Erkenningsnummer P708816 #445

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AUGUST 31, 2016 \ NEWSWEEKLY - € 0,75 \ READ MORE AT WWW.FLANDERSTODAY.EU

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CURRENT AFFAIRS \ P2 | POLITICS \ P4 | BUSINESS \ P6 | INNOVATION \ P7 | EDUCATION \ P9 | ART & LIVING \ P10

BLUE UNION
Minister-president Geert Bourgeois has come out in favour of a possible 'North Sea Union' to ease Brexit trade negotiations
\ 4

TWINNING COMBINATION
Antwerp University graduates – and twins – Joyce and Raissa de Haas are winning over taste buds around the world with their tonic mixers
\ 10

WATER WORLD
Fold up a canoe and wheel it around like a suitcase to explore any city a whole new way, thanks to an ingenious design by two Ghent entrepreneurs
\ 11

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The diagnosis detectives

Medical mysteries are being solved in Ghent, thanks to the 'Dr House team'

Senne Starckx
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A team of four specialists at UZGent are working on curious cases that other doctors have been unable to solve, giving answers to patients who have slipped through the net of the diagnosing system.

The most unrealistic element in the popular TV series *House, M.D.* was not so much the incredible range of diseases Dr House and his team encountered, but the suggestion that there could be a single physician with a command of the entire field of medicine.

"To identify a mysterious disorder in a patient who has run from one doctor to the other, from one hospital to the other, you need a thoroughly multidisciplinary team," Flemish doctor David Cassiman told *De Standaard* in a recent interview.

Cassiman, a specialist in liver and metabolic diseases at UZ Leuven and East Limburg Hospital, spent his summer working in the US, where he was invited to join the undiagnosed disease programme at the National Institute of Health in Bethesda, near Washington, DC. In that programme, a 10-strong team tackles the most mysterious and seemingly unsolvable medical pictures. It's quite an honour for a Flemish doctor to be asked to join the team.

For Cassiman, the past two months have no doubt been an unforgettable experience. But he might equally have made an appointment with his colleagues at Ghent's University Hospital (UZGent).

Since June 2015, UZGent has been home to a similar undiagnosed rare diseases programme, known as Proza. In the programme, a team of four – they are actually referred to as "Dr House's team" in the corridors – work together to help local patients who have slipped through the net of the diagnosing system.

"The profession of a physician, whether they're a GP or a brain surgeon, is in many ways still a trade, a craft," says Wim Terryn, one of the four Proza doctors and an internist specialised in infectious and kidney diseases. "There's no golden protocol every doctor in the world follows to reach a diagnosis. Everyone has their own style, and in some

continued on page 5

The diagnosis detectives

In its first year, UZGent's undiagnosed disease programme has solved 200 cases

continued from page 1

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disciplines diagnosing a patient involves more routine than in others."

To err is human, and so it often happens that a doctor can't make a clear diagnosis when they listen to a patient's complaints or examine their body. That's why our modern health system has both primary (GPs) and secondary health care (specialists).

A GP can refer patients with ambiguous or vague medical pictures to a specialist for further investigation, or to a colleague for a second opinion. For most patients, it stops there: they get the right diagnosis and, hopefully, a treatment is prescribed.

But for a minority, it's the beginning of a journey in which they see more doctors and specialists than the average Fleming encounters in their whole life.

The Proza team consists of four specialists: two in internal medicine, one neurologist and one geneticist. "Many of the rare diseases that are missed in primary or secondary health care are genetic," says Bruce Poppe, the geneticist. So, he explains, it's important to sequence the exome, or the gene-coding part of the DNA, of the patients they deal with. They then try to find a match in the scientific literature with a known disorder.

Many of the genetic, sometimes hereditary, disorders are chronic or progressive – and often life-threatening. And though the diseases are rare, a surprising number of people suffer from one of them.

