39**BIS**
F I L E S

UNIR

Innovating together to reduce diagnostic delay | **in rare diseases**

A **SANOFI** GENZYME initiative in partnership with orange™

Contents

abbreviations

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BNDMR: *Banque Nationale de Données Maladies Rares,* French
national data bank for rare diseases

CCMR: *Centre de Compétence Maladies Rares,* Competence Center for
rare diseases

CNOP: *Conseil National de l'Ordre des Pharmaciens,* French national
chamber of pharmacists

CRMR: *Centre de Références Maladies Rares,* Reference center for
rare diseases

DGOS: *Direction Générale de l'Offre de Soins,* Directorate-General for
Care Provision

EPR: Electronic Patient Record

ERN: European Reference Network

FFRD: French Foundation for Rare Diseases

FSMR: *Filière de Santé Maladies Rares,* Rare disease healthcare network

ICT: Information and Communications Technologies

MRIS: *Maladies Rares Info Services*, an association providing information to
patients, families and healthcare professionals about rare diseases

PMSI: *Programme de Médicalisation des Systèmes d'Information,*
Programme for medicalising information systems

PNDS: *Protocoles Nationaux de Diagnostic et de Soins,* National
diagnosis and care protocols

PNMR: *Plan National Maladies Rares,* National plan for rare diseases

PRIOR: Regional platform for information and guidance
on rare diseases

SNDS: *Système National des Données de Santé,* National health data system

SMR: Shared Medical Record

Editorial

There is a clear benefit to accurately diagnosing a rare disease. Reducing diagnostic delay is a key challenge and a current fight that has stakeholders from the rare disease ecosystem as committed as ever. Diagnostic delay is a complex issue because diagnosis is not an isolated event, but rather the result of an iterative approach involving several separate systems that are difficult to control.

There are many reasons it can take so long to diagnose these diseases: non-expert professionals' lack of experience with rare diseases, difficulties in referring patients, insufficient funding for specialised testing, etc. A delayed diagnosis can also occur because symptoms may be non-specific or uncommon for the disease being considered, scientific knowledge may be limited or there may be no further tests available. Some delayed diagnoses are avoidable while others are not.

Today, the development of digital technologies in the healthcare sector, and more generally in society, inspires hope. This extremely creative sector, supported by public authorities, offers genuine opportunities for progress: for patients and their caregivers, who see in these new technologies tools and options for dealing with their conditions; for healthcare professionals looking to facilitate their daily duties (administrative, medical or research); or for France's public healthcare system as it seeks to optimise care.

Stakeholders are aware of the potential these technologies hold for rare diseases, and are developing projects across all scales, from local to regional, national and international levels. For example, Europe has focused its attention in the area of rare diseases on diagnostic services as well as on European projects to make it easier to identify patients with comparable phenotypes and genotypes (RD Connect). Despite such efforts, the road ahead is long and these initiatives must be reinforced and complemented to eliminate diagnostic delay.

Developing eHealth solutions that are specifically suited to rare diseases is an obvious priority for us: we want to pursue our efforts in digital health innovation and support the initiatives already put in place by the rare disease ecosystem. We believe that digital technologies can help patients and healthcare professionals in areas where missed opportunities persist. These new tools often upend the everyday reality of complex and dynamic human organisational structures. Taking into account the specific needs of patients when designing and implementing these tools is crucial. Challenges abound, but there is a willingness to innovate in the field of eHealth that is stronger than ever.

Mobilising all stakeholders – patients, patient associations, healthcare professionals, researchers, administrators, healthcare and digital specialists etc. – in designing these solutions is essential to ensuring they are fully appropriated. Creating the right conditions and forums for discussion is key to incorporating digital technologies into uses and organisations, as well as ensuring that all stakeholders' rights, limitations and freedoms are respected. This is the conviction that we hold as we opt for open innovation and launch the "UNIR" participatory initiative to work together to speed up the development of eHealth solutions in order to address the needs of patients with rare diseases.

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Foreword

Rare diseases are still a major public health problem. Although they affect fewer than one in 2,000 people, they include more than 7,000 pathologies identified by expert healthcare professionals who are also often researchers in teaching hospitals.
While each pathology is "rare" on its own, together rare diseases affect more than three million French people and more than 350 million people worldwide (Alliance Maladies Rares; PNMR3, 2018).

France has played a pioneering role in fighting rare diseases. Through two National Plans for Rare Diseases (PNMR), major work has been undertaken to improve access to care for patients who have or may have such diseases, namely through the creation of dedicated expertise centers at teaching hospitals. Despite this organisational structure, access to these centers – and therefore to a rare disease diagnosis – can be long and difficult for some patients.

In 2016, following France's second national plan (PNMR2), and thanks to the efforts of all stakeholders (families, patient associations, healthcare professionals and public authorities), the time to diagnosis was estimated to be two years on average in France (MRIS, 2011). However, this average hides large discrepancies, and nearly a quarter of patients waited more than five years to put a name to their disease

(Alliance Maladies Rares, 2016). Despite progress, diagnosis lag time is still too long in many situations. In addition to the heavy psychological toll that a lack of diagnosis can take on patients and their families, delays result in significant missed opportunities for patients. Even when the diagnosis is difficult, or when there are few targeted therapeutic solutions, appropriate and early care can often improve survival rates and quality of life for patients by providing suitable medical-social support. Efforts to improve access to a network of experts – one of the main ways to optimise the diagnosis journey – must be maintained and further expanded.

At the national scale, the specific aspects of rare diseases can be seen through the patients' varied journeys. This results in high analytical complexity and is an enormous challenge for public and private

action to develop a consistent response to a multifaceted phenomenon. Rarity should not be a source of exclusion, and the specific aspects of rare diseases should encourage support for the effort devoted to them.

Today, new digital technologies are at the center of our changing societies and are especially present in the healthcare sector. Sanofi, in partnership with Orange Healthcare, shares the belief that some technologies can help reduce diagnostic delay in rare diseases. Given the number of rare diseases and the many different problems encountered by patients and healthcare professionals, the aim of our participatory initiative, called UNIR,

is to connect stakeholders early on to tackle two priorities: first, refining and gaining perspective on a polymorphic problem, and second, identifying tangible eHealth solutions to reduce diagnostic delay in France. Sanofi will develop and test one such solution.

This white paper aims to share the analyses conducted by Sanofi France through its open innovation initiative as part of its eHealth laboratory, 39BIS, with the rare disease community and beyond. The jointly identified solutions that are proposed in this paper could be used for sharing, inspiration and to support existing initiatives.

Contributions and acknowledgement

We would like to extend our gratitude to all those who contributed to the initiative and supplemented our work.

The participation of nearly 40 stakeholders from patient associations, healthcare networks, researchers and healthcare practitioners, as well as digital start-ups and experts during individual interviews or workshops, provided complementary perspectives on the solutions. We would also like to thank those who were willing to participate in the initiative but were ultimately unable to do so.

Joint teams from Sanofi Genzyme and Open Innovation Sanofi France, in partnership with Orange Healthcare and Orange Consulting, managed the initiative and the drafting of this white paper.

External participants

- **Academic stakeholders**: ICM, INRIA

- **Patient associations**: Alliance Maladies Rares, Association Francophone des Glycogénoses, Maladies Rares Info Services, Vaincre les Maladies Lysosomales

- **Rare disease healthcare networks**: AnDDi-Rares, DéfiScience, FAI2R, Filnemus, MaRIH, Oscar

- Medicen **business cluster**

- **Healthcare professionals from the rare disease expert hospital network**

- **Paramedical and medical professionals** outside the expert network

- **Digital start-ups and experts**: Anamnèse, Orange, Semeia

Project leaders and participants in drafting the white paper

- **Sanofi Genzyme**: Anne-Sophie Chalandon, Public Affairs Manager

- **Sanofi France – Open innovation**: Emmanuel Capitaine, Head of Open Innovation; Guilhem Servant, Open Innovation

- **Orange Healthcare**: Rémy Choquet, Chief Innovation Officer

- **Orange Consulting**: Pierre-Etienne Chazal, Chief Consultant; Lucie Humeau, Senior Consultant

Rare diseases in figures

Prevalence of a rare disease

< 1 case / 2,000 individuals

50% of patients are children under 5

25% of rare diseases appear after the age of 40

50% of patients have not received an accurate diagnosis

> **7000** rare diseases have been identified to date

350 M patients with rare diseases worldwide

3 M patients with rare diseases in France

4,5% of the global population

95% of rare diseases are **incurable**

80% of rare diseases are **genetic**

20% of rare diseases are **not genetic**, or very rare, with unnamed conditions

3200 **genes** responsible for rare diseases have been identified

2/3 of rare diseases are **serious or debilitating**

50% of rare diseases cause **motor or sensory dysfunction or intellectual disability**

9% of patients suffer from a **total loss of autonomy**

50% of rare diseases are **life-threatening**

Sources: DGOS; PNMR3, 2018

Did you know?

Most rare diseases **are genetic**

and some are well known, such as cystic fibrosis, sickle cell disease, trisomy disorders, Huntington's disease and Charcot-Marie-Tooth disease.

Rare diseases also include many **infectious diseases,**

such as those caused by the Zika virus, legionnaire's disease and aspergillosis, as well as autoimmune and autoinflammatory diseases, including scleroderma, relapsing polychondritis and Still's disease

Many cases are idiopathic, which means the cause of disease is unknown.

In France, the term "**orphan disease**" is used to describe a pathology for which no treatment is available

An orphan disease may not necessarily be rare, and a rare disease may not necessarily be an "orphan" one. However, a large majority of rare diseases are orphan diseases and vice versa.

BACKGROUND

Rare diseases and diagnostic delay

This first section provides an overview of the issue through a literature review and interviews with stakeholders in the rare disease ecosystem.

In most cases, rare diseases are severe, chronic and progressive. Their impact on the quality of life of patients and their families is significant. Two-thirds of rare disease cases are serious or debilitating (DGOS), while half are life-threatening (Alliance Maladies Rares). They cause motor or sensory dysfunction or intellectual disability in 50% of cases, and lead to a total loss of autonomy in 9% of cases. Patients affected by a rare disease have their everyday lives completely upended.

On average, three new syndromes are identified and published around the world every week. Gene after gene, the classification of diseases becomes more precise – and considerably more complicated.

FRENCH DOCUMENTATION

Given the number of rare diseases, the impossibility of studying them all, and the time elapsed since doctors were trained, general practitioners – regardless of how competent they are – are unlikely to be able to recognise most rare diseases they may encounter.

FRENCH DOCUMENTATION

Issues in rare diseases

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RARE DISEASES: A SOURCE OF SERIOUS CONSEQUENCES FOR PATIENTS

The family unit and support from healthcare professionals play a critical role in patient support, especially as more than half of rare diseases appear in early childhood.

The many types and the rarity of these diseases hamper research progress and make diagnosis complicated. Around half of patients with a rare disease have not received an accurate diagnosis (MRIS, 2015).

The high cost of treatment can be an additional burden on patients and their families. While a large portion of expenses may be covered (Assurance Maladie, the French national health scheme; top-up insurance; medical-social structures for disabled persons, etc.), some expenses are not and can cause financial hardship for patients: transport to an expert center, hardware purchases, home renovations, or care to improve patients' comfort, which can be essential (HCSP, 2016).

Getting a diagnosis for a rare disease is a crucial step for patients, because a structured and appropriate treatment plan can then be put in place, more advanced testing can be done, and steps can be taken to limit the disease's progression and impacts.

DIAGNOSING A RARE DISEASE: A CHALLENGE FOR THE HEALTHCARE SYSTEM

Diagnosing a rare disease is always a challenge for the healthcare system. The known causes of these pathologies vary. Rare diseases are extremely diverse, and their semiology, nosology, and for most, their natural history have not necessarily been established. Many rare diseases share symptoms with "common" diseases. Others cannot be identified based on current knowledge or are idiopathic or atypical cases. Some are reclassified as they become better understood (for example, today there are 30 different clinical forms of Charcot-Marie-Tooth disease).

Despite increasing knowledge and new imaging or biological technologies, diagnosis remains difficult. Under these conditions, expecting non-expert doctors to diagnose a rare disease would seem unreasonable. The healthcare system must integrate the specific aspects of these pathologies into the "classic" care organisational structure, based on primary and secondary care networks (private practice and hospital networks). To do this, a tertiary network, composed of rare disease experts, was created to ensure management of these pathologies through expert centers (for more detail, refer to the "*Long-established and dynamic public action on rare diseases in France*" section).

The division of care: a necessity in rare diseases

EXPERT NETWORK (TERTIARY)

Rare disease experts

HOSPITAL NETWORK (SECONDARY)

Hospital specialists

PRIVATE PRACTICE NETWORK (PRIMARY)

Private practice specialists

General practitioners
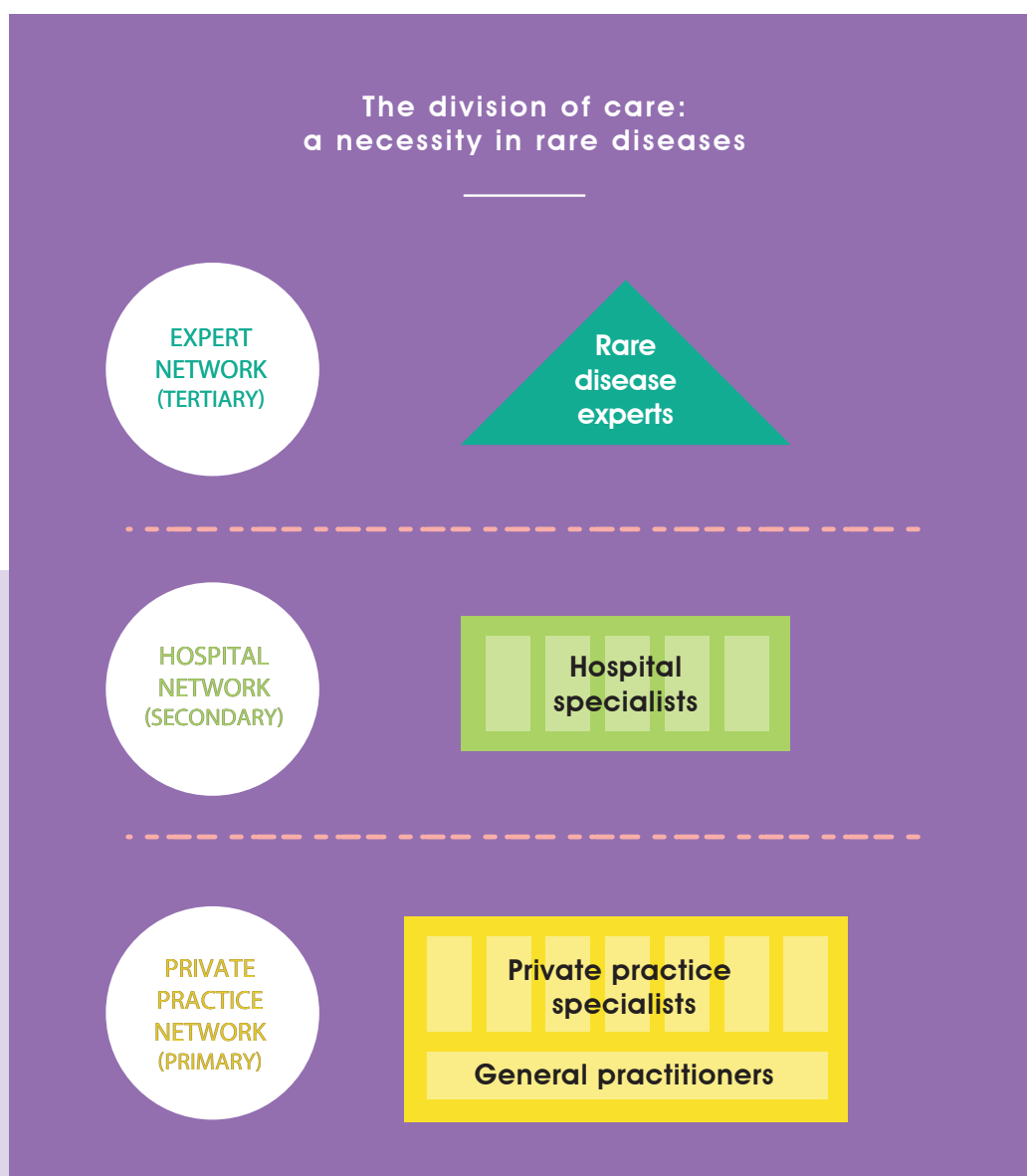
This tertiary network is highly specialised, and although it is well integrated across the French country, identifying and accessing it from the primary and secondary care networks remains difficult for healthcare practitioners and patients. Optimising the care system for rare disease cases is complex and requires organising access to the secondary and then tertiary networks while optimising coordinated care. With this type of organisational structure, the patient's primary care physician, most often a general practitioner, plays a key role as care coordinator. The physician must "sound the alert" regarding an atypical situation and facilitate access to the secondary and tertiary networks.

