy (SMA) and their families were filled with hope as treatments for this rare disease were confirmed to be effective and approved by regulatory agencies around the world.

Previously without treatment and with a limited lifespan for the majority of patients, this progressive disease now has three available drugs that tackle the condition directly.

While getting hold of these drugs was previously a problem for Malaysians, the last year or so has seen the approval of two of these treatments by the National Pharmaceutical Regulatory Agency (NPRA).

They are nusinersen and risdiplam.

The other treatment, the genetic therapy onasemnogene abeparvovec-xioi, is not yet approved in Malaysia, but is possible to access via a special pathway on an individual patient basis (see this Sunday's article in StarHealth for more information).

Although this is one major barrier gone, there is another one preventing patients and their families from getting the life-saving treatment that they need: that of cost.

These are expensive treatments:

Onasemnogene abeparvovec-xioi – which until recently held the title as the world's most expensive drug – costs about US\$2.1 million (RM9.29 million) per shot.

Nusinersen costs between US\$625,000 (RM2.76mil) to US\$750,000 (RM3.32mil) the first year, then about US\$375,000 (RM1.66mil) annually subsequently, and

Risdiplam, which is based on patient weight, costs a maximum of US\$340,000 (RM1.5mil) a year.

Onasemnogene abeparvovec-xioi only needs to be taken once, but both risdiplam and nusinersen are lifelong treatments.

In Malaysia, none of these drugs are covered in public hospitals under the regular Health Ministry budget, i.e. you cannot get them for the heavily-subsidised fee of RM5 as you can for many other more common medicines.

Instead, there have been specific allocations for rare diseases, dating back to 2008 when Hospital Kuala Lumpur received RM250,000 to send patient samples overseas to test for rare diseases.

This allocation has been increased over the years, culminating in RM25mil in the 2023 Budget.

However, the Budget, which was not passed by Parliament due to the calling of the 15th General Election, may be revised when it is tabled in Parliament next month (February 2023).

Even so, WeCareJourney co-founder and president Edmund Lim notes that no SMA patient has benefited from this annual allocation for their treatment.

WeCareJourney is a non-profit organisation that helps provide resources and support for Malaysian patients with SMA and their families, raises awareness about the rare disease, and engages with various stakeholders to help facilitate access to treatments for both Malaysian and Asean SMA patients.

“We would like to see a transparent, equitable way how funding can be allocated between drug therapies based on unmet needs.

“It’s just not clear to us,” says the father of Branden Lim, 12, who has SMA.

“The clarity of the process and the timeline would be nice to know,” he adds, saying that then-Deputy Health Minister Dr Lee Boon Chye had indeed clarified that the allocation was for all rare diseases in Malaysia.

“Without government reimbursement, you will be seeing more and more cases of parents going out and asking for public help to pay for medication for their children,” he says.

The most recent successful case of such crowdfunding was for 17-month-old Reese Tan Rui Xin.

Her parents, accountant Rachel Chung and car engine oil and spare parts salesman Jason Tan, had appealed to the non-profit organisation One Hope Charity and Welfare to help raise RM9mil to pay for onasemnogene abeparvovec-xioi.

As the therapy is only approved for children under the age of 24 months, it was also a race against time for Reese to get the drug.

The huge sum was successfully raised within a week, with a final sum of RM9,002,230 from 26,425 donors.

But with an estimated 50 babies born with SMA in Malaysia every year, this is certainly not a sustainable method of financing

And indeed, not all such crowdfunding efforts are successful.

Lim also notes that it can be difficult to account for how such donations are spent, or what happens to the donated monies that don’t reach the target.

However, as an alternate source of funding for rare diseases, the Health Ministry is also hoping to tap into the generosity of Malaysians with its Rare Diseases Trust Fund established last July (2022), to which the public can donate.

Tax exemption status was given to such donations in the previously-presented Budget 2023, but it remains to be seen if this is still the case in the upcoming Budget.

No insurance plan covers rare diseases in Malaysia either, so parents have no options other than to hope to get into a clinical trial or compassionate use programme that will enable their child to get the treatment for free, or to pay out-of-pocket, which is unaffordable for most families.

As US-based EveryLife Foundation for Rare Diseases Chief of Policy and Advocacy Annie Kennedy shared during the 2022 US National Press Foundation Covering Rare Diseases online conference, a mother of a child with a rare disease once told her: Having no treatment is bad, but what’s worse is having a treatment that is unaffordable. ■

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## Treatment is not a cure for patients with SMA



*Lim (left) and Yap, seen here helping their younger son and SMA patient Branden stretch his muscles, stress that treatment for this rare disease is not a cure and that parents need to be prepared to continue providing care for their child. — ART CHEN/The Star*

Where once parents of spinal muscular atrophy (SMA) patients asked her about what is the best care they can give their child, now they will first ask about treatment.

As the co-founder of the SMA non-profit organisation WeCareJourney and mother to a 12-year-old son with the rare disease, Yap Sook Yee is used to helping and supporting her fellow parents who have been told that their child has SMA.

She says: “When parents hear there’s a drug, they think everything will be cured.” However, this is not the case.

Assuming that their child is able to access one of the three currently-available treatments for SMA, it is crucial to note that certain complications due to the condition might still occur.

In SMA, a child inherits two defective copies of the recessive SMN1 gene.

This gene is in charge of producing the majority of a protein called survival motor neuron (SMN) in the body.

Functional versions of this protein are only produced in small amounts by the SMN2 genes, which are the target of two of the treatments for SMA.

Without sufficient SMN protein, the body’s motor neurons will start to die, impacting the patient’s capability for both voluntary and involuntary muscle movement.

“What treatment does is it stops SMA – certain complications will still occur, e.g. scoliosis and lung infections like pneumonia.

“You still have to do a lot of physiotherapy and all that – the care continues,” says Yap.

In addition, the patient is unlikely to recover whatever motor function they have already lost prior to treatment.

Says her husband and WeCareJourney co-founder Edmund Lim: “If you’re looking at a child or an adult who already has a lot of motor neuron loss, the treatments will not bring back the motor neurons.

“It’s like cutting off a leg – it will not grow back, but if you are bleeding, it can stop the bleeding.

“So people mistake that if you stop the bleeding, the leg will grow back – no, it doesn’t!”

Motor neurons are among the types of cells that have very limited regenerative capabilities, so once they die, the body is unable to replace them.

He adds: “So many families, they have expectations of normalcy with treatment, but the patient will be frozen at their current level of functioning.

“They may get a bit of a bump-up because the disease is stabilised, but it will effectively be what it is.”

Currently, the genetic therapy onasemnogene abeparvovec-xioi offers the closest thing to a cure for SMA.

But even then, it comes with the warning that the patient still has SMA and may still experience symptoms like difficulty in breathing or swallowing, or muscle weakness, after the one-time treatment.

This therapy replaces one of the defective SMN1 genes with a working copy, thus enabling the body to produce sufficient levels of SMN protein.

A phase 3 clinical trial did show that babies who have SMA, developed similarly to healthy babies by 18 months of age when given the therapy before they develop any symptoms.

The study, which was published in the journal *Nature Medicine* last June (2022), had identified the babies via newborn screening.

However, most SMA patients face many hurdles in even getting diagnosed and are likely to have some level of motor neuron loss by the time they are identified as having SMA.

With the issue of financing, their condition is likely to have deteriorated further if and when they are able to get treated.

Therefore, Yap says: “Parents have to be given really good counselling at the start when the doctors are telling them what the treatment can do for their child.

“Not straightaway give them hope that this is a cure.”

Preventive efforts and care to keep their child as well as possible and functioning optimally are likely to still be needed, even with treatment. ■

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## Doctors essential in driving access for rare disease treatment



*The very first treatment for SMA given in Malaysia was administered in UMMC by (from left) paediatrician Dr Tae Sok Kun, Prof Thong and nurse Nur Emylia Jamaludin. — Prof Dr THONG MEOW KEONG*

In any disease, the doctor plays a crucial role in first, identifying or diagnosing the disease, then treating or managing it.

Sometimes, they also have to be advocates for their patients.

This is especially so in rare diseases where access to treatments may be limited, due to either the non-availability of the drug in the country, or cost.

In such cases, doctors play not only a critical part in planning and implementing a management plan for the patient, but also a pivotal role in obtaining the necessary medications.

Take for example, the rare genetic disease spinal muscular atrophy (SMA).

Treatments for this progressive neuromuscular condition only became available over the last decade or so (including through participation in clinical trials), with the first one being approved by the US Food and Drug Administration (FDA) in December 2016.

There are currently three approved treatments for SMA: nusinersen, risdiplam and onasemnogene abeparvovec-xioi.

The first two are registered and approved for sale in Malaysia.

However, as Hospital Tunku Azizah (HTA), Kuala Lumpur, consultant paediatric neurologist Dr Poorani Anandakrishnan shares, neither of them are listed in the Health Ministry's Medicines Formulary, also known informally as the Blue Book.

This means that they are not available for regular prescription in Health Ministry hospitals, nor is their cost covered under the hospital's budget if permission is obtained to prescribe them.

While the past few years has seen a special allocation for rare diseases included in the national budget, Dr Poorani says that her department has not received any of those monies.

And Universiti Malaya Medical Centre (UMMC) consultant clinical geneticist Professor Dr Thong Meow Keong says that although the rare disease allocation is meant for all, it only goes to Health Ministry hospitals, leaving out those under the Higher Education Ministry and the Defence Ministry, which are also part of the public healthcare system.

As these therapies are expensive – their prices range from around US\$340,000 (RM1.5mil) a year for life to about US\$2.1 million (RM9.29 million) for a one-time treatment – this makes them out of reach for the vast majority of Malaysian SMA patients.

## My doctor, the researcher

Fortunately, there are other ways for doctors to help their patients get these treatments, albeit in limited numbers.

As research involving these drugs is still ongoing, it is possible for SMA patients to receive these treatments for free while participating in the relevant clinical trials.

Prof Thong is the lead investigator for the phase 3 clinical trial testing the effectiveness, safety and tolerability of an intrathecal injection of the gene therapy onasemnogene abeparvovec-xioi being conducted at UMMC in Kuala Lumpur.

This one-shot treatment is currently approved by the US FDA for SMA patients less than two years old, to be administered via an intravenous (IV) infusion.

An intrathecal injection is done via a lumbar puncture straight into the spinal cord fluid.

The international, multi-centre clinical trial involves SMA type 2 patients aged two to 18 years old, who have not previously received any drugs for the condition.

Only patients cared for by the doctors involved in the trial, who meet the strict criteria listed, will have an opportunity to participate in it.

While there are a number of factors that go into being chosen as the site of a clinical trial, especially an international one, one of the main reasons is the expertise and research capabilities of its doctors, as well as their willingness to run such trials.

Such access to free treatment is why Dr Poorani is spreading the word for doctors in hospitals that do not have the experience or multidisciplinary teams to manage SMA to refer such patients to HTA.

Aside from providing the patient with the best care, she says: “It is also necessary so that if we have clinical trials for new drugs or any opportunity to try any compassionate access programmes, then we have a ready list where we can pick the patients for all these treatment access programmes.”

She adds: “We want to come up with a patient registry so that it is easier to identify these patients because some of them stay very far away.”

There is no national registry for rare disease patients in Malaysia, although doctors involved in managing these diseases have been calling for one to be set up for years. ■



# Dianah CHIYANGWA

*Zimbabwe*



**Dianah Chiyangwa** is an award-winning, Zimbabwean born photojournalist, documentary photographer, writer, poet and a curator based in Johannesburg. Her work focuses on women and children, migration, health, gender justice, climate change and environmental issues. Chiyangwa uses photography as a powerful role of observation and comment, and she has presented a strong devotion and approach to the craft of photography. Her value is in using the camera as a tool capable of recording with nuance; used to convey an insight, find empathy, make a judgment.

Her journey began in 2014, after she completed her Photojournalism and Documentary Photography at Market Photo Workshop. Since then, Chiyangwa, has won numerous fellowship awards such as and Digital Identity in Africa through Wits-Journalism/Africa China Reporting Project, Climate Change Fellowship, International Women's Media Foundation's Gender Justice Reporting Fellowship, Code for Africa Data Journalism Fellowship, and Africa Women in Media and UNEP Environmental Reporting Fellowship.

## A Rare Disease: Story of Mother Raising Child with Duchenne Muscular Dystrophy



Johannesburg, South Africa: “Mentally it is draining, watching your child’s health crumble and his lovely body deteriorates, but there’s nothing that can be done. Just coping mechanisms are suggested.”

Sibongile Mofokeng a South African mother begins telling her story of resilience while taking care of her sick son.

“Being a first-time mom is a very exciting and memorable experience. I started pushing around two in the afternoon, and the baby came at about six thirty in the evening. As usual, the baby didn’t come head first, I pushed so hard that the baby came out flying to the bed, its skin was pitch-black and at some, I

thought it was a black beauty. After I held him on my bosom, the nurses took the baby away, and when they returned it with a normal pink skin colour.” Mofokeng narrates.

After enduring an 18-hour labour pain, on 16 January 2007, Mofokeng finally gave birth to her beautiful bouncing baby boy whom they named Prosper.

“All was well with King Prosper until when he was a year and ten months old, he stopped mumbling the baby language for weeks, he stopped crying like babies would when they needed something,” said Mofokeng.

Growing up, “King Prosper” as his mother and everyone else affectionately calls him, could walk, but at this stage, he refused to walk unless balancing on something. “He would walk, even lead the way when one held his hand but if you left his hand, my little King Prosper would sit,” added Mofokeng.

### Diagnosis

Upon visiting their then Paediatrician for vaccines, the Dr discovered that King Prosper had a weak muscle tone and requested he is brought back in two weeks for a referral to a see Neurologist. This did not happen as Mofokeng’s strong faith in God convinced her that King’s Prosper condition will see him being able to walk again.

“As a praying mother, I commanded the situation to turn because we were not going back to that doctor,” explained Mofokeng.

Duchenne Muscular Dystrophy is known to result from a defect in a single important protein in muscle fibers called dystrophin and is caused by a fault in a gene that is located on the X chromosome. Boys inherit this gene (with the X chromosome) from their mothers, who are generally not affected.

Duchenne Muscular Dystrophy, is one of the most frequent forms of muscular dystrophy, affecting approximately 1 in 3500 male births. It was described in 1868 by a French Neurologist, Guillaume Benjamin Amand Duchenne, and was named after him. He was of the first people to study muscular dystrophies. Duchenne Muscular Dystrophy is an

X-linked inherited disorder and affected individuals are generally boys, with girls being carriers of the faulty gene.



*King Prosper Mofokeng sitting comfortably at his home in Pretoria/ Courtesy photo.*

Duchenne Muscular Dystrophy accounts for 50% of cases with the most severe form of Muscular Dystrophy affecting children. Similar to King Prosper's condition, most affected boys develop the first sign, which is difficulty in walking, at the age of 1 to 3 years.

“Prosper was clumsy in his walk, he toddles and bumped into walls and hurt himself a lot. His eye coordination was not well coordinated. He also struggled to stand up after sitting on the floor. These were signs of Duchenne Muscular Dystrophy but I didn't know, I was just a concerned Mother” elaborated Mofokeng.

Young boys living with Duchenne Muscular Dystrophy often walk on their toes with their abdomen pushed forward and with a waddling gait. These are early hallmarks of the disorder and result from weakness of muscles of the pelvis, which normally extend to the hips in order to retain the upright position when standing.

When these muscles are weak there is a tendency for the pelvis to tilt forward and in order to compensate for this the affected boy pushes his abdomen forward (called lordosis) and his shoulders backward. Rising from the floor unaided also becomes increasingly difficult which is also due to weakness of the muscles around the hips. This results in what is referred to as Gower's sign (difficulty in rising from the floor), after the physician who first described it.

A genetics test was performed on King Prosper, and when a Neurologist suspected that he could be having a Duchenne Muscular Dystrophy condition, he then requested a Genetics doctor for more investigations. Upon receiving the news of the diagnosis, Mofokeng was shocked. “it was a lot to take in but I believed and still believe we will win this battle God is on our side” she said.

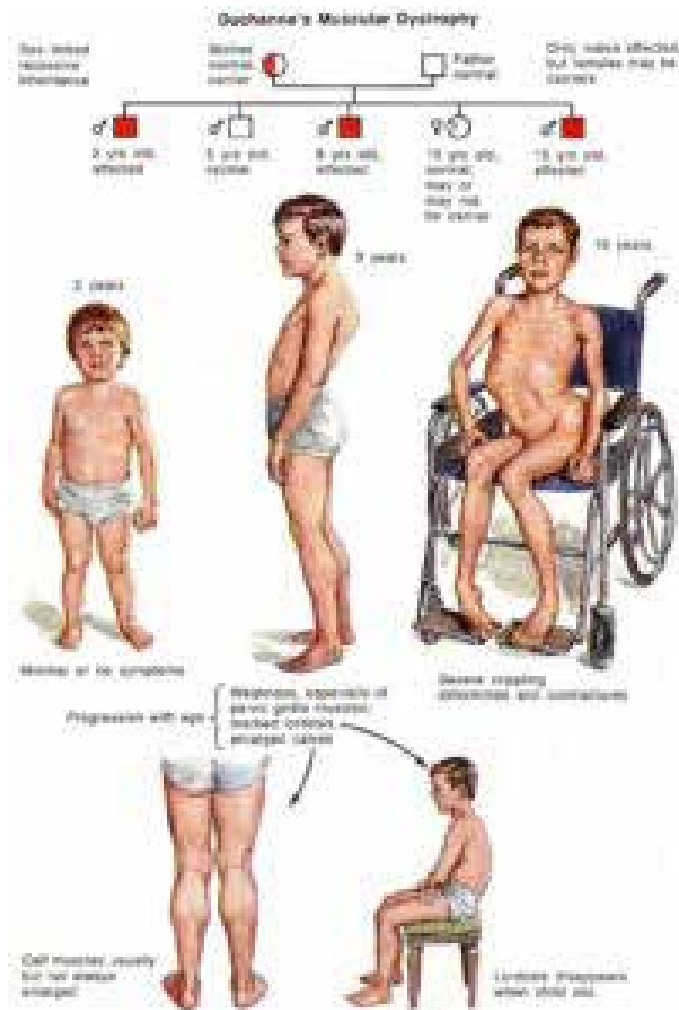
A new journey began for Mofokeng and her family after the diagnosis of King Prosper's condition. Again, like any parent, Mofokeng had big dreams for her son. “I struggled a lot with accepting that the situation is this way now and I need to do a lot to support and love him.”

King Prosper's health condition was not only Mofokeng's challenge at that time. She went through a separation and a divorce from King Prosper's father. Mofokeng, also went through financial challenges and could not afford to take pay for his daycare mother. These challenges led her to depression, and suicidal thoughts.

In the process, King Prosper was also diagnosed with Autism and against all odds, Mofokeng and her family have found a balance in managing King Prosper's condition. “We understand how he communicates using sounds and we read his eyes, sometimes there is a breakdown of communication and meltdowns and we have learned how to cope with those episodes” added Mofokeng.

“I had to really work on myself, so I can be the best mother to my son. God said I should also forgive

King Prosper’s father, so I could love Prosper. I did and it all became much bearable” she said.



A diagram indicating different stages of Duchenne Muscular Dystrophy (Image Source <https://healthjade.net/duchenne-muscular-dystrophy/>)

Despite these challenges, Mofokeng sought help and went for counseling.

“I healed much quicker when my mother started assisting me with King Prosper, she loves Prosper a lot, she prays for us and this is so humbling,” explains Mofokeng.

Educating the family about the two conditions was the first step Mofokeng took in order for them to understand what lies ahead in King Prosper’s life. Fortunately, Mofokeng has a strong family support structure.

Kgomotso Chirinda, King Prosper’s then-day mother said “Prosper is an amazing child, he is very smart, he knows the time, what not to watch, and what not to eat. He loves nice food, soft music, and cartoons and laughs when he watches funny stuff on

TV. I loved every moment, that I shared with them until his grandmother retired and continued taking care of him”.

Mofokeng explained that her family has always been her pillar of strength. “King Prosper is loved and cared for by his nieces and nephews, I made sure I am open with them and allow them to ask any questions regarding his condition,” said Mofokeng.

Speaking about family, Nozipho Rakolota, Mofokeng’s sister said that,” for a very long time as a family we still were in denial, but learning about the condition made us understand and continued to support our sister, and we pray for Prosper each and every day.”

Mofokeng, is a seasoned radio presenter and a week-day host on a show called Heart to Heart, at Radio Pulpit, a Christian radio station based in Pretoria South Africa. Balancing her work and looking after King Prosper, has been a challenge but explained that she is managing because of the support structure she has.

“I am a freelancer at the radio station I work for and I do extra jobs on the side, most jobs that wouldn’t require me to drive out from home, but I am always on the road. So, I make sure to spend quality time with Pro, whenever I am home. Sometimes we drive nowhere slowly, just to spend quality time together, bonding and listening to music” explained Mofokeng.

Mofokeng uses radio and other social media platforms to educate society at large about the condition and their special needs and to challenge stigma and stereotypes.

“We use the opportunity to educate our society when they stare at us or pass comments, or eager to know about the condition, we never get angry at their ignorance but take it as an opportunity to educate them” explained Mofokeng.

“My work has also been so understanding, they have accommodated King Prosper and I, on days where there was no one to look after him, I took him to work and they would feed him and change his diaper’ she said.



*Sibongile and King Prosper spending quality time playing at a jumping castle/ Courtesy Photo.*

## What experts say

Duchenne Muscular Dystrophy diagnosis is done through reliable tests that are available once a boy has been diagnosed as being affected by Duchenne Muscular Dystrophy. Affected boys have very abnormally high levels of an enzyme called creatine kinase (CK) in their blood. Most hospital laboratories can perform the CK test.

Professor Shahida Moosa, the specialist Consultant in Medical Genetics at Tygerberg Hospital and Associate Professor of Medical Genetics at Stellenbosch University, explained that “for families with rare diseases, the journey to a diagnosis becomes an odyssey that is punctuated by multiple tests and investigations, some that are painful and invasive and many that are unnecessary, and that despite consultation with numerous specialists, many are still left without a diagnosis or find themselves on a misdiagnosis odyssey.”

Mofokeng had undergone genetic testing to determine whether she was a carrier or not. Her blood samples were taken and sent to the University

of Witswatersrand (WITS) in Johannesburg for gene testing. Prosper’s test came back positive for Duchenne Muscular Dystrophy and hers were negative that ruling out her as a carrier of this gene.

Unpacking Duchenne Muscular Dystrophy, Dr. Engela Honey, a Paediatrician interested in children with genetic defects, and a senior lecturer at the University of Pretoria said “in case of a family history, we offer prenatal testing to identify where the gene abnormality is.”



*Sibongile and King Prosper spend quality time playing at a jumping castle/ Courtesy photo.*

According to Rare Diseases South Africa (RDSA), statistics indicate that 1 in 15 South Africans is affected by rare diseases. Despite this, the rare community is severely under-represented and remains vulnerable from a medical and policy perspective.

Both Duchenne Muscular Dystrophy and Autism, Mofokeng’s journey with King Prosper requires traveling from one health institution to another. They have been in contact with a Genetics Doctor, Dr. Engela Honey, whom they highlighted has never closed

doors for them, and also has a Physio Therapist. Recently, they met with the Paediatric Occupation Therapy Department at Kalafong Hospital and Pretoria West Hospital Occupation Therapist, who also have been helpful and warm and did their best to make Prosper's life easy.

National Health Institute: Rare Diseases in context, indicates that, despite an 85% GDP spent on health care, South Africa is among the worst performing in the world in terms of health outcomes.

With cases like Duchenne Muscular Dystrophy, Dr. Honey said, "for certain countries the genetics drugs are available, unfortunately in South Africa, we do not have to access these drugs."

Dr. Nicholas Crisp, Deputy Director General National Health Insurance, National Department of Health noted, "all healthcare providers, public and private, should be accessible to everybody purely based on their need for healthcare."

In 2021, the Rare Diseases Access Initiative (RDCI), in Association with Rare Diseases South Africa brought together an expert panel to discuss challenges facing those affected by rare diseases in South Africa and to explore possible solutions. An approach to diagnose care, and for increased equity in health care, for people living with rare diseases was made.

Although there is no cure for Duchenne Muscular Dystrophy, a recent study shows that certain exercises can help with muscular dystrophy. Unfortunately, King Prosper's condition has progressed over the years.

I have to turn King Prosper at night since he struggles to turn himself now, Duchenne Muscular Dystrophy has progressed in the previous years, his back has scoliosis and he is spastic" further explains Mofokeng.

Mofokeng's message of hope to parents and families who are also on a similar journey, but not able to openly speak about their journey because of fear of being stigmatized by society is that "We are stronger and wiser even more than our Physicians most times because we are with the children sometimes all the time. Never be an island, seek help whenever you need it, and get counseling because the journey can be exhausting, especially if you rarely sleep like us. Join a support group, if there's any." ■

*This project was produced as a result of the support from National Press Foundation.*





# Oana DESPA

*Romania*



**Oana Despa** was a TV journalist for more than 20 years. She led Investigation or Event departments at different national TV Stations and was the producer of a TV series of journalistic investigations related to the plundering of Romania after December 1989.

She is now editor-in-chief at the Buletin de București and works as a freelancer for Radio Free Europe Romania. She is also a trainer in media literacy and countering disinformation.

## Nicoleta Vaia, a Bucharest woman with a rare disease who saves the lives of dozens of people year after year in the absence of state aid

**There are 182 patients with mastocytosis in Romania, a form of cancer, included in the list of rare diseases. They learned to take care of each other, in the absence of complete help from the Romanian state. In Romania, too few were diagnosed with mastocytosis due to a lack of specialists, so the needs pushed them to learn to take care of each other.**

Nicholas recently turned 5 years old. He has been fighting the disease since six months. To find a clear diagnosis, his mother went to doctors for months. The first signs appeared after a varicocele operation.

“Some stains on the back. We went to 6-7 doctors who gave us the worst diagnoses. Finally, a private doctor told me it was mastocytosis and urged me to go to a dermatologist. She told me not to read anything about the diagnosis on the Internet, but to talk to Nicoleta Vaia”, recalls Maria, Nicholas’s mother, how their adventure in the fight against the disease began.



Nicoleta Vaia is the president of the Mastocytosis Support Association from Romania. A handful of people you can easily find on social networks. Here they try to convince ordinary people to help mastocytosis patients. Nicoleta is also a patient. He was 22 years old when the first signs of illness appeared. It was 1996 and she went into anaphylactic shock after being anesthetized for dental surgery. Over the next 12 years, anaphylactic shocks followed one after another.

“I had bleeding pustules on my chest and lower back, rashes that had been going on for years,” the woman recalls. He took her from doctor to doctor and even went to a psychiatrist because she thought she was somatizing, but the doctors told her she had an iron psyche. “You are a Survivor.” By all standards it was. He was born at 26 weeks and weighed 900 grams at birth. By 1995, she was on cromoglycate—a drug that unknowingly helped her—which was recommended for former high-grade premature babies. Then the drug was removed from the list of those offered free by the state, because it was too cheap. That was when her problems started.

In 2007, he had an appendectomy. After a 12-hour drive, he arrived at the Bucharest University Hospital and underwent emergency surgery. And in clinical death. His heart stopped because of the anesthetic. Doctors managed to revive her. It had become clear that her illness was not related to the psyche. To make sure the anesthesia was the problem, she tried one more, but the reaction was a severe allergic one.

A year later, in 2008, at the same time, two doctors - Horia Bumbea from Bucharest Emergency University Hospital and Irina Bucur from Nicolae Malaxa Hospital gave him the news. He had mastocytosis, an extremely rare cancer. This is how her story and that of over 100 patients began.

Mastocytosis is a heterogeneous group of diseases characterized by the presence of mast cells (cells involved in the functioning of the immune system that are normally found in mucous membranes and connective tissue) in different organs or tissues

such as skin, bone marrow, digestive tract, bones. Mast cells can develop in all organs except the central nervous system and the retina. Being a rare disease, it is difficult for doctors to have the necessary experience to make a proper diagnosis and treatment.



*Nicoleta is an ardent mountaineer and always tries to have a normal life.*

“The first reaction, I remember like now. It was November, it was raining, heavy rain. I raised my eyes to the sky and said: God, help me, to collect all those with my disease, so that no one will have to go through 12 years of torment to receive the correct diagnosis and treatment and make a center with a network of doctors who know this disease!”, Nicoleta remembers the shock of learning the news.

