RARE DISEASES Magazine

EDITION 2025

Innovative DNA and RNA therapies to tackle rare diseases

How to refer a patient?

The Belgian Rare Diseases Plan: where do we stand today?

UZ LEUVEN

UZ Leuven: a rare diseases function hospital with high ambitions and many dreams still ahead...

Dear reader,

With this second edition of the UZ Leuven Rare Diseases Magazine, we would like to inform you about new initiatives, policy challenges, and UZ Leuven's actions in the field of rare diseases. The magazine also aims to serve as a reference work and information source for referring physicians.

At the national level, several initiatives have recently been undertaken to enable faster diagnosis and improved care for rare diseases. Work has begun on drafting a new Belgian Rare Diseases Plan, which will reorient healthcare organisation. In addition, the generic convention for rare diseases, which had been in preparation for several years, was converted—even before its implementation—into a funding model per function hospital. This will be further developed in the coming period.

UZ Leuven, along with seven other hospitals in Belgium, has been recognised by the federal authorities as a rare diseases function hospital. The corresponding mandate is laid down in Royal Decree 2014/024248. Although UZ Leuven is, in principle, convinced that care for rare diseases is best clustered in hospitals or networks with in-depth expertise, it is also intended that primary and secondary care continue to play an important role.

In this edition, you will also find, among other things, figures on UZ Leuven's activities in the field of rare diseases and information on how to refer patients with (suspected) rare diseases.

Enjoy reading!

Marion Delcroix and Gert Van Assche, Chair and Vice-Chair of the UZ Leuven Rare Diseases Council

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You can subscribe or unsubscribe to the Rare Diseases Magazine mailing list via forms.office.com/e/uPDcUbvFhp.

Previous edition

In the previous and first edition of the Rare Diseases Magazine, you could discover, among other things:

- ✓ what a rare disease is
- ✓ what the European, Belgian, and Flemish stakeholder landscape looks like
- ✓ which national and international networks the UZ Leuven rare diseases specialists participate in
- ✓ the role played by the centre for human genetics in the care and genetic diagnosis of rare diseases

Did you miss the previous edition, or would you like to read it again? A digital version is always available at **uzleuven.be/en/rare-diseases**

RARE DISEASES AT UZ LEUVEN

300 DOCTORS IN VARIOUS DISCIPLINES

> 50 MULTIDISCIPLINARY TEAMS

33,000 PATIENTS WITH RARE DISEASES PER YEAR

IN 2024

12,637 NEW DIAGNOSES

9,792 ADULTS

2,845 CHILDREN

46 REFERENCE AND EXPERTISE CENTRES PUBLISHED ON ORPHANET

10 NIHDI CONVENTIONS FOR MULTIDISCIPLINARY CARE FOR RARE DISEASES

How can you refer a patient with (suspected) rare disease to UZ Leuven?

Without diagnosis of rare disease

1 If symptoms and clinical signs are not related to a single organ: refer to the general consultation of **general internal medicine (adults), paediatrics, or genetics**.

2 If there is a clear clinical suggestion of an organ-specific disease: refer to the relevant **organ specialist**.

Registration via form

✓ In case of suspected rare disease, without knowing where to send the patient: use the **registration form for referring doctors**. Based on this, we will provide you with more information on the appropriate consultation (at UZ Leuven or, if necessary, elsewhere in Belgium or Europe).

Registration form for referring doctors via www.uzleuven.be/en/rare-diseases or directly at qr.uzleuven.be/bgGAs9

✓ The patient can also self-register via the **registration form for patients** (mandatory upload of a referral letter from a doctor or a relevant medical report).