Despite the creation of this expert network specialising in rare diseases, the diagnosis lag time is still long and delays are common for many patients.

My disease has many confusing symptoms. They could be linked to several diseases: rashes, ulcers, neurological and respiratory problems, muscular and bone deficiencies.

The terminal stage of the disease is acute leukaemia. For a long time, it was difficult to connect these symptoms. I had a series of diagnoses – scabies, multiple sclerosis and myopathy – before getting the right one.

PATIENT TESTIMONIAL: HERVÉ, MASTOCYTOSIS (FRENCH DOCUMENTATION)

Diagnostic delay: a major challenge in rare diseases

DIAGNOSTIC DELAY: A MULTIFACETED ISSUE

Diagnostic delay can be defined as the excessive time between symptom onset and diagnosis.

Did you know?

Diagnosis lag time is commonly defined as **the time between the onset of symptoms** noticed by a patient **and a confirmed diagnosis**

(clinical, genetic, biological, etc.) and identified cause (DGOS).

An overly long dignosis lag time can result from two situations

The first is **"diagnostic delay"**, in which lag time is abnormally long at one or several stages of the diagnosis journey. It may also describe a period during which no clear diagnosis can be made due to a lack of sufficiently characteristic clinical signs, leading to suboptimal care.

Diagnostic delay should not be confused with treatment delay:

therapeutic or paramedical care may begin at different points along the care continuum, and in many cases before a rare disease is diagnosed.

The second is **"diagnosis impasse"**, when no specific cause of the disease can be identified due to limited medical and scientific knowledge. A diagnosis impasse can occur for many reasons: the clinical picture is atypical and cannot be linked to a known nosology (even rare) or because biological characterisation is not possible.

Diagnostic delay is a complex issue that encompasses several situations:

• **"Late diagnosis"** situations, which often occur in cases of rare diseases that develop quietly over several years before producing alarming symptoms or an acute episode that brings the disease to light.

• **"Erroneous diagnosis"** situations, which may occur with diseases whose symptoms are similar to other diseases or with a complex differential diagnosis, which is frequently seen in neuromuscular pathologies, for example.

• **"Diagnosis impasse"** situations, which appear in cases of unidentified diseases. These situations will greatly benefit from new whole exome sequencing (WES) technologies. An impasse can also describe a period during which only a partial diagnosis has been made due to a lack of sufficiently characteristic clinical symptoms, which can then sometimes lead to suboptimal care.

The issue of diagnostic delay must be put in perspective based on the point of view – the patient, healthcare professional or care organisation. Diagnostic delay has a number of causes and consequences.

Understand my anger: my husband died at 46 from septicaemia with kidney, heart and lung failure and severe cirrhosis of the liver. It wasn't until he was hospitalised that a diabetologist mentioned the word "haemochromatosis".

For years, he suffered from hand pain and extreme fatigue. His complexion was getting darker and darker, even grey. The two doctors familiar with his issues never considered haemochromatosis.

PATIENT TESTIMONIAL: MADELEINE (FFAMH)

When the first symptoms appeared, I went to see two doctors. After an impressive battery of tests, a diagnosis was made: depression, a tendency to make things up, acute panic attacks. I spoke with my brother, who I didn't see often, and found out that his issues were similar to mine, and he'd had the same medical experience.

He was first treated for a nervous breakdown, and then diagnosed as an alcoholic – even though I had never seen him drink. It wasn't until an article was published in a journal that I realised we might both have haemochromatosis, which was later verified. We're being treated now and things are better.

FAMILY TESTIMONIAL M.B., PARIS, HAEMOCHROMATOSIS (FFAMH)

DIAGNOSTIC DELAY: A PUBLIC HEALTH CHALLENGE

In many cases the diagnosis lag time is still too long, and avoidable delays are seen in the diagnosis journey. These situations have major repercussions on the lives of patients and their families. Reducing this lag time remains a major issue for patients, healthcare professionals and all other involved stakeholders.

FOR THE PATIENT

A delayed diagnosis is extremely harmful for patients and their families because it can lead to psychological and physical consequences (Alliance Maladies Rares, 2016). The later the diagnosis, the more difficulties patients face (academic, family, professional etc.) and the greater the risk that the disease will worsen and that clinical complications will develop. Patients awaiting a diagnosis often find themselves in limbo, which causes considerable anxiety for them and their families, and delays the implementation of a care protocol, leading to serious consequences for their health.

In terms of care, a delayed diagnosis can be a genuine missed opportunity for patients as it leads to delayed access to the most suitable care when available. Depending on the pathology, care may include treating symptoms or,

in very rare cases (<5%), curative treatment. Identifying a rare disease may allow patients to improve their quality of life and chances of survival through paramedical and psychological care adapted to their needs.

A delayed diagnosis also delays access to rare disease centers where patients have access to national and international expertise, through the European Reference Networks (ERNs). Finally, depending on the hereditary nature of the disease, genetic counselling and a family investigation may be offered to patients and their families.

With regard to psychological support, a delayed diagnosis deprives patients of social recognition for their condition, about which they may have felt misunderstood and discouraged for years. Proper patient care also helps support caregivers, who may have had to constantly be more and more involved.

In terms of administration, obtaining a diagnosis for a rare disease facilitates institutional recognition of the patient, who may be eligible for financial support through disability payments or receive an official status for individuals with a chronic disease.

For patients, there is a lot at stake when it comes to reducing diagnosis lag time: access to specific care, treatment to address symptoms or cure the disease, improved survival rate, enhanced quality of life, social recognition of their condition, specific medical-social support, financial support, and academic adaptation.

All patients and their families describe an abnormally long and complicated journey to be heard, gather information and be referred to the competent teams (when they exist) to receive a proper diagnosis.

The result is an enormous waste of time with consultation after consultation, and treatments and medications that are often inappropriate or even dangerous.

CONSEIL ÉCONOMIQUE ET SOCIAL, 2000

FOR HEALTHCARE PROFESSIONALS

For healthcare professionals, identifying the disease is an essential part of beginning care and adapting support for patients. For example, this can lead to adjusting "standard" consultation times, enabling multidisciplinary consultations, promoting data sharing and the use of new diagnostic technologies and therapies, or facilitating access to research.

FOR PUBLIC AUTHORITIES

For regulators and the public authorities in charge of organising care, a delayed diagnosis highlights the limitations of how care is organised, especially when experts are spread out across the country. More generally, for society, long diagnosis lag times for rare diseases can lead to excessive care costs.

Diagnostic delay: challenges
for each stakeholder

PATIENT

DIAGNOSTIC
DELAY

HEALTHCARE
PROFESSIONAL

HEALTHCARE
SYSTEM
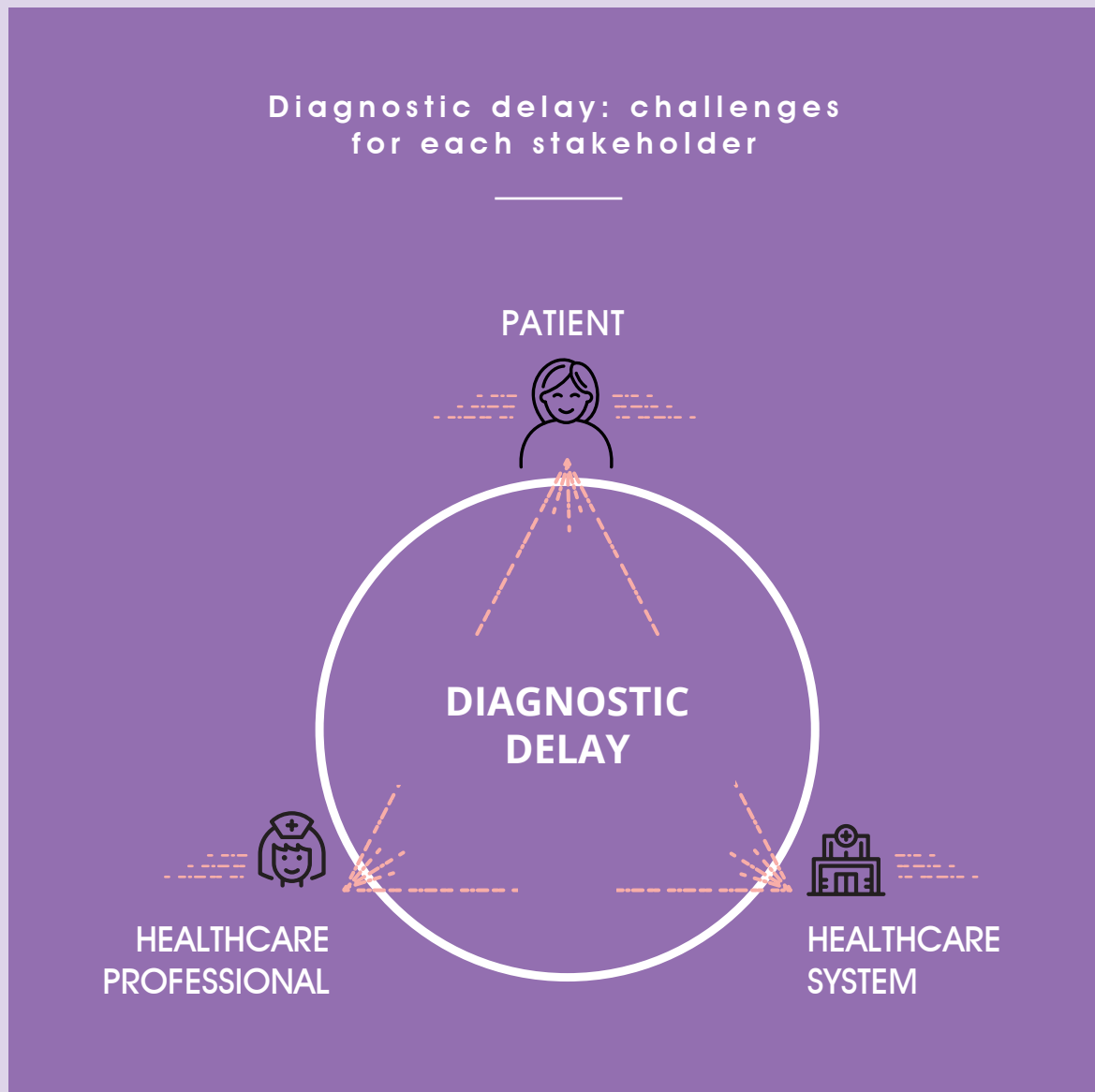
The rarity, diversity and number of rare pathologies make this a highly complex issue requiring public action. Accordingly, reducing diagnostic delay is a major challenge, not only because of the direct consequences, but also because of the missed opportunities due to the lack of a diagnosis. France has played a pioneering role in fighting rare diseases. Considerable progress has already been made to improve the situation for patients, caregivers and healthcare professionals.

Targeted national action to tackle these challenges

LONG-ESTABLISHED AND DYNAMIC PUBLIC ACTION ON RARE DISEASES IN FRANCE

France's efforts to fight rare diseases – including information, research, care organisation or involving voluntary associations – set the country apart on the world stage. France was behind the first national plan for rare diseases in 2005, and initiated a strong dynamic of public action to fight these pathologies at the European scale.

The first National Plan for Rare Diseases (PNMR1) launched the implementation of specialised care for rare diseases in France. Following these efforts in 2005, today in 2018

France has no fewer than 387 certified national reference centers for rare diseases (CRMRs) in French teaching hospitals and 1,757 competence centers (CCMRs) (PNMR3, 2018). ▸▸

» This structuring of the expert network has supported graduated care in the healthcare system: primary, secondary and tertiary care for people with rare diseases. Additionally, this first plan enabled the development of information for patients, professionals and the general public, namely through the Orphanet portal, a global reference in terms of documentation and information on rare diseases.

Launched in 2011, the second National Plan for Rare Diseases (PNMR2) focused on strengthening the actions initiated by the first plan (PNMR1) with regard to care organisation and national and European research, particularly with the creation of the French Foundation for Rare Diseases (FFRD) (DGOS). This foundation supports research projects that study the experiences of patients and their families, in order to analyse the consequences of a rare disease for individuals and society as a whole, and suggest improvements for their journey as well as enhanced care. It strives to create multidisciplinary teams of doctors, researchers and patient association members. The foundation encourages these stakeholders to work together to discuss the consequences of restricted activity in patients' lives and to analyse existing care practices.

In all, 23 rare disease healthcare networks (FSMRs) have been created, and their missions revolve around five areas:

- **Expertise**, by managing stakeholders involved in diagnosis, therapeutic care and monitoring patients with rare diseases that are covered by the network
- **Best practices**, especially through the writing, dissemination and implementation of national diagnosis and care protocols (PNDS)
- **Research**, especially translational and clinical, through the coordination of national and international projects
- **Epidemiology**, through the development of a rational policy on the databases, registers and specific cohorts for the network's rare diseases, in connection with the French National Data Bank for Rare Diseases (BNDMR)
- **Training**, through the identification of existing actions and the implementation of new courses identified as necessary by the network (HCSP – PNMR2 evaluation, 2016)

In 2016, Europe drew inspiration from the rare diseases healthcare networks (FSMRs) to certify 24 European Reference Networks (ERNs) for rare diseases. The French organisational structure is integrated with the ERNs, four of which are coordinated by a French expert center.

National plans for rare diseases have helped drive progress in several areas. Nevertheless, there are still challenges to address, including the issue of diagnostic delay.

French initiatives

1987 — **Téléthon**
created by AFM-Téléthon

Orphan drugs mission
by the Ministry of Social Affairs — **1995**

1997 — **Orphanet,** a global reference database
Eurordis, the European federation of rare
disease patient associations

Alliance Maladies Rares, a French
collective of rare disease patient
associations — **2000**

2001 — **Rare Disease Platform** bringing together the
major French and European stakeholders
(Alliance Maladies Rares, EURORIDS,
AFM-Téléthon, Maladies Rares Info Services,
Orphanet, French Rare Disease Foundation)

**1st National Plan for Rare
Diseases 2005-2008** — **2005**

2011 — **2nd National Plan for Rare
Diseases 2011–2014,**
extended to 2016

**Creation of the French Rare Disease
Foundation,** a foundation
to promote scientific cooperation to speed
up research on rare diseases — **2012**

2017 — New **reference centers**
are certified

**3rd National Plan
for Rare Diseases 2018–2022** — **2018**

European actions inspired by France

1999 — European regulation on orphan drugs

The European Commission makes rare diseases a research and health priority — **2000**

2004 — Creation of the European Rare Diseases Task Force

European Commission Communication on **"Rare Diseases: Europe's Challenges"** — **2008**

2009 — Recommendation from the European Council of Ministers for Health for all countries to develop plans or strategies for rare diseases

Launch of the 24 European Reference Networks (ERNs) on rare diseases to connect expert centers — **2017**

3
French national plans for rare diseases (PNMRs)

23
Rare disease healthcare networks (FSMRs)

387
National reference centers for rare diseases (CRMRs)

1757
Competence centers for rare diseases (CCMRs)

Rare diseases
and diagnostic delay

STATUS ON ACCESS TO DIAGNOSTIC SERVICES IN RARE DISEASES IN FRANCE

The two French national plans for rare diseases have helped bring about major advances in patient care. Diagnosis lag time appears to have shortened, namely due to the creation of the expert network, the allocation of technical means and efforts to inform and train healthcare professionals (HCSP, 2016). However, the average lag time today is between two and four years, with significant discrepancies hidden in these figures: a quarter of patients still wait more than five years to be able to put a name to their disease (Alliance Maladies Rares, 2016).