Then, when she realized how serious her illness was and what her life would look like from then on, she wanted a divorce, “so I wouldn’t be a burden to anyone.”

“I remember how the husband prayed to my father, may God forgive him, and told him to indulge me, that he doesn’t want to divorce even when he’s dead, and my father jokingly told him: I don’t know,

father, now you see how hard it is for me was I 28 with her too?”

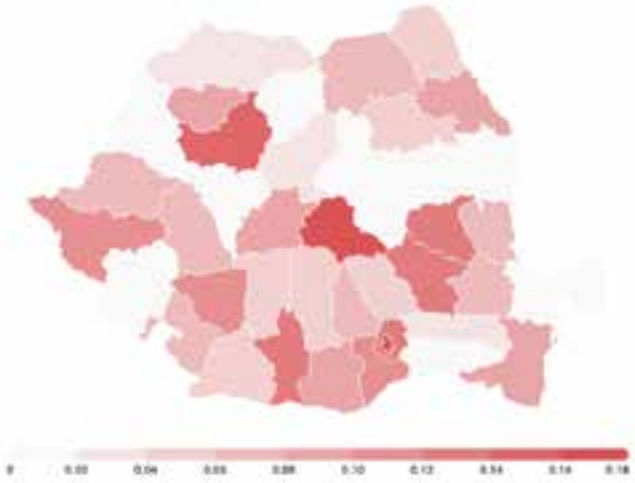
They stayed together to help him and a few years later became the parents of a child.

It was also a shock for Nicholas’ mother. She didn’t understand why this had to happen to her, what she had done wrong, what she should have done for her child. The hardest thing was during the first degranulation when, faced with the reaction of the child’s body, he didn’t know what to do.

“I knew what it was about because I had already documented myself, but it’s still not ok to see how your child swells, that he has a lot of spots on his body and swells like this, they become red and full of water. And you say it’s living flesh. And you see him breathing,” recalls Nicholas’ mother of the first shock.

Because she had already been put through the paces, she didn’t call Salvare, but Nicoleta, who helped her get through the moment. Like Nicholas, there are 67 children with mast cell diseases in Romania, almost half of the total number of diagnosed patients. Nicholas, like Nicoleta, lives near the Capital. The further you move away from Bucharest, the less likely you are to be diagnosed with the disease. Out of 42 counties, cases were registered in only 17. In order to receive a correct diagnosis, you have to go to Bucharest or a big city. Why does this happen, explains Prof. Horia Bumbea, professor at the Faculty of Medicine and Pharmacy in Bucharest.

“We know about 182 patients so far. We believe that it is an underdiagnosed disease compared to certain registers (diagnostic criteria-n.r.) more developed in other countries. We think the incidence is somewhat higher. It was a Danish registry that we had taken into account. Being a rare disease, it is obvious that there are differences from certain areas. What matters is the diagnostic power in that area, that is, having the ability to think about that disease, to make a differential diagnosis. For example, in our country, thalassemia minor is quite common in Romania, we think about it quite a lot, compared to Sweden or Norway where they don’t really do that”, explains professor Horia Bumbea.



*The rate of mastocytosis diseases per 10,000 inhabitants, in the counties of Romania*

Nicholas didn't make it to the hospital the first time he went into shock, but he did make it several other times because his reactions are in the respiratory tract. He has bronchiolitis leading to respiratory failure, so the doctors already know how to get him when he has problems. But, only some doctors.



One summer, he had respiratory failure at the sea, where he was on vacation with his parents. Because the nearby hospital was not ready to take care of him, his parents put him in the car and ran hundreds of kilometers to the ready hospital. They made a 3 hour journey in an hour and a half.

In the absence of specialists, Nicoleta is the man with the most experience in the community. In addition to the diagnosis of mastocytosis, he also learned that he has three out of four mutations on chromosome 7 regarding the production of diamine oxidase (DAO).

Diamine oxidase (DAO) is an enzyme that metabolizes histamine, its action manifesting itself mainly at the intestinal level. Histamine is a chemical mediator, its main physiological activities being capillary vasodilatation, smooth muscle contraction and increased gastric secretion. It is an important cerebral neurotransmitter and the main mediator of the early phase of immediate hypersensitivity.

Basically, her body was producing a maximum of 25% of the required amount of DAO. The news came as a thunderbolt because it came with a ban on 99% of the drugs and 95% of the foods that were pure poison to her body.

Mutations cause mast cells, through the medical process called degranulation, to release 80 substances (mediators) including histamine, heparin or serotonin.

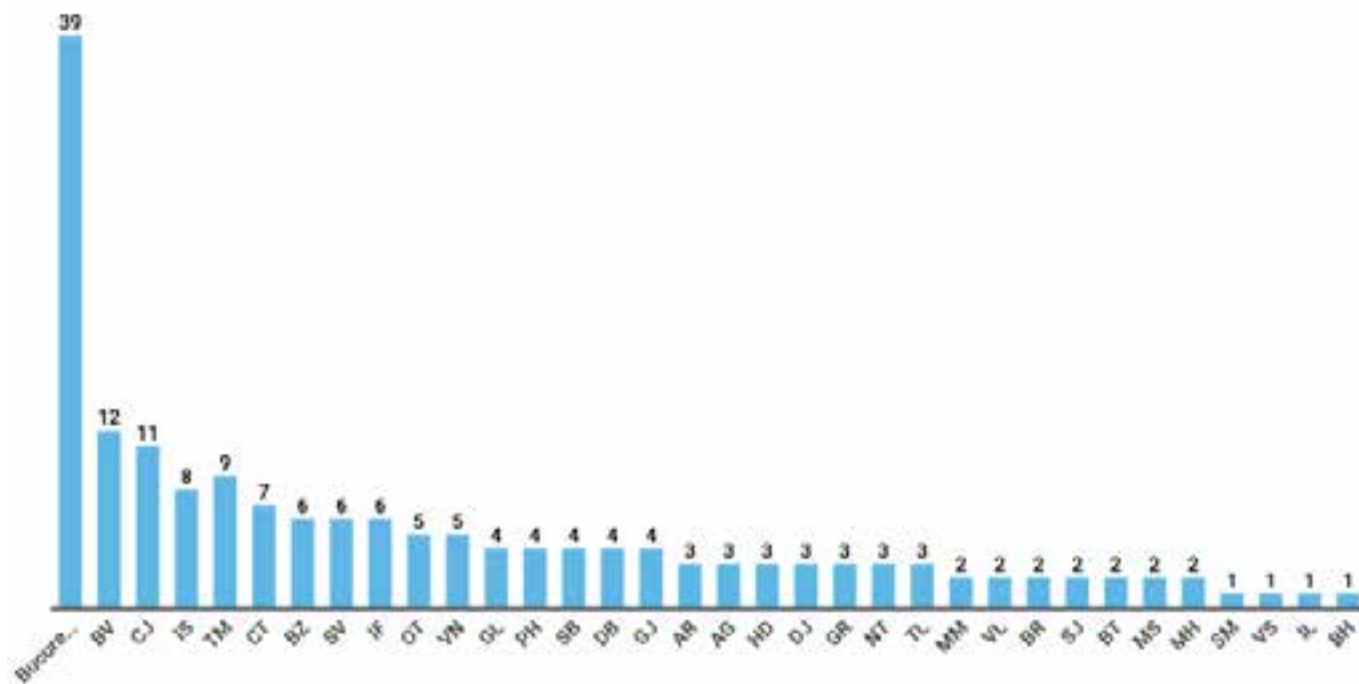
Each of these substances have certain effects on the body. Histamine produces bronchospasm, anaphylactic shock, inflammation, pain and leads to diamine oxidase depletion. Heparin leads to bruising, and serotonin produces serotonin syndrome, of happiness, which can be fatal.

“To sum up, these three mediators alone give the following symptoms while you are in UPU: anaphylactic shock, bronchospasm, generalized edema, generalized pruritus, and hypertension. Here I am unique among all pathologies on earth. In addition, agitation, euphoria, sweating, bradycardia and tachycardia. It's a horrible mix, where you need a super specialized network of doctors, because a lot of it can kill you.”

### What was there to do?

It was 2021 when he found out, 13 years after the first diagnosis. She tried to find the answer to her problem and went from doctor to doctor. He reached the European Center of Excellence in Mastocytosis, the branch in Romania, and the famous Charite hospital in Berlin. He learned that the histamine diet is the only one that can increase the level of diamine oxidase by stimulation.

“Russian Roulette. I remembered the Byzantine kings who were given minute amounts of poison daily to survive a poisoning when they ascended the throne. The principle was the same and I knew



*Distribution of mastocytosis patients by county*

that if I managed to increase my diamine oxidase level, I would change the lives of many patients, especially children with low levels, misdiagnosed as histamine intolerance and mastocytosis patients”, says Nicoleta.

He set his amount at the limit of tolerance, but said he had another chance but to try.

“It’s a strange feeling to know that you can die if the ambulance doesn’t come, but that only by eating like this you can live and help others.”

But the experience paid off. From diamine oxidase level 2, the lowest the machine showed, he went to 9. He repeated the experience every time the level dropped again. A normal diamine oxidase level is between 14 and 35.

“When I eat with histamine, the pain is hellish, my bone practically grows, the malleolus doubles (Each of the protrusions located in the lower part of the tibia and fibula - n.r.), but, looking back, my conclusion is that I managed to get out, from each given, at the port, that I managed to live. And not anyway, but with joy, as every time there were solutions and that is the most important thing”, explains Nicoleta

“It’s like someone is taking a life out of you. After two hours of torture, I manage to fall asleep for another hour and a bit.”

When he wakes up, he instantly throws up the toothpaste. The day starts with a coffee without sugar and 20 of the 40 pills he takes daily.

“I close my eyes and swallow them and that’s it. I can’t eat anything for hours. I prepare my child for school and go to work only by car. Any perfume, smell or viral person to me can mean UPU and oxygen.”

Nicoleta’s life depends solely on others, on how empathy, education, and common sense work or not, but she doesn’t want to rely on that, especially when she goes out into the world. A road with means of transport can cause him serious problems.

He doesn’t eat anything until 1 p.m., the drop in blood sugar is what gives him the signal that he still needs to feed. Eat 150-200 grams of meat, especially pork. Sometimes with a little salad.

“After the feast comes torment, about two hours of great pain, during which I can hardly keep myself from throwing up.” Her pain is not visible at work. She works at the Ministry of Finance in Romania and, for some time, has been a scholarship recipient of the German state. He is now on his fourth scholarship, from the Ministry of Foreign Affairs, at the Goethe Institute Brussel, which aims to implement German as the language of procedure in the European Union.

At home she is a heroine mother. For 12 years she has been the mother of Ianu, a special child as well, born prematurely who needs special diets.

“My child is a special one, a member of MENSA, a child with his own world, of incredible kindness and with a different way of seeing the world, for whose life we have been fighting for 12 years,” explains Nicoleta.



*Nicoleta and Ianu, also a premature baby, in the first days after birth.*

Late in the evening he still eats 200 grams of food - meat, salad or potatoes.

Nicholas’s life also depends on the others. His mother decided to take him into the collective and that implies additional responsibilities that not everyone assumes. Every time he is in kindergarten and asks to go home or says he is not feeling well, Nicholas’ teachers call to take him home. And going to the park can be a problem because any conflict with children can lead to degranulation. However, no one gives up, because if you know what to do and an average variant of the disease, you can have a life expectancy similar to that of people without rare diseases.

Life expectancy decreases for 10% of those who suffer from a severe form that also affects other vital organs.

## **Mastocytosis Association, hope for a better life**

Nicoleta’s fight with the system began in 2008, at the time of diagnosis, after she was prescribed cromoglycate. He had started using it and the reaction of the body was very good. It was

prescribed in mastocytosis since 1980, but in Romania it was not on the list of medicines settled by the National Health Insurance House, so it was no longer available over the counter. Its approval for current use was a complicated procedure that no one undertook.



*Cromoglycate products that the Mastocytosis Support Association buys month after month.*

“Cromoglycate is cheap, but they are drugs for other serious diseases that are very expensive, and if they had approved us, it would have opened a Pandora’s box and they had to be approved for other diseases where the costs would be very high,” explains the woman.

Cromoglycate stabilizes the mast cells that carry oncological information and helps patients to have a life as close to normal as possible, i.e. to stop degranulating – to stop going into anaphylactic shock if it’s cold, hot, if they bump themselves or if they eat E- hate. In children, the pustules stop bleeding.

Romania is the only country in the EU and among the few in the world that does not have legislation regarding the administration and settlement of medicines outside the indications on the leaflet. In the absence of help from the state, Nicoleta manages as best she can. For her and the other 183 mastocytosis patients, she gets money for cromoglycate cream once every few months. As the help must be constant, and the resources of kindness limited, every winter, Nicoleta puts pickles, sauerkraut or makes traditional food that she sells. Sometimes she is overwhelmed by disappointment, but every time she finds the strength to move on. He found a pharmacy willing to produce special cromoglycate soap whenever needed.

A prescription for cromoglycate would cost 30,000 euros per year, a tiny amount, but that would mean that there would be specialists in the Romanian Ministry of Health who could do this and that there would be political will.

Until then, and in 2022, for Christmas, Nicoleta took time off to sell the products she prepared to give hope of a normal life to 182 patients diagnosed with mastocytosis. ■



## Kristina FIORE

*USA*



**Kristina Fiore** leads the enterprise & investigative reporting team at MedPage Today. The team's work shines a light on some of the most pressing challenges currently facing doctors and other healthcare professionals, including the corporatization of healthcare and rising costs. Kristina's work has been recognized by Barlett & Steele, the New York Press Club, the Society of American Business

Editors & Writers, the Association of Health Care Journalists, and others. She has been a medical journalist for more than a decade and has had numerous bylines in both professional and consumer health publications. Kristina is a graduate of NYU's Science, Health, and Environmental Reporting Program, and currently lives in Jersey City, New Jersey with her husband and son.



## COVID Vaccines Made mRNA a Household Name. How Can It Help in Rare Diseases?



This story was supported by a grant from the National Press Foundation in partnership with Fondation Ipsen.

One of the hardest things about managing Jordan Franks' propionic acidemia (PA) was feeding him.

Jordan never wanted to eat. His body seemed to know that food could poison him, so like many kids with PA, he was food-averse.

"My son didn't want to eat anything by mouth," his mother, Jill Chertow, told MedPage Today. "I think the most he would ever eat was like, two pieces of mac 'n' cheese. Or he would lick the salt off of a French fry."

Kids with this rare disease can't metabolize certain amino acids. So Jordan had a regular -- and intense -- schedule of formula feedings that he took in through his gastrostomy tube, or g-tube.

"There was a lot of stress in managing his nutrition," said Chertow, who is president of the Propionic Acidemia Foundation. "He had three different powdered formulas. One was a baby formula, like a Similac. Then there was a second formula that had protein but didn't have the amino acids that were bad for him. And there was a third formula for calories."

The formulas had to be mixed and weighed to the tenth of a gram to deliver precise amounts of nutrients. Depending on the time of day, Chertow also had to mix in medications.

Jordan had six of these g-tube feedings each day, and because fasting is dangerous in children with PA, Chertow turned on a pump every night to make sure he didn't go too long without nourishment.

"It was challenging to manage all the feeds and within a timely manner," said Chertow. "You can't be too far off schedule, or it messes up the rest of the feeds for the day. Everything needs to be done pretty close to on time."

Jordan died in 2016 when he was only 16 years old. There was no treatment for PA during his lifetime, and there still isn't one. But families and researchers are hoping that the technology honed during the COVID-19 pandemic can help change that.

PA is one of a handful of rare diseases being targeted with mRNA therapeutics.

While mRNA mostly became known during the pandemic because of its use in COVID-19 vaccines, the technology had been investigated as a therapeutic long before then -- and it was hoped to have particular potential for rare diseases.

"I think there's great potential for treating monogenic diseases" with mRNA therapies, said P.J. Brooks, PhD, acting director of the Division of Rare Diseases Research Innovation at the National Center for Advancing Translational Sciences at the NIH. "That's what you're seeing with the propionic acidemia and methylmalonic acidemia trials."

One of the companies leading those efforts is, of course, Moderna, which became a household name during the pandemic for its mRNA COVID-19 vaccine (Spikevax). It is among a handful of companies that have advanced mRNA therapeutics for rare diseases into human clinical trials.

Moderna's PA trial is furthest along, followed by its trial for a sister condition, methylmalonic acidemia (MMA). Both conditions are considered ultra-rare, with estimates that each affect about 200 families in the U.S.

The company also just enrolled the first patients into its glycogen storage disease type IA trial, and is set to begin enrolling patients with cystic fibrosis in a clinical trial in partnership with Vertex opens in a new tab or window.

Other companies with human clinical trials of mRNA agents for rare diseases include Ultragenyx with its glycogen storage disease type III (GSD III) therapy, and Arcturus with its ornithine transcarbamylase (OTC) deficiency treatment. Several other mRNA therapies for rare diseases are in preclinical studies.

The technology has its limitations, but patients and families are watching the trials closely in hopes that they will yield a treatment.

## A Step Forward

Paolo Martini, PhD, worked on rare diseases long before he became the chief scientific officer for rare diseases at Moderna. He liked the field because it felt more interconnected than working on diseases with large populations like cancer or cardiovascular disease.

“In rare genetic diseases, it’s almost like a family,” Martini told MedPage Today. “I set up a network of [experts] all over the world, and we know each other well. There’s not much known on rare diseases, so people are very collaborative.”

That collaboration includes patients, patient advocacy groups, doctors, researchers, pharmaceutical companies, and others, he said.

Moderna recruited Martini from Shire in 2015, and within 2 years, Martini and his team -- in partnership with NIH researchers -- had their first major success. Mice with MMA tolerated 5 weeks of treatment with an mRNA drug aimed at the disease.

Their findings, published in Cell Reports opens in a new tab or window, garnered attention for being the first to show that an mRNA therapy can be given repeatedly without soliciting an immune response -- one that could be problematic in and of itself, or that eventually could render therapy ineffective. Martini and team had altered both the mRNA itself and its lipid nanoparticle coating to better evade the immune system and get the drug to the liver, where it is needed.

“With a small modification in one of the nucleosides, we were able to create an mRNA that was silent to the immune system,” Martini said.

The animals didn’t just tolerate the therapy; they thrived, said Charles Venditti, MD, PhD, chief of the Metabolic Medicine Branch at NIH’s National Human Genome Research Institute, who was a co-author of the study.

“The mRNA therapy resulted in the expression of the enzyme in the liver of mice with MMA,” Venditti told MedPage Today. “It has beneficial effects in the mice; it lowered metabolite levels and improved their clinical appearance.”

It also works quickly, and the level of enzyme expression in mice can be measured in a matter of hours, he added, noting that Moderna conducted additional animal studies that were used to inform their human trials for MMA and PA.

The company was just about to enroll the first patient in its MMA trial in March 2020 when COVID-19 hit.

### ‘They Can Get Sick So Quickly’

It would have been impossible to bring kids with MMA or PA into a hospital during the early, uncertain days of the COVID-19 pandemic.

“We could not put anyone at risk,” Martini told MedPage Today. “These patients are very fragile. In some instances they are immune-compromised ... so we stopped everything.”

Moderna also had to divert resources to making its COVID-19 vaccine, though Martini said his team always continued pushing ahead on their rare disease treatments in parallel.

MMA and PA fall into the category of organic acidemias. In both diseases, mutations in a single gene that produces a single enzyme prevents the body from properly metabolizing certain amino acids, which causes toxic metabolites to build up in the blood, potentially leading to a metabolic crisis that can be deadly.

The severity of the condition ranges from patient to patient, depending on their exact mutation: “There’s

an effect by the type of mutation and the amount of residual enzyme activity that a patient has,” Venditti explained.

“There can be patients with a somewhat milder condition,” he added. “That doesn’t mean they don’t have any symptoms or signs of the condition, but they can be not as unstable as someone who has two changes in the respective genes that totally inactivate the enzyme.”

Children with more severe forms of MMA or PA usually have their first metabolic crisis early in life.

Jordan Franks, for instance, was born on a Friday. By Monday, he had to be rushed back to the hospital, his mother, Chertow, said.

“These children can’t even have colostrum,” Martini said. “They can have metabolic decompensation and die because they can’t process it.”

Some children with MMA and PA are frequently in and out of the hospital because of their metabolic challenges, Venditti said. Even a regular respiratory infection can turn into a metabolic crisis.

“Any little thing that happens to them, they can get sick so quickly,” he added. “With these recurrent events happening so frequently, there comes a real chance of death and disability.”

Kids with MMA and PA also can have lifelong neurological damage from these early metabolic crises, Martini said.

Jordan’s early crisis and subsequent crises left him non-verbal, and he also had other behavioral issues, his mother said.

## A Favorable Target

The missing or defective enzyme in MMA is methylmalonyl-CoA mutase, and in PA it’s propionyl-CoA carboxylase. Both are made by the mitochondria, particularly those in liver cells. Without properly functioning enzymes, methylmalonic acid and propionic acid, respectively, build up in the blood.

Essentially, an mRNA therapy that can make it into the liver can allow the enzyme to be produced, and ultimately clear the toxic metabolites.

“mRNA goes into the liver, which is a favorable target, because most of everything that you inject into the blood goes to the liver,” Brooks said. “The enzyme gets made, and metabolizes the toxic metabolite.”

Martini explained how the therapy works. Once the mRNA, encased in a lipid nanoparticle, is given as an infusion, it enters the bloodstream and binds with lipid-like molecules in circulation that have an affinity for hepatocytes in the liver.

The whole molecule is then pulled into the cell, which takes it apart and releases the mRNA. The mRNA is recognized and gets taken up by the ribosomes, which translate it into a protein -- in this case, the missing enzymes in MMA and PA.

“You can imagine that the same approach can be used for a lot of other diseases where you need to correct a genetic defect in the liver,” Brooks said.

Currently, there’s no treatment for MMA or PA. Patients rely mainly on dietary control to restrict the amount of amino acids that can’t be metabolized.

Some can also consider a liver transplant, which is usually reserved for more severe cases because, like any surgery, it has its risks, and there’s a need for lifelong immunosuppression. Questions also remain as to how long a transplant can be effective, and whether it can truly curb damage to other organs over time.

Experts interviewed by MedPage Today said an mRNA therapy could be a replacement for liver transplant in MMA and PA patients, or it could be a bridge to any future treatments that might provide a permanent fix, such as gene therapy.

Martini said Moderna is seeing early signs of hope in its PA trial. At its R&D Day in September opens in a new tab or window, the company reported a decrease in the number of metabolic decompensation events after treatment started, according to preliminary data.

A total of 12 patients have been enrolled in four separate cohorts, he said, and all patients who have completed the study thus far are continuing into an open-label phase, “mainly because I think they believe what’s happening with mRNA and potentially they’re feeling better,” he said.

No patient has discontinued the trial, and some participants have taken more than 15 doses so far and it appears they are still responding to treatment, he added.

“They have some encouraging biomarker evidence that the approach is working as they think it should,” Brooks noted.

Moderna made some modifications to the protocol for the MMA trial that was set to start in March 2020. Martini said the first cohort of three patients has been dosed, and additional patients have been enrolled in the second cohort, totaling about five patients treated so far.

Initial data from both trials are expected in 2023, the company said.

Chertow is positive on the news, but remains cautious. Just because families decide to stay in a trial “doesn’t mean it’s helping,” she said.

Chertow enrolled Jordan in a study of carglumic acid (Carbaglu), a treatment developed for a different condition, when he was about 6 years old.

“I knew it cut his glutamine in half, cut his glycine in half, and his ammonia was pretty good,” she said. “I didn’t see side effects, so I’m like, I don’t know if it’s helping or not, but it doesn’t seem to be hurting.”

“People continuing [into the open-label phase] means, ‘Yeah, I guess it’s safe,’” she said. “But the question is, will it change their quality of life if you have an infusion every 2 weeks?”

### Other Rare Targets

Moderna is not the only company with mRNA therapies in human clinical trials for rare diseases.

Emil Kakkis, MD, PhD, is the CEO of Ultragenyx, a biotech that’s focused on rare and ultra-rare diseases. Kakkis made his name in the rare disease field by developing an enzyme replacement therapy for the rare genetic condition of mucopolysaccharidosis in the 1990s when enzyme replacement therapy was an emerging treatment strategy.

Now, along with other gene therapies and treatment strategies for other conditions, Ultragenyx has an mRNA therapy for GSD III in human trials. The company has dosed patients in its phase I/II trial, which is currently testing different doses, and plans to have early results in 2023.

They focused on GSD III because it appeared that the treatment wouldn’t need to be given as frequently, Kakkis said.

“We found with some others, the [protein or enzyme] didn’t last long enough, and you’d have to give the treatment weekly,” he said. “For GSD III, it appeared that if you could get rid of the toxic carbohydrate that’s building up, it didn’t matter if you didn’t have the enzyme there for a few weeks. The toxic carbohydrate would build up slowly over time and you could clear it again, so there’s the possibility of treating this disease less frequently, maybe once a month.”

“We’ve been looking primarily at situations where you can treat less frequently, so that we don’t keep tickling the immune system constantly,” he added.

Ultragenyx has partnered with Arcturus on that compound, and the latter company is also independently investigating an mRNA therapy for OTC deficiency. That trial is in phase I/II and is expected to report interim data in 2023, according to the company’s websiteopens in a new tab or window. Arcturus did not respond to a request for comment.

This month, Vertex announced that the FDA approved its investigational new drug application for an inhaled mRNA therapy for cystic fibrosis. The company, which is developing the treatment in partnership with Moderna, said it plans to start a single ascending dose trial in the coming weeksopens in a new tab or window.

There are other mRNA therapies for rare diseases in preclinical trials. Moderna and the Institute for Life Changing Medicines are developing an mRNA therapy for Crigler-Najjar syndrome type 1. Moderna is also conducting preclinical work for OTC deficiency and phenylketonuria.

## The Road Ahead

At this time, mRNA appears to be most promising for genetic diseases involving the liver, such as MMA and PA. That's because it's relatively easy to get the mRNA into liver cells.

“When you infuse something into the bloodstream, it gets to the liver first, and then it heads out to the rest of the circulation,” Jerry Vockley, MD, PhD, chief of medical genetics at the Children's Hospital of Pittsburgh, told MedPage Today.

The lipid nanoparticles encasing the mRNA “are seen in the highest concentrations by the liver,” Vockley said. “To get them into the muscle, for instance, in high enough levels, in clinically meaningful levels, it's just a technical challenge right now.”

“We're very interested in finding better ways to deliver mRNA to other cell types,” Brooks noted.

Even in PA or MMA, it might be better to deliver mRNA to both the liver and muscle cells, Vockley said. “The liver is only responsible for about a third of the branched chain amino acid metabolism in the body. Muscle is the bigger part. It's more like half to two-thirds.”

“If you could get something that hits the muscle and the liver, you probably have something that would be close to curative,” he added. “We still don't know if it would fix the brain completely. It's not clear if that's just tied to the metabolic decompensation events, or if it's something that just might show up later in life.”

Another limitation to mRNA therapy is that it would need to be re-dosed often.

“It would be a recurrent therapy, and it's unknown how much they're going to need, what the interval is going to be, what the side effects are,” Venditti explained.

Gerard Berry, MD, director of the metabolism program at Boston Children's Hospital, said the dosing for the MMA or PA trial could end up being about every 2 weeks.

“We're very enthusiastic about mRNA treatment,”

Berry said, “but we're paying attention to all of the different nucleic acid therapies.”

Vockley echoed that mRNA is just one component of the rare disease therapy space. There's gene therapy, which delivers a copy of the gene that's broken or missing, but it has “had a lot of fits and starts,” he said, due to both efficacy issues and side effects, including deaths.

But the gene therapy field has moved on from adenoviral vectors to adeno-associated viral vectors, which should improve safety, Brooks said.

There's also been a move to retroviral and lentiviral vectors for ex vivo gene therapy, which involves removing cells from the body, genetically modifying them, and returning them to the body, he added.

CRISPR also offers another means of gene therapy for rare diseases. Indeed, an ex vivo CRISPR-based treatment for sickle cell disease will be considered by the FDA early next year opens in a new tab or window.

Four other gene therapies have been approved by the FDA in recent years: voretigene neparvovec opens in a new tab or window (Luxturna) for retinal disease, onasemnogene abeparvovec opens in a new tab or window (Zolgensma) for spinal muscular atrophy, etranacogene dezaparvovec opens in a new tab or window (Hemgenix) for hemophilia B, and nadofaragene firadenovec opens in a new tab or window (Adstiladrin) for a type of bladder cancer. Some approved cancer treatments, known as chimeric antigen receptor (CAR) T-cell therapy, are also considered gene therapy, as they involve ex vivo editing of a patient's own T cells to make them target cancer cells.

