Deliverable 5.2

Existing experiences and Guidelines about the coding of undiagnosed rare diseases patients

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By the RD-CODE WP5 members

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More information on the activities of the RD-CODE project can be found at www.rd-code.eu

Table of content

Introduction: the "diagnostic odyssey"

The medical journey travelled by patients with a rare disease (and their families) from initial disease recognition or onset of signs/symptoms to a final diagnosis may involve serial referrals to several specialists and plenty of, often invasive, tests. This journey can be prolonged and, as a result, may have serious unintended consequences for the health of patients.

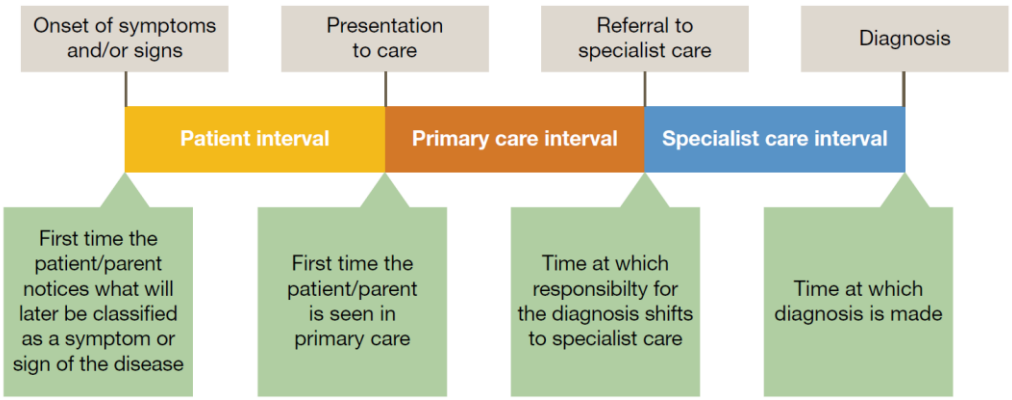

Figure1: *Conceptual framework of the diagnostic odyssey of rare disease patients by Black et al, 2015.*

According to Black *et al*.[1] the "diagnostic odyssey" of rare disease (RD) patients encompasses three different periods: patient interval between disease onset and primary care; primary care interval until referral to a specialist; and specialist care interval until the diagnosis – if findable.

Even without a precise diagnosis, most of the patients have access to proper care and treatment when they are referred to a rare disease specialist (expert centres).

In every step of the way, the patient diagnostic hypothesis is evaluated until it gets confirmed by a test or by another mean for confirmation (compliance with established diagnostic criteria, imaging, etc.). The end of the diagnostic odyssey for conditions that have an easily accessible, highly specific laboratory test is often clearly defined.

When the precise diagnosis is yet to be defined, the journey might be quite long. For instance, in France, more than a quarter of patients have to wait more than 5 years to get a diagnosis (including children) according to the French national plan for rare diseases 2018-2022[2]. Same results were published for Spanish[3] and Australian RD patients[4]. The French national plan for rare diseases 2018-2022 also states that in French RD expert centres, undiagnosed patients can represent up to 50% of the cohort. For the most complex diseases, the journey might never end, leading to a diagnostic impasse. Those patients can be included in research programs such as SOLVE-RD, to try to put an end to the wandering[5,6].

RD patients on their diagnostic odyssey need to be properly identified in Health Information Systems (HIS). The use of ORPHAcodes facilitates a precise coding granularity of diagnosed patients as this nomenclature provides more than 6000 rare disease names and their synonyms, further divided into more granular subtypes. But when the disease is unknown, other means should be available to make possible the description of the patient's condition.

This document is an attempt to propose definitions and documented approaches for the coding of RD when the specific disease is still unknown. We will provide a clear framework of this complex concept of undiagnosed patients. We will then describe how undiagnosed patients were coded in different systems in the RD-CODE participating countries and provide recommendations to better identify undiagnosed patients in health information systems (electronic health records and/or registries) for future implementations.

Definitions

These definitions are to be considered in the frame of the RD-CODE project only. They serve the purpose of making trans-national statistics possible, based on the same indicators.

1. Rare disease diagnosis

1.1. Diagnosis as a process

The word "diagnosis" is widely used to describe different medical situations with many meanings. A diagnosis can represent the name of the disease at some point of the diagnostic odyssey (however, some diagnoses will never have a name, for instance chromosomic abnormalities), or the process that leads to determine which disease or condition explains a person's symptoms and signs.