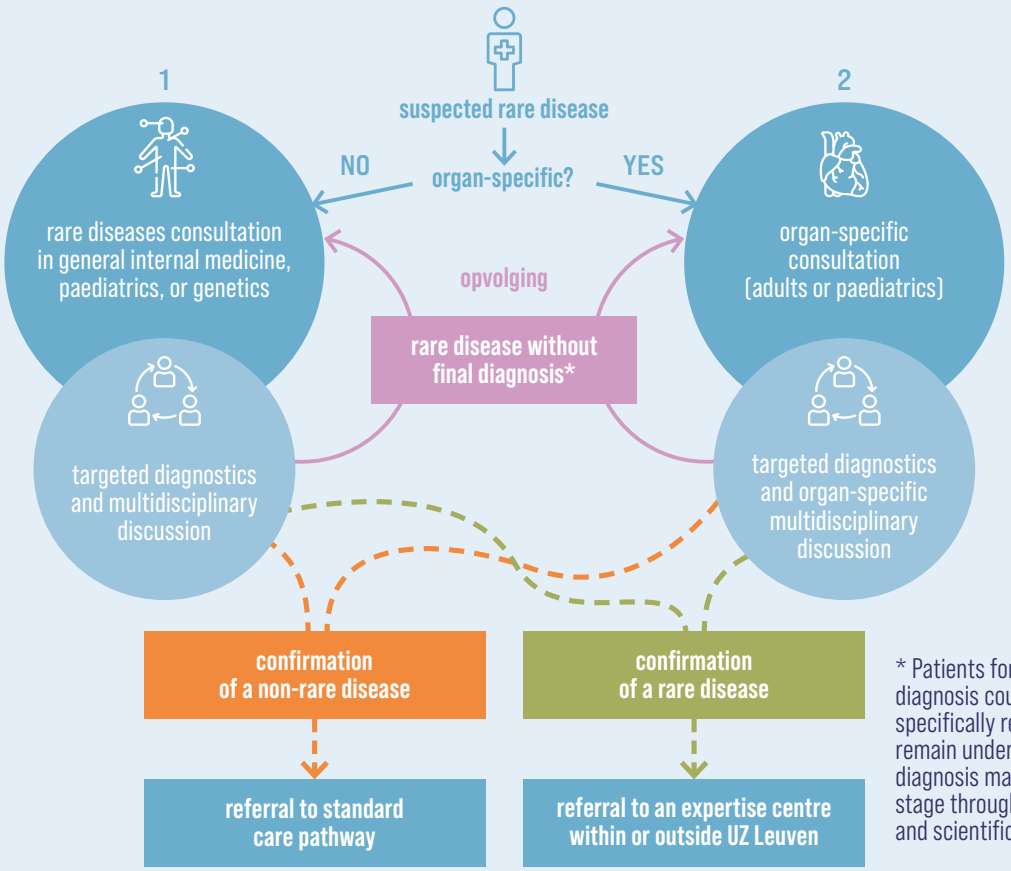
Patient registration form via www.uzleuven.be/en/rare-diseases or directly at qr.uzleuven.be/bgGBOj

With diagnosis of rare disease

✓ With an established diagnosis: refer directly to the **team that is specialised** in the condition.

An overview of the teams can be found at www.uzleuven.be/nl/zeldzame-ziekten/met-diagnose

✓ Some diseases are so rare that **no specialised consultation** exists. However, we may still have the expertise in-house with an individual specialist. Please contact us for this via **rarediseases@uzleuven.be**.



* Patients for whom no final diagnosis could be made are specifically registered and remain under follow-up, so that a diagnosis may be made at a later stage through new technological and scientific developments.

Political debate

On 7 November 2024, UZ Leuven, the patient organisation RaDiOrg and the pharmaceutical consortium RADDIAL organised a policy forum in the Chamber of Representatives entitled *"Equal opportunities in healthcare, including for rare diseases. Patients, experts and policymakers in dialogue".* Nearly one hundred participants attended.

The aim was to engage in dialogue with experts, patient representatives and politicians on measures to address the challenges of rare diseases and improve care for patients with rare diseases.

The organisers stressed that the announced new *Belgian Rare Diseases Plan* must not remain a dead letter but be effectively implemented, taking into account the policy competences of the various authorities and their coherence. This new plan is crucial to achieving a coordinated policy and optimal health outcomes for the more than 500,000 Belgians living with a rare disease and their loved ones.