In MMA and PA, Venditti's team at the NIH is hard at work on gene therapies that are in the preclinical phase, but other companies are pursuing additional strategies as well. That includes two small-molecule drugs being investigated in human clinical trials: one by CoA Therapeutics opens in a new tab or window, and another by HemoShear Therapeutics opens in a new tab or window.

Chertow said the fact that there are three clinical trials that patients with PA can try is “exciting for the families.” It's also a significant improvement over the state of research when Jordan was born in 2000, she said.

Since there were almost no research programs then, Chertow and four other families launched the Propionic Acidemia Foundation in 2002 to accelerate research.

The organization has funded about \$1.5 million in PA research since then, she said. “A lot of our initial research led to PA being a good option for research like mRNA, because there was a mouse model and ... there was some basic science that was done.”

Though that didn't happen quickly enough for Jordan to benefit, the hope is that researchers get closer to a treatment, in whatever form it takes. ■

## Families Push Research Forward in Rare Diseases

— The field has a unique funding model. While fruitful, some question if it needs to change.



*This story was supported by a grant from the National Press Foundation in partnership with Fondation de France. For the main story on how mRNA is being investigated for its potential in rare diseases, [click here](#).*

Kathy Stagni first met Charles Venditti, MD, PhD, at a meeting of her organization, the Organic Acidemia Association, more than 20 years ago.

Stagni's daughter had been born with a rare disease called propionic acidemia (PA) a little more than a decade earlier, and she had long been pushing to increase the visibility and scientific interest in the condition.

At the time, Venditti was a fellow at Children's Hospital of Philadelphia (CHOP), where he was the only postgrad focused on metabolic conditions. That's where he started meeting dozens of families whose children had organic acidemias and other metabolic emergencies.

"Our families just clung onto him" at the conference, Stagni told *MedPage Today*.

"They were saying, please, study our disorders!"

Now, Venditti is the head of the Molecular Medicine Branch at the National Human Genome Research Institute (NHGRI) of the NIH. He said he wouldn't have gotten there without the help of the families he's encountered along the way.

"I always think back to the days when I was starting off in this work. It was really the patients who supported me, listened, and said, 'We believe in you,'" Venditti told *MedPage Today*. "That really

gives people in the research space the boost of confidence to go forward. It's critical."

There's a unique funding model in rare diseases. These conditions typically involve small patient populations, so they don't attract attention from large pharmaceutical companies looking to develop the next blockbuster drug. Often, families are left to do the fundraising on their own, to support the basic science research that would help advance treatments for their child's condition.

The model was portrayed perhaps most famously in the film "Extraordinary Measures," which told the story of John Crowley, a father who quit his job in order to dedicate his life to finding a treatment for his kids' Pompe disease. Crowley is now the executive chairman of Amicus Therapeutics, a biotech company focused on developing therapies for rare diseases.

More recently, families have raised money to design and test their own antisense oligonucleotides targeted to their kids' conditions.

Emil Kakkis, MD, PhD, the founder and CEO of the biotech Ultragenyx, wrote a book, *Saving Ryan*, about his experience developing a therapy for the rare disease of mucopolysaccharidosis type I (MPS I). Kakkis, who at the time was an academic researcher, became very close with his patient, Ryan, and Ryan's family, who also raised money to push the science forward.

Their work together led to the approval of the enzyme replacement therapy laronidase (Aldurazyme), the first treatment for MPS I, in 2003.

In 2017, Ultragenyx won FDA approval of its enzyme replacement therapy vestronidase alfa-vjkb (Mepsevii), the first treatment for MPS type VII, which affects only about 20 patients in the U.S.

"We were able to [develop this drug] because we were really attuned to how to do it," Kakkis told *MedPage Today*. "But the truth is, I can't even do it again because the cost of doing that is still

prohibitive and the product will barely survive making money. It will probably break even, and you can't build a company on those economics."

"I think it's a failing of us, companies, and academia and FDA, to not have figured out an efficient way of getting those kind of rare diseases treated, to leave parents to have to develop their own drugs," he added.

When Venditti was starting his career, many of his mentors told him not to pursue rare metabolic disorders as a research career.

"Decades ago, people said these are not treatable disorders; do not study methylmalonic acidemia," Venditti said.

But Venditti had already developed a deep concern for the families he'd met at CHOP and at conferences. Among the most common conditions he saw during his fellowship, he said, were methylmalonic acidemia (MMA), cobalamin utilization disorders, and PA.

He remembers one patient in particular who helped him see a way forward. This patient had such a severe form of MMA that he had a liver transplant at age 2. One day Venditti got a call from the child's father, who was concerned because the child was spiking a fever of 104 degrees.

The boy was admitted to the hospital, and Venditti ran down to see him.

"He wasn't getting aggressive fluid replacement or adequate calories, which are critical to maintain patients with MMA," Venditti said. "But I just couldn't believe how stable he was. ... I'd taken care of many patients who were so sick from mild

perturbations like a cold or a mild respiratory syndrome, and it was striking to witness that a patient with a 104 fever, receiving minimal support, was totally fine."

"At that point, I knew the way to treat these patients would be to try to develop gene and cell therapies that target the liver," he said.

Venditti made the case for pursuing gene therapy for MMA with his chair of genetics, who opened up

space in his laboratory for the young researcher.

Families raised money for Venditti, too. "That's what really started me on this pathway, that interaction with families from CHOP who encouraged me to do research," he said.

He also won an NIH career development award at the end of his fellowship -- but not long after, the NIH intramural research program came calling. The NHGRI offered Venditti the support to develop a clinically focused program on MMA and cobalamin utilization disorders while, in parallel, developing animal models and working on biochemistry and molecular genetics.

It was bittersweet to leave CHOP and his early career grant, he said, but since he saw his first patient at the NIH in 2004, he and his colleagues have sponsored more than 1,300 patient visits. In 2016, he was able to expand the program to include PA as well.

His team is currently conducting natural history studies focused on both MMA and PA. With his laboratory colleagues, he has led the development of a "whole suite of new genomic therapeutics to treat MMA," including an mRNA therapy, a nuclease-free genome editing treatment, and conventional adeno-associated viral (AAV) vector gene therapy. In partnership with the National Center for Advancing Translational Sciences, and the National Institute of Neurological Disorders and Stroke, he is helping with an initiative called Platform Vector Gene Therapy (PaVe- GT) to facilitate the development of AAV gene therapy for rare genetic disorders, including PA.

"The paradigm of MMA being regarded as an untreatable disorder has dramatically changed. We are now assessing three new advanced genomic therapies that might be effective for patients," he said.

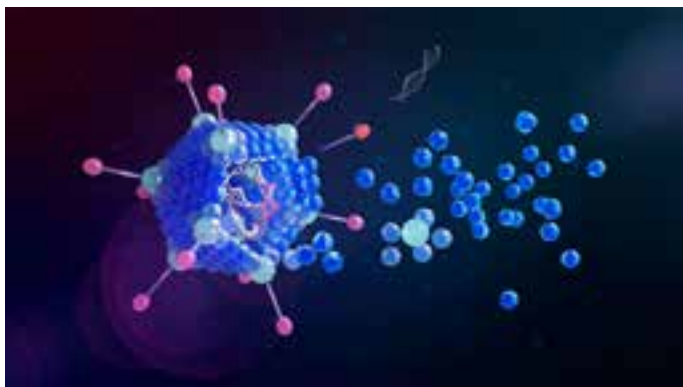
Venditti emphasized the importance of the partnerships he had with the patients and their families for making all of his work possible.

"It has been inspiring to work with the families and have them support our efforts," he said. "We would never be where we are without them."



Stagni echoed his sentiments: “He’s developed a great team at the NIH and he tries to incorporate parents’ views into everything he does,” she said. “I think he really worries about his patients, as well as the parents, and what we have to endure daily.” ■

## NIH Project Aims to Make Gene Therapy ‘Playbook’ Public



As more families raise money for and partner with researchers opens in a new tab or window to develop tailored, personalized treatments for rare diseases, some NIH agencies are trying to help by streamlining the process.

The PaVe-GT program opens in a new tab or window aims not only to blaze a path forward in advancing gene therapy for four rare diseases, but to share its “playbook” for doing so publicly -- including often-proprietary information on manufacturing and FDA filings.

“We’re hoping to pull the curtain back so people can actually see what goes into it ... and have an understanding of the complexity,” said Elizabeth Ottinger, PhD, acting chief of the therapeutic development branch at the National Center for Advancing Translational Sciences (NCATS), which leads the program.

Indeed, the idea behind PaVe-GT -- which stands for Platform Vector Gene Therapy -- was so popular that a second initiative, the Bespoke Gene Therapy Consortium opens in a new tab or window (BGTC), followed not long after to broaden the number of stakeholders involved and the number of diseases being treated.

PaVe-GT launched in 2019 opens in a new tab or window as a pilot program to develop gene therapies for four conditions: two inherited metabolic disorders, and two neuromuscular junction disorders. The two metabolic disorders are specific types of propionic acidemia and methylmalonic acidemia, and the neuromuscular junction disorders are Dok7 deficiency and collagen Q deficiency. Thus, the project involves collaboration with the National

Human Genome Research Institute (NHGRI) and the National Institute of Neurological Disorders and Stroke (NINDS), where those projects live, respectively.

“We’re thinking about the patient groups that are trying to do this for a disease that’s so rare that no biotech is going to be interested,” said P.J. Brooks, PhD, acting director of the NCATS division of rare diseases and research innovation. “We’re aiming to make things easier for them, but ultimately it will benefit the whole field.”

One key component to streamlining the development of gene therapy is to use a single adenoviral vector (AAV)-based platform for multiple diseases, Ottinger said. Another is to standardize manufacturing processes across those diseases. Ultimately, the program aims to minimize redundancies in preclinical development of gene therapies for these rare conditions, she said.

The NIH agencies plan to bring those therapies through the FDA’s standard regulatory process and make public all of their communications with the agency. That includes sharing communications from meetings, as well as any investigational new drug (IND) applications -- something that would be considered proprietary to many drugmakers.

“We’re not a drug company,” Brooks said. “Our goal is to increase translation and the whole process of bringing more treatments to more people more quickly.”

Yet the projects still earn the same valuable components that a drug company might prize. The therapy for one of the rare inherited metabolic disorders -- propionic acidemia caused by a specific mutation in the PCCA gene -- has earned both an orphan drug designation and a rare pediatric disease designation from the FDA, said project leader Charles Venditti, MD, PhD, head of the molecular medicine branch at NHGRI.

If that treatment is approved, the orphan drug designation conveys a certain period of exclusivity, as well as tax breaks, while the rare pediatric disease designation conveys a voucher that can be used for an expedited review of another product.

These vouchers can also be sold, Ottinger said, noting that recently they have garnered around \$100 million opens in a new tab or window apiece.

Venditti's project is currently in the pre-IND phase. Ottinger said the teams have had an "interact" meeting with FDA, which she describes as a "pre-pre-IND" meeting, the "initial engagement to talk about the overall plan of the project." The goal is to have a pre-IND meeting and submit an application by May or June, she added, so that the teams can get the therapy into the clinic by early 2024.

Carsten Bönnemann, MD, chief of the neuromuscular and neurogenetic disorders of childhood section at NINDS, who leads the neuromuscular junction gene therapy part of PaVe-GT, added that the program's transparency initiatives will also bolster the safety of gene therapy.

"Since every single trial has so few patients, if you put all of that information together, you have a powerful database on the immunological impact and safety," Bönnemann said. "Gene therapy not only becomes more affordable, but also safer, quicker."

Meanwhile, PaVe-GT's larger cousin, BGTC, will focus on standardizing and simplifying the development process for gene therapies. It's a public-private partnership run through the Foundation for the National Institutes of Health, which allows NIH experts to partner with industry in a way they otherwise couldn't, Brooks said. In addition to the NIH and the FDA's Center for Biologics Evaluation and Research, the project also involves 10 pharmaceutical companies and five non-profit organizations.

"It's like developing a community where everybody feels they know exactly what the expectations are, and how to move something forward for an AAV gene therapy," Ottinger said.

Although gene therapy had hit major hurdles by the early 2000s, including patient deaths, the field has refined its strategies and has started to show some successes.

One notable change has been the move from adenoviral vectors to adeno-associated viral vectors, which should improve safety, experts said. There's also more work being done in ex vivo gene therapy, which involves removing cells from the body, genetically modifying them, and returning them to the body.

The FDA has approved four directly administered gene therapies in recent years: voretigene neparvovecopens in a new tab or window (Luxturna) for retinal disease, onasemnogene abeparvovecopens in a new tab or window (Zolgensma) for spinal muscular atrophy, etranacogene dezaparvovecopens in a new tab or window (Hemgenix) for hemophilia B, and nadofarogene firadenovecopens in a new tab or window (Adstiladrin) for a type of bladder cancer.

The agency has also approved two ex vivo gene therapies, in which a patient's own stem cells are genetically altered and returned to the body to fight disease: betibeglogene autotemcelopens in a new tab or window (beti-cel; Zynteglo) for transfusion-dependent beta-thalassemia and elivaldogene autotemcelopens in a new tab or window (eli-cel; Skysona) for children with cerebral adrenoleukodystrophy.

In addition, some approved cancer treatments, known as chimeric antigen receptor (CAR) T-cell therapies, are also considered gene therapy, as they involve ex vivo editing of a patient's own T cells to make them target cancer cells. ■



# Portia GABOR

*Ghana*



**Portia Gabor** is a Broadcast Journalist, Producer and News Anchor at TV3 Network Limited based in Accra, Ghana.

She joined TV3 in 2007, carving a niche for herself reporting mainly on persons living with rare diseases and disability. At an immense personal risk, she reported on the COVID-19 outbreak from isolation and treatment centres in Ghana.

Her report on a 7 year old Ayeyi Yiadom Boakye, who had Osteo-Genesis Imperfecta attracted the likes of Ghana's first Lady to raise awareness on the rare disease.

Portia's report on disability also led to the discovery of a blind school dropout, Adelaide the seer, who is now a music sensation in Ghana.

Most of her works have been honored including Best reporter on disability, Disability excellence awards, 2021, Ghana Journalist Awards 2020, Special Award for COVID-19 reporting, Science reporting and Ghana Journalist Awards 2019, Female Journalist of the Year.



## Sickles in my Blood

[Video here](#)



**Erin**

**GARCIA DE JESÚS**

*USA*



**Erin Garcia de Jesús** is a staff writer at Science News. She has a Ph.D. in microbiology from the University of Washington and a master's in science communication from the University of California, Santa Cruz. Erin joined Science News as an intern in January 2020 and has spent most of her career

writing about COVID-19. She and her colleagues earned an Eddie Award for coronavirus news coverage in 2020. Erin also covers gene therapy, immunotherapy and, occasionally, weird animals.

## This child was treated for a rare genetic disease while still in the womb

### Left untreated, infantile-onset Pompe disease typically kills kids before age 2



*Shown here with her mother, Ayla Bashir, now 16 months old, is the first child treated for a rare genetic disorder called infantile-onset Pompe disease while still in her mother's womb.*

A toddler girl is flourishing after receiving treatment for a rare genetic disease. In a first for this disease, she received that treatment before she was even born.

Sixteen-month-old Ayla has infantile-onset Pompe disease — a genetic disorder that can cause organ damage that begins before birth. Babies born with Pompe have enlarged hearts and weak muscles. If left untreated, most infants die before they turn 2. Treatment typically begins after birth, but that tactic doesn't prevent the irreversible, and potentially deadly, organ damage that happens in utero.

Ayla received treatment while still in the womb as part of an early-stage clinical trial. Today, the toddler has a normal heart and is meeting developmental milestones, including walking. Her success is a sign that prenatal treatment of the disease can stave off organ damage and improve babies' lives, researchers report November 9 in the *New England Journal of Medicine*.

"It's a great step forward," says Bill Peranteau, a pediatric and fetal surgeon at the Children's Hospital of Philadelphia who wasn't involved in the work.

Infantile-onset Pompe disease is a rare condition that affects fewer than 1 out of 138,000 babies born globally. It's caused by genetic changes that either reduce levels of an enzyme called acid alpha-glucosidase, or GAA, or prevent the body from making it at all.

Inside cellular structures called lysosomes, GAA turns the complex sugar glycogen into glucose, the body's main source of energy. Without GAA, glycogen accumulates to dangerously high levels that can damage muscle tissue, including the heart and muscles that help people breathe.

While some people can develop Pompe disease later in life or have a less severe version that doesn't enlarge the heart, Ayla was diagnosed with the most severe form. Her body doesn't make any GAA. Replacing the missing enzyme through an infusion can help curb glycogen buildup, especially if treatment starts soon after birth (SN: 4/26/04).

Early studies in mice suggested that treatment before birth showed promise at controlling a Pompe-like disease. So pediatric geneticist Jennifer L. Cohen of Duke University School of Medicine and colleagues launched an early-stage clinical trial covering Pompe and seven similar conditions, broadly called lysosomal storage diseases.

The team began treating Ayla by infusing GAA through the umbilical vein when her mother was 24 weeks pregnant. Her mother received a total of six infusions, one every two weeks. After birth, the medical team has been treating Ayla with now-weekly infusions, and she will continue to need treatment throughout her life.

The therapy was safe for both mother and child, Cohen says. But until more patients are treated and monitored in the trial, it's unclear whether this prenatal enzyme replacement is always a safe and effective option. So far, two other patients with other lysosomal storage diseases have received treatment in the trial, but it's too early to know how they're faring.

Researchers are also exploring in utero therapies for other rare genetic diseases, including the blood disorder alpha thalassemia. And in 2018, researchers described three children who were successfully treated for a sweating disorder before they were born.

Such approaches have the potential to treat other rare diseases in the future, Peranteau says. But it will be important to first show that any newly developed treatments are safe and work when given after birth before trying them in utero.

For now, it's unclear how Ayla and other treated patients will fare over the long term, Cohen says. "We're cautiously optimistic, but we want to be careful and be monitoring throughout the patient's life. Especially those first five years, I think, are going to be critical to see how she does." ■

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# James GRIFFITHS

*Hong Kong*



**James Griffiths** is the Asia correspondent for Canada's *Globe and Mail* and author of *The Great Firewall of China: How to build and control an alternative version of the internet* and *Speak Not: Empire, identity and the politics of language*.

Before joining *The Globe* in 2021, James was a senior producer for *CNN International*. He has reported from across Asia, including Hong Kong, China, Sri Lanka, Malaysia and South Korea.

Originally from Wales, James lives in Hong Kong.





Sharma  
GUNJAN

*India*



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## Researchers from India, Israel, US trying to develop drug to treat rare disease ‘GNB1 Encephalopathy’



Researchers at the Indian Institute of Technology (IIT), Madras, Tel Aviv University and Columbia University are studying a rare genetic brain disease called “GNB1 Encephalopathy” and trying to develop a drug to treat it effectively.

With less than 100 documented cases worldwide, GNB1 Encephalopathy is a kind of brain disease or neurological disorder which affects individuals in the foetus stage.

Scientists say delayed physical and mental development, intellectual disabilities, frequent epileptic seizures, are among the early symptoms of the disease and since genome sequencing is an expensive exercise, not many parents opt for it early on.

According to Haritha Reddy, a former PhD scholar at IIT Madras, a single nucleotide mutation in the GNB1 gene that makes one of the G-proteins, the “G $\beta$ 1 protein,” causes this disease.

“This mutation affects the patient since they are a foetus. Children born with GNB1 mutation experience mental and physical developmental delay, epilepsy (abnormal brain activity), movement problems. To date, less than a hundred cases have been documented worldwide.

However, the actual number of affected children is probably much greater as diagnosis is not widely available since it requires a sophisticated and expensive procedure,” Reddy told PTI from Israel, where she is conducting the research.

“Every cell in the human body has a wide variety

of signalling molecules and pathways that help in communicating with other cells and within itself. The major signalling mechanism used by cells is ‘G-Protein Coupled Receptor’ (GPCR) signalling,” she added.

GPCR is a receptor that receives a signal (e.g. a hormone, light, neurotransmitter) from the outside of the cell and transduces it to the inside of the cell.

“GPCR is present in the cell membrane and has a G-protein (???) attached to it from inside the cell. G-proteins are the immediate downstream molecules that relay the signal received by the GPCR. These G-proteins are present in every cell, and any malfunction will cause disease,” she explained.

Mutations in GNB1 gene cause the neurological disorder (GNB1 Encephalopathy) characterised by general developmental delay, epileptiform activity in the electroencephalogram (EEG) and seizures of several types, muscle hypotonia or hypertonia, and additional variable symptoms, are seen in the patients.

According to Amal Kanti Bera, Professor, Department of Biotechnology, IIT Madras, as GNB1 encephalopathy is a rare and less-known disease, not much research has been done on this.

“We don’t know the mechanisms that underlie the disease. We don’t know how to treat this disease. Therefore, it is important to do research on GNB1 encephalopathy. We have a long way to go. It is not easy to develop a drug for treating this disease effectively,” he told PTI.

“We are in the process of developing preclinical animal models of this disease. Hopefully, in three years we will be able to develop personalised disease models which will be useful in research and drug screening,” he told PTI.

Nathan Dascal, Professor, Tel Aviv University, explained that as the developmental issues start at the fetal stage, gene therapy is the most plausible option to alleviate the effects of the mutation. However, the development of this complicated procedure will take many years and great investment of funds.

“On the other hand, epilepsy can be treated using specific drugs to increase the patient’s quality of life. To treat epilepsy, specific targets have to be identified. Most epilepsies are caused due to altered ion channel function. Ion channels are proteins that underlie the electrical activity of neurons and heart cells.

“It is also possible that a combination of already existing drugs help in a customised treatment line for the rare disease. Like in case of Covid, no new drug was found but already available drugs became part of treatment protocol,” said.

The research was supported by Indo-Israel Binational grant offered by Israel Science Foundation (ISF) and India’s University Grants Commission (UGC).

Professor Dascal pointed out that whole genome sequencing, the elucidation of the full genetic analysis of the baby, can be very helpful in early diagnosis of the disease.

“We have found that a potassium channel called G-protein gated Inwardly Rectifying K<sup>+</sup> (GIRK) channel (present in brain, heart and endocrine glands) function is affected significantly. Then we used specific drugs to correct the channel activity.

“As I80T mutation is the most prevalent variant in GNB1 encephalopathy patients, we are currently focusing prioritising on this mutation alone. We have a mouse models with I80T, K78R and D76G mutations. We have generated induced pluripotent stem cells (iPSCs) from the patient’s fibroblasts with I80T mutation.

“We will differentiate patient-derived iPSCs to differentiate into neurons. Our study paves the way for testing in animal models or patient-derived neurons to develop concrete therapeutic approaches,” he said. ■

## Indian researchers developing treatment for rare genetic disorder ‘Duchenne Muscular Dystrophy’

The current therapeutic options available to treat DMD are minimal and highly expensive treatment.



*Researchers from IIT Jodhpur, AIIMS Jodhpur and DART Bengaluru working on treatment for rare genetic disorder ‘Duchenne Muscular Dystrophy’. | Photo Credit: PTI*

Researchers in India are working on developing an affordable treatment for a rare and incurable genetic disorder called Duchenne Muscular Dystrophy with over 5 lakh cases in the country.

Duchenne Muscular Dystrophy (DMD) is the most common and fatal type of muscular dystrophy, marked by progressive muscle degeneration and weakness due to alterations of a protein called “dystrophin” that helps keep muscle cells intact. The condition is predominantly seen in boys, but in rare cases, it can also affect girls.

The current therapeutic options available to treat DMD are minimal and highly expensive treatment with costs shooting up to Rs 2-3 crore per child a year and are mostly imported from abroad, accelerating dosing costs and putting them out of reach for most families.

The Indian Institute of Technology (IIT), Jodhpur has established a research centre for DMD in collaboration with Dystrophy Annihilation Research Trust (DART), Bengaluru and the All India Institute of Medical Sciences (AIIMS) Jodhpur. The centre aims to develop affordable therapeutics for this rare and incurable genetic disorder.

According to Surajit Ghosh, Dean, Research and Development, IIT Jodhpur, DMD is an X-linked recessive muscular dystrophy affecting roughly one in 3,500 boys, which causes gradual loss of muscle tissue and function eventually leading to wheelchair dependency at approximately the age of 12 years, requirement for assisted ventilation at approximately the age of 20 years and eventually premature death.

Also Read | Pfizer’s haemophilia B gene therapy succeeds in late-stage study

“Currently, there is no cure for DMD, but improvements in integrative treatment can slow down the disease progression and thereby, extend the life expectancy of DMD patients. Patients with DMD have different forms of mutations at varying positions of the protein, resulting in the production of functionally compromised dystrophin ORF,” Ghosh told PTI.

“Despite its severity in terms of systemic muscle impairment culminating into multi organ failure and death, this disease is so far neglected due to lack of proper theranostic tools for in-time diagnosis and treatment. The primary goal of our team is to develop two therapeutic leads for clinical trials on high priority,” he added.

According to scientists, muscle weakness is the principal symptom of DMD. It can begin as early as age 2 or 3, first affecting the proximal muscles (those close to the core of the body) and later affecting the distal limb muscles (those close to the extremities). Usually, the lower external muscles are affected before the upper external muscles. The affected child might have difficulty jumping, running, and walking.

Other symptoms include enlargement of calves, a waddling gait, and lumbar lordosis (an inward curve of the spine). Later on, heart and respiratory muscles are affected as well. Progressive weakness and scoliosis result in impaired pulmonary function, which can eventually cause acute respiratory failure.

The researchers are working on affordable therapeutics for DMD and enhance the efficacy of Antisense Oligonucleotide (AON)-based therapeutics.

According to Arun Shastry, Chief Scientific Officer, DART, Bengaluru, the AON-based therapeutics' idea is to hide or mask specific exons (a segment of a DNA or RNA molecule containing information coding for a protein) in a gene sequence.

“In DMD patients, one or more exons can be masked with specific molecules called AON or molecular patches. Due to these challenges, DMD patients need personalised medicine. We have made significant progress on development of generic version of a utrophin modulator. Further validation in animal model will be initiated soon,” he told PTI.

“In addition, the Duchenne Muscular Dystrophy Drugs Controller General of India (DCGI) has given us a go ahead to conduct a multicentric clinical trial on Antisense oligonucleotide (AON) based exon skipping in DMD patients. Currently, the research team is also working on reduction of AON based therapeutic dose through new molecular tags,” added Shastry.

Until recently, boys with DMD usually did not survive much beyond their teen years. However, with advances in cardiac and respiratory care, life expectancy is increasing.

Researchers in India are working on developing an affordable treatment for a rare and incurable genetic disorder called Duchenne Muscular Dystrophy with over 5 lakh cases in the country.

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## Shiraz HASNAT

*Pakistan*



**Shiraz Hasnat** is a Pakistani Multimedia journalist currently working as a Bureau Chief of country's leading news channel HUM NEWS in Lahore. He is working since 2000 and became a part of many originations including Dawn News, Express etc and also contributed for Aljazeera. Mr Hasnat is an alumni of radio Netherlands training center, Pakistan US Alumni network, ICFJ and East West Center Hawaii. Mr Hasnat was appointed as a correspondent of Dawn TV

Washington in 2016 and covered USA presidential elections. He is also a Finance Sect of Pakistan's biggest journalistic body, Lahore Press Club for 2022. His major area of reporting is Health, Politics and Human rights issues while using investigative journalism tools and data and he also won different awards on his stories. Hasnat is also helping marginalized communities of country through his stories. A cofounder of [www.pakistanpositive.com](http://www.pakistanpositive.com), a website which publish positive stories only.



## Rare genetic diseases are causing 12 to 14 percent damage to the Pakistani economy, says WHO.



Rare genetic diseases are causing 12 to 14 percent damage to the Pakistani economy, says WHO. 6 million people in Pakistan, especially children, are suffering from genetic diseases, German Report Special Research Centers are working to diagnose and cure Rare Diseases, Minister of Health Punjab Cousin Marriages is a great reason for transmitting rare genetic diseases in kids, Head CDC, Dr. Amir According to a report by a German organization working on the diagnosis of rare diseases, 16 million people in Pakistan, especially children, are suffering from some rare genetic diseases. According to the World Health Organization, these rare genetic diseases are causing 12 to 14 percent damage to the Pakistani economy. Because rare diseases have fewer patients, they are not diagnosed, researched, and treated in hospitals like common diseases. Separate research centers are established for them.