These lag times vary considerably depending on the disease, as shown in the table on page 29 of the EURORDIS report. For example, while half of patients with cystic fibrosis are diagnosed 1.5 months after their first symptoms appear, this time lag increases to 14 years for those with Ehlers-Danlos syndrome (EURORDIS). Other factors also play a role in diagnostic delay, such as gender and age (ERRADIAG, 2016, p. 33). These effects should nevertheless be confirmed by a statistical study on a larger scale.

Diagnosis lag time for different diseases, from symptom onset to diagnosis (EURORDIS)

DISEASE	DIAGNOSIS LAG TIME FOR 50% OF PATIENTS	DIAGNOSIS LAG TIME FOR 75% OF PATIENTS
CYSTIC FIBROSIS	1.5 MONTHS	15 MONTHS
TUBEROUS SCLEROSIS	4 MONTHS	3 YEARS
DUCHENNE MUSCULAR DYSTROPHY	12 MONTHS	3 YEARS
PRADER–WILLI SYNDROME	18 MONTHS	6.1 YEARS
MARFAN SYNDROME	18 MONTHS	11.11 YEARS
FRAGILE X SYNDROME	2.8 YEARS	5.3 ANS
EHLERS-DANLOS SYNDROME	14 YEARS	28 YEARS

In the ERRADIAG survey, conducted by Alliance Maladies Rares and published in February 2016, 34% of respondents received a diagnosis within six months, but 22% waited more than five years (ERRADIAG, 2016, p. 35).

• Diagnostic delays are significantly higher for women than for men – even for the same disease (ERRADIAG, 2016, p. 33).
• Children are more likely to suffer longer lag times than adults or newborns (ERRADIAG, 2016, p. 33).
• A patient's socio-professional status has a slight influence on obtaining a confirmed diagnosis while where a patient lives does not play a decisive role (ERRADIAG, 2016, p. 52).

In the survey "Observatory of rare diseases" (Observatoire des maladies rares) published in 2015, diagnosis lag time was six years or longer for 21% of patients (MRIS, 2015).

Rare diseases and diagnostic delay

To date, there are few quantitative studies available to analyse real data on the time required to diagnose rare diseases, and as a result, to assess possible inequality with regard to access to diagnostic services. This is due to a lack of national data on all rare diseases. However, several studies have shown that despite a marked improvement in diagnosis lag times in recent years, the issue of diagnostic delay is key for rare diseases (Alliance Maladies Rares, 2016).

The PNMR2 evaluation report emphasises that the actions from the two first national plans have helped specialist doctors in hospitals become more familiar with expert centers networks (CRMRs and CCMRs) (HCSP, 2016). This has a positive impact on patients because a diagnosis is generally faster once the patient has a consultation at an expert center.

However, access to expertise remains complex outside of genetic testing, especially for progressive diseases and those with non-specific symptoms (HCSP, 2016). The time it takes before being referred to an expert center is still excessive in some cases, especially when patients begin their journey in the private practice network. A more precise qualification and a quantification with regard to when delays happen during the diagnosis journey, established by disease, would seem necessary to identify possible and priority areas for improvement.

Following on from the first two national plans, the Ministry for Solidarity and Health reiterated its support for and commitment to rare diseases with the publication of the third National Plan for Rare Diseases on 4 July 2018. This new plan has five ambitions, the first of which is to enable faster diagnoses for patients, to reduce diagnostic delays and impasses. The plan has 11 areas of work, in conjunction with all stakeholders (health authorities, healthcare professionals, patient associations, academics and industry players).

This plan will coordinate public strategies that can have an impact on rare diseases, such as the National Health Strategy, the National Research Strategy, the National eHealth Strategy and the France Genomic Medicine Plan 2025 (PFMG 2025).

By focusing on diagnostic delay, our UNIR initiative falls in step with the third national plan (PNMR3) and aims to join efforts on shared priorities. UNIR echoes three work areas in the PNMR3:

- **Area 1** "Reduce diagnostic delay and impasse"
- **Area 6** "Promote the emergence of and access to innovation"
- **Area 7** "Enhance the treatment pathway", especially through Action 7-5, which seeks to develop telemedicine and eHealth innovation in rare diseases.

OUR INITIATIVE

UNIR - Innovating together to reduce diagnostic delay in rare diseases

New information and communication technologies (ICTs) have brought about major changes in the healthcare sector as new tools and practices are adopted by patients and healthcare professionals.

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UNIR - Innovating together
to reduce diagnostic delay
in rare diseases

Our aim: take action to reduce diagnostic delay

These new technologies encourage stakeholders to rethink uses and organisational structures, and provide numerous opportunities to improve the organisation and efficiency of our healthcare system.

These changes offer new outlooks for incumbent players but also new stakeholders in the health sector, such as large industrial groups that have long been outside this sector, or specialised start-ups that have found their niche in the ecosystem. This arrival of expertise and skills provides a new approach to innovation, which can complement the action of traditional research and development departments.

The many challenges that need to be tackled to better understand rare diseases within our healthcare system are stimulating innovation. Given the complexity of the diagnosis journey for these diseases, we decided to launch an inclusive and open initiative in which all stakeholders from the rare disease ecosystem can participate to help identify and promote solutions to reduce diagnostic delay.

Using open innovation to drive creativity

Given the many different diseases and problems encountered by patients and healthcare professionals, Sanofi France, in partnership with Orange Healthcare, wanted to give this project a broad participatory dimension.

We developed the project based on a collaborative approach with two methodologies: open innovation and design thinking.

Not only will implementing this type of approach allow us to work with new digital players, but most importantly, it will allow us to include those stakeholders who are impacted by the solutions – healthcare professionals and patient associations – right from the earliest phases of the project. While new technologies are obviously important, we believe that they must be developed by and for users to provide real value and support people, rather than the other way round.

This methodology seeks to bring about new ideas, develop projects with greater value for

users and speed up innovation cycles through sharing and cooperation. Through this open approach, we are looking for every opportunity to best describe the stages of the diagnosis journey, points of difficulty and the organisation of the care network, and to develop the best possible solutions that take into account various points of view. This open innovation initiative brings together 15 experts in rare diseases as well as representatives from six rare disease healthcare networks (FSMRs) and four patient associations for rare diseases. The full list of participants can be found in the annex of this document.
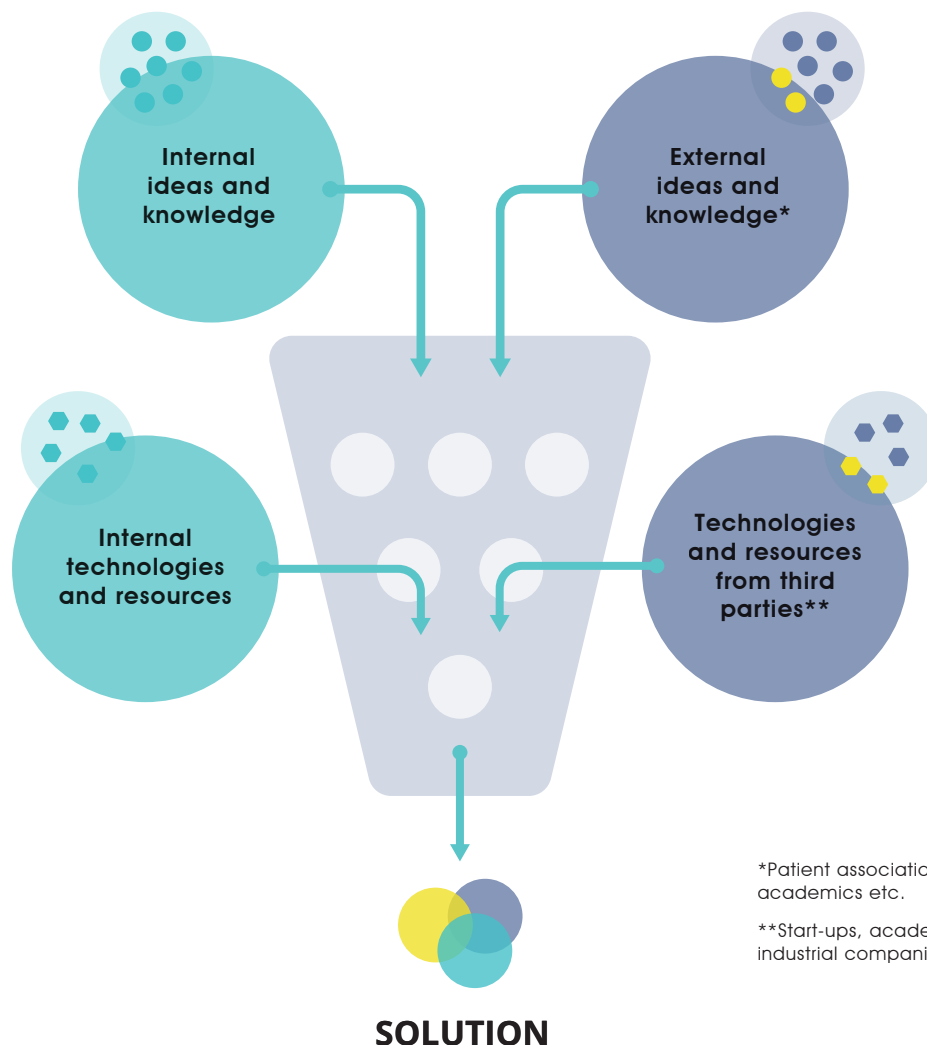
Did you know?

Open innovation

· **The concept of open innovation** was developed in the early 2000s by Henry Chesbrough, an adjunct professor and researcher at UC Berkeley.

· **Open innovation focuses on collective intelligence** and multidisciplinary cooperation by combining input from internal and external stakeholders (patients, patient associations, healthcare professionals, researchers, start-ups etc.).

· **Through this approach to sharing and cooperation**, open innovation lets new and more relevant ideas emerge faster, and speeds up development cycles.

· There are many ways to implement these open innovation processes: **innovation labs, hackathons,** internal and external competitions, co-creation and ideation platforms etc.

· In a similar vein, **Sanofi France's open innovation division created 39BIS, a laboratory dedicated to eHealth**. The UNIR project is run from this laboratory.

Internal ideas and knowledge

External ideas and knowledge*

Internal technologies and resources

Technologies and resources from third parties**

*Patient associations, experts, academics etc.

**Start-ups, academics, industrial companies, etc.

SOLUTION

Did you know?

Design thinking

- **Design thinking is an iterative approach to innovation** developed at the University of Stanford in the 1980s.

- It is based on **co-creation methods and processes** in which the final user of a product or service is the focus. Design thinking promotes observation, experimentation, collaboration and prototyping.

- One particular aspect of design thinking is that it is **people-centered and based on empathy**.

- **Sanofi and Orange Healthcare chose this approach** to tackle the challenge of reducing diagnostic delay for people with rare diseases to identify the real expectations of the various stakeholders along the diagnosis journey, from patients to healthcare practitioners.

The design thinking process

————

EMPATHISE

Better understand the users for whom the product or service is designed
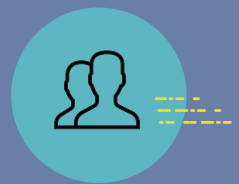
DEFINE

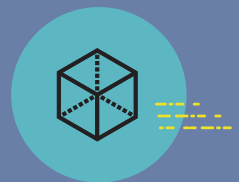**Define the problem** based on the information from the empathise stage

IDEATE

Bring ideas together to **produce creative solutions**

PROTOTYPE

Develop a version of one or several ideas

TEST

Work with other designers and **test everyone's ideas**
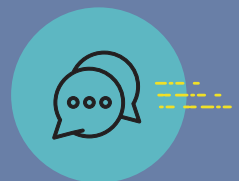
Our initiative

Open innovation and design thinking methods aim to bring out new ideas, develop projects with greater value for users and speed up innovation cycles through sharing and cooperation.

Through this open approach, we are looking for every opportunity to best describe the stages of the diagnosis journey, points of difficulty and the organisation of the care network, and to develop the best possible solutions that take into account various points of view.

This open innovation initiative brings together 16 experts in rare diseases along with representatives from six rare disease healthcare networks (FSMRs) and four patient associations for rare diseases (the full list of participants can be found in the annex of this document). Following 30 individual interviews and three workshops, we were able to create a general diagnosis journey for people with rare diseases, identify 13 obstacles that are sources of diagnostic delay and suggest 14 solutions to reduce such delays.
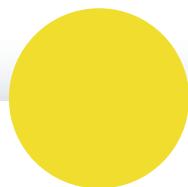
External interviews included 21 participants

- **2 representatives** from patient associations
- **1 healthcare professional from the hospital network** outside the rare disease network
- **6 healthcare professionals from the private practice network**, including 1 general practitioner, 1 school doctor, 1 occupational physician, 1 physiotherapist and 2 psychologists
- **12 healthcare professionals from the rare disease expert hospital network**, including 10 rare disease healthcare network (FSMR) mission heads
- **1 academic research stakeholder**

Participants in the initiative and methodology

- **37 participants** from the rare disease ecosystem
- **23 individual interviews** with stakeholders from the ecosystem
- **6 rare disease health networks** represented
- **16 rare disease experts**
- **4 rare disease patient associations** represented

The workshops included 17 participants

- **3 representatives from patient associations,** including 1 who was also a healthcare professional in the expert network and 1 rare disease healthcare network (FSMR) mission head
- **6 healthcare professionals from the rare disease expert hospital network**, including 4 rare disease healthcare network (FSMR) mission heads
- **2 healthcare professionals from hospitals** outside the rare disease network
- **2 academic research stakeholders**
- **1 stakeholder from an eHealth cluster**
- **2 stakeholders from eHealth start-ups**
- **2 technical experts**

Results

- **1 general diagnosis journey** designed
- **5 categories of difficulties identified**, with 13 "obstacles" encountered during the diagnosis journey
- **14 solutions identified**
- **2 solutions selected** for prototyping

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UNIR - Innovating together
to reduce diagnostic delay
in rare diseases

A structured and participatory approach

THE BASIC PREMISES OF OUR INITIATIVE

Identifying an innovative solution that can help reduce diagnostic delay in rare diseases faces one particular challenge: covering more than 7,000 identified diseases, each with specific characteristics.

To address this challenge, a descriptive and generalist view of the diagnosis journey for rare diseases, along with points of difficulty, was created. This was done based on a series of interviews with representatives of the rare disease community (patient associations, healthcare industry players, rare disease experts, general practitioners etc.). The initiative was divided into three parts:

1

2

3
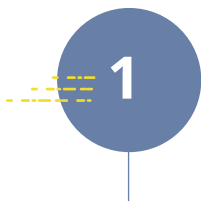
Establishing a shared view of the diagnosis journey for rare diseases.

_ What are the different stages of a diagnosis journey?

_ Who are the stakeholders?

_ What are the information flows?

_ Is it possible to create a comprehensive view?
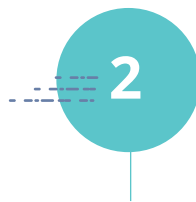
Identifying points of difficulty causing diagnostic delays in the journey.

_ What are the points of difficulty at each stage of the journey?

_ Which of these need to be addressed first to reduce diagnostic delay and missed opportunities?
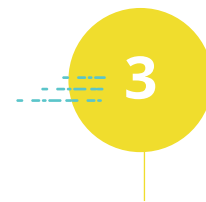
Identifying new solutions to tackle obstacles to diagnosis along the journey.

_ What are the digital solutions for diagnostic support for rare diseases, and what are their limitations?

_ What new solutions could help reduce diagnostic delay?