Three themes were addressed, each introduced by an expert and followed by a debate:

1) European Reference Networks (ERNs) and their integration into national networks
2) Transparent identification of expertise in rare diseases and facilitating access to this expertise
3) Multidisciplinary and integrated care with case management for every person suffering from a rare and complex disease

From the closing Q&A session, it was clear that all participants agreed on the need for a new, workable, updated *Belgian Rare Diseases Plan*, with clarity on the timeline and budget, better coordination between the various levels of government and more efficient data registration. There was also a call for breaking taboos, taking decisive action and ensuring that policymakers remain constantly aware of the importance of making progress.

"Consensus on the need for a new, workable Belgian Rare Diseases Plan"

It was also clear that patient associations play a crucial role in informing patients about important new developments, and that more government support is needed to enable them to fully fulfil their essential role as stakeholders in the healthcare landscape.

Read the full report here: www.uzleuven.be/en/brochure/900564

The Belgian Rare Diseases Plan: where do we stand today?

Since 2013, Belgium has had a *Rare Diseases Plan* aimed at providing patients with responsible and proper access to an accurate diagnosis and to specialised, multidisciplinary care. Unfortunately, certain aspects of this plan have never been implemented, such as the recognition of expertise centres for rare diseases. As a result, patients are still left adrift, and the development and proper funding of expertise in the function hospitals is hindered. More than ten years on, the plan is therefore due for renewal.

Timeline

2009 Establishment of the **Rare Diseases and Orphan Drugs Fund**, managed by the King Baudouin Foundation, tasked with preparing a Rare Diseases Plan

2011 Publication of **recommendations and proposed measures for a Belgian Rare Diseases Plan**

2013 Publication of the **Belgian Rare Diseases Plan** by Minister Laurette Onkelinx

2014 Publication of **three Royal Decrees** describing the structure and missions of the rare diseases function hospitals, the networks, and the expertise centres

Recognition of **seven rare diseases function hospitals**

The **sixth state reform** redistributes political competences for healthcare, leading to great uncertainty. Who holds the mandate to designate the expertise centres?

2017 Establishment of the **Vlaams Netwerk voor Zeldzame Ziekten** (Flemish Rare Diseases Network), with subnetworks per group of rare diseases, but still no procedure for recognising expertise (centres)

2024 In the run-up to the elections, patient organisation RaDiOrg, in collaboration with the Rare Diseases working group of the College of Genetics, publishes a **memorandum** with policy proposals

2025: recent developments

In response to the memorandum, the Minister of Public Health instructed the FPS Public Health to draw up a new plan. After a preparatory phase, a co-creation phase with stakeholders began in May 2025. The plan is scheduled for completion in December 2025. The function hospitals will be tasked with mapping expertise, providing individual care plans and care coordination, and recording data in the central rare diseases register (CRRD), managed by Sciensano.

The aim is to improve the quality of care, treatment, and life for patients with a rare disease and their families. During the co-creation of the new plan, representatives from primary and secondary care will also have the opportunity to contribute to the structure and the main strategic objectives.

Reorientation of the NIHDI conventions

In 2024, it was planned that a generic convention for rare diseases would start for four pilot diseases: epidermolysis bullosa, idiopathic pulmonary fibrosis, multiple system atrophy, and primary immunodeficiency.

However, discussions between Minister Vandenbroucke, the Minister's Rare Diseases policy unit, the NIHDI, and the FPS Public Health, held between December 2024 and March 2025, resulted in a **strategic reorientation of the planned conventions**. It was found that the generic agreement with per-patient funding (based on Article 22, 6° and Article 23, §3 of the HCIA[1]) is difficult to implement in practice, due to the heavy and time-consuming procedure and insufficient resources for the diseases with the lowest prevalence. This method would not deliver equitable progress that benefits all people with rare diseases. Consequently, this approach was abandoned.

The reorientation towards a different framework for the agreements (based on Article 56 of the HCIA) will allow **funding per centre**. Under this method, funding would be provided per group of diseases for:

- Mapping expertise (together with patients)
- Care coordination and an individual care plan for patients with a rare disease
- Data registration

In the short term, an agreement will be concluded, under this method, between the NIHDI and UZ Leuven for the pilot disease epidermolysis bullosa. Subsequently, a funding model will follow for the eight rare diseases function hospitals, with resources allocated based on a mapping of the available expertise within these hospitals. This model is still being developed by the NIHDI.