Minister of Health Punjab Yasmeen Rashid says, “Most important step taken by the Punjab government for rare diseases is a health card. Health card has been given to all 31 Million families of Punjab.” She further said that to date almost 3 million families have benefited from health card. 97 percent of the patients are satisfied with the facilities provided by the health card, says Yasmin Rashid.



Yasmin Rashid said that health care also includes rare diseases. Thalassemia and cancer are being treated through the card. Treatment by cyber knife is also included in the health card.

Dr. Amir Mufti, head of the Communicable Diseases Center Punjab, says that rare diseases are those whose reporting rate is very low. These diseases also vary according to the region. A disease may be rare in Pakistan but its spread rate is high in Africa and other regions. He said that common diseases are detected commonly, Patients come and the treatment continues. There are some diseases whose patients put doctors in confusion about what is it. These diseases are investigated through the labs after which it is estimated what kind of disease it is.

Dr. Amir Mufti said that more than 7 thousand rare diseases have been reported worldwide. Apart from this, there are some syndromes that are very rare. One child in one to two million people is affected by the syndrome.

He said that in rare diseases, the symptoms are detected to some extent; the diagnosis is made through the lab later. As soon as the disease emerges, the government and the private sector make arrangements accordingly. According to Dr. Amir, genetic diseases are transmitted to children through Parents’ genes. One of the main reasons for this is cousin marriages. Hemophilia is an example of this. According to him, due to the marriage of cousins, the chances of hemophilia children are much higher than normal.

He said that research work on these rare diseases is being done on a large scale in Punjab. A large-scale lab is being built at the University of Health Sciences, which will work on genetics. Private universities are also working on it.

He said that he would like to send a message to the people that whenever they see that their disease is not being cured, they should consult the doctors as soon as possible. ■

## 7000 Rare Diseases are listed globally Unfortunately Pakistan has no single institution to diagnose and deal rare diseases

### 7000 Rare Diseases are listed globally Unfortunately Pakistan has no single institution to diagnose and deal rare diseases

If 20 people out of every one Million population suffer from a disease, this disease is considered as a rare disease. More than 7000 diseases are classified as rare diseases worldwide. Unfortunately, there is no institution in Pakistan to diagnose these rare diseases, nor is the data and research being done for treatment.

Among the 7,000 rare diseases in the world's population of 8 billion, there are many diseases that are still incurable. In Pakistan's population of 230 million, there is no proper mechanism for the diagnosis of these rare diseases. Rare diseases that have been diagnosed so far have happened by accident. Pakistan Medical Association blames the health system for this most important problem. President of Pakistan Medical Association, Professor Dr. Ashraf Nizami says, "The state is responsible for it, health is the privilege of every person. Medical experts should understand that if there is an effort regarding the diagnosis and solution for rare diseases, it is necessary to work on it".

According to Pakistan Medical Association, work is being done on rare diseases, their diagnosis and treatment since 2012. Pakistan is also a member of this research group globally, but unfortunately, no research and practical work is being done here.



Rare and complex diseases are affecting children and youth in Pakistan day by day. According to doctors, medical facilities for minor and casual diseases are not available in Pakistan; it is not an easy task to meet the shortage of advanced technology and qualified medical experts for rare

diseases. General Secretary of Pakistan Medical Association Lahore, Professor Dr. Shahid Malik says that most of the rare diseases diagnosed in Pakistan so far have been made possible by accident. If these diseases are diagnosed, the experts will learn their treatment method. If you learn it, you will catch rare diseases.

Doctors say that epidemics like thalassemia in Pakistan have been controlled through mass awareness and treatment.

If a comprehensive health policy is formulated in the same way, not only the diagnosis of these rare diseases will be possible, but through research, Pakistani doctors will also be able to play their role in treatment.



President Pakistan medical association Punjab Professor Dr. Izhar Chaudhry says that there is a comprehensive health policy in promulgation in developed countries. Keeping in mind the futuristic needs of health in these countries, the emphasis is put on what to do in the next ten or fifteen years. It is very thought provoking about Where do the nations stand and where do we stand in terms of health? In the last fifteen or twenty years, it has not been seen what steps we should take for our population. According to medical experts, during the past few years, efforts were made to solve mal nutrition in Pakistan by compiling the results from the data collected with the help of international organizations. A major breakthrough can also be achieved in the case of these rare diseases with the help of international organizations. ■



# Vincent KUGATA

*Uganda*



After sitting for his Uganda certificate of education (UCE) 2014, couple with the lack of fund to facilitate Uganda advance certificate of education (UACE) and bearing in mind the community **Vincent Kugata** comes from together with the corruption in the country (Uganda) and as a long- term admirer, he advices his beloved parent to opt for journalism.

That has given him more knowledge to unearth the rotten societal behaviors that has become a norm. He afterword joint Uganda Radio

and Television Institute (URATI) Lira, (Uganda) that has made him the person he is today after successfully pursuing certificate in Journalism and mass communication before diploma in the same discipline.

From 2016 to date, as part of his activities, He's been reporting on Crime, Politic, Education, health, Environment, public accountability, Security, Land and Property Right among others.

Reports of the disease began in 1997, with first recorded cases in Kitgum

KITGUM

By Vincent Kaguta

Three decades ago in northern Uganda, something unusual and terrible began in the district of Kitgum and, later, Pader and Lamwo.

Children started suffering from seizures, not just occasionally, but several times a day. Their neck muscles would temporarily switch off, causing their heads to nod.

The illness was named nodding syndrome. Nobody knew where it came from, but it devastated several victims, causing developmental delays and psychiatric disturbances. Many died from constant seizures at unexpected times that resulted into burns, falls, or drowning.

GENESIS OF THE DISEASES

Reports of nodding syndrome began in 1997, with the first recorded cases in Kitgum district in 1998. Cases rapidly increased annually, beginning in 2001, with peaks in 2003–2005 and 2008, after a peak in the number of deaths due to war.

No new cases have been reported since 2015, according to the health ministry. However, the disease left more than 3,000 children with lifelong disabilities, overwhelming their families and the region's capacity to take care of them.

Nodding syndrome is an epileptic disorder occurring among certain rural African communities in onchocerciasis endemic regions. It is characterised by repeated head-nodding seizures, developmental retardation and growth faltering.

In Uganda, nodding syndrome is seen in 0.7% of children aged 5–18, but in other districts, the prevalence is as high as 4.6%. A non-profit organisation that operated two clinics and fed and treated many of the children ran out of money and shut down in 2017.

SITUATION NOW

At least 1,000 girls suffering from nodding syndrome in Kitgum and Lamwo districts have been sexually abused in the last four years.

Statistics from the probation department of Lamwo and Kitgum district districts show that 55 of the victims are from Lamwo and 945 from Kitgum. The girls are aged between 15 and 24 years.

Geoffrey Oceana, the Lamwo district probation officer, said 51 of the victims in the district have given birth while four others are expecting. The cases

# Years later, nodding syndrome still a mystery

PHOTO BY VINCENT KAGUTA



A father (seated-back) with two girls who were diagnosed with nodding syndrome

syndrome official and a Village Health Team worker, working at Tumangu Health Centre II in Labongo Akwang sub-county, Kitgum district, said.

Nodding Syndrome remains a public health concern in Uganda, where it is associated with high mortality, severe socio-economic consequences, and social exclusion.

Currently, the natural history, etiological agent and pathogenesis of the diseases remains unknown and there is no specific treatment for those affected.

Despite this, many children receive anti-epileptic therapy, which improves outcomes. However, for effective management and control of the disease, the causative agent of the disease must be identified.

EXPERTS SPEAK OUT

Scientists have voiced their concern, calling for more investigation on nodding syndrome, which is currently a burden to northern Uganda.

According to pathologists, since severe cases are among children born between 1995 and 2005, there is a need to find out what happened in those 10 years in the affected areas, for more investigation.

Prof. Dr Sylvester Onzivua, a pathologist at Mulago Hospital, says nodding syndrome is an unexplained neurological condition characterised by episodes of repetitive drooping forward of the head, often accompanied by other seizure-like activity, such as convulsions or staring spells.

Dr Onzivua associates the disease with malnutrition and onchocerciasis, which have been documented, but remain inconclusive, adding that no underlying cause or cure has been established.

"Nodding syndrome is a mystery beyond Uganda's capacity to unravel," Onzivua says.

It is associated with onchocerciasis transmitted by black flies. Once the infection reaches the brain, there is an autoimmune reaction that triggers convulsions.

In Kitgum district, Labongo Akwang and Labongo Amida are the two sub-counties that are greatly affected by the disease.

Angagura and Palabek Abera sub-counties in Pader and Lamwo districts, respectively, are the most affected.

In December last year, John Baptist Odama, the Archbishop of the Gulu, opened up a care centre at Kitgum Mission to care for about 500 children affected by the nodding syndrome in northern Uganda.

## WAY FORWARD

**Prof. Sylvester Onzivua, a pathologist at Mulago Hospital, said efforts by scientists are in high gear with the University of Toronto to find the solution to the situation of children in northern Uganda.**

**He said much as government has designed a response plan to address nodding syndrome disease, through the health ministry, it should allow the University of Toronto to help in the investigation since they are willing to help.**

**Onkalit Denis Amere, the MP for Kitgum Municipality, appealed to government to provide housing, food and support to the victims of nodding syndrome. Scientists from the World Health Organisation (WHO) and the Centres for Disease Control and**

**Prevention, Atlanta, are now studying possible links between nodding syndrome and onchocerciasis, also known as river blindness.**

**About 93% of all nodding syndrome cases are reported from onchocerciasis-endemic areas, creating a strong hypothesis for common risk factors between the two diseases. Cases have so far been reported in Uganda, South Sudan and Tanzania.**

**WHO advises government to undertake mass treatment of onchocerciasis with ivermectin through out the affected districts and recommending health system strengthening as the best solution to tackle not only nodding syndrome, but other neglected tropical diseases.**

were registered between 2018 and 2021.

Hellen Acan, a mother, said her daughter was sexually abused.

She said her daughter, who is suffering from nodding syndrome, was abused by men who attacked her from water points.

"Government should

introduce stringent measures against such perpetrators to deter others from such shameful acts. I ask government and development partners to continue giving food and livelihood support so that we can grow food," Acan asked

She also requested government to construct a healthcare centre for children

who have acute cases of nodding syndrome.

Jennifer Acola, a resident of Tumangu in Labong Akwang sub-county, said her burden has doubled because she has to take a close watch over her daughter and at the same time provide every basic need for her grandson.

Acola, a peasant farmer

in Labongo Akwang sub-county, said the burden is heavier on grandmothers, who must tend their gardens with babies strapped behind their backs.

She said educating their grandchildren, who were all born without the nodding syndrome will help them lead productive lives in future.

Constance Omona, a 68-year-old man in Labongo Akwang sub-county, whose daughter and two boys were diagnosed with nodding syndrome, said his daughter has been sexually abused twice. He now takes care of his two children, who are six and three years old.

Omona said because of his age, he cannot practice farming on a small scale to earn enough money for basic needs.

CARE AND SUPERVISION

Children with nodding syndrome require constant supervision because a seizure could strike at any moment. The disease hinders their behaviour and decision-making abilities.

"These children are not easy to handle. Most of them are neglected by their parents, who have to provide for the rest of the family, Joe Otto, a nodding



# Alice MARTINS MORAIS

*Brazil*



**Alice Martins Morais** was a reporter for the newspaper *Diário do Pará*, senior communications analyst for *Temple Comunicação*, and also she was a Communication Consultant for the United Nations Population Fund (UNFPA). Nowadays, she's a freelance and she's working as a reporter on the Liberal Amazon project.

In 2018, she was the only candidate from the North region selected to participate in the training of the Women in Science Workshop,

promoted by the British Council, through which she covered the Women of the World festival.

In October 2020, she was the winner of the Northern region of the FactCheckLab program, from *Agência Lupa*, with a project to check facts about vaccination, aimed at children. As an award, she joined the International Visitor Leadership Program (IVLP) of the US Embassy, with a professional exchange in the country in 2022.

## Lack of specialists and resources impact the treatment of rare diseases



*Juliana Rodovalho is one of the three geneticist doctors who work in Maranhão – Photo : Matheus Melo*

Almost nine years ago, in January 2014, the Federal Government instituted the National Policy for Total Care for People with Rare Diseases, which reinforces the right to free total care for people with rare diseases within the Unified Health System (SUS). The offer of this care, in some cases, should start when the couple plans a pregnancy, with the advice of a medical geneticist. However, of the 322 geneticist doctors in Brazil, only 10 are based in the Amazon, according to the professionals' registry at the Federal Council of Medicine (CFM). Therefore, this follow-up is not always possible for the families in the region.

Considering that about 80% of rare diseases are of genetic origin, genetic counseling should be done with a medical geneticist, who assesses whether there is risk of a genetic disease occurring in a family and, together with a multi-professional team, guides when there is already a case in the family, explaining how to deal with this scenario. During prenatal care, this follow-up is indicated for couples

who have a consanguineous relationship (among relatives), or a history of fetal loss (when the baby is lost during pregnancy) and also when there is someone with a rare disease in the family.

However, the percentage of medical geneticists represents only 3.10% of the national total. And the only three states in Brazil that do not have this specialty are in the region: Amapá, Roraima, and Tocantins - these, along with Rondônia, also do not have any specialized public care services. To have an idea of the regional inequality, the 10 doctors who work in the Amazon are equivalent to 10% of the total number of professionals in São Paulo, the state with the largest number of doctors with this specialty (100 professionals registered in the CFM).

Maria Juliana Rodovalho is one of those who are part of this select regional group. She is today one of the three geneticist doctors who work in Maranhão, but, for a long time, she was the only one to work in the state. “I spent 14 years as the only medical geneticist here, I had only a few professionals who came, sporadically, and others were seen by telemedicine, with doctors from other states. Even so, the first challenge I faced was to be incorporated into the job market”, she recalls.

When she started her career, she noticed little interest from public hospital managers in incorporating this specialty. Even now, Juliana says that there are no medical geneticists working in Maranhão with a career plan, through public exams. She provides services to the Health Secretariat as a legal entity and, through her company, she invited another medical geneticist to be a partner and to share the services. “There is a lack of structure in the public service for hiring specialized professionals and training for those who work in Primary Care and are the first contact for the patient. And there is still a lack of incentive for medical students to enter the area”, she says. Today, the residencies in Medical Genetics, necessary formation to become a specialist, are concentrated in the South and Southeast regions and, when passing through this stage, many professionals end up not returning to the Amazon to work, according to Rodovalho's perception.



Heel prick test investigates at least six rare diseases - Photo: Thiago Gomes

## Heel prick test is an important ally for diagnosis

Long before the 2014 Ordinance, the so-called “Teste do Pezinho” (Heel prick test) already existed in SUS, incorporated into the system in 1992. It is a neonatal screening, a right of all children born in Brazil, and is a preventive test done by collecting drops of blood from the feet of newborns, performed in maternity hospitals and health units throughout the country. The test investigates at least six rare diseases: phenylketonuria and other hyperphenylalaninurias, congenital hypothyroidism, sickle cell disease and other hemoglobinopathies, cystic fibrosis, congenital adrenal hyperplasia, and biotinidase deficiency. “These are diseases that manifest themselves in early childhood and can be treated, besides being highly reliable tests,” says Rodovalho. The ideal is to perform the collection 48 hours after the beginning of breastfeeding, as soon as possible, although the neonatal period is up to 28 days and collections are accepted without medical request until this period.

Since 2021, the Federal Government has increased to 50 the number of diseases that can be detected by the Heel prick test offered by SUS. However, many health units are still not able to perform this list of tests. “For all screening tests, time is important because we need to detect the pathology as soon as possible so that the child has the least possible sequelae, or no sequelae at all, which is ideal, and does not die. We are waiting for the Ministry of Health to organize with the state secretariat the

necessary structure to expand the test to more diseases,” says Ana Thalyta Costa, a nurse from the Association of Parents and Friends of Exceptional Children (APAE) in São Luís (MA).

APAE São Luís is the Reference Service in the state, receiving the Heel prick test samples from all municipalities in Maranhão and performing the laboratory analysis. Besides identifying the diseases, the federal program of neonatal screening recommends that, if the child is diagnosed with any of these conditions, it receives the appropriate treatment by SUS consecutively to the test result.

In Maranhão, this step is done in three different places - for some diseases, such as phenylketonuria, for example, the treatment is at APAE itself. “At APAE, we provide multi- professional support, with a geneticist doctor, nutritionist, psychologist, among other specialties, and we also provide rehabilitation services, such as therapies, prosthetics and wheelchairs, when necessary,” explains Rosilene Cutrim, coordinator of the state’s Newborn Screening Reference Service (SRTN), at APAE São Luís.



Heel prick test samples for the laboratory analysis - Photo: Matheus Melo

## Institutions seek access to federal resources

The National Policy for Total Care for People with Rare Diseases determines that the health establishments may receive financial incentive from the Federal Government to offer exams, consultations with a multi-professional team, treatment, among other services that integrate the integral care and specialized attention to rare diseases.

With the qualification, the units can become a Reference Service in Rare Diseases or a Service of Specialized Attention in Rare Diseases and can receive up to R\$41,480.00 per month. To do so, the establishment needs to prove that it has the technical conditions, physical facilities, equipment and human resources suitable for providing this service to patients, meeting a series of prerequisites to be able to plead for the qualification.



*Isabel Neves, pediatrician at Bettina Ferro's Hospital - Photo: Matheus Melo*

This is what APAE São Luís has been seeking. In Pará, the Bettina Ferro de Souza University Hospital is also trying to qualify. Together with Hospital Barros Barreto, the Bettina Ferro makes up the Hospital Complex of the Federal University of Pará (UFPA)/ Brazilian Company of Hospital Services (Ebserh), which centralizes all specialized care to rare diseases in the state.

Doctor Isabel Neves has been a pediatrician for 28 years at Bettina Ferro and, because of her dedication to children, she became closer and focused on working with rare genetic diseases. She is part of a multi-professional team at the hospital, which includes a medical geneticist. “The qualification at the federal level will make a big difference, because we will have the resources to ensure more complex exams, which today depend a lot on the research projects of the university itself and of the Evandro Chagas Institute, and sometimes need to be sent out

of the state. We will also qualify the service, be able to hire more professionals, and better supply the patients’ demand”, she ponders.

In her experience, Isabel has closely followed the difficulties many patients have in accessing diagnosis and treatment, and has been engaged in the fight for improvements in quality of life for these people. “Sometimes the patients’ journey from the first symptoms is very long; it can take years to reach a service that makes the correct diagnosis. With all the difficulties in the Amazon, even the logistical ones, we also need to ensure that there is a greater decentralization, that there are specialized services and trained professionals in the interior of the states”, she declares.

For her, having qualified centers can also ensure that patients have follow-up in adulthood, because, in most cases in the region, the service is available in maternity hospitals and pediatric sections - as it is in the Bettina Ferro.

### Universities fill gaps in the health system

Just as the Bettina Ferro depends on the partnership with the laboratories of the UFPA (Laboratory of Innate Errors of Metabolism and Laboratory of Human and Medical Genetics) to perform the genetic tests of patients, in other states the reality is repeated.

In Rondônia, there is only one geneticist doctor, who attends in a private clinic, and no state reference center in the public health system. Thinking about the repressed demand, a group of researchers from the Federal University of Rondônia (UNIR) decided to expand a research project to also become an extension program, called “Caring for the rare”, in 2016. “Until then, it was a research work. We followed up with families who had patients with rare diseases and, during home visits, we realized that their situation was so complex, so difficult, that we couldn’t just stay in research, we needed to help as we could,” says Professor Vivian Susi, a professor in UNIR’s Human Genetics Laboratory and a member of the program.

The professor says that, in the absence of a state reference center, some patients get transfers through the public health system to undergo treatment in São Paulo, Goiânia and Porto Alegre. “But few



people have this opportunity, most stay here and it is difficult because we see that their living conditions could be much better, with proper assistance,” she adds.

According to her, the group took advantage of the field trips, with the initial goal of collecting data for studies, to also take social assistance actions, collection of material for laboratory tests, and other services to improve the quality of life and well-being of the patients. “Many patients live in rural areas, far from urban centers, and have difficulty accessing information and being part of SUS,” she recalls.

Among the guidance provided is also the direction for families to get the Benefício de Prestação Continuada (BPC), a federal government guarantee that provides one minimum salary per month, to the elderly and to people of any age who have some condition that makes it impossible for them to participate “fully and effectively in society.”

The activities strengthened in 2019, after the program received the donation of a van, which made it possible to expand home visits, even reaching municipalities in Amazonas and Rondônia. On each trip, a multiprofessional group followed, including professionals from Medicine, Biologists, Social Work, and Physical Education, and volunteers from Nutrition, Psychology, and Dentistry, among other specialties.

Besides the communities benefited by the project, UNIR’s undergraduate and post-graduate students also gained with the initiative a space for learning in practice.

### **Budget cuts harmed actions**

In the last two years, in addition to the impacts of the pandemic of social distancing and economic crisis, the federal budget cuts to universities made it impossible to advance the project and even to continue the activities that were already being done. “At the moment we are without supplies for the laboratory, which is an important part of the project, because it is where we analyze the samples and make diagnoses. We lost many of them during the pandemic because they expired and we still can’t find the resources to buy them again,” explains Professor Vivian Susi, from UNIR’s Human Genetics Laboratory.

The Laboratory of Genetics and Molecular Biology (LabGeM) at the Federal University of Maranhão (UFMA) is going through a similar situation. There is state-of-the-art equipment available and trained professionals to perform tests such as the karyotype, which analyzes all the chromosomes present in a person’s DNA and can detect conditions such as Turner’s Syndrome, which happens when a woman is born with only one X chromosome (instead of two) and causes symptoms such as short stature.

However, the equipment is currently being used exclusively for research, as there are no resources to serve the community as a whole. The LabGeM coordinator, Silma Pereira, points out that, from 2002 to 2008, the laboratory opened its doors to meet the demands of the population, receiving referrals from UFMA’s University Hospital. “I used the resources from my research projects to bring this service. Meanwhile, we tried with the University to seek agreements with the state and municipal health secretariats so that we could attend the patients in a more definitive way, but it never went ahead,” she says. Until 2019, the professor performed some exams on her own. “The demand is there and it’s very high. It’s a pity we can’t expand it for the population to enjoy,” she believes.

### **Patients’ families are important partners in the actions**

In the Amazon states, rare disease patient associations play a fundamental role in multiplying qualified information and directing those who seek a reference service. The groups are usually organized by mothers and fathers who have learned on a daily basis how to deal with the pathologies and exchange experiences with each other. This is the case of Ligia Lopes, who is the mother of a Williams Syndrome patient, whose symptoms include unusual facial features, such as a smaller and more prominent nose than usual, as well as coordination and balance difficulties. In 2014, she founded the Para Williams Syndrome Association, which has grown over the years and now includes other rare diseases. “We have patients from more than 28 types of rare genetic diseases in the association and together we fight for guaranteed rights, fight for public policies and conduct lectures, home visits and other actions to support families,” explains the founder.

The Association’s performance was so important in the state that it mobilized the creation of a specific

department for Williams Syndrome in the Bettina Ferro Hospital. “Through the mobilization of the mothers, we started to receive more and more patients likely to have the disease. They helped to give visibility and referral to people who might never receive the correct diagnosis and treatment, points out Isabel Neves, a doctor at the hospital.



Photo: Matheus Melo

## Where to look for specialized attention in rare genetic diseases in the Amazon

### ACRE

Women’s and Children’s Health Care System (Sasmc) at the Hospital da Criança e Maternidade Bárbara Heliodora

Outpatient Clinic of the Acre Hospital Foundation (FUNDHACRE)

### Rio Branco Cancer Hospital

Specialized Rehabilitation Center (CER) Tucumã Polyclinic

### AMAZONAS

Adriano Jorge Hospital Foundation - FHAJ

Genetic Counseling Clinic of the University Hospital - UFAM Genetic Medicine Outpatient Clinic of APAE Manaus

### MARANHÃO

Reference Service in Newborn Screening of Maranhão of the Association of Parents and Friends of the Exceptional of São Luís (Apae São Luís)

Medical Genetics Service of the Maternity of High Complexity of Maranhão (MACMA)

Medical Genetic Service of Juvêncio Mattos Children’s Hospital

### MATO GROSSO

Medical Genetics Service of Júlio Müller University Hospital - UFMT

### PARÁ

Federal University of Pará Hospital Complex (UFPA)/ Brazilian Company of Hospital Services (Ebserh)

Amapá, Rondônia, Roraima and Tocantins do not have official specialized care services for genetic rare diseases. In these cases, treatment is guaranteed to patients through the Out-of- Domicile Treatment policy.

In the case of Tocantins, there is a technical group for rare and/or degenerative diseases, which prepares clinical protocols and/or studies with the presentation of an opinion regarding the feasibility of incorporating technology in health care at the state level. ■

Sources: Brazilian Society of Medical Genetics (SBGM), NGO Many We Are Rare (MSR) and state health secretariats.

## People with rare diseases and the challenge of living in the Amazon



(MA), where she was born. She is one of seven albino people living in this small community, which shows a proportion well above the world average of one in up to 20,000 people, according to the United Nations (UN).

Ilha dos Lençóis is 150 km away (about 93 miles) from the capital of Maranhão, São Luís in a straight line, and is officially part of the municipality of Cururupu (MA). The City Hall does not have accurate official data concerning the number of inhabitants on the Island, but extra-official estimates are that as many as 365 residents live there. It is a calm and very silent place, hot sun all year round and very windy at night. There are no paved roads, cars or motorcycles. Everyone walks with their feet in the sand, crossing the mangroves and the white dunes.

### Listen to the comment on this news

Albinism is a rare, hereditary, non-contagious genetic condition. There is no cure and the major health risk is the high propensity for skin cancer. The World Health Organization (WHO) reports that “in some countries, most people die between the ages of 30 and 40 from skin cancer caused by the extreme sensitivity of albinos to the sun. But the disease can be avoided when albinos have access to health services”, explains the organization.

On the island, residents say that there have been about 20 albino people there, a fact that has attracted researchers and the press since the 1970s. It is believed that the high incidence of cases is due to the number of consanguineous relationships, that is, between people of the same family, which represents one of the risk factors for this genetic disorder.

The community lives mostly from fishing and shrimp harvesting. Edna’s non-albino parents were also fishermen and she, herself, started fishing when she was 10 years old. “I really like fishing, but nowadays I can’t do it anymore because of sensitivity to the sun, my skin dries up all over, sometimes it forms sores, it hurts a lot when I go to bed, I need to apply a lot of moisturizer”, she says. She stopped fishing eight years ago, when she started receiving the Benefit of Continued Provision (BPC), a guarantee from the federal government that grants a



*Edna Silva, one of the seven albino people living in Ilha dos Lençóis, in Maranhão - Photo: Matheus Melo*

“I will only leave this island when I die”, says Edna Silva, 42 years old, who, despite having very sensitive skin to the sunlight and sand, has chosen to spend her life on Ilha dos Lençóis, in Maranhão

minimum wage per month, to the elderly and to the people of any age who have some condition that makes it impossible to participate “fully and effectively in society”.

According to Edna, this adaptation for albinos is complicated, because it is not part of the local culture to take extra care with their skin, so it is as if this behavior took a wrong course, opposite from the habits of the rest of the community. Today, she spends her day at home,

taking care of house chores. Only after 5 pm, when the sun begins to “go down” or “cool down” (as they say in the region about dusk) is she able to go out normally to visit relatives and friends and occasionally go fishing at night. “This situation complicated the budget a lot because part of the money we receive from the government is spent with sunscreen, buying long-sleeved shirts, I really don’t have enough income, now I depend a lot on my husband’s fishing”, says Edna.



*Ilha dos Lençóis is 150 km away (about 93 miles) from the capital of Maranhão, São Luís in a straight line - Photo: Matheus Melo*

There is only one health center on the island. Despite the commitment of the team of professionals working there, the building is old and the facilities are humble, to meet basic demands. “It is very difficult to see a doctor here. When I go (to the doctor), I pay private consultation so as not to run the risk of taking too long to get an appointment or an exam”, she informs. But the logistics to get around Ilha dos Lençóis are not simple. There is no official “line” boat that makes the trip to the nearest town, Apicum-Açu. To overcome this limitation, it is necessary to take advantage of getting a ride on a fisherman’s boat heading in the desired direction and who charges R\$ 30.00 per person for the “ride”, which lasts approximately three hours.