The following definition of a medical diagnosis can be found on several scientific journals websites: "A diagnosis, in the sense of diagnostic procedure, can be regarded as an attempt at classification of an individual's condition into separate and distinct categories that allow medical decisions about treatment and prognosis to be made. Subsequently, a diagnostic opinion is often described in terms of a disease or other condition."[7-8]

For the Committee on Diagnostic Error in Health Care, getting the right diagnostic "provides an explanation of a patient's health problem and informs subsequent health care decisions. The diagnostic process is a complex and collaborative activity that unfolds over time and occurs within the context of a healthcare work system. The diagnostic process is iterative, and as information gathering continues, the goal is to reduce the diagnostic uncertainty, narrow down the diagnostic possibilities, and to develop a more precise and complete understanding of the patient's health problem"[9].

In the frame of the RD-CODE project, it was agreed that a diagnosis is a process that leads to assigning a disease name to a patient's clinical situation, or to the undiagnosed status. Thus, the name of the suspected disease can evolve over time (*cf.* "Coding granularity" chapter).

In this document, this definition will be referred to as "diagnostic process" and the term "diagnosis" will be used to designate the nosological[1] category assigned to a patient.

1.2. Type of confirmation and diagnostic assessment

The diagnosis can include different situations and levels of confirmation.

1.2.1. Clinical assessment

On one hand, a diagnosis could refer to a clinical description of a health situation, based on signs and/or symptoms identified through advanced investigations: malformations, clinical manifestations, histological features, laboratory results including biomarkers, imaging findings, etc.

The clinical description can lead to a **suspected clinical diagnosis**, meaning that despite the clinical description and further investigations, the disorder is not really identified. In this case, a general and imprecise term for the condition can be attributed to the patient's situation. This term will most likely cover a heterogeneous group of patients with possibly different disease courses (e.g. a patient with «unclassifiable» polyarthritis as evaluated by rheumatologists). This suspected clinical diagnosis can be a step towards an

[1] Nosology is the science of classification of diseases.

established clinical diagnosis when the results of an investigation or the investigation method itself is not available yet (*cf.* chapter 4 "About diagnostic tests").

Conversely, the clinical description can lead to an **established clinical diagnosis**: a precise clinical diagnosis (naming the disorder) would be ascribed by RD experts to homogeneous and precisely defined phenotypic elements (including biomarkers), even when it has no identified causality (VATER association, for instance).

Finally, the presence of a constellation of signs and symptoms that cannot be named (e.g.: a child with cleft lip, thumb hypoplasia, epilepsy and agenesis of the corpus callosum: no syndrome name) can be considered as an **unknown clinical diagnosis**.

1.2.2. Etiological assessment

On the other hand, a diagnostic process could also lead to identifying the cause (genetic, autoimmune, infectious, environmental…) of the patients' disease. Etiopathogenic diagnosis is especially relevant for genetic diseases. When the cause has been identified, the etiological diagnosis will be considered as **established**; if not, as **unknown**.

1.2.3. Diagnostic assessment

In the frame of the RD-CODE project, the following diagnostic assessment has been decided considering the type of confirmation:

Clinical diagnosis	Etiological diagnosis	Diagnostic status for RD-CODE
Established	Established	Diagnosed
Established	Unknown	Diagnosed
Suspected	Established	Undiagnosed
Suspected	Unknown	Undiagnosed
Unknown	Established	Undiagnosed
Unknown	Unknown	Undiagnosed

Table 1: RD-CODE diagnosed and undiagnosed status by type of diagnostic assessment

In the frame of RD-CODE, the "undiagnosed patients" term will be used to describe patients with no established clinical diagnosis.

"Diagnosed patients" have an established clinical diagnosis related to a **confirmed rare disease**, even without an etiological diagnosis.

A clinical diagnosis may be the final diagnosis without the need for any additional procedure (for instance, when established diagnostic criteria are fulfilled). However, further research into the disease etiology is always to be considered in regards with the patient's situation in order to provide better care, a possible treatment or genetic counselling.

1.3. Undiagnosed RD patients

We define the undiagnosed patients as patients who are somewhere in the long pipeline of investigations and referrals of the diagnostic process, from primary care to specialist care, and did not get yet a confirmed and final diagnosis.