The project's methodological approach

Bibliographic analysis
(REPORTS FROM PNMR, HSCP, ALLIANCES MALADIES RARES AND EURORDIS; PATIENT HISTORIES)

Individual interviews
(7 INTERNAL INTERVIEWS, 23 EXTERNAL INTERVIEWS)

STEERING COMMITTEES TO OVERSEE PROGRESS

CROSS-REFERENCING OF INFORMATION

Preliminary diagnosis journey

Preliminary list of points of difficulty

Preliminary list of solutions

WORKSHOP 1 — Patient associations, FSMR

WORKSHOP 2 — Patient associations, FSMR, expert and non-expert practitioners

SURVEYS AND INTERNAL EXPERT COMMITTEE

STEERING COMMITTEES TO OVERSEE PROGRESS

General diagnosis journey

List of **priority** points of difficulty

List of **priority** solutions

WORKSHOP 3 — Start-ups, eHealth experts, rare disease technical experts

Priority solutions described

UNIR - Innovating together
to reduce diagnostic delay
in rare diseases

1

**Establishing a shared vision of the
diagnosis journey for rare diseases.**

**The first phase of work was based on two
datasets collected in different ways:**

• **A bibliographic analysis**: mainly drawn
from the national plans for rare diseases
(PNMRs) and their assessment reports by
the High Council for Public Health (HCSP),
the ERRADIAG report from Alliance Maladies
Rares, the EURORDIS Care 2 and 3 reports
and patient testimonials (Pompe disease, Fa-
bry disease).

• **30 individual interviews:** seven internal pre-
liminary interviews with managers from the
Sanofi Genzyme Rare Disease Division, fol-
lowed by 23 individual interviews with various
stakeholders selected from different stages of
the patient diagnosis journey (patient asso-
ciations, paramedical personnel, healthcare
professionals expert and non-expert of rare

diseases, school and workplace doctors etc.).
These individual interviews were used to draw
up a situational analysis according to the diffe-
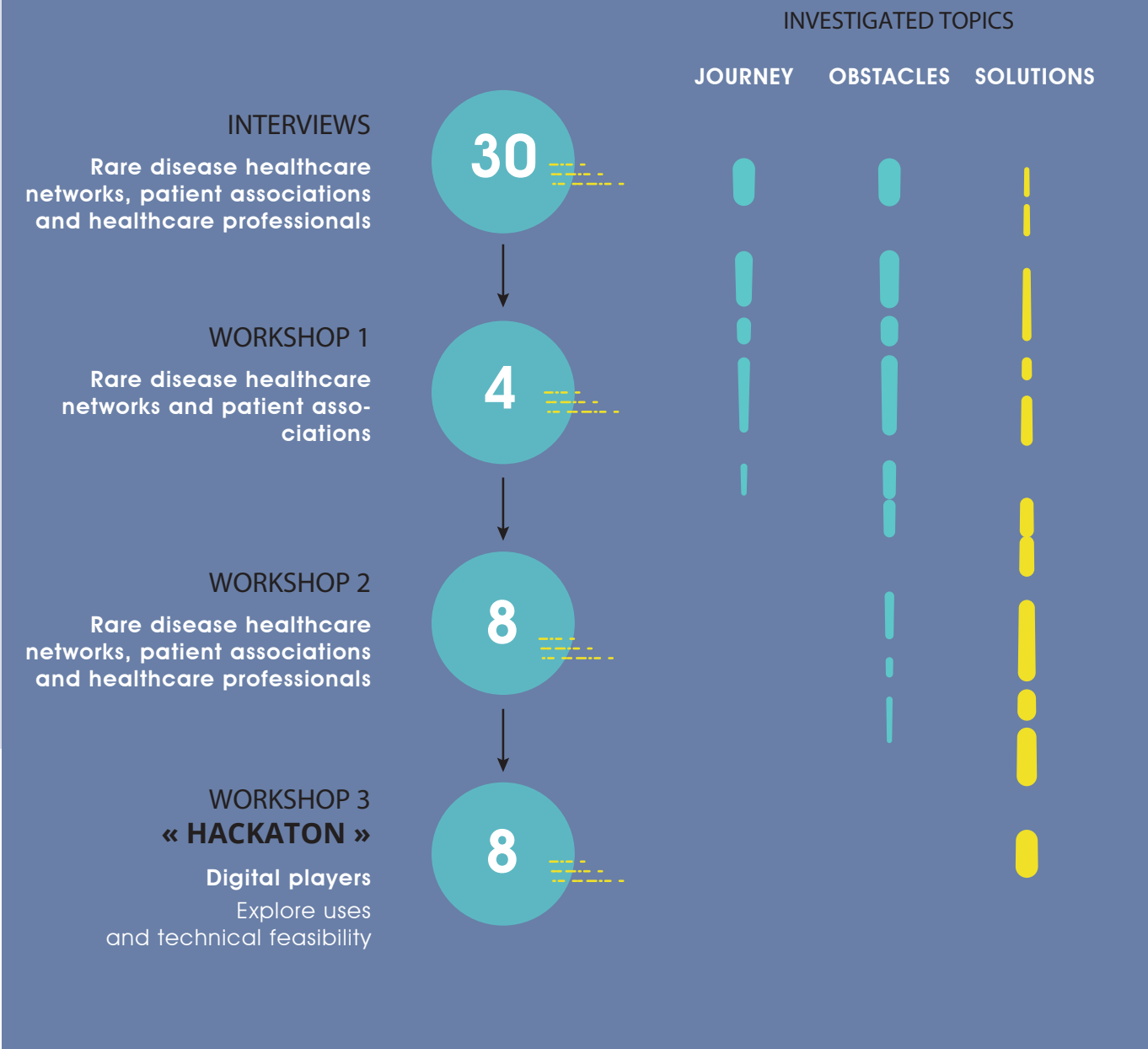rent points of view of the professionals ques-
tioned. Each person was asked to describe
their take on diagnostic delay in rare diseases,
the current patient journey and points of dif-
ficulty. The variety of these discussions pro-
vided a well-rounded and high-quality pers-
pective on the current situation, taking the
plurality of cases and diseases into account as
much as possible.

The information gathered helped us develop
a preliminary view of the general diagnosis
journey for patients with rare diseases and an
initial mapping of points of difficulty along the
journey. We were also able to get information
on existing digital solutions.

A qualitative initiative inspired by design thinking and open innovation

INVESTIGATED TOPICS

| JOURNEY | OBSTACLES | SOLUTIONS |

INTERVIEWS

Rare disease healthcare networks, patient associations and healthcare professionals

30

WORKSHOP 1

Rare disease healthcare networks and patient associations

4

WORKSHOP 2

Rare disease healthcare networks, patient associations and healthcare professionals

8

WORKSHOP 3
« HACKATON »

Digital players
Explore uses
and technical feasibility

8

Note on the methodology

It is important to remember that the work described here is based on a qualitative approach that aims to identify innovative solutions to reduce the main causes of diagnostic delay. Although the size and diversity of the sample of stakeholders questioned are representative, our approach does not attempt to be exhaustive. The information gathered did not undergo a quantitative statistical analysis, which could reinforce the observations shared in this white paper at a later point in time.

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UNIR - Innovating together
to reduce diagnostic delay
in rare diseases

2 **Identifying points of difficulty causing
diagnostic delays along the journey**

**Professionals discussed their various
points of view during two multidisciplinary workshops and refined the information
gathered during phase one:**

• **The first workshop focused on getting patients' points of views** by bringing together
patient associations (Alliance Maladies Rares,
Association Francophone des Glycogénoses,
Vaincre les Maladies Lysosomales) and a representative from a rare disease healthcare
network (MaRIH).

• **The second workshop brought together
a representative from a patient association** (Vaincre les Maladies Lysosomales) **and
seven healthcare professionals, experts
and non-experts in rare diseases**, including three who represented rare disease
healthcare networks (DéfiScience, FAI2R,
Filnemus). These participants discussed the

preliminary diagnosis journey established
and the main points of difficulty with regard
to missed opportunities for patients. Among
the identified difficulties along the diagnosis journey, a shortlist of priority issues was
drawn up by participants based on two criteria: the estimated impact on diagnostic delay
and the level of required action.

Experts from Sanofi Genzyme were also called
on to challenge the work undertaken through
surveys and regular committee projects.

These discussions provided input for our work
and we were able to create a shared map of
the points of difficulty causing delays along
the journey. These obstacles were ranked by
priority by our project committee and a panel
of experts according to impact and required
action.
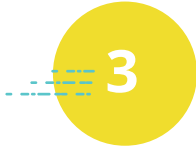
3 Identifying new solutions to tackle obstacles to diagnosis along the journey

A third workshop was held to discuss possible results of our work with regards to digital innovation:

• The third workshop brought together a healthcare professional and seven digital stakeholders, including two French start-ups working in fields that are very similar to the envisioned solutions (artificial intelligence, algorithms etc.). This workshop, designed as a hackathon, aimed to see the selected innovative solutions from the perspectives of digital stakeholders. This made it possible to develop value propositions in line with our ambition by focusing on uses. The workshop also sought to study the technical feasibility of the identified solutions.

• Sanofi Genzyme's experts were called on to discuss the selected solutions.

Following this phase, two innovative solutions to reduce diagnostic delay for rare diseases were selected for further consideration.

This methodology led to three deliverables

1
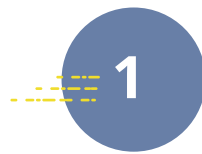
A general diagnosis journey
presenting the main stakeholders and diversity of patient flows.

2
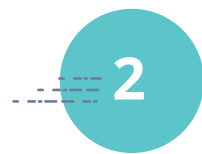
A list of 13 priority points of difficulty to address,
divided into five categories and characterised according to the issues covered.

3
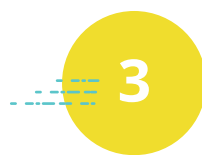
A list of 14 solutions
addressing the main points of difficulty, set as priorities during our workshops and interviews.

RESULTS

The diagnosis journey, points of difficulties and identified solutions

The organization of health care in France is complex. To better understand the types of diagnostic pathways, we drew up a diagram of the possible pathways based on the 30 interviews and first two workshops.

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The diagnosis journey,
points of difficulties and
identified solutions

The diagnosis journey

THE STAKEHOLDERS AND ORGANISATIONS

The diagnosis journey was designed by placing the patient and the goal (i.e., a confirmed diagnosis) at either end of the journey. The organisational structure was modelled based on the following stakeholders and organisations:

- Patients and their environment
- The private practice network
- The hospital network
- Technical testing platforms
- Rare disease organisations involved in coordinating care

Patients and their environment are the first unit of the journey. This unit includes the patients and people in close proximity to them, such as their family and friends, as well as social networks that may alert or inform them of a possible rare disease diagnosis.

The private practice network is the second unit of the journey. It is divided into three groups: "generalist" medical stakeholders, "specialist" medical stakeholders and peripheral stakeholders and organisations.

- **Private practice general practitioners and paediatricians** comprise the first group. These professionals are, in the French healthcare system, most frequently consulted as a first resort. Through a "generalist" consultation, they perform an initial filtering and refer patients to specialists who are better equipped to deal with uncommon diseases.

- **Private practice specialists,** regardless of their speciality, comprise the second group. Patients are frequently referred to these professionals following one or more consultations with "generalist" professionals. These professionals refer patients they cannot or do not know how to treat to hospital organisations.

- **The group of peripheral stakeholders and organisations** is a more varied unit, comprising school and workplace doctors, child and maternal welfare agencies and pharmacists, as well as paramedical stakeholders (e.g., physiotherapists, psychomotor specialists etc.), medical-social stakeholders (e.g., residential care homes for the severely disabled or for adults with special needs etc.) and finally private psychologists. These stakeholders and organisations are not directly involved in the diagnostic process, but may detect atypical situations and refer patients to "generalist" or "specialist" practitioners. The term "peripheral" is meant to describe only where along the diagnosis journey they are involved. These stakeholders are key in treatment and in patients' daily lives.

Whether they are generalists or specialists, working in private practices or hospitals, primary care physicians play an essential role in coordinating care and guiding and monitoring patients throughout their journey. In particular, they handle the following: becoming familiar with and monitoring patient medical records, informing and connecting patients with other healthcare professionals if necessary, helping establish ❯❯

The different diagnosis journeys of patients with rare diseases

THE PATIENT

?

PATIENT ENVIRONMENT

INTERNET SEARCHES

SOCIAL MEDIA

FAMILY AND FRIENDS

RD* COORDINATION SUPPORT STRUCTURES

- MRIS / PRIOR
- PATIENT ASSOCIATIONS

PRIVATE PRACTICE NETWORK

Specialist consultations

- PRIVATE PRACTICE SPECIALISTS

Generalist consultations

- GENERAL PRACTITIONERS
- PAEDIATRICIANS

RD* NON-EXPERT HOSPITAL NETWORK

Specialist consultations

- INTERNS
- ORGAN SPECIALISTS
- CLINICAL GENETICIST

Peripheral practitioners and organisations

- SCHOOL AND WORKPLACE DOCTORS, CHILD WELFARE AGENCIES
- MEDICAL-SOCIAL, PARAMEDICAL
- PHARMACISTS
- PSYCHOLOGISTS

DIAGNOSTIC DECISION SUPPORT TOOLS

Hospitalisation

Expert consultations

Competence centers

EXPERT NETWORKS

Reference centers

A&E departments

RD* EXPERT HOSPITAL NETWORK

RETURN HOME

REVISED DIAGNOSIS

TECHNICAL TESTING PLATFORMS

- BIOCHEMISTRY - BIOLOGY
- GENETIC TESTS
- FUNCTIONAL TESTS
- IMAGING ETC.

LIKELY RD* DIAGNOSIS

MAIN JOURNEY

SECONDARY JOURNEY

DIAGNOSIS CONFIRMED BY A HEALTHCARE PROFESSIONAL OR MC**

*RD = rare disease
**MC = Multidisciplinary consultation

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The diagnosis journey,
points of difficulties and
identified solutions

›› a treatment protocol in the event of a chronic disease etc. The general practitioner is a cornerstone in patients' diagnosis journeys, and has a comprehensive view of their health conditions.

The hospital network comprises the third unit along the journey. A rare disease center is generally a part of a hospital that is otherwise not specialised in rare diseases, rather than a specific hospital center. A continuum (from light green for non-experts to dark green for experts) indicates on our journey the degree of expertise of practitioners working in hospital centers today.

• **Consultations with specialists at hospitals** comprise the first group of the "non-expert" hospital network for rare diseases (in light green). These are a core component of hospital care and may be performed by interns, specialists or clinical geneticists.

• In addition to specialist consultations, two direct points of access to the hospital network are shown: hospitalisation and emergency care. The use of these two points of access occurs when a patient develops acute symptoms or complications that require immediate care.

• Finally, **consultations with hospital practitioners who are experts in rare diseases** comprise the final group (in dark green). This network of "experts" includes all practitioners from expert centers (CRMRs and CCMRs) and rare disease healthcare networks (FSMRs), which support practitioners by managing and coordinating actions between stakeholders involved in patient care.

Technical testing platforms are the fourth component of the journey, and provide support with clinical exams. Regardless of type, these tests – biological, biochemical, histological, imaging, genetic or functional – are an essential diagnostic tool for clinicians and allow them to confirm or rule out some possible diagnoses.

In addition to the private practice and hospital networks, a unit named Rare Disease coordination support structures was created. This unit gathers several stakeholders of the rare diseases ecosystem, including: Alliance Maladies Rares, AFM-Téléthon, the French Foundation for Rare Diseases, EURORDIS, Maladies Rares Info Services and Orphanet. It aims to give patients the means to be actively involved in advancing their care, from research to medical-social services. This platform also helps guide patients: if a rare disease is suspected, whether by a practitioner or a patient, these stakeholders can guide patients more quickly to the expert network as a "shortcut" through the diagnosis journey. Other regional initiatives have been developed and also play this role. This is the case for instance with the PRIOR network, a regional initiative that seeks to develop information and training on rare diseases, implemented in western France (Pays de la Loire region) with the support of Professor Dominique Bonneau. This is also the case with the Réseau Méditerranée, a care support network for professionals, patients and their families in south-western France (Occitanie region), which relies on screening by an on-call emergency physician. ››

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The diagnosis journey,
points of difficulties and
identified solutions

▶▶ **At the center of the diagram are the diagnostic support tools used by these stakeholders.** These tools correspond to all of the digital tools available to the different stakeholders to help them share information, research possible conditions and determine a diagnosis. An overview of identified tools is given in the section entitled *"The various existing solutions identified within an ecosystem undergoing digital transition"*.