Arriving in Apicum-Açu for her consultation, Edna goes either to Cururupu, located more than 78 km (or more than 48 miles) away, about 1 hour and 30 minutes by car, or to the state capital, São Luís, a trip that can take around six hours, considering road trip and ferry boat. “(Adding up all the expenses), every time I have to go on a trip like this, I spend a thousand reais”, she summarizes.

Due to the complicated logistics, many albinos choose to move to the nearest cities, to make it easier to access all kinds of services, from shopping to solving bureaucratic issues. For Edna, the choice to stay involves an affective link with the place: “It’s a quiet beach, the food is natural, I really like it. Many islands are not good, wonderful, like this. Here, we can even sleep on the street and nobody messes with us”, she justifies.

Prejudice - Even though the presence of albinos on Ilha dos Lençóis is relatively common, there is still prejudice against them. For this reason, Edna reveals that, sometimes, she thinks it would be good to have been born “Morena [brunette]”, as she calls non-albinos. “I’m not ashamed of being what I am. I’m very proud of my skin (...). But being ‘brunette’ could have been better because I wouldn’t suffer prejudice, right? I’ve been called a lot of things, ‘hairless’, ‘rotten skin’”, she laments.

### Parents fight for the well-being of children with hereditary disease



João was only two days old when blisters started appeared on his face and hands - Photo: Matheus Melo

Unlike albinism, most rare conditions are difficult to diagnose. Currently, it is estimated that 13 million Brazilians suffer from some rare disease. However, there is no global consensus on what is considered a rare disease, as each country has its own criteria.

In Brazil, a disease is considered rare when it affects up to 65 people in every 100,000 individuals. Due to this context, it is difficult to correctly and quickly diagnose and provide treatment when something unusual is noticed in someone.

When João Pereira was two days old, blisters appeared on his face and hands. His parents were immediately worried and surprised, and tried to find out what was going on. The family is from Bagre, a municipality in the interior of Pará, located in the Marajó Archipelago (also known as Ilha do Marajó), 12 hours away by boat from the capital, Belém.

But João was born at the Regional Hospital of Breves, the health center with the largest facilities in the archipelago. When it was noticed that the patient needed greater care, he was transferred to Belém, to the maternity hospital of the Santa Casa de Misericórdia do Pará.

After some possibilities were discarded, it was there where he received the correct diagnosis: epidermolysis bullosa. The disease is hereditary and causes the formation of blisters on the skin when minimal friction or trauma occurs. There is no cure, and it is not a contagious disease. According to information from the Ministry of Health, it is estimated that around 500,000 people worldwide suffer from the disease - 802 of them are in Brazil.

Similar to albinism, one of the risk factors for the disease is having parents who are blood relatives, as it is also João's case. His mother, Eloisa Pereira 25, a Natural Sciences teacher, is her husband's cousin, Valdir Teixeira, 27, a pedagogue.

After his birth, João was hospitalized for three months in Belém, and Eloisa remembers that period with tears in her eyes. "When I see the photos from that period, what I feel is pain. We had no answers and we had to rent a small apartment to stay there during that time", says the mother. According to Eloisa, what helped the family at that moment was talking, through social networks, with doctors and other mothers of patients with epidermolysis bullosa. "I met a specialist from another state who guided us on the most recommended procedures in his case, since, in the hospital, there was not this more specialized service", she recalls.

The next step, then, was to be discharged from the hospital, because there the boy was more susceptible to infections, as his skin was fragile. Afterwards, the parents found a specialized treatment service at Hospital Barros Barreto. This institution, together with the Bettina Ferro Hospital, integrates the Hospital Complex of the Federal University of Pará (UFPA)/ Empresa Brasileira de Serviços Hospitalares (Ebserh), where diagnoses and treatments are offered for several rare diseases.

"In the beginning, we had to go there every week and the trip was even more complicated than it is now. We had to go to an island near Bagre, in a riverside house, in the middle of the river stem, waiting for a boat to pass by to pick us up. It wasn't a structured port, we had to cross a bridge straight to the boat, holding the baby and our stuff in our arms, it was such a mess", she shares. Each trip to the capital, according to Eloisa, costs around BRL 1,000 Reais, including tickets, taxi, accommodation and food, which is almost the entire amount that the family receives from the Benefit of Continued Provision.

## The region lacks qualified reference centers

Now at four years old, João has the disease under control. His parents already know what to do when blisters appear and how to avoid more serious wounds. Trips to Belém are now twice or three times a year for medical care. But, to reach this stage, it took intense dedication from the parents, something very common to happen in cases of rare diseases.

"We know that there is a type of bandage specially made for this disease nowadays, which is much more comfortable for João", explains the mother. SUS offers these special bandages free of charge, but there is a bureaucratic procedure before getting them. So, Eloisa has a whole prior schedule to ensure the access to the free bandages for her son. "Once, I checked out the price to buy them on my own and, in addition to being very difficult to find, they cost about R\$ 1,200.00 Reais, just enough for three days of treatment", says Eloisa.

Treatment - Since 2014, There is the National Policy for Total Care for People with Rare Diseases in Brazil, a policy which reinforces the right to complete care, free of charge, for people affected with rare diseases by the Sistema Único de Saúde (SUS) [Unified Health System] and It also establishes financial incentives to qualified reference centers, which must provide exams, consultations with a multidisciplinary team and treatment, among other services. Of the

12 qualified centers in the country, none is situated in the Legal Amazon. In each state in the region, health units, hospitals and universities fill this gap in patient care. The Hospital Complex of the Federal University of Pará (UFPA)/Empresa Brasileira de Serviços Hospitalares (Ebserh) is one of the places that offer diagnosis and treatment and, at the moment, is seeking authorization at the federal level. ■



## Debra MATABVU

*Zimbabwe*



**Debra Matabvu** is a journalist with The Sunday Mail, the largest weekly newspaper in Zimbabwe. She has eight years' experience and holds a Bachelor of Science degree in Journalism and Media Studies. Her

beats include health, local governance and education. She has received numerous local and regional awards including the 2020 APO African Women in Media Award.

## NEW: A day in the life of a patient with a rare disease



For some time, Tafadzwa Mutumbi of Glen View suburb in Harare struggles to climb onto the living room sofa to take a seat.

He finally manages after two unsuccessful attempts.

Although he is 13-years-old, Tafadzwa is only 50 centimetres (cm) in height.

His diminutive stature is a result of a rare genetic condition called mucopolysaccharidoses, which affects one in 25 000 children globally.

The teenager, who also suffers from a myriad of illnesses such as arthritis and poor eyesight, leads a difficult life.

His mother, Sinikiwe Aaron (38), says the condition has robbed her son of a normal life. “We first noticed the condition when he was a year old after he was diagnosed with umbilical hernia,” she told The Sunday Mail Online recently.

“He was operated on twice between the ages of one and three years. “Still, he did not get better.

“No one could correctly diagnose what he was suffering from, and we were referred from one doctor to the other; from one hospital to the next.

“When he was three-years-old, he stopped growing. But his head continued to grow in an unusual manner and his joints became stiff.”

Four years ago, Tafadzwa was finally diagnosed with mucopolysaccharidoses, a condition caused by

the absence of or malfunctioning enzymes needed by the body to break down sugars and carbohydrates in cells.

Without these enzymes, large amounts of starch and sugars accumulate in the cells, resulting in skeletal abnormalities, stunted growth and stiff joints.

Besides the physical pain, Tafadzwa suffers emotional turmoil due to this rare medical condition.

There is no infrastructure for people of his stature in public places, especially schools.

As a result, he has difficulties accessing rest rooms, as well as using classroom furniture. He also suffers stigma in his community since most people do not understand his condition.

“There are days he does not want to go to school. At times he goes to school only twice a week,” Sinikiwe added.

“The chairs and desks were not designed with people like Tafadzwa in mind.

“Because of his skeletal deformities, he cannot sit for a long time because he suffers a lot of discomfort.

“In addition, other children bully him because of his condition, and this has affected him immensely.”

While local doctors have proposed that he undergoes corrective surgery to place enzymes inside his body in the United Kingdom, his family does not have financial resources to fund the procedure.

### Underreported

Tafadzwa is not the only child suffering from rare and underreported diseases.

About 33km from Glen View, five-year-old Natasha Zinyuke from Mabvuku suffers from Congenital Adrenal Hyperplasia (CAH).

CAH is caused by a deficiency of enzymes needed



to make specific hormones that gauge the body's response to illness or injury and regulate salt and water levels.

This condition causes low circulating blood volume, abnormally low blood pressure and early puberty.

The disease affects one in 15 000 children globally.

Although Natasha has normal internal female reproductive organs, she was born with both male and female external genitalia.

In an interview, Natasha's mother, Anna Zinyuke, said the family cannot afford to fund corrective surgery for their child.

"I understand she will have to take medication for the rest of her life for the low blood pressure and hormones regulation, but for now I would want her to have the corrective surgery," she said.

"Having both male and female genitalia is confusing her, and I do not know how to explain it to her.

"I can tell that although she is young, the issue worries and confuses her, especially when other young children tease her about her condition."

Ms Zinyuke also says she can barely afford CAH medication, which costs US\$30 a month.

A rare disease is a health condition affecting a small number of people compared to other diseases that commonly affect a community.

According to the World Health Organisation (WHO), there are about 5 000 and 8 000 common diseases in the world affecting an estimated 400 million people.

Zimbabwe has no registry of people suffering from rare conditions; as a result, the actual number of people affected by rare diseases is unknown.

Founder of Child and Youth Care Zimbabwe, Ms Trudy Nyakabangwe, said the absence of data and the minimal number of people living with the conditions has left many suffering in silence.

Child and Youth Care Zimbabwe is an organisation that advocates for needs of people living with rare conditions, and also offers physiological support.

"Most organisations and Governments go for numbers. So, who is going to worry about two people with a rare medical condition?" Ms Nyakabangwe questioned.

"It seems as if people with rare conditions are excluded and not accommodated in national health budgets.

"In addition, when pharmaceuticals are producing for a few people, it is costly for them, as a result, the end user is also going to get the product at a very expensive price."

Ms Nyakabangwe also bemoaned lack of knowledge of some conditions by medical personnel, as well as members of the community.

Most African countries, she said, have not invested in researching treatment and screening of rare conditions.

"When you are born with a rare condition, not all health professionals are going to know what you have.

"Parents move from one hospital to another and at times it takes five to six years for a person with a rare disease to get a correct diagnosis," she added.

"This lack of knowledge is also passed down to communities, which then stigmatise the patients and their families.

"In my line of work, I have also realised that people with rare conditions suffer from mental health issues, as their conditions degenerate as they get older."

She called on Government to fund rare diseases treatment and research through policy frameworks and national budgets.

"The right to health is enshrined in the Constitution and international treaties, which Zimbabwe is signatory to.

“Thus, we call upon the Government to include funds for rare diseases in budgets and national health policy frameworks.”

Sally Mugabe Central Hospital CEO Dr Christopher Pasi, who is also a specialist in Neglected Tropical Diseases, said there is need for regional cooperation when it comes to treating rare diseases.

“Most countries in Africa have inadequate budgets to treat the common diseases, so it becomes very difficult to have budgets for rare diseases, which may be affecting not more than 10 people at a time,” he said.

“Therefore, what we need is a registry of the number of people with rare diseases in the country.

“After that, we put them into groups, and then we cooperate with partners and other countries in the region on their additional diagnostics, treatment and medication.”

Dr Pasi also bemoaned the lack of enough knowledge and expertise on rare diseases in the health sector. ■

*This project was produced with support from the National Press Foundation*



# Hawken MILLER

*USA*



**Hawken Miller** is a features writer and columnist for BioNews, where he reports on stories about the rare disease community, including point of views from patients, caregivers, family, physicians, advocates, and biotech executives. Hawken also contributes to The Washington Post Gaming Section by producing and running YouTube livestreams and

writing content focused on video games and esports. Prior to his role at BioNews, Hawken wrote for The Sacramento Bee, KTLA 5 News, The Washington Post and Epoch Times. Hawken attended the University of Southern California's Annenberg School for Communication and Journalism, where he graduated with honors in 2019.

# Rare Disease Fellowship Teaches Me About Genomics and Empathy

Columnist Hawken Miller considers his dual role as a patient and journalist

The Duchenne muscular dystrophy community is reaping the benefits of innovations in rare disease diagnosis, research, and care. That's part of what I learned last week while training to cover rare diseases with the National Press Foundation (NPF).

I was selected for the NPF's Rare Disease Journalism Fellowship. As part of it, I'll receive a grant to report a story of my choice. Last week's three-day training, in which I learned from the brightest in the rare disease advocacy community, biotech industry, and government, was part of this fellowship.

Not only did I learn, but I also had a chance to think more about my dual role as a Duchenne patient who covers his own rare disease community, among others. My perspective on rare diseases changed because of the diverse group of international fellows and panelists I was with.

Individualized medicine was referenced several times. It's taking hold as cheap and rapid whole genome sequencing becomes available in the U.S., better systems for clinical data analysis are employed, and more conditions are added to newborn screening panels. This also helps the development of Duchenne therapies.

Gene therapy and gene editing, at least for now, have shown the most promise, according to Peter Marks, PhD, director of the Center for Biologics Evaluation and Research at the U.S. Food and Drug Administration. He told NPF fellows it was the most straightforward way to treat rare conditions.

With gene therapy, scientists can identify defects in a mutated gene and correct them. I believe that as this technology is deployed, we can address certain issues, such as an immune response and the size of the therapies' viral vectors, so that people with Duchenne are helped. (Viral vectors are used to deliver genetic material into the body's cells.)

All sessions were recorded, so fellows didn't have to take notes and could think about story ideas instead.

It also gave me time to reflect on where I, as a journalist and patient, fit into rare disease coverage. I realize that my experience as a patient gives me empathy for the people I interview and brings a rich amount of background knowledge to every story.

## A journalist's empathy is heightened

We heard a powerful story from Richard Engel, chief foreign correspondent of NBC News, who lost one of his sons, Henry, to Rett syndrome. I asked Engel, who was coming to us via Zoom from a military convoy in Odesa, Ukraine, how and why he went public with Henry's story. He was quick to say that anything he reported on Henry was not necessarily journalism, but rather sharing his personal story with the hope that it would move research forward.

Engel also said that caring for Henry revived his compassion for the people he sees displaced, killed, or injured in war zones. The decades of reporting he's done in these areas had given him compassion fatigue. But seeing Henry as a bundle of light despite his disease renewed Engel's empathy.

I always attempt to be objective and unbiased in the articles I write. I still believe that objectivity is the standard for journalism. But Engel showed me it's OK to use my storytelling to help the Duchenne community in a nonjournalistic capacity, as well as as a reporter. He showed me that I should be leaning on my experience as a Duchenne patient as I ask sources questions, write articles, and approach other patients for interviews. As much as I don't want to admit I have a complex neuromuscular condition, it's part of me and can be used to deepen my coverage.

Empathy is so important when covering rare diseases, as Engel described in his segment. That's especially true in developing nations, which are sorely behind in genomic medicine.

Attendees from these nations, including Kenya, Mongolia, and Pakistan, referenced their countries' lack of access to doctors, clinical trials, and genomic data. I imagined being born with Duchenne in a

country with no knowledge of the condition or its treatment options. It made me feel blessed to live where I do, but I also felt a responsibility to help reveal the difficult situations of rare disease patients across the world.

Journalists are often catalysts for change. They're among the ones who bring to light what was once in the dark. With this training and fellowship, I hope to continue that achievement in the rare disease field.

As a Duchenne patient myself, I'm also excited for what the future holds as individualized medicine and the study of genomics accelerate. The more that data about the human genome are collected and analyzed, the more we can uncover the secrets of our DNA and save people's lives.

These were three long days of fellowship training, but they'll no doubt provide me years of inspiration. ■

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## Finding Joy by Focusing on What Duchenne Has Given Me

“We rejoice in our sufferings, knowing that suffering produces endurance, and endurance produces character, and character produces hope, and hope does not put us to shame, because God’s love has been poured into our hearts through the Holy Spirit who has been given to us.”

I nervously recited this Bible verse from the book of Romans (ESV). About 450 people were intently staring at me from behind their Michelin-star dinner and exquisite wine.

What I was trying to show in my speech for my parents’ foundation, CureDuchenne, was that while Duchenne muscular dystrophy has taken a lot from my life, it’s also given me a lot — a big family of supporters, the endurance to face the inevitable peaks and valleys of life, critical thinking, maturity, and mental fortitude.

The crowd I was addressing was one of those gifts. A diverse group from all walks of life had put their time and money into curing Duchenne, a disease that ravages the muscles of one in 3,500 boys and an estimated one in 1 million to 50 million girls.

Without Duchenne, I wouldn’t have met and developed relationships with the likes of NHL star Ryan Getzlaf, NFL linebacker Clay Matthews, and world-class guitarist Zane Carney. The fight to cure Duchenne has led my parents and me to celebrity golf tournaments. We’ve made connections that amplify awareness of the condition, finding people that have the means and ability to help drive that mission. On the way, we’ve met too many incredible individuals to count.

We’ve also connected with innumerable other families around the world who are also affected by Duchenne. We recently returned from meeting two such families in Hungary. I’ve made friends with other young men with Duchenne who understand what it’s like to have your mind trapped in your body. They’ve either already gone through the same challenges as I have, or will face them in the near future. We’ve developed strong relationships because of it.

### Finding the lessons in hardship

As the apostle Paul writes in his letter that I quoted above, suffering truly gives us the ability to withstand future trials and tribulations. Paul himself dealt with beatings, imprisonments, and hunger. While I haven’t faced anything of that magnitude, I’ve learned to roll with the punches because of Duchenne.

Every year there’s something new that I can’t do, whether it’s going to the bathroom on my own, walking independently, or being able to sit in a regular chair. I mourn the part of me that’s lost, but I also move forward the best I can, adapting through technology, outside help, and a little bit of ingenuity.

For example, I’ve had to find personal care assistance, which is a challenge because of a nationwide caregiver shortage. Between finding an assistant, attempting to receive caregiving pay through the state, and learning how to interface with new people 24/7, I’ve encountered a lot of challenges and tough learning experiences.

Each problem that I solve and every time I prevail in a challenging season of life, I build endurance for the future. Having a disability like Duchenne is a kind of suffering, but it makes me strong — not physically, but mentally. As the old saying goes, diamonds are formed with time and under pressure.

I’ve learned countless life lessons much earlier than the average person. I’ve had to manage employees that care for me, instilling in me leadership abilities. I’ve had to explain to people I just met how to transfer me out of my wheelchair, helping to improve my communication skills. I’ve learned to eat a healthy diet and find time to rest to reduce the disease’s progression, building increased discipline. I owe all of that in some way to Duchenne.

Through awareness and fundraising with CureDuchenne, I’ve made connections with people from every walk of life and seen places that most never will.

I would rather be able to simply ride a bike, work out with friends, play a sport, or travel as much as I can, but it's also valuable to realize what I've been given in spite of this terrible condition. Knowing what I've gained from having Duchenne keeps me going when the going gets tough. If I'm dealt this hand, I might as well do the best I can to win with it. ■

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## How I'm Destressing My Life With Duchenne

Adult life is overwhelming. There's so much to do. You have to hold down a job, pay rent or mortgage, prepare for retirement, spend quality time with those you love, learn new skills, find time for rest, and pursue a hobby or passion.

Then add Duchenne muscular dystrophy on top of it. That probably means you're scheduling doctors' appointments, balancing medication side effects, making sure your wheelchair and medical devices are functioning properly, and figuring out the best care for a disease that few know how to pronounce.

As I've gotten older and more independent, the weight of the world has felt even heavier. That's been catching up with me lately, and it's been elevating my stress levels and thus negatively affecting my health.

Many have called stress a silent killer, and I believe that's true. I've recently had heart palpitations, and while I don't know why I feel them more now than before, it's been yet another wake-up call that I need to reassess my life and find some calm.

In the last couple of weeks, I've learned to breathe better, limit my worry over things I can't change, focus on one task at a time, and put less pressure on myself. I've felt my health has improved as a result, and with a condition like Duchenne, that should be my No. 1 priority.

Part of my improved health comes from being in tune with my body, knowing when something is wrong, and making sure I address that issue. But being in tune with my body starts with taking a second to breathe. Taking big breaths through my nose and exhaling through my mouth has helped me feel more relaxed when it feels like there's no stop to the stream of thoughts going through my brain.

This practice seems so simple, but it can pay dividends down the road, especially as I deal with a complex disease. There are a lot of things to think about — working with insurance, managing my caregivers, ensuring I find enough sleep at night, and purchasing new accessibility tools, such as a shower chair that fits better in my bathtub. Breathing gives my mind time to compartmentalize and focus on the

task at hand rather than everything all at once.

I haven't yet created a system to take time to breathe and meditate, but every time I remember it, my to-do list feels less overwhelming. I plan to rely on my Apple Watch to remind me to breathe and guide me through mindfulness exercises.

I think too much, not unlike most people. How did that person react to my attempt at a joke? Am I being a good friend? I lie in bed going through my journalism stories, reminding myself I need to call a source or fix a random sentence in the middle of the article. I remember to drink water, but then I realize I can't because it's late at night, and I don't want to wake my assistant more than necessary so I can go to the bathroom. I think about ways to insert myself into a conversation and then settle with the line I think is least embarrassing.

All of that thinking is stressful and unnecessary. To combat it, I try to focus on what's going on in front of me. I don't need to be writing and thinking about what to say to insurance when I inevitably fight them on my next power chair. When it's the right time, I'll come up with something. That has freed up more brain power and made me more peaceful.

In my 25 years of life, I've found that I put too much pressure on myself to perform professionally and grow my career. That stems from comparing myself with able-bodied people. The reality is I have Duchenne, a fatal, muscle-wasting disease. I need rest. I can't push myself to the same limits they do.

It helps me when I relax and remember everything that I've already done. I'm learning to be satisfied with myself. I have to keep reminding myself that I'm OK with where I'm at. Obviously, pushing oneself is important, but like all things, there are limits.

I preach about finding peace and calm, but sometimes even I can't find it. In the midst of doctors' appointments, relationships, pursuing my passions, and advocating for others with Duchenne, it can be extremely difficult to find that inner Zen. But it is possible, and over the last couple of weeks I've proved to myself it can be done. My body is thanking me. ■



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## A Recent Hospital Visit Taught Me How to Self-advocate

On Thursday, Nov. 17, I went to bed with what I thought was a bad stomachache. It felt like someone was sticking a knife in my left flank.

Then I realized: This was undoubtedly a kidney stone. I'd had three others, and the pain was exactly the same. But this time, the pain didn't go away, and I was left counting down the hours to when I could take another Tylenol. I knew something was different. Rather than coming in waves, the pain stayed the same.

Around 3 a.m. the next morning, I relented and asked my assistant to get me dressed and drive me to the emergency room (ER). It turned out to be the right decision as the stone was stuck, causing an infection. I had to have a surgical procedure to put a stent in my ureter to allow urine to flow through and stop the infection from spreading.

I've been to the hospital before, but this was the first time I was on my own, without my parents. I had to advocate for myself. My parents, who live nearby, were this week halfway across the world on vacation. With a rare condition like Duchenne muscular dystrophy, I had to ensure that doctors understood the disease and my unique needs. It was a scary moment, but also a valuable learning experience.

The first and most important part was telling the ER nurses and doctors about Duchenne. Most people in the medical world know that Duchenne exists, but nothing much beyond that. And I wouldn't expect them to, given that it's a rare disease and they'll probably never see another patient like me.

I told them about my muscle weakness and how I need help getting up to use the bathroom or transferring to a gurney. The charge nurse joked with me, "We're used to lifting dead bodies out of cars. Your situation shouldn't be a problem." Even so, I explained the best places to grab me to lift me up.

I also wear a MyID Hive Medical ID Bracelet for situations like an ER visit. I was able to have doctors scan a QR code that led to a landing page with my medications and general information about Duchenne. I'm on a high dose of the steroid Emflaza (deflazacort), and missing a day can cause

an acute adrenal crisis. I made sure I had the steroids I needed after realizing I'd be staying in the hospital for a few days.

The extra information helped me better communicate with the doctors. For example, I knew that certain anesthesia methods would be dangerous for me, but I didn't know the specifics. I felt a lot more comfortable knowing the details were outlined in the MyID bracelet. A compound called succinylcholine is often used in surgery, but can have dangerous side effects (such as elevated potassium levels) for someone with Duchenne. The anesthesiologist immediately understood the situation and went through extra measures to ensure the operating room was wiped clean of it.

I also learned from this experience that I need to rely more on friends and family. I was a bit slow to ask for visitors. I didn't have anyone with me when I went under for the operation, which probably wasn't the smartest decision, looking back. But after some lectures from close friends, I realized it's important to have someone else there who knows my condition and can advocate for me in case I can't.

Thankfully, the procedure to put in the stent was a success, and I was released from the hospital that Sunday. And on Thanksgiving, I passed the 4 mm kidney stone that had been causing all these issues.

This time I was in the hospital for a low-risk surgery, but I never know what the future will hold. It was almost like a dry run for any future hospital visits (though I hope there are none). I need to selfishly take extra time with the doctors and explain my situation, wear my MyID bracelet, and have a list of close friends and family ready.

The reality is that many people, even in the medical field, don't know about Duchenne. I was fortunate to be in a great hospital with smart doctors and caring nurses, but that may not be the case next time. Because of that reality, the onus is on us to quickly teach people about Duchenne so they can make the best medical decisions possible.

That's the power of self-advocacy. ■

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## Technology Helping to Make Registries, Databases More Efficient

### Advances in AI, computing, and smartphones aid efforts to collect data



In amyotrophic lateral sclerosis (ALS), as in many diseases, patient registries, biorepositories, and natural history studies are helpful both in planning clinical trials and as tools for scientists to learn more about how a person’s lifestyle, genetics, and environment can potentially lead to ALS. These databases also might help in finding new ways to treat the disease.

ALS is a rare condition for which not much data are available. But ALS-related institutions are making it easier and more efficient to collect data housed on platforms such as registries, thanks to technological advances in artificial intelligence (AI), computing, and smartphones.



*Erin Dittoe uses her power chair when she becomes tired.  
(Photo by David Petkiewicz)*

Erin Dittoe, 55, was diagnosed with ALS two years ago and is sharing her health data in a number of different ways.

She has registered with the National ALS Registry from the Centers for Disease Control and Prevention (CDC), taken part in genetic testing, and wears a watch that tracks her movements for an observational clinical trial (NCT05276349). That trial is seeking to determine if at-home measurements might replace repeated in-person clinic visits.

Diagnosed with sporadic ALS — the most common type, where there is no family history — in November 2020, Dittoe’s disease progression has been slow. She can walk with assistance, speak (albeit slowly), and work from home.

The Ohioan hopes the information she contributes will help scientists better understand what causes ALS and how to treat it.

“I kind of feel as though [it’s] for the people that can’t answer questions for one reason or another, it’s for them,” Dittoe said. “It’s doing my part.”



*Fernando Vieira is the CEO and chief science officer of the ALS TDI. He has been with the nonprofit for 20 years.  
(Courtesy of ALS TDI).*

he ALS Therapy Development Institute (ALS TDI), a nonprofit focused on disease research, is enlisting Google's help to streamline its data analysis and use of patient data. Google's application programming interface forms the analytical backbone of its Precision Medicine Program (PMP), which currently has data covering 813 fully enrolled patients — those who contributed three or more months worth of information. The PMP project, initiated in 2014, stores information about a patient's movement abilities, medical history, genetics, biomarkers, and clinical measurement scores, as well as voice recordings.

According to Fernando Vieira, MD, CEO and chief scientific officer of the ALS TDI, Google's Looker platform, as the interface is called, is a big data analytics platform used primarily for business intelligence. The powerful tool allows researchers to look up people's information — as detailed as their genome, for some — and compare it to their disability progression, as measured by the ALS Functional Rating Score-Revised (ALSFRS-R).

Identifiable information — including participants' names, Social Security numbers, or email addresses — is not available to researchers. Data that could identify any individuals are protected under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 in the U.S. Each participant is only referenced as a number.

To date, ALS TDI has captured 9,873 voice recordings, 19,404 ALSFRS-R scores, and 7,422 weeks of data from patients wearing accelerometers, which calculate how much each wearer is moving.

ALS TDI considers it important to share the collected data with patients, Vieira said, so they can track their own health.

“A key tenet of our program from the beginning has been to treat our participants as partners,” Vieira said. “That, I think, has been key to maintaining compliance and commitment to the efforts, and I would encourage that.”