Referring to table 1, **undiagnosed patients can either have suspected clinical diagnosis (using unspecific term) or unknown clinical diagnosis (that cannot be named).**

How quickly the patient will be diagnosed depends on the condition but also on the expertise and tests available. This is why the up-to-date status of rare disease diagnosis has to be determined by expert centers in the field, to make sure state-of-the-art medical efforts have been made.

1.3.1. Undiagnosed patients with suspected RD clinical diagnosis

Suspected RD patients can be described by a generic, unprecise disease category to describe their signs and symptoms. Clinicians have not validated the hypothesis of the suspected disease yet because the search for the final diagnosis has not yet been successful.

Patients with such **suspected rare diseases** can usually be identified in health information systems: even without an etiological explanation, it is still possible to describe and code the disease with uncertain diagnosis (also called "primary diagnosis" or "working diagnosis"). Imprecise terms or groups of diseases are usually used (such as "epilepsy", "intellectual disability" or "neurodevelopmental disorder")[10].

This coding will be helpful for billing purposes, epidemiological purposes or to be socially enabling for patients. In addition, patients will be findable in databases so that their inclusion in research programs can be promoted (see "Reasons to identify undiagnosed patients" section below).

1.3.2. Undiagnosed patients with an unknown clinical diagnosis

Some diseases are so rare, complex or still unknown that it is not possible to diagnose the patient given the current knowledge and diagnostic tests. It may be because the patients' clinical picture has not yet been recognized as a specific clinical entity. In that case, neither the recognizable clinical description nor the etiologic explanation has yet been reached.

Those patients with **undetermined diagnosis** are difficult to identify in health electronic system as their condition cannot be described using an ORPHAcode, however, an unspecific ICD or the regular codification terminology used (for instance SNOMED-CT) can be used. Phenotypes can also be reported (e.g. using Human Phenotype Ontology).

As a conclusion, in the frame of the RD-CODE project,
undiagnosed patients are patients for whom no clinically known disorder could be confirmed by a RD expert center after up-to-date state-of-the-art diagnostic workup.

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2. Diagnostic delay

The diagnostic delay refers to the time during which the patient has not yet been diagnosed.

2.1. From the first signs to the expert center referral

According to the International Joint Recommendations to Address Specific Needs of Undiagnosed Rare Disease Patients[11], the diagnostic delay includes cases of patients who live with an undiagnosed condition that should be diagnosed but haven't been because they have not been referred to the appropriate clinician due to common, misleading symptoms, or an unusual clinical presentation of a known rare condition. On the conceptual framework of the diagnostic odyssey of rare disease patients by Black et al. 2015, it would be equivalent to the "patient interval" and "primary care interval".

> The reason for visit and a potential diagnosis can be coded with ICD codes in Health Information Systems. However, those patients cannot be traced as they are not yet identified as rare disease patients.

2.2. From the expert center referral to the diagnosis

The notion of diagnostic delay also includes patients that are already in the expert RD network but diagnostic investigations are still ongoing.

> Information about those patients can and should be coded in Health information systems as they are identified as (suspected) rare disease patients. Those patients can also be part of (disease) specific databases (registries, cohorts...) when the suspicion of a diagnosis is high but the confirmation hard to get.

The International Rare Disease Research Consortium (IRDiRC) proposed, as an ultimate goal for 2017–2027, to enable all people with a suspected RD to be diagnosed within one year of presentation, if the disorder is known[12].

3. Diagnosis impasse

The diagnostic impasse refers to the situation where the patient's disease is impossible to diagnose after undergoing all available investigations as of today[13].

It can also refer to patients for whom a diagnostic test is not yet available since the disease has not been characterised and the cause has not yet been identified[14].

In the case of genetic diseases, Wise *et al*.[15] describe those patients as "Patients who received an appropriate, extensive clinical evaluation on the basis of their presenting signs and symptoms, and yet remain without an etiological diagnosis. They might also have received targeted genetic testing or low-resolution chromosomal copy number analyses (e.g., chromosomal microarray) on the basis of their clinical presentation, or have a suspected diagnosis, or both, but no genomic-based diagnosis of the disease has been made".

4. About diagnostic tests

For some conditions, an easily accessible, highly specific test is available (for instance biochemical or genetic test), allowing confirmation of the diagnostic hypothesis. But other conditions can only be diagnosed clinically (consensual criteria based on observation) by an experienced clinician. In addition, some disorders do not require an etiologic test, even if it is available, as the clinical diagnosis is sufficient to adequately treat the patient.