1 The HCIA is the Law on compulsory health care and benefits insurance. You can find the articles mentioned on the NIHDI website, on the page for the coordinated law of 14 July 1994 (https://bit.ly/4cKoreV), under Title III on insurance for health care.

Rare but numerous

For many years now, the last day of February has been dedicated worldwide to rare diseases. Through various actions and initiatives, Rare Disease Day draws attention to this theme. By sharing the campaign colours (blue, green and pink), you show your support for people living with a rare condition.

As a reference hospital, UZ Leuven also supports this day each year through its internal and external communication channels. This year, staff members were invited to submit photos showing them sharing the campaign colours. Under the central theme '**Rare but numerous**', we showcased the diversity of rare diseases through photos and stories from nine patients with a rare condition.

Read and share in the experiences of Lou, Niya, Luca, Marion, Johan, Lio, Bruno and Wendy on our website.

www.uzleuven.be/en/news/rare-disease-day-2025

Innovative DNA and RNA therapies to tackle rare diseases

One of the major challenges in the field of rare diseases remains providing every patient with an adequate and affordable treatment. Thanks to groundbreaking research worldwide, progress is moving at lightning speed and innovative therapies are delivering impressive results. Together with Professors Kristl Claeys and Liesbeth De Waele, neurologists at UZ Leuven for adults and children respectively, we highlight two pioneering treatments that are already making a difference. Rik Gijsbers, professor at the Faculty of Medicine of KU Leuven and researcher into rare conditions and gene technology, takes a closer look at the DNA and RNA mechanisms underlying them.

Missing gene

Spinal muscular atrophy, or SMA, is one of the rare neuromuscular disorders for which treatment has made a huge leap forward in the past decade. You may recall baby Pia: in 2019, Flanders raised €1.9 million by text message so that she could receive the drug Zolgensma®. This innovative gene therapy for SMA is administered once intravenously and tackles SMA at its root: the congenital genetic defect.

Professor Liesbeth De Waele explains: "In this disease, the SMN1 gene is missing. This gene enables the production of the protein that protects the motor neurons in our spinal cord from dying off. Without this gene, and therefore without that protection, the motor neurons gradually die, and the nerve signal to the muscles weakens, causing them to become weaker and waste away. Children with SMA therefore develop increasingly

"The majority of babies treated before the symptoms of SMA develop go on to have an almost normal motor development. That is revolutionary."

Prof. Dr. Liesbeth De Waele

Viral vectors: an inactive virus as an efficient vehicle for genetic information

Professor Rik Gijsbers: "Gene therapy such as Zolgensma® is designed to address genetic defects at their source. In the case of SMA, a correct version of the coding information for a vital protein, SMN1, is administered to the patient. This genetic information is introduced into the cells using **recombinant viral vectors derived from the adeno-associated virus**, or rAAV. These viral vectors are created in the lab and combine the best of both worlds. On the one hand, they use the same access routes as the viruses they are derived from to efficiently recognise target cells in the body – in the case of SMA, the motor neurons – and then enter them. On the other hand, the genetic information for making new viruses has been removed and replaced with the correct version of the gene that causes the disease."

"Through a single infusion, the viral vector delivers the genetic code for the protein to the nerve cells so they can start producing the protein themselves again. This way, the nerve cells are protected once more and further muscle deterioration can be halted. Although Zolgensma® does not completely cure the disease, it can halt disease progression and improve patients' quality of life. The earlier it is administered, the greater the effect."

severe motor limitations. Without treatment, patients with the most severe form, SMA type 1, die before the age of two from respiratory failure. What gene therapy does is introduce a correct version of the SMN1 gene into the cells, enabling the patient to produce the protective protein and halting the nerve degeneration."