## Recognizing patient ‘voices’

In 2018, ALS TDI also partnered with Google on Project Euphonia, which aims to use artificial intelligence to help people with impaired speech (dysarthria) — a common ALS symptom —

interface with voice recognition on its platforms, such as the Google Pixel smartphone.

Google is using available PMP voice recording data to train its AI in interpreting speech with dysarthria. The first publicly available tool to come from Project Euphonia, Project Relate, is an app that's now in beta testing.

Speech recognition software, such as that used with Siri or Google Home, recognizes wavelengths that correspond to spoken words. It pieces those words together and, through a series of steps, arrives at an understanding of someone's speech and commands — for example, “Turn off the lights.” But it can only interpret phrases based on the quality of the voices used to train it. People with speaking impairments, whose voices typically are not part of a software's training parameters, often struggle to use this technology.

Loss of vocal clarity and strength are common with ALS. In a YouTube Original documentary about AI, the father of former NFL linebacker Tim Shaw recounts his son's frustrations with his increasing lack of clarity in speaking. As his ALS progressed, the former football player had to change his phone's contact information from “Dad” to “Yo-yo” because it couldn't understand Shaw's command to “call Dad.”

ALS TDI's work with Google also created an algorithm, derived from machine learning, that might better track changes in disease severity based on a patient's speech and movement data than do ALSFRS-R tests taken at a given time. The code behind the tool has been made available for scientists to use and continue to improve.

While such technology still is being refined, its use continues to grow. As part of her trial, Dittoe is recording her voice into an application that aims to track disease progression through changes in speech.

## What blood samples and earlier HIV work might teach

With its PMP project, ALS TDI also is collecting data from patients' blood samples, looking for biological measures of disease progression. This work is supported by a \$281,000 grant awarded the institute in March by the Congressional Directed Medical Research Programs, part of the U.S. Department of Defense.

ALS TDI plans to send blood samples, collected quarterly over one year, to SomaLogic, a Colorado company, “to observe the concentrations of thousands of cytokines, growth factors, ... kinases, structural proteins, hormones, and other proteins in each sample” that might serve as biomarkers.

Vieira compares the race to cure ALS to the charge to find treatments for HIV.

In the mid-1990s, scientists conducting a natural history study of HIV found a certain genetic variation conferred resistance to the virus. Specifically, they discovered that people with genetic mutations leading to a “nonfunctional,” or inactive, CCR5 receptor protein were “highly resistant” to the infectious disease. This pointed to CCR5 as a promising target for preventing HIV infection.

Through a study “designed to teach you,” Vieira said, scientists were able to more quickly develop “drugs targeting that receptor” and better treat HIV.

“They were able to reveal that you can go into a natural history study knowing nothing and allowing it to show you something,” he said, adding, “And that’s how, I think, we’ve gone into this [ALS data] ... assuming we know very little, collecting as much data as we can, and then allowing it to show us what is important over time.”

Like that HIV natural history study, whose scientists “didn’t know how many people they needed, or how long they’d have to look ... we don’t know how many people we need or how long we’re going to have to look,” Vieira said. “But it will be the source of a lot of our answers.” ■

*This article is the second of a three-part series published as part of the Rare Disease Fellowship through the National Press Foundation.*

# Big Data a Source of Better ALS Insights, Trials, and Hope

## Value in studying points that unite and distinguish patients with rare diseases



## Healthcare has long harnessed the power of big data

Examples range from the Human Genome Project, a worldwide 13-year effort to map DNA, to the adoption of electronic medical records— allowing doctors to quickly access patient information at points of care — and the rise of personalized medicine, which tailors treatments to an individual based on data collected about traits like a person’s genetic makeup.

Increasingly, big data now is making inroads into rare disease research. Numerous databases — run by academic institutions and nonprofits, healthcare groups, and governments — have come online to address rare diseases like amyotrophic lateral sclerosis (ALS), estimated to affect between 18,000 and 32,000 people in the U.S.

These databases collect large amounts of information on patients over time. Scientists use these data in studies into a condition’s origins and progression in hopes of shedding new light on both causes and prognoses. Such studies include natural history, or what happens if there is no treatment given, and analyses of blood biomarkers and changes in proteins and genes.

A shared big data goal: improving patient treatment and care, and designing better clinical trials needed to advance therapies.



*Fernando Vieira, CEO and chief scientific officer of the ALS Therapy Development Institute, at right, and researcher Alan Premasiri analyze accelerometer data collected on ALS patients. (Courtesy of ALS TDI)*

Among the larger of these efforts in ALS are the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database, the Precision Medicine Program from the ALS Therapy Development Institute (ALS TDI), and the National ALS Registry from the Centers for Disease Control and Prevention (CDC).

Along with others, these three pair data points tracking patients’ progression with information collected on their genetics, family history, medical and lab exam results, overall health, lifestyle, and environment.

The aim is to help explain why some people develop ALS, how it might be prevented, and how to better treat it.

“To have the more profound effects that we hope for clinically, we’ll need to have a better understanding of the underlying biology: whether or not there are subsets of ALS, who may have what areas of biology engaged, and whether that changes over time during the disease,” Fernando Vieira, MD, CEO and chief science officer of ALS TDI, said in an interview with ALS News Today.



*Avi Kremer with his daughter Ella, 6. (Courtesy of Avi Kremer)*

here's a lot to be learned, Avi Kremer, co-founder of Prize4Life, which helped create PRO-ACT, said in an email interview. Prize4Life is now part of the ALS Association.

“Why did Lou Gehrig progress so fast and Stephen Hawking so slowly?” Kremer asked. “What do the ‘Stephen Hawkings’ have in common?”

Kremer points to natural history studies, which look at disease progression in the absence of an effective treatment, as essential in planning good clinical trials.

“It enables us to understand how the disease changes over time and this way learn ... [how a treatment] can change the course of the disease,” said Kremer, 47, who can no longer speak due to ALS.

“The best thing for a clinical trial is for it to be short and decisive — to get the effective drugs to patients and the ineffective drugs out of the way to not take away resources. Natural history data and disease progression biomarkers are the drivers of that,” he said.

PRO-ACT, recognized in 2021 for its work in ALS research, has collected more than 11,000 de-identified patient records from 23 clinical trials, with both treatment and placebo trial arms. Its data also cover disability progression scores as measured by the ALS Functional Rating Scale-Revised (ALSFRS-R), use of ALS medications and their side effects, lung function, and muscle strength test results.

## What do databases collect, and protect?

Patient databases combine a person's disease history, collected through questionnaires or surveys, with information about the individual's work, residency, and lifestyle, which may suggest risk factors. They also collect information on clinical measurements, such as ALSFRS-R scores and tests of breathing and muscle strength.

These data are protected in the U.S. under the Health Insurance Portability and Accountability Act (HIPAA) of 1996. Personal identifying information available to researchers is strictly limited and protected by safeguards.

What registries and databases collect often varies. Smaller ALS registries, like that of Massachusetts, mostly count ALS cases in given areas. Larger ones, like the PRO-ACT database and the National ALS Registry, tally cases and collect disease-relevant data, as well as demographics like a patient's age, sex, place of residency, and work history, all of which could potentially establish risk factors. These larger collections also keep a repository of patient biospecimens for research.



*Paul Mehta runs the National ALS Registry, which has collected over 100,000 survey responses from people with ALS. (Courtesy of Paul Mehta)*



The National ALS Registry’s biorepository has collected biospecimens — including blood and urine samples, brain and nervous system tissue, cerebrospinal fluid, and other tissue samples — from 1,469 participants. A recent collaboration with the ALS Postmortem Tissue Core, started in 2013 by Lyle Ostrow, MD, PhD, has expanded access to patient tissues and data.

Fluid samples can determine levels of ALS biomarkers like oxidative stress, while tissue samples can peer into changes marking this disease, including mutations in genes like C9ORF72 or SOD1.

About 300 of these samples went through whole genome sequencing, said Paul Mehta, MD, a medical epidemiologist and principal investigator of the National ALS Registry.

“Their data is very, very valuable,” Mehta said. “If you can figure out what the risk factors are, you could potentially prevent ALS.”

The registry’s collaboration with the Johns Hopkins ALS Postmortem Tissue Core, directed by Ostrow, began in 2021; these efforts are in the process of moving to Temple University. At the National ALS Registry’s 2022 annual symposium, Ostrow presented results from a detailed survey of ALS researchers’ biosamples and data needs. “Our transition to Temple University and continued partnership with the National ALS Registry is enabling us to harmonize and integrate additional tissue and data resources, to best meet the evolving needs of ALS researchers,” he said.

To date, national registry samples have been shared with scientists at at least 22 sites — mostly universities, but also laboratories and pharmaceutical companies.

“There’s no end to the utility of having access to tissues because you can look at anything from exposures to genetics to pathology. And if you have frozen tissues ... you can even culture cells,” said Elijah Stommel, MD, PhD, a neurologist with Dartmouth Hitchcock Medical Center in New Hampshire who’s approved to use registry fingernail samples in his research into environmental pollutants and ALS.

## Big data and ALS: Promises and challenges. Potential for better trials, faster treatments

Big data is helping clinical trials become more efficient, aiding physicians in detecting signs of disease earlier, and assisting scientists in moving therapy discoveries from the lab into the clinic, known as translational science.

Amylyx Pharmaceuticals, which markets Relyvrio (sodium phenylbutyrate and taurursodiol), a newly approved ALS treatment, recently gave PRO-ACT data from the placebo arm of its CENTAUR Phase 2 trial (NCT03127514).

PRO-ACT also helped Amylyx. Patient information in the database was valuable in CENTAUR’s design, allowing researchers to define enrollment criteria — that marking fast disease progression — using models drawn from those data, said Sabrina Paganoni, MD, co-director of the Neurological Clinical Research Institute at Massachusetts General Hospital and the trial’s principal investigator.

The result was a smaller, quicker, and ultimately successful study.

“We knew that [patient group] was predicted to progress at a relatively homogenous and fast pace. So we targeted the population,” Paganoni said. “And we knew that we had enough statistical power to see a treatment effect, based on those simulations, with a trial of relatively modest size.”

Merged with artificial intelligence, data points on patients also improve the time to diagnosis, said Asaf Shiloni, CEO of the Israel-based company Kadimastem, which is developing a stem cell therapy called AstroRx. That therapy is expected to move into a clinical trial next year at sites that include centers in the U.S.

“I think that this is where a lot of the big data experts are looking at: how can we collect enough data that, if you connect a few dots from complaints from the patient, you can point to ALS earlier,” Shiloni said.

Such work could get a person into treatment at a time when there is still “a chance to hold the disease or to slow the disease ... and to continue with something closer to a normal life,” Shiloni said.

Big data also is aiding translational science. According to the ALS TDI's Vieira, the institute developed tegoprubart (then called AT-1501) partly through gene expression analyses of the SOD1 mouse ALS model that identified the CD40 ligand protein as a key target for the disease.

Analyses of patient blood samples also showed co-stimulatory pathway signaling, a regulator of immune system responses that acts via the CD40 ligand, to be overactive in 56% of ALS patients.

“When we modulated that pathway in the animal model with an antibody targeting CD 40 ligand ... we decided, well, we need to now create a human antibody, this is a lead drug,” Vieira said.

Use of tegoprubart, a monoclonal antibody designed to block the CD40 ligand, was found to slow weight loss, delay paralysis, and extend survival in the mice.

Eledon Pharmaceuticals, which has since acquired tegoprubart, tested it in a Phase 2a trial (NCT04322149) in 54 ALS patients in the U.S. and Canada. Top-line results, announced by the company in May, showed safety and tolerability at ascending doses, a main trial goal, as well as lower levels of multiple pro-inflammatory biomarkers.



*ALS TDI researchers collaborate on a project in the lab. (Photo courtesy of ALS TDI)*

larger trial is being planned, Vieira said, adding that this discovery underscores the need for much more data collection.

That's one reason ALS TDI's Precision Medicine Program — a translational research study launched

in 2014 — is gathering data on ALS progression. PMP is tracking patients' blood samples over time, along with ALSFRS-R scores, voice recordings, and movement captured through wearable accelerometers.

“Even the instances that we think are simple,” like discoveries using an ALS mouse model, “may not be,” Vieira said. “And it will take an immense amount of data, well beyond even what we have here — and we have a lot — to really tease these complexities out.”

Data collected via PRO-ACT and the CDC registry also are helping in tracking various clinical interventions — from respiratory devices to vaccines — that doctors are using with patients over time. That's important, said Neil Thakur, PhD, chief mission officer of the ALS Association, because changes in care might be better, or equal, to currently approved ALS therapies.

Combining that information with specimens “gives us an opportunity to think about how to optimize clinical care,” Thakur said. “When do you do a specific kind of intervention? What kinds of services and support do we need to help prevent infections and falls and other kinds of complications of ALS that can shorten life and certainly makes the disease even more miserable than it is?”

The ALS Association is working to build a central data system to track disease complications to better spot and prevent them.

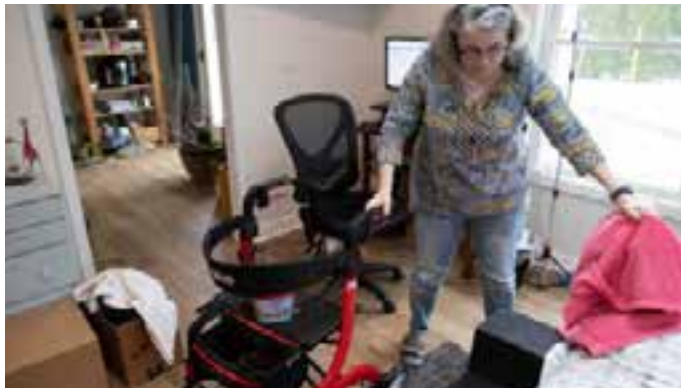
### **Concerns about overlap, data siloing, limited diversity**

Data are collected on thousands of people every day and housed in many different, isolated databases. In data science, experts refer to this as data siloing, and it results in a lot of repeat data being gathered.

From the patient perspective, it can seem like there's considerable overlap among institutions collecting information for databases or conducting clinical trials. Erin Dittoe, 55, who was diagnosed with ALS in November 2020, wears a watch that tracks her movements as part of a clinical trial (NCT05276349) that's seeking to determine if at-home measurements can replace repeat visits to a clinic.

## Dittoe has seen other similar studies on remote tracking.

“It’s difficult sometimes to differentiate who’s doing what,” Dittoe said. “Early on I tried to fill out as many questionnaires as I could and some of the details got lost. It would be nice if everyone was working together at the same time, instead of multiple people doing the same research at the same time.”



*Erin Dittoe moving from her desk chair to her walker. (Photo by David Petkiewicz)*

ut different institutions collecting various types of ALS data and storing them in different ALS-related repositories is not necessarily a bad thing, Thakur said. He thinks streamlining silos could happen too quickly and go too far.

“It’s a judgment call. I think we can always spend more time on coordination and get some benefit, but you do start to get diminishing returns,” Thakur said. “And you get a layer of bureaucracy that may end up slowing things down if we over-coordinate and stifle creativity.”

Vieira agreed some parts of registries should be standardized, but said each institution should look at new ways to collect and analyze data gleaned from patients.

“If at the very least, we develop common denominator data sets, where each of the groups always captures ALS Functional Rating Scale, and always asks some surveys the same way, then we can relate the unique elements of each of our programs and start to tease apart what might be more useful and powerful,” Vieira said.

Collaborating on data and biospecimen collection was discussed at the National Institutes of Health (NIH) Strategic Plan Workshop in October. The

two-day virtual event highlighted priorities that scientists, patients, clinicians, and advocates would like the NIH to pursue.

Discussion also touched on potential drawbacks to standardizing data.

“If you do everything the same way, you’re gonna all make the same mistakes,” said Thakur, who listened in to the meeting. “I think that’s a real feature of that conversation.”

For Thakur and the ALS Association, however, the priority is getting better care and treatments to patients.

“We’re focused on speed,” he said. “We want more clinical trials, we want to find new treatments and cures as quickly as possible.”

Big data, from registries to biospecimens and gene sequencing, are tools to help get there.

Another challenge is getting data from diverse patient groups.



*Neil Thakur, chief mission officer of the ALS Association, favors speed in ALS research. (Photo courtesy of Neil Thakur)*

Most data come from predominantly white patients in Western countries. Overall, this could be expected, because white people are generally more affected by ALS than minorities.

National ALS Registry data, current as of 2017, showed white people made up 73% of all its cases, Black people 6%, and the remaining 23% classified as other or unknown.

“It is challenging because some groups don’t want to join,” said Mehta, noting 100,000 surveys have been completed for the national registry. “There’s even a distrust for government in certain [groups] and geographical areas of the U.S.”

That’s partly a legacy of the Tuskegee study of the 1930s that left Black men with untreated syphilis after penicillin became available.

Still, Mehta’s confident of bringing more minority cases into patient counts, genomic data, and biorepositories. A CDC request to the U.S. Office of Management and Budget, if approved, would add data collected by health maintenance organizations (HMOs), other insurance companies, and nonprofits. These groups are likely to have more diverse — racially, ethnically, and geographically — patient populations contributing relevant information, he said.

What’s next? Data about ALS is improving, thanks to awareness efforts and national research funding. Last year’s ACT for ALS Act, for instance, expanded the U.S. Food and Drug Administration’s treatment research program for this and similar diseases. Meanwhile, Congress earmarked \$200 million for ALS research and programs for the 2022 fiscal year, which ran through Sept. 30.

But Dittoe, possibly like many ALS patients, says more federal support is needed, including for big data collection and analysis.

“Because the illness has been so underfunded, not a lot is known about it,” she said. “As more is learned about it, we’re going to see where it relates to other motor diseases as well as other brain diseases.”

That’s why Dittoe wants to share her data, especially as she’s “been fortunate in that I’m slowly progressing.”

“It’s doing my part,” she said of participating in the trial.

Many ALS patients are “very altruistic individuals,” Mehta said. “They want to help others, and they want to join the fight against ALS, when it comes to being part of the research.”

A credit analyst, Dittoe still works full time and occasionally uses her power wheelchair to get around. She’s taking Radicava (edaravone) to help slow disease progression.

Even understanding why Dittoe — like Hawking — is advancing less rapidly than that considered typical requires more time, more questions, more data, and more analysis, according to researchers. But at the bottom of all this could be a much-wanted breakthrough.

“We’re just not there yet,” Dittoe said. “It’s important to try to connect the dots where we can.” ■

## State ALS Registries Collect Valuable Data, but Few Are in Process

**Only Massachusetts has a mandatory registry, though 2 more are on the way**



Patient registries help record how many cases of a particular disease there are across the country, and many also log related genetic, clinical, and biological information.

Some U.S. registries, including those dealing with infectious diseases, have mandatory reporting requirements. But for many other diseases, including amyotrophic lateral sclerosis (ALS), they do not.

The National ALS Registry, for example, is run by the Centers for Disease Control and Prevention (CDC) and collects data from the federal government, such as the U.S. Department of Veterans Affairs and the Centers for Medicare & Medicaid Services. It also collects voluntary data from people with ALS who sign up via its web portal.

Clinics across the U.S., however, are under no obligation to report a case of ALS, which means some diagnoses may be missing. That's where state-level registries, which are gaining traction in the Northeast, could come in.

These registries can make mandatory requirements for clinics in their jurisdictions in a way that can't always be done at the federal level. Scientists hope that might help pave the way for the National ALS Registry to become mandatory.

"It would be best if the national registry is reportable and mandatory, but it's not. And it's harder to get things on a country's national level versus a state level, because it's a smaller operation and probably [has] fewer hurdles," Elijah Stommel, MD, PhD, a neurologist with Dartmouth Hitchcock Medical

Center in New Hampshire, said in an interview with ALS News Today.

Stommel sees ALS patients across the Northeast and is researching how the environment there could be a risk factor for developing ALS.

Massachusetts leads the way with state registries

Right now, only one state — Massachusetts — has a fully functioning ALS Registry. Some states are working on developing their own registries, and governors have signed bills to establish them in Vermont and Maine. But only Massachusetts has one that's up and running.

"There's been a hunger with patients and groups asking for what's happening in my backyard," said Paul Mehta, the principal investigator of the National ALS Registry. "And we want to go ahead and provide more granular information at the state level."

More in-depth, state-level information about ALS cases could bring state legislatures to allocate more funding for ALS research and clinical care. Such knowledge also could help in linking ALS cases to environmental issues, such as airborne pollutants.

Just as cancers and infectious diseases have environmental risk factors and are tracked in registries, scientists are learning neurodegenerative diseases have similar risk factors, so a state registry makes sense for ALS, Stommel said.

Smaller states, such as Vermont, are expected to have about 20–25 new patients a year, he added. Maine might get double that. While a few dozen people might seem of little relevance, connecting their cases to databases that show residency over time can be quite powerful.

"If you get all the cases reported in a state ... you can really do some analyses of what patients had done and what they had been exposed to," Stommel said. "It's also useful for the patients. If they're in a registry, then they're going to be informed of ALS clinics. They're going to be informed of potential clinical trials. If they're [Veterans Affairs] patients,

they'll be informed about benefits that they might not know about. It's a two-way street."

The legislation that created the Massachusetts registry makes ALS a reportable condition, which means the state Department of Public Health will collect medical records from healthcare providers of those diagnosed with the disease. The fine for not reporting ALS is up to \$500 a day and can result in revoking or changing the license of a healthcare facility or related party.

Part of the reason why Massachusetts was an early registry adopter is because a former governor, Paul Cellucci, was diagnosed with the disease after leaving office, and he died of disease complications in 2013. State officials named the registry after him.

State registries also don't have to contend with the kinds of regulatory and political hurdles for reporting that exist on the national level, Stommel said.

## Where state registries stand in US

Governors in Vermont and Maine signed bills in May to set up registries in their states. Maine's CDC confirmed to ALS News Today that it's drafting rules for its registry, and rule-making will be initiated during this legislative session, which opened Dec. 7.

Some efforts are underway in other states. With federal funding from the CDC, officials in Ohio, working with Stommel and others, set up a two-year registry of new cases. From October 2016 through September 2018, the registry identified 333 newly diagnosed ALS patients.

Registry analyses also found age- and gender-standardized incidence to be 1.71/100,000 person-years (meaning that 1.71 out of 100,000 people living in Ohio would be diagnosed with ALS in a given year). This statistic tracks closely with the national incidence rate measured in the National ALS Registry, between 1.5 and 1.7 per 100,000 people.

With Massachusetts, the National ALS Registry is working to match existing cases in their respective registries. It's part of a CDC registry goal to provide information on disease burden to help inform public health policy, such as ALS research in federal government funding bills.

"ALS is a very relevant and relatively opportune neurodegenerative disease to research and can shed light on some of the more common neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease," Stommel stated in a written summary of testimony to state Sen. Virginia Lyons of Vermont. It "also would be very helpful to patients and their families who ... often have no direction from ALS experts."

A real need exists "for states to come together to help create a mandatory national registry. Setting a precedence on the state level will likely make this happen," Stommel added. "If large states such as California, Michigan and Florida follow suit, we would be on our way to a mandatory National ALS Registry."

That registry, in turn, could help researchers tease out why certain areas of the U.S. have higher ALS rates than others and potentially discover ways the disease could be prevented. ■



## Parikshit NIRBHAY

*India*



**Parikshit Nirbhay** is a Medical & Science journalist based in “Amar Ujala”, a daily Hindi National Newspaper, New Delhi. He is passionate about uncovering the gaps in access to healthcare and writing about public health policies. He has won Merck Foundation’s MASK UP INDIA Award for Health writing in 2021, the International Center for Journalists (ICFJ)’s Journalist of the year Award in 2020, the Laadli Media Investigative Award for Gender Sensitivity in 2021,

the Press Council of India (PCI)’s development Reporting Award 2017. He has also received Excellence Award 2019 from All India Institute of Medical Sciences (AIIMS) Delhi, Swasth Bharat Abhiyan, Federation of Resident Doctors Association and AMIM Cancer Trust. He is fellow of “REACH” in 2019-2021 and “LAADLI” Media Fellowship 2022. He was previously with Dainik Bhaskar, IANS, Navbharat Times National Newspapers.

## Imprisoned in policy papers, patients are not getting benefits, life of people suffering from rare diseases is in danger

Doctors believe that if a single dose of a patient suffering from rare diseases is missed due to any reason, it has a profound effect on the health. Delay in treatment leads to loss of cost and effect of previous treatment.



### Detailed

The lives of more than 400 children suffering from rare diseases in the country depend on donations. They have to be treated in lakhs and crores of rupees and they have to go through various medical procedures throughout their life. A long time ago, the central government started raising online crowdfunding to save the lives of these children suffering from rare diseases, but statistics show that out of 80 crores, so far the government has been able to collect only two lakh rupees for them.

According to information received from the Ministry of Health, two types of services are being provided to patients suffering from rare diseases. Under the National Policy 2021, they are being helped up to Rs 50 lakh and the second service is related to crowdfunding, for which an online platform under the ministry was started last year. Under this, a total of 429 children suffering from rare diseases registered in 10 different hospitals of the country have to spend more than Rs 80 crore. So far a total amount of Rs 213,008 has been collected from 250 donors. However, if we look at the statistics, the amount received is not even equal to the treatment amount of a patient in comparison to the total expenditure given by the hospitals.

### Due to lack of help, treatment is not started

Saurabh Singh, director of Rare Disease India Foundation, said, the life of rare patients is going through a lot of difficulties. The government started crowdfunding but has been able to collect only Rs 2 lakh so far in more than a year.

While taking crowdfunding, it was decided that an appeal would be made to private companies for this, but till now not a single company has joined it through CSR.

The government has given the status of Center for Excellence to 10 hospitals across the country, but due to lack of financial help, the treatment of these children has not started.

### Did n't even get a message...

I had registered for crowdfunding. I have not received a single message till date and no phone call. I have spinal muscular atrophy. It has damaged nerve cells in my spinal cord. Delhi's Maulana Azad Medical College has reported an expenditure of Rs 6.70 crore. Every day I am sad to see my helpless father and mother with tears in eyes but what can I do? Anubhav Pal, spinal muscular atrophy patient, even after reprimand from the High Court, the order has not yet been implemented

Last week, the Delhi High Court had also raised questions on this crowdfunding system of the government. The court had clearly said that the responsibility of the government is not fulfilled only by creating a website. This crowdfunding platform should be publicized for those suffering from rare diseases so that more and more people can get information about it. Saurabh says that even after the order is issued, it is still not cognizance. ■





## Jackie OPARA

*Nigeria*



**Jackie Opara**, regional deputy editor [jackie.opara@scidev.net](mailto:jackie.opara@scidev.net). Jackie is a Nigerian science journalist and is responsible for coordinating correspondents and news coverage for SciDev.Net Sub-Saharan Africa region. She is English-speaking and won the IDRC/Research Africa Science Journalism award in 2014. Jackie coordinates the affairs of the Nigerian Association of Science Journalists (NASJ). As a journalist, her works have been published in various parts of the world including

Africa, South Africa and the UK. She has a profound interest in science journalism and science communication, she dedicates her time to speak to universities and their vice-chancellors in Nigeria on the importance of science communication. She also moderates conference sessions, one of which is moderating at the EuroScience Open Forum (ESOF2020) on ‘Agriculture on the front line, what the world can learn from African Scientists.’

## Collaborative R&D vital to stem rare diseases in Africa



Patients waiting to see a doctor. Copyright: DFID, CC BY-NC-ND 2.0

[LAGOS] At the Ipakodo Health Centre in the Nigerian city of Ikorodu, nurse Biola Daniels collects medical information on the antenatal ward from pregnant women with a history of anomalies.

“We have made it a point of duty to collect the history so we can pay more attention and refer them for testing or newborn screening for anomalies,” says Daniels, adding that such anomalies could help in diagnosing rare diseases.

The definition of a rare disease varies between countries and regions. The European Union defines a rare disease as one that affects one in 2,000 people, while the United States considers it a medical condition that impacts less than 200,000 people.

A study published in the Orphanet Journal of Rare Diseases in June says that almost six per cent of the world’s population could be affected by a rare disease.

According to the European Organisation for Rare Diseases, 72 per cent of rare diseases can be transferred genetically to children, with others resulting from infections, allergies and environmental factors.

### Rare disease screening ‘out of reach’

While newborn screening can help identify rare diseases early, such services are often inaccessible, say health professionals.