It is important to highlight that the confirmation method for a given disease can differ from one country to another, or even from one expert centre to another inside a country, mainly because some of the tests are not available. National or cross-border collaboration is often required.

It can be recommended to try to have the etiological diagnosis of genetic diseases (genetic confirmation) when the cause has been described in the medical literature and when it may have an impact on the care or the cure of the condition (in the broad sense, including genetic counselling for instance). For non-genetic diseases, clinical gold standards should be published by European or international medical societies. Production of decisional trees and national recommendations based on the available tests should also be promoted.

Reasons to identify undiagnosed patients

1. Impacts on the patients

As stated in the International Joint Recommendations to Address Specific Needs of Undiagnosed Rare Disease Patients[16], undiagnosed rare disease patients should be recognised as a distinct population with specific unmet needs by national authorities to enable the development of personalised health and social care.

The RD-ACTION "Review document of existing technical implementations for RD coding"[17] underlined that identifying rare disease patients within health information systems is a key requirement to accelerate patient recruitment for clinical trials or observational and longitudinal data collections such as registries for research and public health purposes. This is also true for undiagnosed patients, who could be better identified to get access to genomics platforms throughout Europe for instance. Through the ERNs Clinical Patient Management System (CPMS), they could benefit from the shared knowledge of all the whole RD community in the medical field of interest to accelerate their diagnosis.

One of the main IRDiRC goals for 2017-2027 is that "[…] all currently undiagnosable individuals will enter a globally coordinated diagnostic and research pipeline", which requires the patients to be identifiable in care systems.

In addition, the diagnostic delay can lead to the identification of "pathways breaks" towards diagnosis, which happens when the patient is no longer interested in searching for a diagnosis because he/she does not believe anymore in the possibility of finding a diagnosis. It can also happen during the paediatrics to adults care transition. For the patient, this is a loss of chances to receive adequate treatment, which could be prevented if alerts in electronic health systems were in place.

Finally, the recognition of the rare disease status can be necessary for patients, even though they do not have a precise diagnosis. It can facilitate reimbursement of care, as well as being socially and psychologically enabling.

2. Impacts on the health authorities

A better RD coding and, consequently, an increased visibility of undiagnosed RD patients in health information systems can also inform health authorities about patients' care pathways and their use of health services, a necessary step in the care planning process and health economic costs impact evaluation.

Diagnostic delays prevent patients from accessing specialized healthcare and social services in a timely manner[18]. They may experience a progression in their disease, leading to potential disabilities and even preventable life-threatening complications. They may undergo unnecessary and painful procedures, and multiply medical appointments which can have serious impacts on their professional and personal life in addition to be potentially expensive for them and add major costs to the health care system[19].

Being able to assess the population of rare diseases patients, including undiagnosed patients, will enable greater political measures including financing for care and research programs throughout Europe. The comparable epidemiological statistics in EU countries will be a powerful tool to highlight the needs of patients, clinicians and researchers in the field.

Coding granularity

The term used for a diagnosis of rare diseases can be more or less precise. The granularity level of the term used can evolve along the patient's diagnostic pathway. The closer to the diagnosis confirmation, the more precise it can get.

Even when a RD is only suspected, it is important to try to classify it, as in some countries, reimbursement of care depends on a list of disorders. The clinician can thus provide the patient with the name of a family/group of disease, or even the suspected disease (primary / working diagnosis). Each time there's a revision to the working diagnosis, this should be communicated to the patient.

However, even when a precise term could be used, a broader one can be chosen depending on the purpose of the diagnostic label (clinical description in health information systems; biobanking; research in registries/cohorts; reimbursement...). Some patients do not need the etiological explanation of their disease to get the appropriate care as they usually get treated for the symptoms and not the cause. Yet, for genetic counselling, access to clinical trials and inclusion in research programs, the most granular level is needed.

Orphanet has developed a rare disease-specific nomenclature organized in a multi-hierarchical classification allowing a precise representation of all rare diseases. The entities of the Orphanet classification system (and their unique identifiers) are organised into groups, disorders and subtypes.