TYPICAL DIAGNOSIS JOURNEYS

We were able to identify four distinct points of access along the diagnosis journey for rare diseases:

1 - Consultations with a general practitioner or a paediatrician
2 - Hospitalization and/or emergency hospital care
3 - Consultations with specialised hospitals, especially in clinical genetics
4 - Peripheral private practice stakeholders and organisations

Access through one of these points may also depend on the combination of several criteria:
• The patient's age when symptoms appear
• Conditions of symptom onset (acute crisis, progressive and/or chronic)
• Family history of disease

While each patient's diagnosis journey is unique, each of these points of access is associated with one or more "typical" journeys. These journeys are representative of the experiences of most patients, whose journeys share certain characteristics. They reflect the discussions we had with stakeholders along the journey throughout our work, and do not claim to be exhaustive or to statistically represent all possible cases.

The different points of entry to a rare disease diagnosis journey

POINT OF ENTRY	TYPICAL PATIENT PROFILES ENTERING EACH JOURNEY
PRIVATE PRACTICE: CONSULTATION WITH A GENERAL PRACTITIONER OR A PAEDIATRICIAN	**NEWBORNS & TODDLERS (0-2 YEARS)** with a progressive disease, with minor, diffuse or non-specific symptoms
	CHILDREN (2-18 YEARS) with a progressive disease, with minor, diffuse or non-specific symptoms
	ADULTS (>18 YEARS) with a progressive disease, with minor, diffuse or non-specific symptoms
HOSPITALIZATION AND/OR EMERGENCY HOSPITAL CARE	**NEWBORNS & TODDLERS (0-2 YEARS)** presenting with acute or early onset symptoms **NEWBORNS & TODDLERS (0-2 YEARS)** presenting with a visible dysmorphic feature at birth
	CHILDREN (2-18 YEARS) AND ADULTS (>18 YEARS) presenting with a crisis episode with acute symptoms
CONSULTATIONS WITH SPECIALISED HOSPITALS, ESPECIALLY IN CLINICAL GENETICS	**PATIENTS OF ALL AGES** with a suspected genetic rare disease and their family members
PERIPHERAL PRIVATE PRACTICE STAKEHOLDERS AND ORGANISATIONS	**PATIENTS OF ALL AGES** with a slight or moderate intellectual deficiency receiving care from a medical-social organisation
	PATIENTS WITH A SLIGHT OR MODERATE PHYSICAL DISABILITY receiving paramedical care
	CHILDREN WITH A PROGRESSIVE DISEASE RECEIVING CARE FROM A SCHOOL DOCTOR or adults receiving care from a workplace doctor

* This qualitative estimate is formulated by the UNIR project committee, and does not rely on a documented statistical study

MAIN STAKEHOLDER GROUPS INVOLVED	DISEASE EXAMPLES	RISK OF DIAGNOSTIC DELAY*
• Private practice paediatricians • Paediatricians and other non-expert hospital specialists • Specialists from the rare disease expert network	Severe combined immunodeficiency	
• Private practice general practitioners/paediatricians • Paediatricians and other non-expert hospital specialists • Specialists from the rare disease expert network		MODERATE
• Private practice general practitioners • Private practice specialists • Non-expert hospital specialists • Specialists from the rare disease expert network	Adult-onset Pompe disease (mucopolysaccharidosis 1 or MPS1)	HIGH
• Hospital paediatricians • Non-expert hospital specialists • Specialists from the rare disease expert network	Infantile-onset Pompe disease	LOW
• Emergency doctors • Non-expert hospital specialists • Specialists from the rare disease expert network	Fibrodysplasia ossificans progressiva	MODERATE
• Clinical geneticists • Specialists from the rare disease expert network	Fabry disease	LOW
• Paramedical or medical-social professionals • General practitioners • Private practice specialists • Non-expert hospital specialists • Specialists from the rare disease expert network		MODERATE TO HIGH DEPENDING ON THE SITUATION

The diagnosis journey, points of difficulties and identified solutions

Point of access: consultation with a general practitioner or paediatrician
A consultation with a general practitioner or paediatrician is the main point of access to the diagnosis journey when symptoms do not appear at birth and are not acute.

Often, children seen by a private practice paediatrician are referred to a hospital paediatric department in the event of an atypical clinical picture or persistent symptoms following a limited number of consultations. Indeed, the robust structure of the paediatric network (smoother communication between private practice and hospital practitioners, existence of paediatric health networks etc.) makes it easier to refer young patients and enables generally quick access to suitable experts. Fast referrals also usually help reduce the time it takes to get a diagnosis. However, it is interesting to note that, according to the results of the ERRADIAG study, the time to be referred to a hospital varied based on the age of the child when the symptoms appeared, and was longer for children (2–18 years) than for adults (>18) or newborns (0–2 years) (ERRADIAG, 2016, p. 32).

For children and adults beginning their journey with a consultation by a general practitioner, several consultations with generalist or specialist private practitioners may be necessary depending on how specific and chronic the symptoms are. If patients present with an atypical case, they may be referred to the hospital network. If the referring doctor has a good knowledge of rare diseases and their ecosystem, patients may be directly referred to a competent expert center (CCMR or CRMR). Patients are generally referred to the non-expert hospital network for additional consultations and analyses. Repeated generalist and/or specialist consultations can increase the risk of erroneous diagnoses and can be a source of considerable diagnostic delay for patients (ERRADIAG, 2016, p. 32).

This is often the point of access for patients experiencing symptoms that are progressive, mild or vague. These diseases generally present like more common diseases and make identifying the atypical clinical picture especially complex for healthcare professionals.

Point of access: hospitalisation and/or emergency care
Hospitalisation and emergency care are a point of access for many patients with a rare disease. Among them are two "typical" cases.

The first is that of patients presenting with a visible dysmorphic feature at birth or when acute symptoms develop between zero and two years of age. At this age, any symptom is closely monitored. Newborns are quickly hospitalised and generally do not leave until a diagnosis or referral is made. Referrals to the appropriate experts are generally made quickly and diagnostic delay is relatively limited in this type of situation.

The second case is that of patients with delayed symptom onset (children aged 2 to 18, or in adults over 18), with acute episodes of symptoms. The patient is immediately admitted, either to the hospital for consultation or to the emergency department. While a rare disease may be suspected at this point, this suspicion will depend on the type and presentation of symptoms as well as whether a rare disease expert is available in the hospital. For some diseases, such as Fabry disease, it is common for patients to have several acute episodes affecting different organs before a rare disease is finally suspected.

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The diagnosis journey,
points of difficulties and
identified solutions

Point of access: clinical genetics

For diseases with a known genetic cause, or a suggestive family history, a consultation with a clinical geneticist is a direct point of access to the diagnosis journey.

When a patient receives a diagnosis of a hereditary disease, genetic consultations are offered to other family members to detect those at risk. These consultations offer the family support for the diagnosis, genetic counselling, treatment, prenatal testing and research. This consultation is a point of access that strongly limits diagnostic delay. Access to expertise, if deemed necessary following the consultation with a clinical geneticist, is very quick. However, this point of access is not always used by patients, because the fear of a serious diagnosis (possible for parents and offspring) may cause family members to feel anxious or guilty and lead them to postpone care.

Point of access: peripheral stakeholders in the primary care network

Peripheral stakeholders in the primary care network are also a point of access to the diagnosis journey.

The suspicion of a rare disease – or an atypical clinical picture – may, for example, be suggested by a school doctor (e.g., during medical visits, in the event of repeated trips to the nurse's office etc.) or by residential care homes, such as those for children or adults with special needs. Cases may also be suspected during consultations with a workplace doctor or by paramedical practitioners, such as physiotherapists for neuromuscular issues. In some cases, these practitioners can help the patient begin the diagnosis journey by referring them to their general practitioner, sometimes noting the suspicion of an atypical case. Our approach did not allow us to estimate the number of patients concerned by these points of access, particularly those in residential care homes whose personnel may have alerted the appropriate healthcare professionals.

Accordingly, the study of these typical journeys shows that diagnostic delay varies depending on the symptoms and how they present, patient age and previous history. From this observation, we focused our work on identifying the obstacles to diagnosis that were prioritised as most important by the community, especially for journeys deemed to have the greatest risk of diagnostic delay, in order to put forward relevant solutions.

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The diagnosis journey,
points of difficulties and
identified solutions

Difficulties
in the diagnosis journey

The interview and joint workshop discussion phases enabled us to identify more than 13 "obstacles" to diagnosis, divided into five categories, shown in the table on pages 60–61. Identified obstacles were prioritized by degree of impact on the delay assessed by experts.
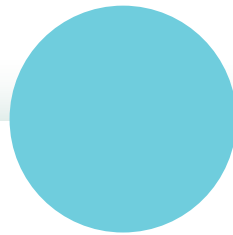
Note on the methodology

A qualitative analysis:

A qualitative approach cannot guarantee the exhaustiveness of the information gathered. However, the number of interviews, range of profiles and critical assessment by various professionals during the workshops helped make them generally representative. Most of the points of difficulty identified were shared by several people we spoke with, and the marginal amount of new information highlighted during the final interview phases was very limited.

The diagnosis journey,
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**Identified points of difficulty along the diagnosis journey:
estimated level of impact and required action**

TYPES OF DIFFICULTIES	OBSTACLES IDENTIFIED
DIFFICULTIES IN ACCESSING CARE FOR PATIENTS	• Scattered and unequal care options • Rarity of rare disease expertise • Lack of and unequal access to experts
LIMITING FACTORS RELATED TO PATIENTS	• Delays in taking symptoms seriously • Denial of the supposed diagnosis • Partial communication of results from prior consultations
LACK OF SCEPTICISM	• Difficulty recognising some clinical signs of rare diseases • Lack of awareness when seeing atypical situations • Cognitive bias in medical practice • Isolation of expertise
DIFFICULTIES REFERRING PATIENTS TO RARE DISEASE EXPERTS	• Lack of familiarity with and visibility of rare disease networks
DIFFICULTIES IN SHARING INFORMATION AMONG HEALTHCARE PROFESSIONALS	• Difficulty obtaining a comprehensive view of the patient's history • Difficulty exchanging information between professionals

*The level of impact is defined here as the impact of the point of difficulty on missed opportunities for patients (number of patients, resulting delay etc.)

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MAIN STAKEHOLDERS AFFECTED	ESTIMATED LEVEL OF IMPACT*	ESTIMATED LEVEL OF ACTIONABILITY**
• Private practice paediatricians • Paediatricians and other non-expert hospital specialists • Rare disease experts	MODERATE	MODERATE
• Patients / Family members	MODERATE	LOW
• GPs / Paediatricians • Private practice specialists • Non-expert hospital specialists • Rare disease experts	HIGH	HIGH
• GPs / Paediatricians • Private practice specialists • Non-expert hospital specialists	MODERATE	HIGH
• GPs / Paediatricians • Private practice specialists • Non-expert hospital specialists • Rare disease experts	MODERATE	HIGH

**The level of actionability is defined here as the ability to tackle the point of difficulty (perceived and estimated complexity, time to implement, organisational impacts etc.)

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Inequality in access to care, especially in rural areas, is a reality and an obstacle that can have a significant impact. This is even more true for rare diseases. However, addressing this challenge remains difficult.

TRANSCRIPT OF A WORKSHOP
DISCUSSION BETWEEN HEALTHCARE
NETWORKS AND PATIENT ASSOCIATIONS

A major limitation in the expert centers is the number of patients. The time it takes to see an expert – from three to 12 months at times – can be a real problem. Then there is the added time for performing some analyses.

EXPERT CENTER COORDINATOR

The first major hurdle in the expert network is the time it takes to get an appointment. The second is the lag time to do the tests. It varies considerably. A CGH array can be done in a month because it has been a routine test for ten years. For an exome, it can take three months to a year, because the waiting list is long and sequencers are shared with other centers.

TRANSCRIPT OF A WORKSHOP
DISCUSSION BETWEEN HEALTHCARE
NETWORKS AND PATIENT ASSOCIATIONS

DIFFICULTIES IN ACCESSING CARE

In many cases, the diagnosis of a rare disease first begins in the primary care network following a consultation with a private practice generalist or specialist doctor.

However, access even at this level can be complicated for patients living in areas with few medical facilities, which is increasingly true in many places.

Around 8% of the population, or more than five million people (ARS-Santé), may face problems accessing care in France in 2018, from long waiting times for appointments to having to travel long distances to a doctor's office. Such unequal access to care can also lead patients to forego care if symptoms are "tolerable". These situations lengthen the diagnostic delay for rare diseases. Expertise, which is extremely concentrated in hospital centers, increases difficulty of access and further increases the distances patients must travel when they live in rural areas or far from the expert center for their suspected disease.

Once an appointment has been made at an expert center, the extreme concentration of expertise can create lengthy waiting times for testing and analysis. Conducting and interpreting numerous tests and analyses for rare diseases becomes difficult outside of large expert hospital centers. In some centers, consultation waiting times can be between nine and 18 months, to which analysis waiting times must then be added. For example, an exome analysis can take three months to one year depending on the center. These waiting times, combined with multiple consultations and testing, significantly lengthen the time it takes to get a diagnosis.

In addition to these factors, the disparity of resources allocated to centers can lead to a lack of funds. Expert centers have observed a lack of certain clinical skills and suitable tools, such

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as those to investigate a family history. Moreover, waiting times for some analyses (e.g., biological or genetic testing) vary from one center to another. Most of these analyses are performed by public laboratories, whose resources (staffing, equipment and funding) vary. Finally, such reduced means limit renewed testing for patients who still do not have a confirmed diagnosis, even as technologies evolve quickly and could make it possible to detect new cases.

Inequality in care access around the country and varying resources are hurdles in the rare disease diagnosis journey that complicate and slow access to experts.

The role of analytical testing laboratories is very important. To properly diagnose a rare disease, you need a good laboratory.

Tests may come back negative from one lab and positive from another more specialised laboratory.

DIRECTOR OF AN ANALYTICAL AND
DIAGNOSTIC TESTING LABORATORY

Given the constant changes in knowledge and techniques, it is important to redo analyses regularly for patients without a confirmed diagnosis.

However, due to staffing and equipment issues, such analyses are often only performed during a routine visit or when symptoms change, based on a clinician's intuition.

MANAGER OF AN ANALYTICAL
TESTING LABORATORY

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*Patients who adapt to their
condition over the years
without consulting a doctor
are quite common.*

MISSION HEAD
AT A RARE DISEASE HEALTHCARE
NETWORK

*Steinert's disease is an example
of a disease where patients
won't complain, even when
experiencing issues (digestive,
neurological). They rarely
seek out care, and experts
have to reach out to them.*

*Ignoring symptoms is common
when they are not serious. The
"pain" element is usually the
trigger for going to see a doctor.*

EXPERT CENTER COORDINATOR

LIMITING FACTORS
FOR PATIENTS

Some difficulties affecting patients or their families may cause longer diagnostic delays.

Rare diseases that progress gradually are often characterised by initial symptoms that are non-specific or mild. Pain or discomfort may appear banal and be ignored by patients and their families. In some cases, patients gradually become accustomed to the disability and develop workarounds in their lives. However, recurring or accumulating symptoms should be a warning sign. These situations are frequent in cases of neuromuscular disorders, such as inclusion body myositis, channelopathies or central core disease.