Revolutionary

A crucial factor in the effect of the treatment is the timing of the gene therapy. Once a child shows symptoms, a large proportion of the motor neurons has already died. That situation cannot be reversed. By halting the further death of motor neurons, the disease can be stabilised. That alone can make the difference between life and death. But the truly impressive results come when gene therapy can be given before symptoms appear. Here, neonatal screening by Guthrie or PKU test, a.k.a. the heel prick, plays a key role.

"Since the end of 2022, every baby has also been tested for SMA during the Guthrie test carried out in the days after birth," says Professor De Waele. "Implementation took a long time and was not straightforward, because this is a genetic test – a new type of neonatal screening in addition to existing metabolic protein tests. But the impact is enormous. The majority of babies treated presymptomatically go on to have an almost normal motor development. You can call that revolutionary. And everyone benefits: not only these children and their families, but certainly also our healthcare system."

Hereditary diseases in later life

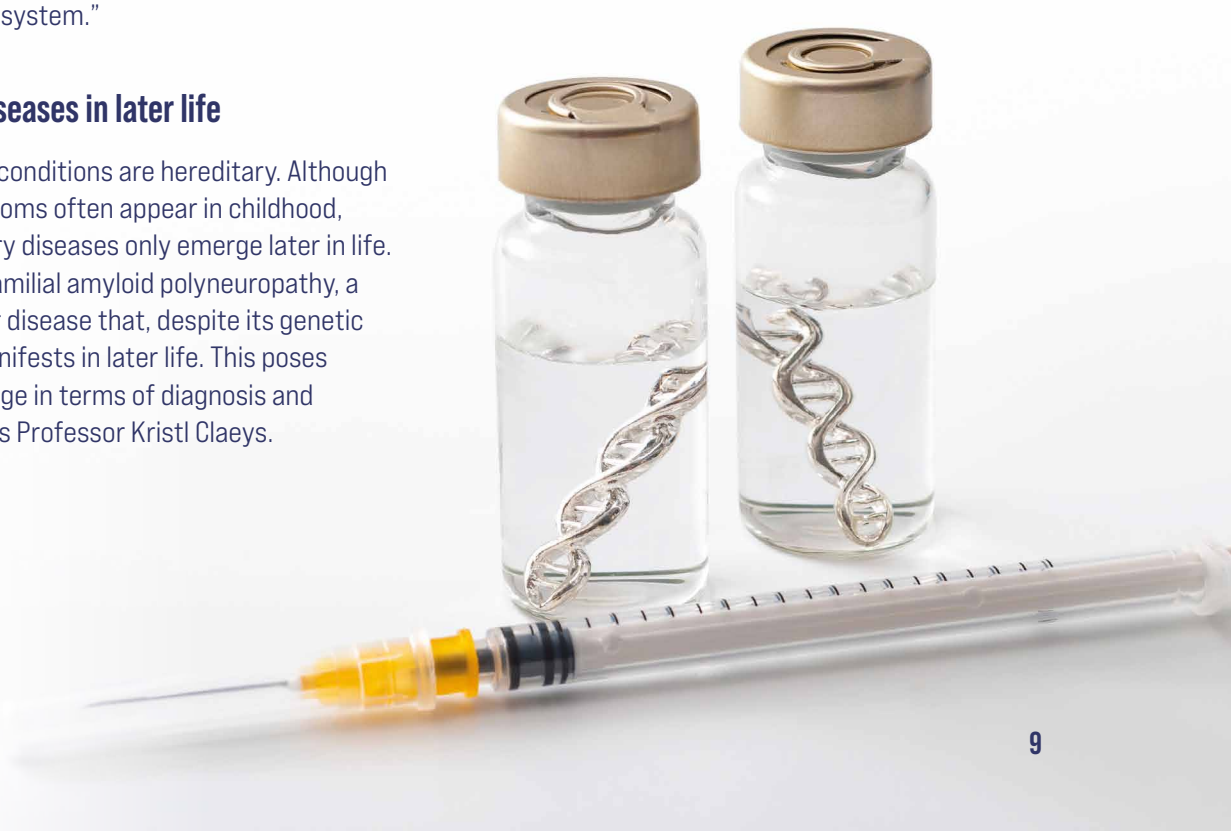
72% of all rare conditions are hereditary. Although the first symptoms often appear in childhood, some hereditary diseases only emerge later in life. For example, familial amyloid polyneuropathy, a neuromuscular disease that, despite its genetic cause, only manifests in later life. This poses a major challenge in terms of diagnosis and treatment, says Professor Kristl Claeys.