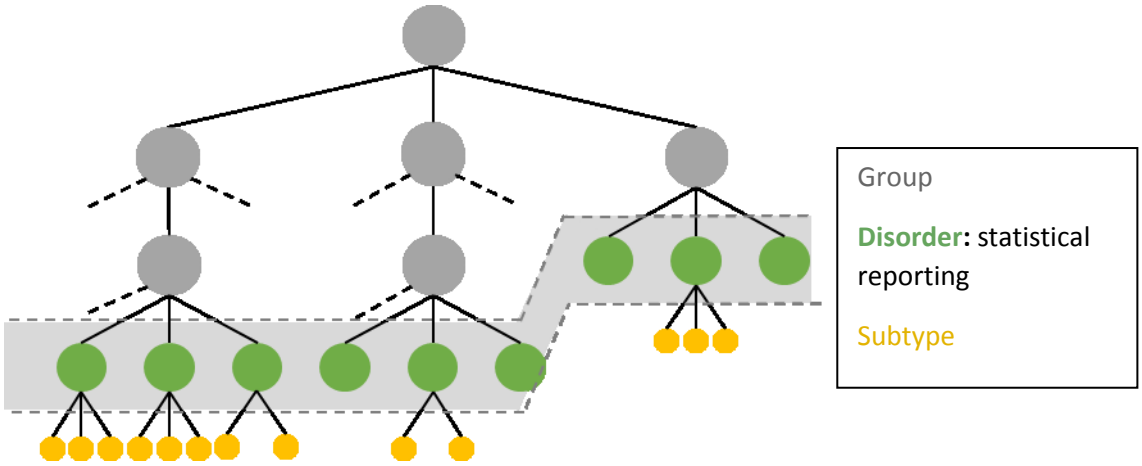

Figure 2: The Orphanet classification representation: groups of disorders, disorders and subtypes.

A disorder in the database can be a disease, a malformation syndrome, a clinical syndrome, a morphological or a biological anomaly or a particular clinical situation (in the course of a disorder)[20].

A 'group of disorders' is not considered as a precise diagnosis because it includes several heterogeneous disorders.

However, whether a term at the disorder level can be considered as a precise diagnosis when subtypes exist is an open question. Experts in the field will need to settle such matter – and it can differ from a disorder to another, but also from a country to another and even from an expert centre to another, depending on the access to diagnostic tests among other things.

At the EU level, the RD-ACTION project recommended to "code the data in a way that the reporting can comply to the granularity of the international recommended list of ORPHAcodes" (Guideline 2)[21] which is the disorder level. When generating data sets for international comparability, the subtypes can then be aggregated to the level of disorder to provide comparable data.

Experiences of coding undiagnosed patients

To complete this part of the document, a bibliographic study was conducted, and all RD-CODE partners were consulted through several rounds of review that are open for comments and two dedicated workshops.

This work concludes that the experience in coding undiagnosed patients in electronic health records (EHRs) or patient registries is scarce. Most of the experiences in the field are research oriented (see Annex 1), which prevent perspectives of epidemiological data comparison.

The French experience, the only one dealing with the subject in details, is described in Annex 2.

This work also pinpoints the need to differentiate coding in EHRs from coding in registries, as the possibility to make the tools evolve is very different according to the system (registries being more flexible).

Guidelines for coding undiagnosed patients

1. JRC Set of common data elements for Rare Diseases Registration

A Working Group coordinated by the EC's Joint Research Centre (JRC) and composed of experts from EU projects which worked on common data sets (EUCERD Joint Action, EPIRARE and RD-Connect) produced a "**Set of common data elements for Rare Diseases Registration**"[22].

It contains 16 data elements to be registered by each rare disease registry across Europe, which are considered to be essential for further research and **interoperability of RD registries**. They refer to patient's personal data, diagnosis, disease history and care pathway, information for research purposes and disability.

The item 6.3 of the "diagnosis" section is about "undiagnosed case": how the undiagnosed case is defined. The coding options proposed in the set of common data elements can be done with two descriptors:

- **Phenotype with HPO** (Human Phenotype Ontology)
- **Genotype with HGVS** (Human Genome Variation Society) – HGVS is a grammar (structure rules) used to describe the variant. They don't use identifiers as the variant itself is unique.