Additionally, situations where patients are in denial about the diagnosis can also occur when a rare disease is suspected, whether by an expert or a non-expert physician. The seriousness of the rare disease diagnosis may lead the patient to see other practitioners in hopes of a different diagnosis. These situations are generally linked to fear with regard to family, social and economic consequences of a rare disease diagnosis. They are also observed during family screenings, which are offered when a member of the family has been diagnosed with a hereditary disease, and which can cause strain for the family. Diseases linked to the X chromosome are one example. Denial of the diagnosis, even temporary, is a major obstacle to confirming a diagnosis and implementing appropriate care.

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The refusal to undergo genetic testing in cases of hereditary disease is a problem.

There is a real missed opportunity for the patient. What is important is sharing information with potential patients, but this is sometimes difficult when members of the family are no longer speaking to each other.

EXPERT CENTER COORDINATOR

Sometimes patients are not satisfied with the supposed diagnosis and deliberately hide details during later consultations. In reality, patients should come with all the information they have, because some connections between medical examination results can be an obvious link for a specialist. The doctor should be the one sorting through the information.

MISSION HEAD
AT A RARE DISEASE HEALTHCARE
NETWORK

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Medical students are not taught to maintain a sufficient level of scepticism during their studies, and that can be felt in private practice medicine as well as in some hospital departments. There is no role-playing during training to learn to say 'could this be a rare disease'?

EXPERT CENTER COORDINATOR

Many rare diseases develop progressively and slowly. Symptoms can be minor and non-specific, such as fatigue, pain, depression or cramps. It can be difficult to recognise a rare disease with those. However, when the symptom persists or worsens, the doctor must be more careful. Several minor, worsening symptoms taken together is a warning sign. A common error is to diagnose a psychological or psychosomatic disease.

EXPERT CENTER COORDINATOR

Emergency departments are an important focus for networks, because emergency doctors also lack scepticism. Much too often, urgent or acute symptoms are treated without looking for the underlying cause.

MISSION HEAD
AT A RARE DISEASE HEALTHCARE
NETWORK

DETECTION DIFFICULTIES IN ATYPICAL SITUATIONS

Several factors can complicate the detection of atypical situations in the non-expert network.

First, basic training on rare diseases in medical school is brief, and limits non-expert practitioners' knowledge of these diseases. Additionally, non-expert practitioners rarely come across cases of these diseases, which means they are not likely to consider this type of atypical diagnosis. This leads to several questions: How can doctors encourage and maintain the reflex to consider rare diseases over time? How can practitioners be encouraged to keep rare diseases in mind, even when symptoms are common?

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Given the complexity and diverse character of rare diseases, it would seem unreasonable and irrelevant to believe that non-expert doctors would be in a position to diagnose a rare disease. However, it is crucial for them to be able to detect atypical situations in patients. Such a "culture of scepticism" when they see an atypical case would allow them to address the patient's symptoms differently, to expand the possible diseases considered and, if necessary, refer the patient more quickly to an appropriate expert. It is important to emphasise that constant scepticism from doctors is not desirable either. However, erroneous diagnoses and incorrect diagnostic possibilities remain a source of diagnostic delay for patients, as noted in the EURORDIS Care reports (EURORDIS).

General practitioners risk having tunnel vision when they are overly focused on a part of the clinical picture to formulate possibilities. Tunnel vision is also a risk for specialists: when a patient consults several specialists without informing each of the practitioners, this can lead to a silo effect as a specialist attempts to make a diagnosis. Specialists are trained to consider the system or organ in which they are specialised, sometimes putting aside symptoms that fall outside of this system. While this diagnostic reasoning by system can achieve results in most cases, it can complicate the diagnostic process for rare diseases, which tend to present as multisystemic cases, and can increase the time needed to detect an atypical situation.

Practitioners need to know their limits and when to make a referral, rather than continuing on pointlessly. This is especially true since incorrect diagnoses, such as a psychosomatic disorder, create bias and can be a factor in mistakes or increase diagnostic delay because it is even more difficult to challenge an established diagnosis.

RARE DISEASE EXPERT

Non-expert specialists generally have excellent knowledge of their speciality and network. But they often have poor knowledge of other specialities. The problem with some rare diseases is that they are multisystemic.

EXPERT CENTER COORDINATOR

There are also problems in interpreting analyses. Having a rare disease expert review a test can identify an anomaly for an image or result that initially appeared normal. From pathology to scanners, non-expert specialists are not trained on rare diseases and only see what they're looking for.

EXPERT CENTER COORDINATOR

Did you know?

Cognitive bias

Numerous studies

have shown that diagnostic failures depend on various factors.

Psychological factors

are key in influencing the cognitive function of the decision-maker.

Other research suggests that **environmental and contextual factors**

can create risky situations that dissuade decision-makers from making a decision.

For more information, refer to the following two scientific articles:
Diagnostic Errors, 2008; Cognitive Debiasing, 2013; **recommended by Professor Olivier Steichen, a specialist from one of the expert networks participating in this initiative.**

Fatigue, sleep deprivation

and cognitive overload appear to be decisive factors.

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DIFFICULTIES IN GUIDING PATIENTS TO RARE DISEASE EXPERTS

Once a non-expert doctor identifies an atypical clinical picture, they can encounter difficulties in guiding the patient through next steps.

Many non-expert doctors lack knowledge as well as familiarity with the rare disease expert network. They may have questions regarding the most appropriate institution, competency or person to take over the patient's care. To date, there is no simple tool that non-expert doctors can use to quickly identify the nearest expert based on the identified symptoms. Patient referrals largely depend on the doctor's personal network. This situation increases regional inequality: it is easier for a doctor who practices medicine in or near a teaching hospital to make a referral than for an isolated doctor in a private practice or a local hospital.

Furthermore, doctors face difficulties in identifying another component of the expert network: analytical testing laboratories. Non-expert doctors may not know where they are located, the analyses they can do, their procedures (administrative and technical) etc., all of which can be a barrier for practitioners who want to further their diagnostic research using complementary analyses, especially in the non-expert hospital network.

The additional time spent on such situations contributes to diagnostic delay for patients, even though there are ways to address these issues.

Access to information is a real problem still today. The expert network is fairly well-rounded (CRMRs, CCMRs, FSMRs), but it is not widely known. And patients are not immediately redirected to experts.

EXPERT CENTER COORDINATOR

The creation of the rare disease network with the expert centers constitutes real progress. It has also helped bring in funding. But the hierarchical structure and names are not well understood outside the expert network.

RARE DISEASE EXPERT

It is rare that a general practitioner will find the center's address alone. Often, it's the patient who finds the center and address after an internet search.

EXPERT CENTER COORDINATOR

There is no database that would simplify the search for expert analytical testing laboratories. I know what kind of testing I want to do, but it is not easy to find the appropriate laboratory. And no information is available regarding the procedure to send samples, the forms to fill out, the sampling methods to use, clinical information to include, etc. Simplifying the procedure would make it easier to deal with complicated diseases.

NON-EXPERT DOCTOR IN A HOSPITAL CENTER

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DIFFICULTIES IN SHARING INFORMATION AMONG HEALTHCARE PROFESSIONALS

Organised and secure sharing of information among professionals treating a patient is the foundation of care coordination. Although all stakeholders understand the need to share this information, actually doing it can be time consuming and hampered by a range of issues.

These issues may be technical. The difficulty and even impossibility for a doctor to have a comprehensive and exhaustive view of the patient's information (reports, analyses, history, etc.) complicates diagnosis, especially

Many patients do not know their own records well.

Communicating information is difficult when there is no shared record. Many practitioners do not respond when they are asked about their conclusions from their consultation.

MISSION HEAD
AT A RARE DISEASE HEALTHCARE
NETWORK

for multisystemic pathologies such as rare diseases. An operational shared medical record (SMR) could be one solution.

Access to expertise located far away is still a difficulty for non-expert practitioners as well as for professionals in the expert network due to a lack of appropriate tools. For non-expert practitioners, access to an expert opinion following a suspected atypical case depends on their knowledge of the rare disease network and their personal network of contacts. Facilitating access to expertise via shared tools designed for such use (user-friendly, secure, etc.) would speed up doctors' decisions and help them more efficiently refer patients to the rare disease network. For practitioners in the expert network, the situation is similar when a second opinion is needed from an expert in another national or European center. Today, practitioners use their personal networks and available tools (email, Skype etc.) to access non-local expertise. This brings up the issue of securing health data. Moreover, the lack of suitable tools also limits multidisciplinary consultations between distant sites, which require finding a time when all stakeholders are available to meet in person.

Finally, the compartmentalisation between care sectors (health, medical-social, social) is also a potential obstacle to sharing information among professionals. Access to direct and simple communication pathways between these sectors would simplify requests for second opinions or reporting complex patient cases from one sector to another. In their everyday practices, school and workplace doctors or paramedical practitioners meet patients with atypical health conditions, which leads these professionals to refer patients to the primary care network along with an advisement to take note of the atypical clinical picture. The means available to these professionals are sometimes considered too limited today. Regarding cases of intellectual deficiency, medical-social structures are not ▸▸

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>> responsible for monitoring their patients' conditions, and as a result, some patients may have symptoms that have not been identified. Gradually increasing cooperation between medical-social and healthcare sectors (especially expert centers, CRMRs and CCMRs) could make patient referrals to expert centers more efficient.

Points of difficulty have been identified at all levels of the diagnosis journey, from the patient to the expert network. While their importance and impact on diagnostic delay varies, hurdles that slow referrals of patients to an expert center appear to be the main sources of delay along the diagnosis journey. In particular, developing "scepticism" among non-expert practitioners is an important area of focus to move patients from the non-expert to the expert network more quickly.

Even within the expert network, sometimes it's not possible to get a second opinion from other experts, to reinterpret analyses (scans, biopsies etc.) for example. This is possible in a hospital, but it is still difficult with remote centers. There needs to be a national network that connects the different centers.

MISSION HEAD
AT A RARE DISEASE HEALTHCARE
NETWORK

To communicate about patients, we generally use email, because multidisciplinary consultations do not exist within the expert network or between remote sites. Ideally, there would be a very simple and suitable standardised tool, and regular multidisciplinary consultations.

NON-EXPERT DOCTOR
IN A HOSPITAL CENTER

There are a lot of patients without a diagnosis in medical-social structures. They may refer patients without a diagnosis in the event of a major intellectual disability. But the local expert center is not in close enough contact.

EXPERT CENTER COORDINATOR
MISSION HEAD AT A RARE DISEASE
HEALTHCARE NETWORK

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Solutions to reduce diagnostic delay

THE VARIOUS EXISTING SOLUTIONS IDENTIFIED WITHIN AN ECOSYSTEM UNDERGOING DIGITAL TRANSITION

France has long been working to digitalise the healthcare and medical-social sectors according to a range of objectives, first starting in the hospital system: administration and financial management (PMSI, Programme for medicalising information systems); electronic patient records and paperless clinical documentation; digitalisation of biological tests, imaging, hospital electronic prescribing and the hospital medication pathway.

More recently, several key areas of digitalisation have gradually been developing and have changed practices: telemedicine, digitalisation of patients' hospital care, the pharmaceutical record and the shared medical record, secure health messaging system etc. Meanwhile, private practice doctors' offices are also using software to digitalise their tools for patient management, prescriptions, billing and payments, and appointment booking. More recently, new stakeholders have positioned themselves in the sector with a "platform" approach for telemedicine consultations with doctors or experts with some supplemental insurance companies. Accordingly, projects are being implemented on different levels:

- **National projects:** genomic platforms, data collection for data banks, patient medical records, vigilance portal
- **Regional projects:** telemedicine, treatment information portals, shared imaging platforms
- **Hospital projects:** digitalising the outpatient care pathway, online appointment booking, clinical data warehouses to identify patients who are eligible for therapeutic trials etc.

Initiatives are also under way at the European level, such as research projects or projects to create European platforms to facilitate cross-border patient care.

In France, the most recent oSIS report (Observatory on health information systems, Observatoire des systèmes d'information de santé) by the Fench Directorate of Health Care Supply (DGOS) indicates that the maturity of the information systems intended to support patient care in French health establishments (teaching hospitals, hospital centers, clinics, private establishments etc.) is increasing (DGOS, 2018). However, only 58% of patient records and treatment plans have been digitalised in the 2,665 establishments surveyed, which accounts for 84% of French healthcare establishments. The process to digitalise the healthcare system is continuing but is not yet complete. Furthermore, investments by hospitals in France (1.7% of operating expenses for hospital information systems) are well below European levels (3% on average) in this area.

With regard to the general public, digital tech-

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nologies are gradually becoming more commonplace. According to a recent study (BVA), more than a quarter of French people track their health data using digital technology, and nearly 30% book medical appointments online. The popularity of health apps and connected devices is also growing. Nearly seven out of 10 French people and doctors say that connected devices are useful for tracking their health. Eight out of 10 French people and seven out of 10 doctors find health apps useful. However, the actual rate of use of these apps and connected devices remains limited, with just one out of five French people actually having used them. Despite the slow adoption of these technologies, doctors' trust in the opportunity they offer has remained steady or risen: four out of 10 say they recommend health apps to their patients, while two out of 10 say they use connected devices to track their patients' health status.

Accordingly, our work was both focused on identifying the types of existing tools as well as solutions that could be developed to reduce diagnostic delay. The illustration on the following page shows a non-exhaustive overview of the types of tools identified during our work. Specific examples of tools are given in brackets on the following page.

Overview of rare disease diagnostic support solutions

PATIENT ENVIRONMENT

PRIVATE PRACTICE NETWORK

General health information sites (Doctissimo)

Rare disease information sites (MRIS, patient associations)

Patient communities (RareConnect)

Internet search (Google)

Rare disease serious games (SOCRATE)

Generalist diagnostic support systems

Shared medical record

Pharmaceutical record

DIAGNOSTIC DECISION SUPPORT TOOLS

Medicinal product database (Vidal)

Clinical decision support (CDS) tools (Diagnostic Help)

Databases (MatchMaker)

Medical knowledge bases (Cartagénia / GeneMatcher)

Shared imaging platform

Biomedical literature databases (PubMed)

Medical knowledge bases (OrphaNET, HPO)

National Diagnosis and Treatment Protocols (PNDS)

Multidisciplinary consultation software

Rare disease patient registries (BNDMR)

Data science platforms (Dr. Warehouse)

Clinical data warehouse (CDW)

Rare disease diagnosis tools (OrphaNET, Phenomizer, Findzebra, Possum, Isabel Healthcare)

Rare disease information exchange and data processing platforms (RD-Connect, Beacon)

TECHNICAL TESTING PLATFORMS

NON-EXPERT HOSPITAL NETWORK

RARE DISEASE EXPERT HOSPITAL NETWORK

○ Category of value-added solutions
() = Existing support solutions

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Overview of solutions identified during the initiative

THE DIAGNOSIS JOURNEY	Patients and family members	Private practice network	Non-expert hospital network	Expert hospital network

• *Shared medical record**
• Patient intake form to prepare consultations

Solutions to support the identification of atypical clinical pictures

• Initial and continuing training on rare diseases (culture of scepticism)
• Red flag "atypical case warning"
• Diagnostic decision support tools

• Imaging platform and detection algorithms
• Observational study of patient histories
• Semantic search tool for electronic patient records

• Platform to analyse the patient medical record by the expert network (second opinion)

Solutions to support coordination between stakeholders and patient referrals

• Expertise mapping
• *Digital solution for rare disease information and guidance**

• Telemedicine with the expert network (patient record exchange platform)
• *Multidisciplinary consultation between non-experts and experts**

Solution to share national (FSMR) and international (ERN) expertise

• Multidisciplinary consultation management tool

* Solutions that fall outside the UNIR initiative and which were not explored further.

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FOURTEEN SOLUTIONS IDENTIFIED TO REDUCE DIAGNOSTIC DELAY

Our initiative sought to expand the range of solutions that already exist to support the diagnosis journey by identifying needs that have yet to be addressed.

Within this extremely dynamic context, where digital tools can help enhance the efficiency of the care system and the quality of care itself, we worked to identify tools that could reduce diagnostic delay. Nevertheless, we are aware and fully believe that these tools must be developed to support people and be designed with their uses and needs in mind.