"Less than one in 2,000 people in Flanders are affected by an officially recognised 'rare disease'," says Poppe, "but because there are more than 8,000 variations of such diseases, the total number of patients in Flanders lies somewhere between 30,000 and 50,000."

One of those rare disorders is Fabry's disease, known for its misdiagnoses among clinicians. Terryn wrote his PhD thesis on it. "Fabry's disease is an ultra-rare disorder that produces symptoms and complaints that can easily be misunderstood," he says. "I recall a young man who was hospitalised with a high fever and severe pain in his arms and legs, just after his GP had sent him home telling he just had a severe sinus infection."

It was only after the patient had a stroke that another doctor remembered a similar case from a conference he'd attended a while before. The patient was quickly sent to Poppe, and, after an exome scan, they discovered the real cause: Fabry's disease.

Fortunately, there's a treatment for Fabry's disease, although it requires a hospital visit every two weeks for the rest of your life.

When Terryn says that a doctor remembered a similar case entirely by coincidence, he hits the nail on the head. One of the reasons Poppe and his three colleagues started the Proza programme a year ago was their desire to decrease the role of chance in whether or not a patient receives the right diagnosis in time.

"We want to abolish routine in the practice of diagnosing," says Terryn, "as it's clear that this routine hasn't solved the cases that reach us. I believe a multidisciplinary approach is an important key to our success, combined with the fact that we sit together and brainstorm with each other when we discuss a file or see a patient in person."

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The Proza team, from left: Wim Terryn, Dimitri Hemelsoet, Steven Callens and Bruce Poppe

> "Making the right diagnosis depends heavily on what questions you ask and what answers you give priority to

The Proza team meets twice a month, once to discuss new files, the second time to see the patients whose files were not clear enough to make a diagnosis. In the first meeting, they discuss which of the new files, submitted by physicians across Flanders, offer the most hope of a diagnosis.

If a file is admitted, the Proza doctors don't necessarily see the patient behind it. On the contrary, in most cases the medical mystery is solved based solely on the information in the file. If it isn't, the patient is invited for a consultation. "Since we've started, more than a year ago, we've diagnosed more than 200 patients," Poppe says. "Of those 200, we saw 50 in person for a consultation."

It's a heavy workload for a team of four who do this as a kind of volunteer work. And, according to Poppe's statistics, the number of requests isn't decreasing.

During a consultation, a patient meets all four Proza doctors together. "Making the right diagnosis depends heavily on what questions you ask and what answers you give priority to," explains Terryn. "We try to find as much as objective information as possible and avoid vague complaints, like fatigue, which is almost impossible to measure. It's all about trying to find clues that put us on the way."

When the team eventually come up with the diagnosis, it's not necessarily a rare genetic disorder no one has ever heard of before. Sometimes the final outcome even seems a little banal – but of course no less serious for the patient.

Terryn: "I recall a woman who was suffering from pain in her joints and chronic fatigue and had already been diagnosed eight years earlier with fibromyalgia. We discovered that, before the complaints started, she had undergone gastric bypass surgery. A rare but well-known consequence of such an operation – if it's not carried out well – is a syndrome that causes fibromyalgia-like symptoms. We were able to help the woman; after six weeks of treatment, she felt fit as a fiddle."

Like so many conditions, Fabry's disease was named after its discoverer, a German named Johannes Fabry. Is there a chance that, someday, a patient at UZ Gent will be diagnosed with Poppe's disease or Terryn's syndrome?

"Thousands of rare genetic disorders have already been discovered and described, so there's not much chance we'll find a new one," Terryn says. "But it's not zero. At UZGent, we have a unique set of sequencing machinery by which we can scan a patient's exome and immediately compare the results with the existing genomic data in the scientific literature."

Even if there's no match, he says, "we can continue our search and look for genetic anomalies in the patient's DNA that resemble known mutations. This bio-informatics approach could lead us to yet undiscovered genes and, yes, to undiscovered disorders."