GROUP	ELEMENT N°	ELEMENT NAME	ELEMENT DESCRIPTION	CODING	COMMENT
6 Diagnosis	6.1.	Diagnosis of the rare disease	Diagnosis retained by the specialised centre	Orpha code (strongly recommended – see link) / Alpha code/ ICD-9 code/ ICD-9-CM code / ICD-10 code	http://www.orphadata.org/cgi-bin/inc/product1.inc.php
	6.2.	Genetic diagnosis	Genetic diagnosis retained by the specialised centre	International classification of mutations (HGVS) (strongly recommended – see link) / HGNC / OMIM code	http://www.hgvs.org
	6.3	Undiagnosed case	How the undiagnosed case is defined	• Phenotype (HPO) • Genotype (HGVS)	

These recommendations are quite broad and leave room for interpretation. As a result, they could be implemented in different ways.

Moreover, how to identify that the patient is undiagnosed is not indicated.

2. Generic recommendations for coding undiagnosed patients

As stated in the RD-ACTION "Standard procedure and guide for coding with Orphacodes"[23], in the process of differential diagnosis, some diagnoses are tested and excluded during the investigations. Capturing this information might be helpful but is not mandatory on an international level.

The RD-ACTION Guideline 3 can still be recommended in the frame of undiagnosed patients coding:

Recommendation #1:

Whenever possible capture the information of the diagnostic assertion for all RD cases. Use the options "Suspected rare disease", "Confirmed rare disease" and "Undetermined diagnosis". Additional options might be helpful.

In addition, as different levels of the Orphanet classification are needed, regardless of the chosen solution, it can be useful to keep the granularity information available (i.e. group of disorders, disorder, or subtype) together with the Orphacode for future data exploitation.

3. Specific guidelines for coding undiagnosed patients in registries

In addition to the 2 generic recommendations, registries should also provide a phenotype and a genotype description of undiagnosed patients to be compliant with the JRC Set of common data elements for Rare Diseases Registration.

Recommendation #2:

In registries, each undiagnosed patient should be described by its phenotype, using HPO. When available, the genotype should be associated to help future diagnosis, using HGVS. Additional phenotypic descriptors could be used (for instance ICD; SNOMED…) as well as genetics descriptors (HGNC genes…).

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4. Specific guidelines for coding undiagnosed patients in EHRs

Even though the previous recommendations could also apply for coding undiagnosed patients in EHRs, it might be difficult to modify all diverse EHRs to collect new items.

The focus should thus be made on being able to identify undiagnosed patients to count them and produce comparable statistics in the different countries, without adding any new item.

In the frame of the RD-CODE project, the best solution was to rely on the Orphanet classification that is currently implemented in the participating countries.

Three options were discussed:

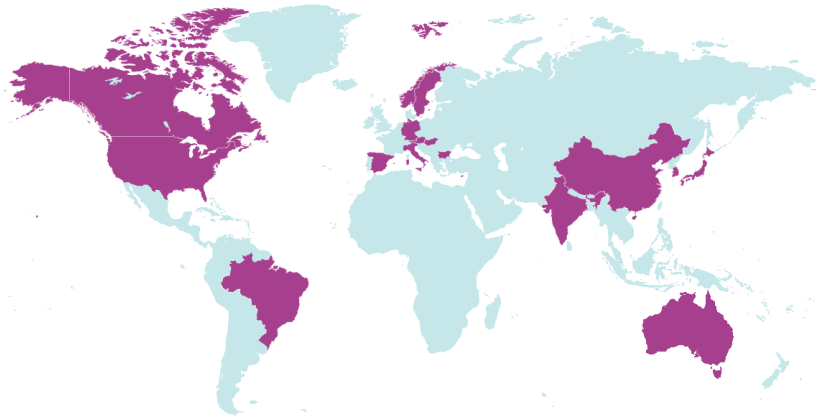
- Use of the Orphanet classification group levels (the higher up the lower the level of diagnosis definition)
- Use of a new dedicated Orphacode specifying the "undiagnosed" status
- Use of a normalized prefix / markers

Those three options will be tested in the voluntary implementing countries to make sure the final recommendation will be based on the most reliable option.

Annexes

1. Annexe 1: Undiagnosed Diseases Network International research program

A few countries have started dedicated national research program for undiagnosed patients such as Japan[24], Western Australia[25], USA[26] or Canada[27]. Based on their success, an international network to establish global programs for patients with rare and undiagnosed diseases have been formed: the Undiagnosed Diseases Network International (UDNI)[28]. Fifteen countries (including European ones) joined the network have to comply with the general principles of the UDNI (http://www.udninternational.org/).