Fourteen proposed solutions emerged from our efforts and are aimed at various stakeholders along the diagnosis journey. These solutions can be associated with three major priorities:
• **Improving the identification of atypical clinical pictures**
• **Supporting coordination between stakeholders** and patient referrals
• **Facilitating the sharing** of national and international **expertise**

Some solutions (in italics on the diagram on page 76) fell outside the scope of this initiative, and so were not explored further. These include organisational solutions and/or solutions beyond the scope of rare diseases that face regulatory hurdles.

Each solution was evaluated on a qualitative basis according to two criteria:
• **The level of impact on diagnostic delay** as estimated by the project committee
• **The level of technological maturity**, estimated based on the existence and development stage of similar projects (R&D, start-ups, industrialised solutions).

Solutions to support the identification of atypical clinical pictures

1 - Shared medical record (SMR)*
The SMR is a secure digital record that tracks patients' health conditions, treatments and insurance reimbursements. SMRs are managed by Assurance Maladie, France's national health insurance agency, with a view to facilitating multidisciplinary patient care by sharing medical information online with private practice and hospital practitioners. By providing a more comprehensive view of a patient's medical history, the SMR is a precious tool to aid diagnostic and therapeutic decision-making (AMELI). Since December 2016, a new SMR system is being tested in nine pilot administrative départements in France.

Because the roll-out and widespread use of the

SMR is still in its early stages, patients remain the main aggregators of their medical information and must share it in the most exhaustive way possible with the practitioners they see. For rare diseases, a 360° view of a patient's medical history is crucial for professionals to identify their suspicions. The SMR appears to be one of the tools that could help improve the diagnosis journey by having all useful data available in a single, standardised and shared system for all stakeholders (patients, doctors, insurance companies etc.).

The SMR could draw from and, eventually, even be integrated with the pharmaceutical record, a shared electronic health record available using the Carte Vitale - the French national health insurance card - and overseen by the french national chamber of pharmacists (CNOP). For all public health insurance (Assurance Maladie) ▸▸

*The feasibility of these solutions was not explored further as part of the UNIR initiative

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>> beneficiaries who so desire, the pharmaceutical record identifies all medication given in the previous four months, whether prescribed by a doctor or recommended by a pharmacist, and today has more than 37 million active records (CNOP, 2018). The pharmaceutical record was initially developed in pharmacies, but has gradually been adopted by healthcare establishments and helps improve care coordination between private practices and hospitals.
The importance of the use of the SMR was mentioned in Action 7-5 of the third national plan for rare diseases (PNMR3) to facilitate the identification of patients with rare diseases, especially for emergency care and to avoid some risk situations.

• Priority target: Patients/non-expert and expert practitioners
• Level of estimated impact on diagnostic delay: N/A
• Level of technology or solution maturity: Industrialised solutions
• Level of complexity to implement: High

2 - Patient intake form

When an SMR is not available, a doctor meeting a patient for an initial consultation must create a complete record with ample information obtained during the consultation (symptoms, history, allergies, comorbidity etc.). This takes time, even as waiting times to get an appointment are getting longer, especially in the expert network. The time spent on creating a complete patient history could be avoided by gathering information beforehand using a patient intake form.

This would make it possible to transfer organised and targeted information to the healthcare provider before the consultation, and

would also facilitate the gathering of information related to the patient's own and family history to save a significant amount of time that could then be spent talking to the patient and on the clinical exam. The patient intake form would be based on questionnaires that could be adapted based on the network and the initial information provided by the patient. The patient could be asked to complete it before the consultation either online or via an app, for example after an online appointment is made, or could be filled out in the doctor's waiting room.

• Priority target: Rare disease experts
• Level of estimated impact on diagnostic delay: Low
• Level of technology or solution maturity: Start-ups
• Level of complexity to implement: Low

3 - Platform to analyse the patient medical record by the expert network (second opinion)

It is not rare for patients to be the first to suspect a rare disease following multiple consultations that have not led to a diagnosis, or after an online search of their symptoms. The development of online health forums, for example, enables patients to do in-depth research on their symptoms prior to a consultation and leads some patients to question healthcare professionals' opinions. Some patients contact the MRIS platform, patient associations or expert centers directly to discuss their situation.

To manage this type of request and prevent centers from becoming overly busy, an online "second opinion" platform could be developed. This platform could make it possible to download the entire medical record and obtain >>

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➤➤   an expert opinion on the possibility of a rare disease, without booking an in-person appointment. However, strong involvement from the expert centers (CRMRs and CCMRs) would be necessary to analyse and respond to requests.

- Priority target: General practitioners/ paediatricians/private practice specialists/hospital specialists
- Level of estimated impact on diagnostic delay: High
- Level of technology or solution maturity: Start-ups
- Level of complexity to implement: High

4 - Enhanced initial and continuing training on rare diseases (culture of scepticism)
Since the first national plan for rare diseases (PNMR1), rare diseases have been a major public health priority. However, the initial training of practitioners today includes only a few hours of classes on rare diseases. While critical, this instruction is not sufficient to create a "culture of scepticism" in practitioners over the long term. And yet approaching atypical cases with scepticism and referring patients to the dedicated network is crucial to reduce diagnostic delay in the non-expert network.

Including more instruction on rare diseases in initial medical training could help reduce diagnostic delay. Moreover, the implementation of continuing distance training through e-learning systems could sustain or improve knowledge, whether via courses such as Massive Open Online Courses (MOOCs), resulting in a degree or not, or serious games.

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One example is the serious game called So-crate, developed by Sanofi Genzyme. It aims to raise awareness among general practitioners about rare diseases and facilitate referrals to expert centers. Through a series of six clinical cases, the goal of this game is to encourage general practitioners to develop their scepticism and stimulate their reflex of sending atypical cases to a reference or competence center. **Continuing training for doctors is a key priority in rare diseases, the importance of which is emphasised in Action 9-3 of the third national plan (PNMR3).**

- Priority target: General practitioners/ private practice specialists/hospital specialists
- Level of estimated impact on diagnostic delay: High
- Level of technology or solution maturity: Industrialised solutions
- Level of complexity to implement: High

5 - Red flag "atypical case warning"
Identifying a patient with a history of an atypical disease is complex, especially in cases where the symptoms are non-specific. This early warning tool would generate automatic alerts, indicated by a "red flag" for example, through practitioners' software to signal a possible rare disease, allowing them to adapt their support.

Two red flag cases are possible and could be linked to make the warnings more reliable. A first "delay" red flag would apply to the patient's journey. For instance, it could appear when the patient has seen numerous different specialists in a short period of time, or had multiple consultations with different general practitioners. A second "atypical situation" war-ning could appear when a patient mentions or a doctor notices an atypical combination of symptoms and/or symptoms affecting multiple organs.

Two methodological approaches could be foreseen to manage these warnings. The first would be to create empirical rules based on experts' experience. The second would be to take advantage of machine learning to identify journey profiles or atypical symptoms by using existing data as a training dataset. Several sources of data could be used to produce these alerts: data from the National Health Data System (SNDS: SNIIRAM, PMSI), electronic patient records (SMRs, medical practice management software, EPRs), rare disease database (BND-MR), hospital data warehouses etc. The predictive character of these data sources would need to be assessed. Finally, filters would likely need to be added to prevent too many false positives, which would overload expert centers.

- Priority target: General practitioners/ paediatricians/private practice specialists/hospital specialists
- Level of estimated impact on diagnostic delay: High
- Level of technology or solution maturity: R&D
- Level of complexity to implement: High

Did you know?

Machine learning

Marvin Lee Minsky defined **artificial intelligence as**:

"The science of making machines do things that would require intelligence if done by men."

Machine learning and statistical learning

are fields of study in artificial intelligence that involve developing methods to allow a machine (in broad sense) to learn through iterative learning and complete difficult tasks using more traditional algorithmic means. To achieve results, machine learning requires large amounts of data.

Artificial intelligence

draws from computational neurobiology (neural networks), mathematical logic and informatics. It uses tools to imitate human functions (recognition, reasoning, decision-making).

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6 - **Diagnostic decision support tools for rare diseases**

Several diagnostic decision support tools exist today and can be integrated into information systems used by private practice or hospital practitioners. However, these software programs are oriented towards researching common diseases and are not suited to identifying rare diseases. In the expert network, specific software is available to these specialists, but they are not suited for use by non-expert practitioners due to the complexity of the symptoms in the programs.

Developing a non-expert diagnostic decision support tool designed for rare diseases would be especially helpful for general practitioners and paediatricians when facing atypical clinical pictures and are considering the possibility of a rare disease. A doctor could enter specific information (clinical, biological or phenotypic symptoms) and the program would offer suggestions of possible rare diseases, or rare diseases clusters. The aim would not be to make a diagnosis, but rather to support or rule out a suspected atypical case in order to guide the patient to the appropriate center or to a national information and referral platform.

- Priority target: General practitioners/ paediatricians/private practice specialists/hospital specialists
- Level of estimated impact on diagnostic delay: High
- Level of technology or solution maturity: Start-ups
- Level of complexity to implement: Moderate

These last two solutions – red flag warnings and diagnostic decision support tools – could support Action 1-1 of the third national plan (PNMR3), which aims to speed up the diagnosis journey by referring patients to expert centers (CRMRs or CCMRs).

7 - **Imaging platform and detection algorithms**

The use of digital images in medicine is increasingly common for biological analyses (e.g., biopsies) or medical imaging (e.g., MRIs and CAT scans). The analysis of these images is often a reliable way to confirm or rule out some rare diseases.

These images are generally archived in the electronic patient record (EPR) at the hospital and sometimes sent to other practitioners for further review. Efforts today are being made to create centralised platforms for imaging databases between establishments. Whether images from MRIs, biopsies or even dermatological conditions, the creation of these centralising imaging platforms would make it possible to test innovative detection approaches for rare disease cases. Machine learning could be used to test detection of patterns specific to different diseases based on the training dataset, and to develop prefiltering algorithms for new images. Only "suspicious" cases would be kept for further analysis by a specialist. These methodologies are complex but have already been shown to be effective in oncology.

- Priority target: Experts/analytical testing laboratories
- Level of estimated impact on diagnostic delay: Low
- Level of technology or solution maturity: Start-ups/industrialised solutions
- Level of complexity to implement: Moderate

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8 - **Observational study on patient histories**
Patient histories, which recount patients' journeys, are an extremely important source of information regarding diagnostic delay. And yet, the gathering and analysis of these "histories" is not systematic today. To remedy this, the creation of an observational study on systematically collecting the histories of patients with a rare disease is a possible solution proposed following our study. This type of study would aggregate information from patients as well as from practitioners consulted throughout the diagnosis journey. Information could be gathered by rare disease networks and expert centers or through a research platform open to patients and healthcare professionals. The involvement of rare disease healthcare networks (FSMRs) in creating such studies could be part of the new complementary missions set out in Action 10-1 of the third national plan (PNMR3).

This aggregated database of patient histories could be used for research, especially to identify common patterns in rare diseases based on declared symptoms or journey details. These patterns could be projected on accessible health databases to identify possible cases of rare diseases (see "atypical case" warning solution). The need to have a way to filter and avoid overloading expert centers would be essential.

- Priority target: Experts
- Level of estimated impact on diagnostic delay: Moderate
- Level of technology or solution maturity: R&D
- Level of complexity to implement: High

9 - **Semantic research tool in electronic patient records**
Electronic patient records include a large amount of textual data (reports). To better exploit these data in free text, various knowledge bases allow machines to better understand medical language (UMLS, SNOMED CT, HPO, Orphacodes). Used in conjunction with natural language processing in search engines, it is possible to perform a contextualised search in a vast volume of structured and unstructured data. Such initiatives have already been launched, such as the Dr Warehouse data warehouse in France, developed with the support of the Imagine Institute and public hospitals.

Applied to rare diseases, a semantic search engine could be used for retrospective searches in hospital data to find patients with comparable clinical episodes or phenotypes, for example. Entire patient records could be searched to find patients without diagnoses when a molecular diagnostic test becomes available. Using this type of tool could help identify patients awaiting a diagnosis.

- Priority target: Experts/analytical testing laboratories
- Level of estimated impact on diagnostic delay: Moderate
- Level of technology or solution maturity: Start-ups
- Level of complexity to implement: Moderate

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Solutions to support coordination between stakeholders and patient referrals

10 - Expertise mapping

The rare disease network in France was created and strengthened during the first two National Plans for Rare Diseases. While this network is highly structured, understanding how it is organised and accessing information about it is not easy for non-expert practitioners (and sometimes even for experts). A map of the medical expertise was drawn up and published by Orphanet, and more recently by rare disease health networks as well. However, visibility remains limited because the way information is presented is not suited to the needs of non-experts.

The map of rare disease expertise, integrated into an intuitive tool, could bring information about the expert network together for quick and easy access by non-expert professionals: location of expert clinics, practitioner names and contact information, contact forms, etc. For non-expert practitioners, this map could help practitioners refer patients with a suspected rare disease more quickly to the nearest and most appropriate expert center based on their symptoms. The tool would help reduce haphazard patient referrals, which are still largely dependent on practitioners' personal networks. Finally, a clear map of analytical testing laboratories, including the analyses that can be performed and the sample submission process, could make it easier for hospital practitioners to request a particular analysis.

This solution echoes Action 1-2 of the third national plan (PNMR3), which seeks to improve the visibility of how technical diagnostic platforms are organised and coordinated, and to share this information with healthcare professionals and the general public.

- Priority target: General practitioners/paediatricians/private practice specialists/hospital specialists
- Level of estimated impact on diagnostic delay: Moderate
- Level of technology or solution maturity: Industrialised solutions
- Level of complexity to implement: Moderate

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11 - **Telemedicine consultations between healthcare professionals**

Rare disease expertise is concentrated in some healthcare establishments. In-person access to this expertise is complex, both for patients and for practitioners seeking a medical opinion from an expert colleague about a patient with an atypical clinical picture. Yet, the decision to refer a patient to an expert center, which may be located far away, depends on the initial diagnostic details that a non-expert doctor may have trouble piecing together. The use of telemedicine between non-expert doctors and the expert network could be an effective way for non-expert doctors to get further insight from an appropriate specialist. These telemedicine tools could also apply to interactions between national and international experts.

How to bill for telemedicine services has long been a key issue that has held up the full expansion of this practice. Previously, patients had to actually come to the hospital for an expert practitioner's activity to be recognised financially by the hospital. However in France, recent negotiations on the issue are intended to remove this barrier to allow the practice to take root from September 2018. Payment is planned for both the requesting and responding healthcare professionals.

Today, information about patient cases is often exchanged through unsecured software, and calling on experts depends on the general practitioner's personal network. The creation of a secure system for non-expert and expert practitioners to share information would help promote access to expertise and faster patient referrals while preventing expert centers getting overloaded. To encourage this type of solution, a user-friendly design for practitioners is key.

These telemedicine tools are right in line with Action 7-5 of the third national plan (PNMR3), which seeks to develop telemedicine and eHealth in the rare disease networks.

- Priority target: General practitioners/ paediatricians/private practice specialists/non-expert hospital specialists
- Level of estimated impact on diagnostic delay: High
- Level of technology or solution maturity: Start-ups/industrialised solutions
- Level of complexity to implement: Moderate

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12 - **Digital solution for national rare disease information and guidance***

Today, a national information and support system on rare diseases, Maladies Rares Info Services (MRIS), exists alongside other local initiatives such as the PRIOR network. The MRIS system could be strengthened and expanded to centralise the information and guidance of patients and non-expert healthcare professionals when a rare disease is suspected. This would require creating a structure that brings together social, medical-social and medical resources to meet the needs of patients looking for information as well as non-expert healthcare professionals needing additional information, to connect with an expert or to help refer patients to the most appropriate expert.