“As much as we’re mobilising resources and working on the awareness, we can’t do it alone as a public health institution.” Noella Bigirimana, Rwanda Biomedical Centre

“Newborn screening is not easily available in many government hospitals,” says Abiola Ejidokun, a gynaecologist at the General Hospital Ikorodu, in Nigeria’s Lagos state. “In the hospitals where they are available, they are expensive and many mothers who come here can barely afford it.”

Ejidokun tells SciDev.Net that even when newborn screening is available, healthcare workers tend to screen for one medical condition, usually sickle cell disease.

Faith Manuwa, the chief medical director of Malens Medcare Limited, a Nigerian medical diagnostics and biomedical services company, says the non-availability of diagnostics makes it difficult for the health sector in Africa to tackle rare diseases holistically.

“We see that some of the diseases that present more recently are inherited metabolic diseases, but then nothing happens beyond that,” she explains.

### Inherited metabolic diseases

A study published in the European Journal of Human Genetics in May, explains that inherited metabolic disorders (IMD) are examples of rare diseases linked to genes.

“The disorders are individually rare. They represent a common group of diseases with a prevalence of 1 in 784–2,555,” the study says. “Currently, over 1,400 IMDs are recognised. Early disease recognition, accurate diagnosis, and treatment are lifesaving in many cases.”

Peter Bauer, chief medical and genomic officer at Centogene, a healthcare company focused on rare diseases tools, explains that an integrated diagnostic approach is needed for improving the diagnosis and early detection of IMDs.

“Some IMDs are treatable. Many are included in newborn screening programmes in various countries, but are very low in Africa,” says Bauer, a co-author of the study.

Bauer led a team of researchers to develop a new next-generation sequencing panel with more than 200 genes which integrate genetic and biochemical testing performed in the same laboratory to allow the efficient diagnosis of more than 180 metabolic diseases.

## Diagnosing rare diseases in Africa

Barriers such as insufficient funding, lack of political support, and weak health systems make diagnosing rare diseases difficult in Africa, says an article published in the Orphanet Journal of Rare Diseases by the rare disease working group of the H3Africa Consortium.

The lack of diagnostic tools increases the chances of false positives and wrong classification of germs that cause rare diseases, the article adds.

Manuwa urges African governments to boost the infrastructural capacity at government hospitals and facilitate collaboration between government and private hospitals to increase diagnosis of rare diseases. She believes training of healthcare workers on rare diseases is also vital.

“Newborn screening is meant to be the norm but it is not available.” Faith Manuwa, Malens Medicare Limited Nigeria

“We also need inter-regional research to find sustainable solutions and build a formidable genomic data hub,” says Manuwa.

Diseases that should be curbed at the newborn stage “linger on and cause the patient damage at adulthood”, she says, adding: “Newborn screening is meant to be the norm but it is not available.”

## Endometriosis: ‘a silent rare disease’

One such disease is endometriosis, which occurs when tissue that usually lines the womb can be found on the ovaries, fallopian tubes or the intestines.

Abayomi Ajayi, a co-founder of African Endometriosis Awareness and Support Foundation and managing director of Nordica Fertility Centre in Nigeria, says that endometriosis is a silent rare disease often misdiagnosed and mismanaged in Africa.

“One in ten women, representing 200 million women and girls are living with endometriosis globally,” Ajayi adds. “The pain usually disturbs their normal chores. They also experience abnormal bleeding which can come from the navel and cough out blood.”

Ajayi tells SiDev.Net that about 40 to 50 per cent of women living with endometriosis could have fertility issues.

Kgomotso Mpho Gagosi, Botswana-based co-founder of African Endometriosis Awareness and Support Foundation, says that she was misdiagnosed several times when doctors did not understand while she was bleeding so much since she was 14 years old.



Kgomotso Mpho Gagosi, Botswana based co-founder of African Endometriosis Awareness Support Foundation and Endometriosis survivor

“I was told I have sexually transmitted disease when I have never had sex in my life. One doctor even told me I had undergone abortion because I was bleeding heavily,” Gagosi says.

She adds that she had several tests but nothing could point to what she was going through.

“Early diagnosis is important. Unfortunately, endometriosis has no cure,” says Ajayi. “This is a condition that they have to live with, till the stage of menopause.”

## Collaboration ‘crucial’

Noella Bigirimana, a public health expert and deputy director-general of the Rwanda Biomedical Centre, says that regional collaboration and consolidation of efforts are key to controlling rare diseases in low-income countries.

“Rare diseases affect a lower proportion of people and may not receive attention,” she explains.

Bigirimana says that investment in primary healthcare has benefited both infectious and chronic diseases such as HIV, and hopes that rare diseases will also get the needed attention.

Bigirimana calls on public health workers to collaborate with organisations that focus on such diseases to increase their awareness in communities.

“As much as we’re mobilising resources and working on the awareness, we can’t do it alone as a public health institution,” she explains, adding that families and communities should also be actively engaged to help patients with rare diseases. ■

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## Chimwemwe PADATHA

*Malawi*



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He is a Media and Communication professional with a Bachelor's Degree in Communication and Cultural Studies acquired from the University of Malawi. Apart from that, Chimwemwe is a holder of a Certificate in Film Radio and

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Chimwemwe is a 2016 fellow for the International Journalist Programme (IJP) through which he underwent a monthlong mentorship program at Radio DW. He is MISA Malawi's 2018 Supply Chain of Essential Medicines awardee.

## Untold Stories Of Duchenne Muscular Dystrophy



*The Mulowa Family*

Peter Mulowa is a boy aged 17. This boy has a condition known as Duchenne Muscular Dystrophy (DMD). DMD is a genetic disorder that weakens a person's muscles over time.

Peter has difficulty standing. His posture is clearly poor. When he walks, Peter is almost tip-toeing. This is Chibagala village in Blantyre, the village is in BCA Hills area.

He is in the early stages of Duchenne Muscular Dystrophy (DMD), according to experts.

And this, is Chibagala village in Blantyre. The village is in the BCA Hills area. On our visit this day, Zione, mother to Peter is busy pounding flour for the day's meal. That speaks to the home's ability to afford basics; food, shelter and clothing.

The mother has to pay K30,000.00 rentals every month for the two-bedroom house. Her only means of income is sales of tomatoes and onions. The husband in the home has no means of income

The Mulowa family has seven children, four of which are male and have the condition. One child died a year ago of the same disease condition, as recalls the father James Mulowa.

“He was not born with this condition, this disease started developing when he was about 10 years, one of children died in September last year at the age of 18. We lack a lot of necessities such as food as I am always supposed to look after the children. I bath them and take them where ever they want including visiting the toilet,” said Mulowa.

And yet, it is not only Peter they have to look after with the DMD condition. There is also Noel. He is 24. He too has Duchenne Muscular Dystrophy. He developed the condition when he was 12. At the time, he was in primary school.

Noel fell frequently. He had frequent muscle cramps. Noel has difficulty standing on his two feet. Now he even has speech problems.

“The disease started when I was in primary school. I used to fall a lot and stopped going to school. I feel that my future is shattered, I cannot do anything on my own now,” Noel recalls.

Duchenne Muscular Dystrophy is a multi-systemic condition, affecting many parts of the body, resulting in the deterioration of the skeletal, heart, and lung muscles. People with this condition gradually lose the ability to use their limbs.

In 2002, Malawi adopted the Integrated Disease Surveillance and Response strategy. The strategy was meant to help implement comprehensive public health surveillance and response systems.

Dr. Jonathan Ngoma is Chief Medical Specialist at Kamuzu Central Hospital in Lilongwe. Here he explains some factors in regard to this condition in Malawi at the moment.

Said Ngoma; “We need more specialists because you see how most of these cases are managed, how to make diagnosis even without diagnostic capability.”

Peter Mchilima is a physiotherapist. He works at Kachere Rehabilitation Centre in Blantyre.

The center is the only medical facility designed to provide intensive rehabilitation to people who have met disabling conditions such as Duchenne Muscular Dystrophy in Malawi.

Mchilima also asserts that, for some reason, the disease affects males more often than females.

“Muscular Dystrophy is more common in males or boys than girls. At the moment we don't know why it is like that. We don't have a special place or special people who have specialized in Muscular Dystrophy,” said Mchilima.

Chairperson of the Parliamentary Committee on Health, Dr. Mathews Ngwale, says financial constraints have led to poor health care for diseases such as Muscular Dystrophy in Malawi.

He says the committee is exploring options on how to improve the situation.

“Because of the limited resources of funds, government looks at the more critical cases first but diseases like Muscular Dystrophy are not given as much attention as they should, we are aware of what the situation is for government” he pointed out.

Health rights activist, Maziko Matemba, agrees that the disease is associated with socioeconomic constraints. This, he says, is due to high demand for healthcare and non- health care resources.

Matemba suggests a new approach to reaching out to communities mainly those with the condition.

“Government need to make sure that issues of health financing are also being given attention because if you have enough resources, some of these conditions can be dealt with”

Despite its life-threatening nature, Duchenne Muscular Dystrophy has no cure. Physiotherapists only work on improving muscle and joint function. And physiotherapy is largely in urban areas.

The majority of public health facilities in these areas do not offer physiotherapy treatment.

Dorothy Chinguwo is deputy director in curative and medical rehabilitation services responsible for rehabilitation in the ministry of health.

“We have the services readily available for the population, the disease is generally very, very rare. Even in the development countries, they don’t

have equipment to detect but you only diagnose the condition through the signs and symptoms presented,” Added Chinguwo

Duchenne Muscular Dystrophy has evident negative socio implications on affected families in Malawi. There are experiences of discrimination, rejection and socio-cultural mythical beliefs.

In some cases, marriages have broken up when children develop the incurable condition.

Hawa Williams is a mother of five children. She has had to move from Lilongwe city to a village in Nthenje because of her situation.

For Williams, at least hospitals should be able to detect the disease before childbirth.

“I would request government to find a way of detecting this disease before a child is born. This can reduce the burden that families have. I have been affected as I was forced to live alone since my husband left me because of the condition of my children,” said Williams

The United Nations (UN) General Assembly adopted a resolution in 2021 lobbying countries to recognize the need to promote and protect rights of persons Living with Rare Disease Worldwide.

These include those with Duchenne Muscular Dystrophy living in Malawi.

Provision of specialized care for such people may appear to be a tall order but the absence of the same is, therefore, a violation of that UN resolution.

Malawians living with Duchenne Muscular Dystrophy deserve, as a right, health care like do all. ■



# Sachin RAWAT

*India*



**Sachin Rawat** is a freelance science writer and journalist based in Bangalore, India. He holds a master's degree in biotechnology. He writes

about the bioeconomy and everything that impacts or is impacted by it. Find him on Twitter at [@sachinxr](https://twitter.com/sachinxr).



## Drug repurposing emerges as viable option for rare disease treatment



With few options available for the treatment of rare diseases, the practice of drug repurposing has gained traction as an effective strategy. With genome sequencing revealing new rare diseases, it is now known that at least 5% of the world population lives with a rare disease. Drug development must pick up the pace to keep up with rare disease diagnoses. This is however incredibly difficult for a lot of reasons, but mainly the fact that rare diseases, by definition, have few patients for clinical trials.

Beyond expedited regulations and incentives, drug development for rare disease patients needs creative solutions that accelerate the pipeline. Drug repurposing, also known as drug repositioning, is one such increasingly popular solution. The approach navigates existing literature and data on disease mechanics and the action of potential therapeutics to identify new uses for existing drugs.

Compared to a full-blown drug development process, drug repurposing significantly reduces time and costs, making it a more economical option for rare disease drug development. This is because it is already known that a particular drug is safe for use and only its efficacy in treating a different condition is in question.

### Drug repurposing: old drugs, new benefits

Drug repurposing has found wide success in the treatment of non-rare conditions. The most famous example is that of aspirin, which was first developed to treat pain and was later repurposed for heart diseases. More recently, researchers around the world repurposed multiple drugs for COVID-19.

The rationale behind drug repurposing is that almost all drugs interact with multiple biological pathways and that similar drugs should act on similar targets.

Unlike serendipitous discoveries of the past, biotech researchers and companies now actively seek new applications for existing drugs, including those that made it to clinical trials but were not commercialized. High-throughput screening assays allow companies to investigate the action of drugs on multiple pathways at once, enabling a systematic approach to drug repurposing.

Scottish biotech NovaBiotics does exactly this with a focus on immunology assays. The company is repurposing cysteamine, a drug that has been used for the treatment of cystinosis, a rare metabolic condition, for decades. The company is reformulating this drug as a potential cure for the treatment of cystic fibrosis (CF), another rare metabolic condition. The repurposed drug, Lynovex, has received orphan drug designation in both the U.S. and Europe.

Speaking of the company's technology, CEO Deborah A. O'Neil said that it "uses innate immune effector molecules as templates for novel therapeutic approaches for an unmet disease where there is an inflammatory and/or infectious component."

With this, NovaBiotics is able to test and develop the same drug for multiple conditions. For example, Novabiotics "developed NM001 for CF in oral and inhaled (dry powder) form."

Early results show that the oral form helps with intermittent episodes in which CF symptoms worsen and the inhaled form maintains healthy lung function during treatment.

Additionally, the company is repurposing cysteamine for the treatment of community-acquired pneumonia, a far more common condition. Repurposing the same drug for multiple conditions in this manner has the potential to further derisk the process for companies.

### Computational approaches reveal hidden mechanisms

Conventional drug repurposing works well when investigating a drug that's similar to a drug that already works for the same disease, or when

investigating the action of a drug on a disease that's similar to the one it already works for. Such data are often not available for rare diseases when it comes to looking deeper into the interactions between drugs and targets.

For rare diseases, computational drug repurposing offers a quicker and more scalable method. Over the last two decades, biologists have produced tons of omics data for all kinds of conditions. There is a lot of other data available thanks to the digitalization of clinical trials and healthcare in general. Artificial intelligence (AI)-based approaches make these data accessible to drug designers looking to find new purposes for existing drugs. AI-based solutions tease out hidden interactions between drugs and phenotypes, allowing researchers to better understand disease mechanisms and identify drugs that target them.

U.K.-based biotech Healx tackles this challenge with its graph-based approach to computational drug repurposing. The graph here refers to the complex network of interactions between drugs and target molecules. Scientists traverse these networks and find shared pathways between mechanisms of drugs or diseases.

By integrating omics and phenotyping with this approach, Healx advances a hypothesis-free model of drug discovery. Instead of looking at one drug's action on one disease at a time, it looks into multiple possibilities for enhancing existing drugs, repurposing them, or combining them for improved action at once.

Daniel O'Donovan, principal machine learning engineer at Healx, said that their model analyzes “structured and unstructured data sources and uses a variety of algorithms to solve different problems in the drug repurposing pipeline.”

Healx's main focus is on Fragile X syndrome, a rare genetic disorder that causes intellectual disability in patients. It is repurposing sulindac, a drug originally developed decades ago as a treatment for inflammatory conditions.

Donovan added that Healx's AI platform analyzes interactions of multiple drugs with pathways involved in the Fragile X disease mechanism. This way, it identifies combination therapies as well as relative concentrations required to

optimize synergistic activity between the drugs in combination therapy. The company is testing sulindac in combination with gaboxadol, a drug that failed in clinical trials for Angelman syndrome and as a sleeping pill at another pharma company.

## Bridging the gap

Rare disease patients may also benefit from personalized repurposed drugs. This is true for ultra-rare diseases with only one or few patients globally as well as rare diseases for which existing therapies produce highly variable responses in different patients. In recent years, there has been a steady rise in N-of-1 studies for drug repurposing. As the name suggests, these are studies with a sample size of one individual for highly personalized drug repurposing.

A successful case of N-of-1 drug repurposing for a rare disease is that of Dr. David Fajgenbaum. When diagnosed with the life-threatening Castleman disease, he found a cure by researching known drugs that prevent cytokine storms, a characteristic trait of this disease in which an overproduction of cytokines sends the immune system into overdrive.

Like Dr. Fajgenbaum, much of rare disease drug development is led by patients or those close to them. However, they don't always have the resources required to research or repurpose a drug. The industry needs new business models that allow rare disease patient groups to commercialize drug repurposing. For example, patient-led decentralized autonomous organizations empower patient groups to crowdfund research and have a financial stake in drug development.

Most of the nearly 7,000 rare diseases known to date have no cure. Sustained innovations in drug repurposing are necessary to better serve rare disease patients. Bridging the gap between its promise and cures requires incentives for systematic drug repurposing — including those particularly targeted at rare diseases, new methods to repurpose drugs for individual patients, and better computational tools that gather as many insights as possible from a few patients.

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# Hellen SHIKANDA

*Kenya*



Ms **Hellen Shikanda** holds a Bachelor's degree in Communication and Journalism from Moi University in Kenya. She received a post-graduate diploma training in Multimedia Journalism from the Graduate School of Media, Aga Khan University. She has been a reporter for three years now specializing in producing multimedia content in Health and Science for the Nation Media Group. She is a fact-checker, a

leader and climate change enthusiast. Ms Shikanda is an alumna of the Bettina Fund Mentorship Program, the Oxford Climate Journalism Network, Africa Resilience Network and the Africa Academy of Open-Source Investigation. She is currently a Women in News fellow. She is a member of the Media for Environment, Health, Science and Agriculture (MESHA).

## Autoimmune disease

## Rare disease defers ex-bank employees ambitions, for now

Jefitha Murimi had perfect health, relishing his job, until he hit 30



Jefitha Murimi Gichuki who suffers from Stiff Person Syndrome during an interview at their home in Ngong on December 18, 2022. EVANS HABIL IN NATION

BY HELLEN SHIKANDA

There is one thing that Jefitha Murimi misses; his job. He says it with the gusto of a highflier. While his dreams were deferred by a rare genetic condition that has left him immobile – the stiff person syndrome (SPS) – his determination is still in beast mode, and his mind continues to sparkle, fervently waiting for the next opportunity.

*Healthy Nation* finds him seated on a couch at his sister's house in Ngong, Kajiado County. The house, which sits on top of a hill, is cold, and the breeze from the trees sneaks in fresh air that makes our interview settling.

Jefitha has his crutches by his right hand, one which has become his newfound identity. In fact, in July, he got an official identification card from the National Council for Persons with Disability, something he never imagined in his wildest of dreams.

Jefitha tries to talk, but he is stuttering and takes ages to respond. His sister, Pauline Njeri, who doubles as his caregiver, takes over and explains what really happened to her brother.

"My brother always had perfect health, until he turned 30. At the time, he was working at a bank after successfully completing his degree and aced two levels of a professional course with the Association of Chartered Certified Accountants (ACCA). His career was taking shape and we

all knew his future was bright," Pauline says.

Before he detoured from the path he had hoped would elevate his life, he lived with the mother of his two children. It is there that the unusual muscle spasms first manifested. It is from there that he was first wheeled to hospital unconscious. It is from there that the late renowned neurologist Prof Paul Kioy diagnosed him with SPS.

How did he take the news that he had a rare and incurable condition?

"I was shocked and full of fear," he says, dramatising the shock, and fear. "I was told that my condition affects people when they get to the age of 30, and that it is genetic; there is nothing I could do to reverse that."

It took some time before they got the proper diagnosis.

"We struggled to know what was going on. We did a lot of scans. At some point he would faint and we didn't know what was happening," Pauline tells *Healthy Nation*.

The search for the correct diagnosis took forever, but the family is glad that they finally got closure. Pauline says the family also took time to let that news sink in.

Even before they confirmed what he was suffering from, Prof Kioy, based on the symptoms that Jefitha had, suggested that he could be a candidate for SPS. The diagnosis confirmed his viewpoint.

"We trusted Prof Kioy. My brother's

**We struggled to know what was going on. We did a lot of scans. At some point he would faint and we didn't know what was happening**

Pauline Njeri



blood samples were flown to South Africa for analysis and the results came back. He was diagnosed with the stiff person syndrome. We had never heard of that disease before and we had to accept it. We are a family that does not believe in witchcraft and we did not think that anyone had bewitched him. It is just a disease like any other and we have learnt to live with it," explains Pauline.

As he learnt to live with the disease, they sought a second opinion from an orthopaedic surgeon. Pauline says they regret visiting that doctor, who dismissed his brother as pretentious. "There is a doctor that did not find

anything wrong with my brother after doing all the tests. Instead of giving us options, he told us [my brother and me] that my brother was just afraid to work, and that he should face his fears and go back to work. I could see the rage in my brother's eyes when such vile words were said. You know, it is only him that can tell how his body feels. He even didn't want me to pay for the consultation. We did, anyway, but left in agony," she narrates.

All this time, Jefitha was still working at the bank, until he got fired under mysterious circumstances and his dues, to date, have not been paid. At some point, he completely lost his speech and could barely move. His friends vanished and his solace came from family only.

"When he stopped talking, we had to take him to India. The doctors in India applauded Prof Kioy for the treatment he had given my brother and the apt diagnosis," says Pauline.

After the treatment, he began to talk once again, albeit with difficulty.

"This disease is mysterious; one time my brother is okay; the next minute he is in pain," she says.

## Sudden change

Pauline shows us a photo of Jefitha in September on his birthday. Jefitha is standing on his feet, surrounded by children who seem eager to devour the cake that was being cut. He seemed genuinely happy, and in no pain. The next day, however, Pauline tells us Jefitha could barely move. The muscle spasms came in full throttle, as though they were reacting to his new age.

"We were shocked. Someone who doesn't understand how this disease manifests could easily say he is pretending, but in reality, my brother was in pain."

On his brighter days, like the day we interviewed him, he finds time to apply for jobs because he still has the grit in him.

"Even after my brother was fired at the bank, he still worked online; unfortunately, his account was closed," Pauline says.

It may seem like a burden for his sister Pauline to take over and care for Jefitha, her younger brother, but she says she doesn't feel the load.

"I will move the mountain for my brother. I will not complain even if he stays here for 20 years, so it is okay."

It is not just the spasms of pain, and the deformed back that have afflicted in his life. At times, he is affected by things like noise. Lately, he has been managing because of the medicine that he takes as well as physical activities, when the pain fades away.

After losing his job, he did not have medical insurance and had to get money to buy medicine. In a month, he could spend about Sh5,000 on medicine, and some more money on physiotherapy and consultation, when need be. He is lucky to have a brother who owns a chemist and gives him most of his drugs for free.

"We know that there's no cure for this condition just yet. Prof Kioy used to tell us to just take the medicine and see what happens. We have always been positive that he will one day be okay," says Pauline.

So, what really is this disease?

To date, scientists do not know the real cause of this autoimmune dis-

ease.

According to the Rare Disease website, autoimmune diseases occur when the body's natural way of defending itself against diseases starts attacking healthy tissues for unknown reasons. It further explains that most people who have SPS have more antibodies to glutamic acid decarboxylase (GAD), a protein found in the body.

Even so, there is an ongoing study by the US National Institute of Stroke and Neurological Disorders that focuses on understanding the cause of the disease and the role of the anti-GAD antibodies.

When Jefitha's results came from South Africa, the report shows that he had more than 500 GAD in his blood—it was labelled as 'high'.

It is, however, difficult to diagnose this disease.

The Rare Disease website explains: "A diagnosis of SPS is made based upon identification of characteristic symptoms, a detailed patient history and a thorough clinical evaluation. Additional tests can be used to support a diagnosis and to rule out other conditions."

## Types of SPS

There are about five types of SPS: classic, focal, jerking, progressive encephalomyelitis with rigidity and myoclonus, and paraneoplastic-related SPS.

According to the Stiff Person's Syndrome website, some of the symptoms include muscle spasms, hyper-rigidity, debilitating pain and chronic anxiety. Muscle spasms can be so violent that they dislocate joints and even break bones.

They explain that SPS likely occurs when the immune system of people with the disease mistakenly attacks an enzyme, which plays a role in producing a vital neurotransmitter called gamma-aminobutyric acid (GABA). This then decreases the amount of GABA in the body, resulting in the aforementioned symptoms, which mostly occur in middle age. While most studies show that people experience it in middle age, a rare occurrence published in the *African Journal of Neurological Sciences* shows that a 12-year-old Kenyan girl was diagnosed with the disease.

"The serum anti-glutamic acid decarboxylase (GAD) level was greater than 2,000 (normal 0-10 IU/ml), strongly supporting the diagnosis of stiff-person syndrome plus. The patient recovered with diazepam, baclofen, and supportive care," states the study.

Besides the symptoms that Jefitha experiences, some patients react to touch and are often in distress. The disease affects one in a million people and more women than men are likely to get it. While there is no cure, there exists treatment options that help in suppressing the pain.

"There are two main treatments for SPS: GABAergic (gamma-aminobutyric acid) therapy and immunotherapy. For treatment, we suggest starting with benzodiazepines as first-line treatment. We recommend adding levetiracetam or pregabalin if symptoms persist," says a study published by the *Cureus Journal of Medical Science*.

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## Moudud Ahmmed SUJAN

*Bangladesh*



**Moudud Sujan** is a Dhaka-based journalist with in-depth reporting experience on science, public health, health inequality and government corruption, environment, migration, diplomatic relations and labour rights.

Currently, he has been working as a health reporter at The Daily Star -- a national English daily in Bangladesh. During the Covid-19 pandemic, he provided crucial front-page coverage every day from mid-2020 to late-2021. He has specialisation in reporting on AMR; his award-winning report on antimicrobial resistance in 2019 prompted the

country's judiciary as well as the executive authorities to take measures to stop over-the-counter sale of antimicrobials. This report was also quoted by The Telegraph in London.

Before joining The Daily Star, Moudud covered diplomatic affairs at the Bangladesh Post, another Dhaka-based national English daily of Bangladesh.

As a young journalist, he looks forward to taking his health and science reporting skills and knowledge to the next level.

## The unheard plight of those with rare diseases

Amid dearth of treatment options, patients suffer due to misdiagnosis, lack of awareness



In 2014, Iraboti Roy, 40, a patient with the disease Myasthenia Gravis, died a day after a doctor in the country's top neurological hospital used a sedative on her.

Myasthenia Gravis is a rare, long-term condition that causes severe muscle weakness and often remains undetected in patients, leading to misdiagnosis and wrong treatment.

“Had the doctor not jabbed her with that injection, my sister could have survived. But I would not blame the physician because most doctors are unaware of rare diseases present in the country,” said Shashanka Baran Roy, Iraboti's brother.

Myasthenia Gravis is one of approximately 7,000 rare diseases discovered so far. These conditions affect the lives of around 300 million people worldwide at any time, according to Global Genes -- a US-based organisation that works for individuals and families fighting rare and genetic diseases.

Being rare, there is a lack of awareness among physicians about these diseases, and medication to treat them is not widely available, leaving patients helpless.

For instance, Jakia Abedin, a 36-year-old Myasthenia Gravis patient in Munshiganj, lost two babies just days after giving birth to them in 2006 and 2014.

Before conceiving the second child, Jakia asked her doctor -- who first identified her as a Myasthenia

Gravis patient in 1999 -- whether her disease was responsible for the death of her first baby.

“My doctor told me there was no connection. But now I know there was and my baby would have lived if we had taken precautionary measures,” Jakia told The Daily Star.

Abandoned by her husband, Jakia, now lives in a rented house in Munshiganj all alone. She needs Tk 4,000 a month to buy medicines for her rare illness but cannot afford the regular doses.

“I take medicine only when I need to move from my bed,” said Jakia between her sobs.

Jakia's life could be easier if her thymus gland were removed through surgery, which her doctor advised back in 2004. But she could not manage the required amount -- between Tk 2 to Tk 10 lakh -- for her surgery.

Amid the absence of policy and government funds, many patients with Myasthenia Gravis and other rare diseases lead a miserable life in Bangladesh, where out-of-pocket expenditure for treatment is 68.5 percent of the total cost.

Meanwhile, nine-year-old Anisur Rahman has been suffering from a rare complication, what the district-level physician suspects is a premature ageing problem. The physician suggested his parents to take him to a specialist in Dhaka. “We cannot even afford enough food for ourselves, let alone take my son to Dhaka. If anyone helps us, we would be grateful,” Anisur's mother told The Daily Star.

### LACK OF AWARENESS LEADS TO MISDIAGNOSIS

Most rare diseases are genetic and affect a person throughout their life, even if symptoms do not immediately surface.

As a result, it takes more time to diagnose such conditions.

For instance, Iraboti was on medication for three months to address nutritional deficiencies, as diagnosed by a doctor, until her brother suspected that she had something else and took her to a neurologist.

In Jakia's case, an accurate diagnosis took over a year. But for Sumona Monzur, who also has Myasthenia Gravis, it took 12 years, even though she lived in Dhaka and belonged to a privileged family.