"When a patient aged fifty or older presents with symptoms, hereditary diseases are often no longer considered. Moreover, familial amyloid polyneuropathy is a very progressive disease once symptoms appear. Patients deteriorate quickly, and the more damage there is, the harder it becomes to intervene. This is the reality for many rare diseases: a race against time, from a difficult diagnosis to the fastest possible treatment."

"The reality for many rare diseases is a race against time, from a difficult diagnosis to the fastest possible treatment."

Prof. Dr. Kristl Claeys

In familial amyloid polyneuropathy, protein builds up in the nerves, causing sensory disturbances and pain that begin in the feet and legs and gradually move up to the hands. The heart, kidneys and eyes can also be affected. The first treatments did not succeed in stopping disease progression. More recent and innovative therapies do, by acting at the RNA level. This counterpart to our DNA converts genetic information into proteins.



Impact via RNA

"These therapies destroy the piece of RNA responsible for producing the harmful, accumulating protein," explains Professor Claeys. "This is done using small interfering RNA or antisense oligonucleotides, which break down this RNA code. This prevents the production of the protein and thus addresses the cause of the disease. This makes a real difference for the patient. Progression stops, and sometimes we even see a slight improvement."

"By intervening at RNA level, you tackle the root cause of the disease. That's how you make a difference for the patient."

Prof. Dr. Kristl Claeys

Here too, timing of administration is crucial. "We can only give this therapy in stages one and two of the disease course, when the patient can still walk with or without aids. Patients already dependent on a wheelchair are generally no longer included in studies of new medicines and will also not be eligible once the products come to market."

When they come to market, these medicines are also very expensive. The smaller the market, the higher the price. This is perhaps the most painful thorn in the side for most people with a rare disease and their families. "The price of such orphan drugs can reach absurd proportions. As long as the approval and reimbursement process is not completed, the patient has their back against the wall. By actively participating as a university hospital in groundbreaking international studies, we contribute step by step to the development of and access to innovative therapies."

RNA interference: well-aimed messages for our protein producers

Professor Rik Gijsbers: "The mechanism behind RNA therapies, such as patisiran or vutrisiran for familial amyloid polyneuropathy, is RNA interference, or RNAi. This is a natural process that takes place in our cells anyway. During this process, small pieces of RNA, called siRNA, recognise certain messages (mRNA) in cells that contain the instructions for producing proteins. The siRNA pieces bind to those messages and cut or block them, preventing the corresponding protein from being produced. We can also create these small siRNA molecules ourselves in the lab and make them target specific messenger molecules we want to hit, such as an mRNA coding for a faulty protein. We then administer these interfering RNA molecules to patients whose disease is caused by the faulty production of certain proteins."

Support the Rare Diseases Fund

The Rare Diseases Fund of UZ Leuven and KU Leuven promotes research into rare conditions and appropriate patient care.

Professor Gert Van Assche, Medical Director of UZ Leuven and manager of the fund: "For patients with rare diseases, research into disease mechanisms and new treatment options is extremely important, as there is often still no adequate therapy. KU Leuven and UZ Leuven wish to pool their unique expertise to offer precisely these patients and their children a better future. Your support for this research can truly make a difference."

More information about the fund and donations can be found on the Rare Diseases Fund website: qr.uzleuven.be/bgGB9R

KU Leuven launches the Institute for Rare Diseases

In December 2024, a new institute aimed at rare diseases, the *Leuven Institute for Rare Diseases* (Leuven.IRD), was launched at KU Leuven. Its mission is to bring together KU Leuven researchers from different disciplines around the theme of rare diseases. By pooling expertise in rare diseases within KU Leuven and UZ Leuven, the Institute provides an important platform for groundbreaking research and improvements in care in the field of rare diseases.