• Priority target: General practitioners/ paediatricians/private practice specialists/hospital specialists
• Level of estimated impact on diagnostic delay: N/A
• Level of technology or solution maturity: N/A
• Level of complexity to implement: Moderate

13 - **Multidisciplinary consultations between non-expert practitioners and rare disease experts***

Multidisciplinary consultations are an increasingly common practice in hospital medicine. Healthcare professionals from several fields with complementary skills that are necessary to take the appropriate decisions meet to outline coordinated care for complex cases.
For rare disease cases, the solution proposed here would be to implement regular "rare disease" multidisciplinary consultations for non-expert practitioners, whether in private practice or a hospital setting. Managed by the rare disease healthcare networks, they could have one or two experts from different networks join each consultation. These consultations would allow professionals to discuss "atypical" cases and to confirm or rule out the need to refer a patient to an expert center.

• Priority target: General practitioners/ paediatricians/private practice specialists/non-expert hospital specialists
• Level of estimated impact on diagnostic delay: N/A
• Level of technology or solution maturity: N/A
• Level of complexity to implement: High

These last two solutions could draw on the rare disease expert platforms described in Action 10-6 of the third national plan (PNMR3) and be used to sort through information and get second opinions in support of telemedicine services provided by experts.

*Solutions that fall outside the **UNIR** initiative and which were not explored further.

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**Solution to share national (FSMR)
and international (ERN) expertise**

14 - **Multidisciplinary consultation mana-
gement tools for rare diseases**
The complexity of cases and the multisyste-
mic nature of many rare diseases requires
collaboration among experts from several
medical specialties through multidisciplinary
consultations. These consultations often still
require each doctor to be physically present,
which considerably complicates the planning
of consultations and expert doctors' schedules.
These issues are even more challenging when
practitioners are located far away from each
other, especially within a single rare disease
healthcare network.

The proposed management tool would be a sof-
tware program or an app that would facilitate
some or all of the planning of multidisciplinary
consultations (scheduling, agenda, follow-up
etc.). It could also integrate a telemedicine
component (secure video sharing, audio and
documents) to facilitate teleconferencing, both
in France and with international ERN practitio-
ners, whose expertise could be complementary
or even more specialised for some pathologies.
Such tools already exist at the European level,
and ERNs can use the Clinical Patient Manage-
ment System (CPMS), a secure record sharing
platform developed by the European Commis-

sion.
One of the key challenges will be to develop
national tools that are interoperable with the
CPMS and patient databases to prevent dupli-
cate record entry in the different tools. It will
also be important to identify the needs that are
not yet covered, as well as practices for plan-
ning multidisciplinary consultations so that
centers can more easily integrate such a tool.
As such, ASIP Santé (the French agency for di-
gital healthcare), is surveying the needs of rare
disease professionals as part of a feasibility
study on creating a multidisciplinary consulta-
tion management tool for expert centers.

**This tool could support Action 1-5 of
the third national plan (PNMR3), which
aims to systematically hold multi-
disciplinary consultations and as a
result maximise diagnostic cooperation at
the supranational level for very complex or
rare cases.**

- Priority target: Experts/Analytical testing
  laboratories
- Level of estimated impact on diagnostic
  delay: Moderate
- Level of technology or solution maturity:
  Industrialised solutions
- Level of complexity to implement:
  Moderate

**This wide range of solutions, both in their form and scope of action, demonstrates that a single
solution cannot resolve the issue of diagnostic delay entirely and that a combination of solutions
will be required.**

Solutions identified by UNIR that could reduce diagnostic delay for rare diseases

SOLUTIONS IDENTIFIED BY UNIR	DESCRIPTION
SHARED MEDICAL RECORD*	A secure digital record that tracks patients' treatments and insurance reimbursements. Speeds up and facilitates information exchange between care providers.
PATIENT INTAKE FORM	A questionnaire or other method to gather patient medical information prior to the appointment to optimise the time with the expert.
PLATFORM TO ANALYSE THE PATIENT MEDICAL RECORD BY THE EXPERT NETWORK (SECOND OPINION)	An online platform to discuss a suspicion of a rare disease with the rare disease network without overloading expert centers.
INITIAL AND CONTINUING TRAINING ON RARE DISEASES (CULTURE OF SCEPTICISM)	Developing e-learning tools or serious games to support the continuing training of care providers by encouraging their scepticism.
RED FLAG "ATYPICAL CASE WARNING"	An automatic alert tool that issues a warning when an atypical patient journey or combination of symptoms is noticed by the practitioner's software.
DIAGNOSTIC DECISION SUPPORT TOOLS	An alert tool that issues a warning when a combination of atypical symptoms is entered by the practitioner's software or the practitioner.
IMAGING PLATFORM AND DETECTION ALGORITHMS	A platform that centralises the data from medical imaging and biological analyses to develop automatic detection models.
OBSERVATIONAL STUDY OF PATIENT HISTORIES	Systematically collect patient histories to have a complete database for research on detection models.
SEMANTIC SEARCH TOOL FOR ELECTRONIC PATIENT RECORDS	A semantic search tool to retrospectively search medical data texts to support research on detection models.
EXPERTISE MAPPING	A tool to aid faster access to appropriate specialists, a dedicated tool that can be integrated with/linked to other diagnosis support tools.
TELEMEDICINE WITH THE EXPERT NETWORK (PATIENT FILE EXCHANGE PLATFORM)	A tool that provides easy, organised and secure access to an expert opinion without requiring an in-person meeting.
DIGITAL SOLUTION FOR RARE DISEASE INFORMATION AND GUIDANCE*	A way to bring together social, medical-social and medical resources to refer patients to the right experts in the expert network.
MULTIDISCIPLINARY CONSULTATION BETWEEN NON-EXPERTS AND EXPERTS*	A telemedicine platform to improve remote coordination between non-expert and expert healthcare professionals.
MULTIDISCIPLINARY CONSULTATION MANAGEMENT TOOL	A telemedicine platform to simplify and organise the creation of multidisciplinary consultations between experts.

*Solutions that fall outside the UNIR initiative and which were not explored further.

PRIORITY TARGETS	LEVEL OF ESTIMATED IMPACT ON DIAGNOSTIC DELAY	LEVEL OF MATURITY	LEVEL OF COMPLEXITY OF IMPLEMENTATION
Patients/non-expert and expert practitioners	N/A	INDUSTRIALISED SOLUTIONS	HIGH
Rare disease experts	LOW	START-UPS	LOW
General practitioners/ paediatricians/private practice specialists/hospital specialists	HIGH	START-UPS	HIGH
General practitioners/private practice specialists/hospital specialists	HIGH	INDUSTRIALISED SOLUTIONS	HIGH
General practitioners/ paediatricians/private practice specialists/hospital specialists	HIGH	R&D	HIGH
General practitioners/ paediatricians/private practice specialists/hospital specialists	HIGH	START-UPS	MODERATE
Rare disease experts/ analytical testing laboratories	LOW	STARTUPS / INDUSTRIALIZED SOLUTIONS	MODERATE
Rare disease experts	MODERATE	R&D	HIGH
Rare disease experts/ analytical testing laboratories	MODERATE	START-UPS	MODERATE
Rare disease experts	MODERATE	INDUSTRIALISED SOLUTIONS	MODERATE
General practitioners/ paediatricians/private practice specialists/hospital specialists	HIGH	START-UPS / INDUSTRIALISED SOLUTIONS	MODERATE
Rare disease experts	N/A	N/A	MODERATE
General practitioners/ paediatricians/private practice specialists/hospital specialists	N/A	N/A	HIGH
Rare disease experts	MODERATE	INDUSTRIALIZED SOLUTIONS	MODERATE
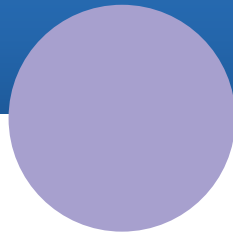
The next steps

The enthusiasm encountered throughout our work reflects the topical nature of this issue and its ability to unite rare disease stakeholders who want solutions. We are extremely grateful to all those who participated in **UNIR** and for the quality of their contributions. Sanofi France decided to make the results of this work accessible at no cost to encourage knowledge sharing and open innovation.

We would now like to turn our attention to developing two of the solutions identified, which will take the shape of a tool for clinical investigation and guidance and an early warning tool to support the work of healthcare professionals, especially those in the primary care network. To do this, we will draw up the functional and technical foundations of these solutions to test their feasibility and use before possibly scaling up their development. Accordingly, a quantitative study is currently being studied in line with work such as the ERRADIAG report (Alliance Maladies Rares, 2016) and the EURORDIS Care 2 and 3 surveys (EURORDIS).

The study will be based on the analysis of databases that retrace the care of patients with rare diseases, with two priorities in mind: describe the observations of diagnostic delay and the idea of missed opportunities, and create a system to evaluate the impact of solutions following their implementation.

Discussion

The mobilisation of stakeholders from the rare disease ecosystem, supported by proactive public policies, has encouraged many actions to better diagnose and treat rare diseases in France and Europe. The creation of a specific network for rare disease care and the certification of expertise in hospital centers are two specific examples of important progress made in the past 15 years.

Despite this progress, diagnostic delay remains a current challenge stakeholders are still working to tackle. Diagnostic delay varies from one pathology to another due to a combination of factors, from organisational to institutional and technical. In 2016, nearly a quarter of patients with a rare disease waited more than five years between symptom onset and being referred to a hospital center (Alliance Maladies Rares, 2016). This delay in diagnosis has major impacts on patients, with social, psychological, financial as well as health consequences, because the longer it takes to get a diagnosis, the greater the risk of erroneous diagnoses and worsening symptoms (Alliance Maladies Rares, 2016). Based on this information, the participatory UNIR initiative was launched by Sanofi in partnership with Orange Healthcare to identify innovative technological solutions to help reduce diagnostic delay for rare diseases.
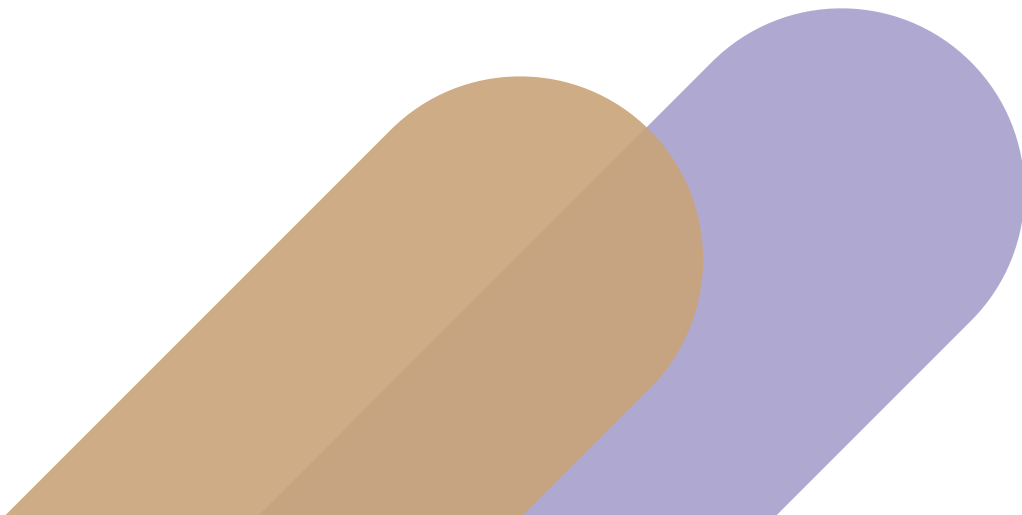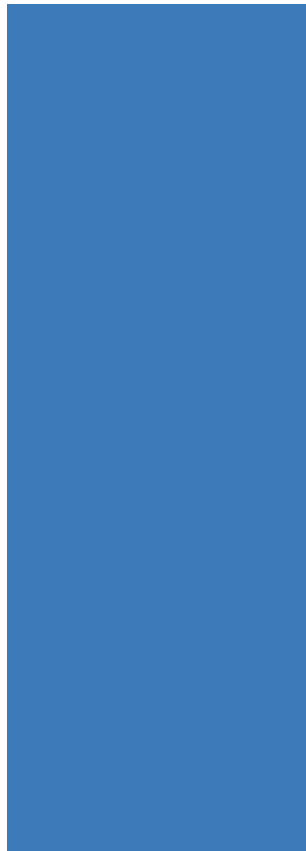
Our initiative allowed us to describe a general diagnosis journey for patients with rare diseases and to map out and characterise the remaining obstacles to diagnosis. The diagnostic delay caused by these obstacles varies considerably, as does the ability to remedy them. Although there are no precise quantitative studies on the issue, during our work we focused on analysing the possible causes and solutions that could reduce diagnostic delay (or the time lag before referring a patient to a rare disease center) in the primary care network. Collective discussions late in the research process helped identify 14 possible solutions to reduce diagnostic delay, with various possibilities: diagnostic decision support tools, information exchange platforms, professional training tools etc. As this wide range of solutions suggests, a single solution would not be able to resolve the issue of diagnostic delay; rather a combination of actions, some- ››

›› times complementary, will be required. In line with the observations made throughout the UNIR initiative, most of the identified solutions are centred on a specific part of the diagnosis journey: speeding access to expertise by better identifying atypical cases and improving the patient referral process. We wanted to share all of the results of the joint collaboration in this white paper so that other stakeholders could make use of the information.

New technologies, including artificial intelligence, have inspired new hope in the healthcare sector for healthcare professionals as well as for patients and institutions. These technologies call into question and sometimes upset established practices and human interactions, and require a certain amount of time and support for users to become comfortable with them. These two points are prerequisites to adopting and integrating technologies into common practices in the sector. The impacts vary in terms of care coordination, journeys, communication and more. These technologies also raise questions about ethics and security, which must be taken into account to ensure that technology use becomes firmly rooted in modern practices.

A number of challenges must still be tackled along the rare disease diagnosis journey. The choice made by UNIR to target our expertise on a specific segment should be part of a broader dynamic for action (organisational, regulatory, communication etc.) and bring together the full range of stakeholders from the rare disease ecosystem. Public and private stakeholders should continue their commitment to the issue, because France is a pioneering country that should keep driving improvements in the care of rare diseases. These actions should also remain in step with the European programmes and tools, in order to extend their reach. The UNIR initiative would like to underline the importance of complementarity in every stakeholder's participation to be able to address this difficult challenge.

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Annexes

List of participants
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Individual interviews

————————

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Workshop 1

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Workshop 3 - Hackathon

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Ms LIVIA AOUIZERATE	BUSINESS CLUSTER	MEDICEN
Mʀ IONEL TOTHEZAN	EXPERT NETWORK	ORANGE IMT
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Dʀ THIERRY CARDON	NON-EXPERT NETWORK	RHEUMATOLOGIST

Rare diseases affect more than three million people in France and are a major public health issue. Since 2005, the mobilisation of stakeholders from the rare diseases ecosystem, supported by proactive public policies, has improved the patient diagnosis journey and care. However, only one of every two patients with a rare disease has an accurate diagnosis, and nearly a quarter of patients must wait more than five years to get a diagnosis (Alliance Maladies Rares, 2016). This diagnostic delay has considerable impacts and is an enormous challenge for the healthcare system in France.

Today, new technologies have inspired renewed hope in the healthcare sector. Sanofi France, in partnership with Orange Healthcare, believes that reducing diagnostic delay in rare diseases will only be possible through a combination of actions and solutions (technical, organisational, communication etc.) that bring together the full range of ecosystem stakeholders: patient associations, medical and medical-social sectors, researchers, health industries and digital players. This is why the participatory UNIR initiative was launched, with a view to identifying innovative technological solutions to help tackle this challenge.

The initiative helped formalise a typical rare disease diagnosis journey and pinpoint ways to take action to reduce diagnostic delay. Fourteen technological solutions were identified, a majority of which are focused on speeding up access for the non-expert network to the necessary expertise, the main area of improvement identified in our discussions with stakeholders along the diagnosis journey.

In line with the open innovation approach adopted by Sanofi France for the UNIR initiative, this white paper summarises the work of this collaborative project and is intended for all stakeholders to share, capitalise on and adopt the ideas it lays out.