“Initially, my parents even discouraged me from discussing my illness, assuming that it was all in my head. Later, physicians too made mistakes time and again. And throughout this time, I was the one who suffered,” Sumona, coordinator of Bangladesh Myasthenia Gravis Patients Society, told The Daily Star.

Currently, a total of 58 patients are under the platform, using which they help each other by sharing information.

“One thing we all encountered is that even renowned physicians made mistakes,” Sumona mentioned.

Prof Mohammad Hosen, dean of the neurosurgery faculty at Bangabandhu Sheikh Mujib Medical University (BSMMU), said that patients struggle to find the appropriate medical facility due to the lack of information.

“We have highly qualified physicians, but access to them is an issue. Besides, even the country's top hospitals often lack state-of-the-art technology for diagnosis,” he added, further pointing out the absence of a referral system as the major cause behind delayed diagnosis.

## A SYSTEMIC GAP

According to Prof Ahmedul Kabir, additional director general (administration) at Directorate General of Health Services, there are two main reasons behind physicians lacking knowledge about rare diseases, which often leads to wrong treatment or late diagnosis.

Firstly, medical students are often taught that while evaluating a patient, they should first consider a common diagnosis, not a rare one. Secondly, the country's health system has no systematic approach to addressing the needs of patients with rare conditions.

Kabir said the medical community is aware but there is a need to revise the current educational curriculum so that students are aware of the many possible diseases symptoms can point to.

“It should start from the undergraduate level,” Kabir, who co-authored the book “101 Interesting Cases in Clinical Medicine”, told The Daily Star.

He agreed that a government policy on rare diseases is needed. “The treatment cost for a rare disease is very high. We need to raise a separate fund to support patients with such conditions,” he said.

“In fact, we have been considering such a policy for the next health-sector plan,” he added. ■

## Helplessly, rare disease patients soldier on



### THE PROBLEMS

- › Lack of awareness among doctors
- › Medication expensive, not widely available
- › No govt policy, fund
- › Arrangement for diagnosis inadequate
- › Flaws in educational curriculum
- › Absence of referral system

“Initially, my parents even discouraged me from discussing my illness, assuming that it was all in my head. Later, physicians too made mistakes time and again. Throughout this time, I was the one who suffered.

**SUMONA MONZUR**  
Who has Myasthenia Gravis

“We have highly qualified physicians, but access to them is an issue. Besides, even the country’s top hospitals often lack state-of-the-art technology for diagnosis.

**PROF MOHAMMAD HOSEN**  
Dean of neurosurgery faculty at BSMMU

*Bangladesh’s stretched healthcare system has no room for rare disease treatment, leaving patients with misdiagnosis*

In 2014, Iraboti Roy, 40, died a day after a doctor in Bangladesh’s top neuroscience institute hospital in Dhaka administered her a sedative.

“Had the doctor not given that injection, my sister would have still been with us,” said Shashanka Baran Roy, Iraboti’s brother.

But Roy is not blaming the physician: his sister was suffering from Myasthenia Gravis (MG), a rare, long-term condition that causes severe muscle weakness and often remains undetected in patients leading to misdiagnosis and wrong treatment.

The reason MG is so difficult to pin down is that its primary symptom, which is weakness, is a common precursor of many ailments. Complicating matters is the fact that the symptoms may be vague, fluctuate or only affect certain muscles.

And MG doesn’t “perform” on demand; the eyelid that droops at 7:00pm may not show for a 9:00am doctor’s appointment.

Suspecting her weakness was due to nutritional deficiencies in early 2006, Iraboti took medication for that but to no avail.

Other than feeling weak, her muscles would freeze randomly, leaving her as good as paralysed. Suspecting something was wrong with her hypothalamus, Roy took Iraboti to a neurologist, who was finally able to diagnose her condition.

Like MG, there are about 7,000 such rare diseases that affect the lives of about 300 million people worldwide, according to Global Genes, a US-based non-profit advocacy organisation for individuals and families fighting rare and genetic diseases.

Due to their rare nature, there is a lack of awareness among physicians and a lack of availability of medication to treat them, leaving sufferers mostly helpless.

For sufferers of such rare diseases in Bangladesh, a country where healthcare infrastructure is said to be inadequate for its populace and out-of-pocket expenditure accounts for 68.5 percent of the total cost for treatment, their ordeal is particularly heart-breaking.

Even if it gets diagnosed in time, no government policy or state funds for rare diseases means only the very well-off can afford the expensive treatment.



Take the case of Jakia Abedin, who has been diagnosed with MG in 1999 after a year's suffering.

In 2004, her doctor advised the removal of her thymus gland as an option to effectively manage the symptoms of MG. The procedure would cost Tk 2 to Tk 10 lakh (\$2000-10,000), but Jakia, who was then a housewife in Munshiganj, could not manage the funds.

Her condition has since gotten worse, leaving her incapable of leading a normal life.

“At times, I am unable to even swallow my food or move my limbs. Out of nowhere, I get the spasms and I turn to stone and drop to the floor.”

She needs Tk 4,000 a month for the full dose of her medication that would prevent her muscles from freezing at random.

“But I can't afford it. I only take the medicine when I have to pull myself out of bed,” she said.

Like Jakia, Anisur Rahman's parents are passing their days in a state of helplessness. Their nine-year-old son is displaying symptoms of Progeria, an ultra-rare disease, according to local physicians, that shortens the lifespan of children to 13 to 14.5 years.

A medicine that costs Tk 6.68 crore could extend Anis's life to 17 years, which his parents are unable to afford.

Let alone afford the expensive treatment, his parents are so poor that they can't even pool the funds needed to make the trip to Dhaka from Lalmonirhat to see a specialist to diagnose Anis's condition.

“We are so poor that we can't even afford enough food for ourselves. But I still dream my son will get proper treatment and will recover one day,” said Anis's mother.

Without some divine intervention, a fate like Faridul Islam's awaits Anis.

In 2015, Farid died at the age of 14 of Fibrodysplasia Ossificans Progressiva, a rare genetic disease that causes human connective tissue to turn into bone.

Although FOP has no known cure yet, with medical attention, such patients on average have a lifespan of about 56 years.

“Due to poverty, I could not ensure a comfortable life for him. I had to watch my son die right in front of me and I couldn't do a thing,” said Mazidul Islam, Farid's father.

Ahmedul Kabir, who co-authored the book “101 Interesting Cases in Clinical Medicine”, called for a government policy on rare diseases.

“The treatment cost of a rare disease is very high. We need to raise a separate sickness fund to support patients with rare diseases,” he said.

The absence of a referral system is the major cause behind the delayed diagnosis of rare diseases, said Mohammad Hosen, dean of the faculty of neurosurgery at the Bangabandhu Sheikh Mujib Medical University.

“We have highly qualified physicians, but the diagnosis arrangement is systematically inadequate. The patients can't reach the right physicians due to the lack of information,” he added.

Sumona Monzur, the coordinator of the Bangladesh Myasthenia Gravis Patients Society, echoed the same.

Bangladesh Myasthenia Gravis Patients Society has 58 patients who help each other by sharing information.

“One thing we suffered in common is that even..... renowned physicians made mistakes.”

Were there any specific platform centrally for rare diagnosis, physicians would send suspected cases there, said Sumona, who suffered for 12 years before her MG could be diagnosed.

“Initially, my parents even discouraged me from discussing my illness assuming it was an imagined illness. Later, the physicians too made mistakes time and again. But I was the one to suffer,” she added.

Medical students are often taught to consider a common diagnosis for evaluating a patient and not a rare one. There is a need for adjusting a clinical challenge-oriented curriculum to address the existing gaps, Kabir said.

“It should be started at the undergraduate level,” said Kabir, who is also the additional director general (administration) at the Directorate General of Health Services.

## Spare a thought for patients with rare diseases

**They are being undone by misdiagnosis, lack of awareness, and limited treatment options**



In a country where the vast majority of ordinary patients – those with easily diagnosable diseases – are often deprived of the care and treatment that they deserve, it's easy to overlook the small minority of patients afflicted with rare diseases. But their plight is no less dismal. As well as enduring problems that patients in general do in terms of access, cost and quality of care, those with rare diseases also suffer from misdiagnosis, lack of awareness on the part of doctors, limited treatment options, etc.

As a recent report by this daily shows, these factors, coupled with lack of policy response from the health authorities, make this group of patients suffer disproportionately. The report presents a number of cases to illustrate their vulnerability. There is the case of Iraboti Roy, 40, a patient of the rare Myasthenia Gravis disease, who died a day after a doctor used a sedative on her that allegedly caused the death; the case of Jakia Abedin, 36, another Myasthenia Gravis patient, who lost two babies just days after giving birth to them in 2006 and 2014; the case of Anisur Rahman, 9, suspected to be suffering from a premature ageing problem, the treatment of which is not available in his home district; the case of Sumona Monzur, also a Myasthenia Gravis patient, who had to wait for 12 painful years before her condition could be diagnosed.

Myasthenia Gravis – a chronic autoimmune, neuromuscular disease – is one of approximately 7,000 rare diseases said to have been discovered so far. These conditions affect the lives of around 300 million people worldwide, according to an estimate. Being rare, it's understandable that doctors may not always be aware of them, nor is medication to treat them widely available. Delayed diagnosis or misdiagnosis is another factor, which may lead to potentially dangerous wrong treatment.

Cases examined in our report have shown that patients with rare diseases mostly suffered because of lack of awareness and information. Most rare diseases take more time to be diagnosed and treated, at a comparatively high cost, of course. But delays in detection and treatment – in a country where out-of-pocket health expenditure is 68.5 percent of the total cost – only increase the costs further. This makes poor patients like Jakia and Anisur even more vulnerable among their peers. Unfortunately, the policy response to this threat remains woefully inadequate – with no separate fund for rare diseases, no policy guidelines, no research, no awareness drive for patients and doctors, no change in how medical students are taught to approach symptoms, etc.

This lack of response represents a lack of priority in our already stretched healthcare system. But those suffering from rare diseases deserve as much attention and care as ordinary patients. And the onus for that falls squarely on the health authorities, both at the policy level and at the medical college/hospital level. They must combine to form a national policy that addresses the threat of this growing challenge in the country. ■



## Bijal P. TRIVEDI

*USA*



**Bijal P. Trivedi**, senior editor for science at *National Geographic*, is the inaugural winner of the Sharon Begley Award for Science Reporting.

Trivedi is the author of the 2020 book *Breath from Salt: A Deadly Genetic Disease, a New Era in Science, and the Patients and Families Who Changed Medicine Forever*, tracing the century-long scientific quest to understand and treat cystic fibrosis. *Breath from Salt* made the longlist for the 2021 PEN/E.O. Wilson Literary

Science Writing Award. The book was also included in Bill Gates' 2020 list "5 Good Books for a Lousy Year."

Among Trivedi's previous awards are the Michael E. DeBakey Journalism Award (2006), the Wistar Institute Science Journalism Award (2005), and the NIH Plain Language Award (2009). Her *Scientific American* piece "The Wipeout Gene" was selected for the 2012 edition of *Best American Science and Nature Writing*.

## This crippling disease often goes under-diagnosed—unless you're white

Anyone, of any ethnicity, can get cystic fibrosis. But for decades it has been overlooked in people of color, leading to misdiagnoses and dismal health disparities.



*Terry Wright takes a pulmonary function test at the University of Arkansas for Medical Sciences in Little Rock, to monitor the state of his lungs. Wright has cystic fibrosis, an inherited genetic lung disease, and wasn't diagnosed until age 54, and has sustained significant, irrev... Photographs ByTerra Fondriest*

Terry Wright spent his childhood in Little Rock, Arkansas, struggling with severe stomach pain. “That initial blow when you first get kicked,” he says, “that was the pain, and it didn’t go away.”

He vomited after every meal, and the crippling stomachaches discouraged him from trying to eat or drink more, leading to severe malnutrition. Each trip to the emergency room yielded a different diagnosis—ulcers, a virus, the flu—and then doctors would inject him with painkillers. “That would just

kind of hold me for a few hours. And then the pain would start back again,” he says. As he grew up, he had frequent sinus infections, and bronchitis and pneumonia, causing such severe sickness that he spent at least two-and-a-half weeks in the hospital every three months.



*People with cystic fibrosis are at risk for two common bone diseases: osteoporosis and osteopenia. Here Terry Wright, who has CF, gets a bone density scan with UAMS employee Melissa Bryan while his wife and advocate Michele Wright waits by his side.*



*Patient Terry Wright and Larry G. Johnson, director of pulmonology and critical care medicine in the department of internal medicine at the University of Arkansas for Medical Sciences, talk during a routine cystic fibrosis check up. Johnson is the pulmonologist who has been caring for Terry since he was diagnosed at 54.*

Wright, a fitness trainer, prize-winning master gardener, and naturalist, has struggled with these serious health issues his entire life. But he wasn’t diagnosed with cystic fibrosis—a rare, life-threatening genetic disease—until he was 54. He’d come close to being correctly diagnosed in 2000 when he was 38: A doctor told him, “If you were not Black, I would say you had cystic fibrosis.”

Wright, a fitness trainer, prize-winning master gardener, and naturalist, has struggled with these serious health issues his entire life. But he wasn't diagnosed with cystic fibrosis—a rare, life-threatening genetic disease—until he was 54. He'd come close to being correctly diagnosed in 2000 when he was 38: A doctor told him, “If you were not Black, I would say you had cystic fibrosis.”

## Why is CF considered a ‘white’ disease?

Dorothy Andersen, a pathologist based at Babies Hospital in New York, first characterized cystic fibrosis, and published the seminal account in 1938. From the beginning, she recognized the disease could affect anyone—not just white people. “One of the patients of the Babies Hospital was a Negro, and the parents of the others came from Puerto Rico, Italy, Germany, Ireland,” she wrote.

But over the course of the next eight decades, the inherited condition became perceived as a white disease. Taylor-Cousar, who is the adult patient care representative on the Cystic Fibrosis Foundation's Board of Trustees, suspects that was because the people who founded the foundation in 1955 were a small group of affluent white parents, the doctors were predominantly white, hospitals were still segregated in most places, and “so when the textbooks got written, they got written by the people with the money in the majority,” she says. “There wasn't enough of a voice of people of color to counteract that.”

Because these texts were used in medical schools, it led to the perception that CF was a white disease, “and of course, that perpetuates itself,” leading to health inequities for people of color, says Taylor-Cousar.

Today, the idea that CF is a white disease is a “misperception by those who have not been deeply involved in CF care,” says Mike Boyle, a pulmonologist who led the Johns Hopkins University Adult CF Program for 20 years and is the current CEO of the Cystic Fibrosis Foundation in Bethesda, Maryland. Physicians at Boyle's CF center cared for many Black and Middle Eastern patients. But, he admits, that was unusual. Most health workers around the country have had limited exposure to CF patients, and those they meet are usually of Caucasian descent. This has led to missed and delayed diagnosis of CF, says Boyle,

and contributed significantly to health outcome disparities for people of color.

## Why are more white people affected by CF in the United States?

To develop cystic fibrosis, a child must inherit a genetic mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene from both parents. Since the gene was discovered in 1989, more than 2,500 mutations have been identified, many of which can alter the structure of the CFTR protein and cause the disease.

Anyone, of any ethnicity, can get this disease. But which mutations a person carries usually depends on ancestry. One in 25 white people in the U.S. whose ancestors came from western Europe carry a mutation in their CFTR gene called F508del—which is believed to have arisen about 5,000 years ago. It is the most common CF-causing mutation in the country.

Currently there are believed to be about 40,000 people with CF in the U.S.—of these 91.4 percent are white, 3.5 percent African American, and 5.1 percent are of other races. But these stats are now being regularly revised as new mutations are identified in people of color.

In other countries where people migrated from western Europe, the F508del mutation is also present, but less common. And mutations that have arisen spontaneously in Egypt, India, or China, for example, are completely different and are not included in routine genetic screening. Children with those genetic mutations are typically diagnosed late and can suffer permanent organ damage with dire consequences.

When Andersen published her description of cystic fibrosis in the early 20th century, the disease could kill a baby before its first birthday—with malnutrition and/or lung infections often the main causes of death. But after she created a diagnostic test, the administration of digestive enzymes extended life expectancy to about 12 years old. In the 1990s, inhaled antibiotics and drugs that help clear deadly mucus from lungs pushed life expectancy into the early 30s.

But in the past 10 years, breakthroughs in drug development have created revolutionary treatments.

For those carrying certain mutations, the treatment is so effective that it is essentially a cure. And patients who receive these treatments in infancy are expected to live full lives, perhaps without any symptoms. Newborn screening and testing for all mutations, even the rare ones, is what allows these early life-changing interventions.



*Michele Wright greets her adopted stray cat Max, or Max-y poo-poo as she affectionately calls him. Terry Wright, Michele's husband, jokingly complains that Michele has spoiled Max who used to be his gardening partner. He says that Max now just visits for food, to steal Terry's chair, and to sleep with Michele.*



*Terry and Michele Wright share a bowl of green curry soup at The Root Cafe after a morning of medical appointments.*

## Terry's story

In 1999, Terry Wright met Michele Wise, who founded the National Society of Black Engineers at the University of Tennessee Space Institute but had pivoted to a career in pharmaceutical and biotechnology sales following a tenure as an electrical and industrial engineer. At the time, Terry's inability to digest food became life threatening. Surgeons performed an operation on his damaged pancreas, rerouting digestive juices so they could reach his gut and enable him to absorb nutrients. But his lung infections got worse. During each hospital stay, doctors treated him with heavy

doses of antibiotics and oxygen.

When they married in November 2000, Michele knew she was stepping into the role of wife, caretaker, and advocate. She sensed from Terry's medical history, and from the frequent visits they made to the emergency room every week, that the doctors were missing critical clues. "It was nothing but pain, suffering, and devastation" for the next 16 years, Michele says.

In 2016, antibiotics failed to vanquish an infection in Terry's lungs—and he spent Christmas and New Year's in the hospital. Frustrated and desperate for another perspective, Michele took Terry to the University of Arkansas for Medical Sciences where she sought out an infectious disease specialist. After examining Terry, Keyur Vyas said that his symptoms seemed consistent with those of cystic fibrosis. He ordered the gold-standard diagnostic for the disease: a test that measures the salt concentration in sweat, which is particularly high in people with CF because the CFTR protein in the sweat glands malfunctions and releases too much salt.

Terry tested positive for CF. Twice.

## CF newborn screening and health disparities

Since 2010, all 50 states have implemented a two-part newborn screening test for CF. The first part tests for high levels of a chemical called immunoreactive trypsinogen—which is a chemical made by the pancreas. If levels are too high, the baby's DNA is screened for mutations that could cause cystic fibrosis. When a mutation is identified, early interventions that improve nutrition and lung health can save lives.

But as Meghan McGarry's study showed, the types of genetic mutations used to diagnose CF vary from state to state and have dramatically different impacts on detection of CF in various ethnic groups.

In Mississippi, the tests only screen newborn DNA for the most common CF-causing mutation in the Caucasian population: F508del. As a result, the state detected only 53.7 percent of African American babies that had the disease; 64 percent of Native Americans and Alaskans; 42 percent of Asians; and 66 percent of Hispanic patients. It identified 87.5 percent of white babies with CF.

Even states that used more comprehensive genetic tests, which screened for 139 mutations, were not infallible. They detected only 83.4 percent of African Americans babies with CF; 91 percent of Native Americans and Alaskans; 90 percent of Hispanics; and 72.4 percent of Asians. But the tests found 96.7 percent of CF cases in white people.

“But they didn’t look at all the mutations,” says Taylor-Cousar, “because we weren’t acknowledging that disease existed in other people.”

## Diagnosed through IVF

That was the case when a pulmonologist in Portland wrote in Sowmya Bobba’s medical chart that he suspected she had cystic fibrosis but wasn’t going to test her for it “because she was of an Asian race.” Bobba, who moved from Vijayvada, India, in 2013, had always suffered from coughs and colds but had never been treated with anything other than antibiotics, inhalers, and some steroids.

In 2018, after Bobba and her husband had been trying to conceive for a couple of years, she had a genetic test done as a standard part of an in vitro fertilization procedure. The tests revealed her ovaries were healthy and her husband’s sperm count was good. But the doctor who authorized the tests called her and asked, “Did you know you have cystic fibrosis?”

“I had a lot of mixed reactions,” Bobba says. “I was very happy that I was diagnosed and knew that, OK, something was wrong with me.” But it also made her feel vulnerable and scared, paranoid of getting sick and fearful of dying young.

In 2020, Bobba set up an appointment with Aaron Trimble, who directs the adult cystic fibrosis center at Oregon Health & Science University. There, a team of experts schooled her in nutrition, the hours-long nebulizer treatments, physical therapy she would need to do daily at home to keep her lungs healthy, and all the other aspects of living with the disease.

“The adults who lived like Sowmya for 30 years with symptoms...are the ones who tend to get overlooked,” Trimble says. “They were just sick enough to go to a doctor, get some antibiotics, get an inhaler, get something, get sort of better, and just get passed along.”

The drug Trikafta had been approved in 2019 for patients who carried the F508del mutation—the one that is most common in the U.S., not the one Bobba has. But the drug maker Vertex Pharmaceuticals kept testing the drug on cells with less common mutations, one by one, to see whether it would work for those.

In 2021, Trimble delivered good news. The U.S. Food and Drug Administration said the drug could also treat Bobba’s rare mutation. He encouraged her to delay IVF treatments because he knew that women with CF-related infertility had conceived naturally after taking the drug.

Bobba began taking Trikafta—just a single pill every day—beginning in November 2021. By early February 2022, she was pregnant. In October 2022, she gave birth to a healthy girl and is feeling great. With Trikafta she is freed from the hours spent doing breathing treatments.

These days when Trimble is working with medical students or with residents in the intensive care unit, he’ll ask them to share what they know about CF. Most know that cystic fibrosis causes chronic lung disease and limits lifespan. They know that the F508del mutation is the most common. “Most will say it is more common in people who are white or of European descent,” says Trimble.

When he asks how common that mutation is in white people, only a few are aware that one in every 25 Caucasians carry it. But when Trimble asks about non-whites, “Nobody has any idea.”



*Terry Wright and his wife and advocate Michele Wright on the front porch of their home in North Little Rock, Arkansas. Their large, hillside yard has a view of downtown Little Rock and is filled with herbs, fruit trees, and other medicinal plants that Terry, a certified master gardener, harvests. Terry was finally diagnosed with cystic fibrosis at age 54 after having suffered his entire life from the disease. He has immersed himself in learning about medicinal plants as a way of combatting his illness over the years.*

## CF in other countries

This disease affects people from every ethnic background, says Samya Nasr, a pediatrician and director of the Cystic Fibrosis Center at the University of Michigan. The incidence might be lower in other countries and among people of non-European ancestry, but statistics on its frequency are spotty or nonexistent because the mutations have not been identified and genetic testing isn't common. "In the U.S., we see it in African Americans, we see it in Hispanics, we see it in Chinese Americans, Japanese Americans ... Asian Indians. So it's everywhere." And that includes Egypt.

When Nasr attended Ain Shams College of Medicine in Egypt, she was taught that CF didn't occur in the country. "But that was false. Because really, if you don't test for something, you're not going to find it."

In the early 2000s, Nasr began collaborating with faculty at Cairo University's pulmonary and gastrointestinal clinic. They began testing the saltiness of patients' sweat with equipment donated by a company in the U.S., and they found that 12 of the 60 patients they tested carried the disease.

When the results were published, Cairo University invested in their own testing equipment and began diagnosing patients. So far, between 800 and 1,000 people have been diagnosed with cystic fibrosis,

Nasr says. Since Nasr was able to arrange donations of sweat testing equipment to several universities in Egypt in 2021, the number of new patients has escalated.

But without access to digestive enzymes to help children with nutrition and treatments to clear their lungs, survival for CF patients is about eight years in Egypt; in the U.S., it's now 53.

Nasr has teamed up with the Michigan-based Bonnell Foundation to get medicines and chest-clearing equipment donated to Egyptian patients, and to spread the word that people of color can get CF.

## Going forward

After he was diagnosed in 2017, Terry Wright, with his wife Michele, founded the National Organization of African Americans with Cystic Fibrosis (NOAACF) to raise awareness of the disease among African Americans.

In 2021, Trikafta was shown to be effective for Terry's mutation, and he began taking it immediately. Even though his health was improving, he was keen to make sure that others didn't repeat his medical odyssey. Working with Taylor-Cousar, the Wrights created a free screening tool to help



Black, Indigenous, and other people of color, or their medical providers, determine whether they have symptoms that match CF.

Boyle, the Cystic Fibrosis Foundation's CEO, says the group is working with state health officials to explain the importance of expanding newborn screening to include a broader range of mutations that cause CF. The foundation is also addressing health inequities by independently testing cells carrying rare CF-causing mutations to find ones that may respond to Trikafta so more people of color may benefit.

Lathronia Jefferson, whose 12-year-old son Khaleb has CF, has had her share of run-ins at the ER when doctors have asked her whether she is sure that her son has CF. But her frustrating experiences have motivated her to work with the Cystic Fibrosis Foundation to educate medical providers.

“If I’m having this much trouble, and my child is only 50 percent African American, what about someone who is 100 percent and has this disease? How are they dealing?” Now when someone says to her that CF is rare in African Americans or people of color she says: “It’s just underdiagnosed in people of color. The light has just not been shone on the fact this is not just an Anglo-Saxon disease. People of color have this.”

Editor’s Note: This article originally misstated the state that uses only a single variant—F508del—for CF newborn screening. It is Mississippi.

Editor’s Note: Bijal P. Trivedi is a senior science editor at National Geographic and author of *Breath from Salt: A Deadly Genetic Disease, a New Era in Science, and the Patients and Families Who Changed Medicine Forever*, which chronicles the fight to develop personal, mutation-specific treatments for cystic fibrosis. ■

## **About Fondation Ipsen**

There are 7,000 rare diseases affecting 300 million people worldwide. 75% of patients are children. 1 in 2 patients do not have an accurate diagnosis. A quarter of patients wait 4 years to get a diagnosis. Our program brings together world experts to improve this dire situation.

## **About The National Press Foundation**

The National Press Foundation is a 501(c)(3) whose mission is to “make good journalists better.” We educate journalists on the complex issues of the day and train them to use the latest reporting tools and techniques. The foundation recognizes and encourages excellence in journalism through its awards and fellowships.

Since 1976, the foundation has provided in-person professional development opportunities to thousands of editors, producers and reporters, helping them better understand and explain the effects of public policy on readers and viewers. All NPF programming is free and on the record.

National Press Foundation is funded by journalism organizations, foundations, corporations and individual benefactors. We are grateful to our funders who are listed here.

Prior to the novel coronavirus, NPF programs were held in the nation’s capital, around the United States and overseas. During the global pandemic, we are offering all-virtual training, and continuing to bring journalists together with leading authorities to discuss significant issues ranging from health and economics to politics and policy. NPF produces digital curriculum from these fellowships and briefings that are posted to our website, allowing journalists across the world to access the best expertise and enhance their reporting.

Journalists are currently under fire, overworked, underpaid, and too often threatened with violence. The landscape for media continues to deteriorate with widespread layoffs, newsroom closures, mistrust, and disinformation. Against this grim background, the National Press Foundation’s mission—making good journalists better—has become more necessary than ever.

## **About the collaboration**

The National Press Foundation and Fondation Ipsen plan to select and train a delegation of the world’s leading journalists to focus on Rare diseases. The goal of this meeting is to connect leading Science journalists to patients, scientists, caregivers and patient groups.

The National Press Foundation and Fondation Ipsen will select a group of international journalists to participate in a four-day training program to offer them the opportunity to interact with scientific experts and learn better ways to communicate information on rare diseases to the general public (detection, diagnosis, molecular biology, symptoms, etc.). The convening will reveal newly published scientific information and facilitate interaction between journalists, scientists and patients.



## **Book# 06.4.2**

Have your say!

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**Book# 06.4.2**  
Have your say!

One of the great challenges faced by people living with rare diseases is that the public knows so little of their struggles, challenges, and the need for unrelenting resilience in a world that doesn't understand. Coupled to the 300 million people living with rare diseases are hundreds of millions of caregivers who sacrifice time, work and money in the name of love. Working with the National Press Foundation, top world journalists highlight in these writings the plights of patients living with rare diseases and those who care for them. The stories are informative, dramatic, and heart-rending. I thank most the patients living with rare diseases and the people who love them for sharing their stories with these gifted journalists.

**James A. Levine**

*MD, PhD, Professor, Fondation Ipsen, Paris*

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