The institute as a bridge builder

"At KU Leuven and its university hospital, there are many experts conducting pioneering research on rare diseases," says director Professor Marion Delcroix. "Due to the lack of a common platform, this expertise was until now difficult to locate, causing common themes for interdisciplinary collaboration to remain under the radar. Yet such collaborations are highly valuable for finding innovative solutions to the many challenges posed by rare diseases."

"An Institute also ensures that we can better showcase KU Leuven's expertise externally, which will benefit collaborations with other institutions."

At present, around a hundred researchers have already joined. "But in the coming years, we hope to be able to identify even more expertise and attract additional researchers."

Four research themes

The Institute will work around four concrete programmes. The focus will not be solely on scientific breakthroughs, but also on bridging the gap between research and clinical care, and on social, ethical, and societal issues.

- ✓ Mapping the diverse expertise and making it accessible to KU Leuven researchers and external parties.
- ✓ Strengthening cooperation between healthcare providers and the genetics centre, with the aim of stimulating research into the genetic components of rare diseases and speeding up diagnosis.
- ✓ Identifying the unmet needs of patients with a rare disease and their families.
- ✓ Taking action to promote faster diagnosis and the development and use of advanced therapies for rare diseases.

This initiative will lead to better care and support for patients, both in Belgium and worldwide.

More info

Website: **kuleuven.be/ird**
LinkedIn: **linkedin.com/company/leuven-ird**
Contact: **rarediseases@kuleuven.be**

OVERVIEW OF USEFUL LINKS

UZ Leuven rare diseases

www.uzleuven.be/en/rare-diseases

- ✓ For what and through which channels can patients turn to UZ Leuven in case of suspected or diagnosed rare disease?
- ✓ More info about the teams specialised in diagnosing and treating rare diseases
- ✓ News and events

Registration form in case of (suspected) rare disease

Patient registration form via www.uzleuven.be/en/rare-diseases or directly at qr.uzleuven.be/bgGB0j

Referring doctor registration form via www.uzleuven.be/en/rare-diseases or directly at qr.uzleuven.be/bgGAs9

Support the Rare Diseases Fund with a donation: qr.uzleuven.be/bgGB9R

E-learning transition from paediatric to adult care: www.uzleuven.be/kindergeneeskunde/onderweg

Leuven Institute for Rare Diseases (kuleuven.be/ird)

- ✓ Brings together expertise in rare disease research within KU Leuven and UZ Leuven

Flanders

Vlaams Netwerk Zeldzame Ziekten (Flemish Rare Diseases Network – www.departementzorg.be/vlaams-netwerk-zeldzame-ziekten)

- ✓ Organisation in which Flemish university and general hospitals, GP circles, and numerous patient associations join forces.

Belgium

NIHDI (www.riziv.fgov.be)

- ✓ NIHDI agreements: via *Thema's* > *Verzorging: kosten en terugbetaling* > *Ziekten*, you can see for each disease which care the health insurance fund reimburses.

RaDiOrg (www.radiorg.be)

- ✓ The Belgian umbrella association for people with a rare disease. RaDiOrg joins together more than 80 associations for specific rare diseases as well as hundreds of individual members with a disease for which no association exists. RaDiOrg is the national alliance of EURORDIS, the European federation for rare diseases.

Europe

Orpha.net (www.orpha.net)

- ✓ International information portal on rare diseases and orphan medicines, aimed at patients and professionals. Orphanet manages the nomenclature and classification of rare diseases, and publishes for each disease the reference centres recognised in Europe for diagnosis and treatment. For Belgium, you will recognise the centres of expertise for each specific disease by this logo (without the additional RC symbol):

European Reference Networks (health.ec.europa.eu/rare-diseases-and-european-reference-networks_en)

- ✓ Overview (from the European Commission) of the European Reference Networks for rare diseases, within which members exchange knowledge and information.

European University Hospital Alliance (EUHA) (www.euhalliance.eu)

- ✓ Network of eleven major university hospitals in Europe. A specific working group is handling a number of improvement projects on rare diseases.

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