Such programs are especially focused on finding the genetic etiology of the disease. They involve a combination of deep phenotyping of the patients by interdisciplinary expert panels, exhaustive genetic analysis by utilizing phenotype-driven next-generation sequencing and clinical and genomic data sharing. Data are collected in forms that are not using controlled and structured vocabulary, but recommendations on specifying a code is provided. Those forms are not linked to the hospitals' electronic records as they are specific to the research program.

The UDNI provides templates for case submission[29]. Once a diagnosis hypothesis is provided to the patient, the results are produced via the "Diagnosis Coding Tool" using descriptors such as:

- ⇨ Diagnosis Name (free text)
- ⇨ Phenotype (MIM Number)
- ⇨ Gene (MIM Number)
- ⇨ ICD Number

The certainty of the diagnosis is also assessed:

The overall certainty of the diagnosis.

- ☐ Certain
- ☐ Highly Likely
- ☐ Tentative
- ☐ Low (still on differential diagnosis, but lacking clear evidence)

2. Annexe 2: undiagnosed patients coding in FRANCE

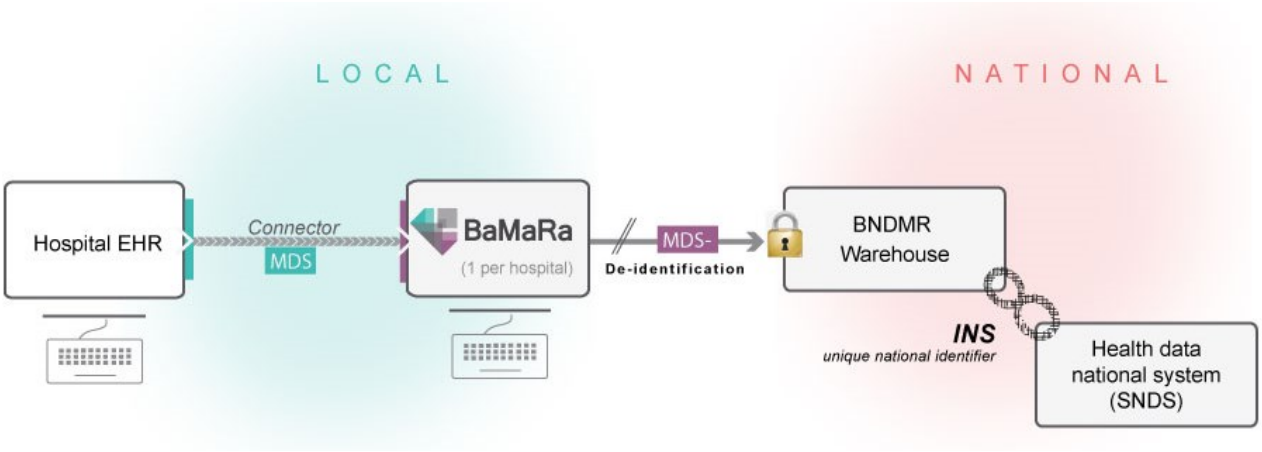
In France, more than a quarter of patients have to wait more than 5 years to get a diagnosis. In French RD expert centers, undiagnosed patients can represent up to 50% of the cohort. The national registry for rare diseases (BNDMR) provides ways to code patients in the database and in EHR (Electronics Health Records). In addition, the French national plan for RD dedicates more than 3M€ per year to tackle diagnosis delay and impasse reduction (action 1.7). It will help create an observatory of the diagnosis and provide more human resources to coordinate the work of the expert centers on the diagnostic coding and shared expertise.

The French registry on rare diseases (BNDMR) works on data collected only in RD expert centres. As a consequence, the national definition of the diagnostic delay does not include the "patient interval" period of the diagnosis journey - that is called "care-access delay"-. As this period is focused on finding the right infrastructure/centre of expertise to have access to the appropriate tests in order to make it possible to find a diagnosis.

2.1. French Implementation options in EHR and RD national registry

A national Minimal Data Set (MDS) was adopted during the second national plan for rare diseases[30]. The data collection can be done by **RD expert centers only**, either in a web app (BaMaRa) or in EHR. In the end, all the collected data is sent to the RD National registry (BNDMR). In France, the contribution to the BNDMR is mandatory (regulation) for expert centers and linked to a specific financing mechanism.

Out of the 16 items of the set of Common data elements of the European Commission (*see previous paragraph*), 13 items are available in the French MDS – and at least one more could be aligned soon (the patient identification with EUPID).



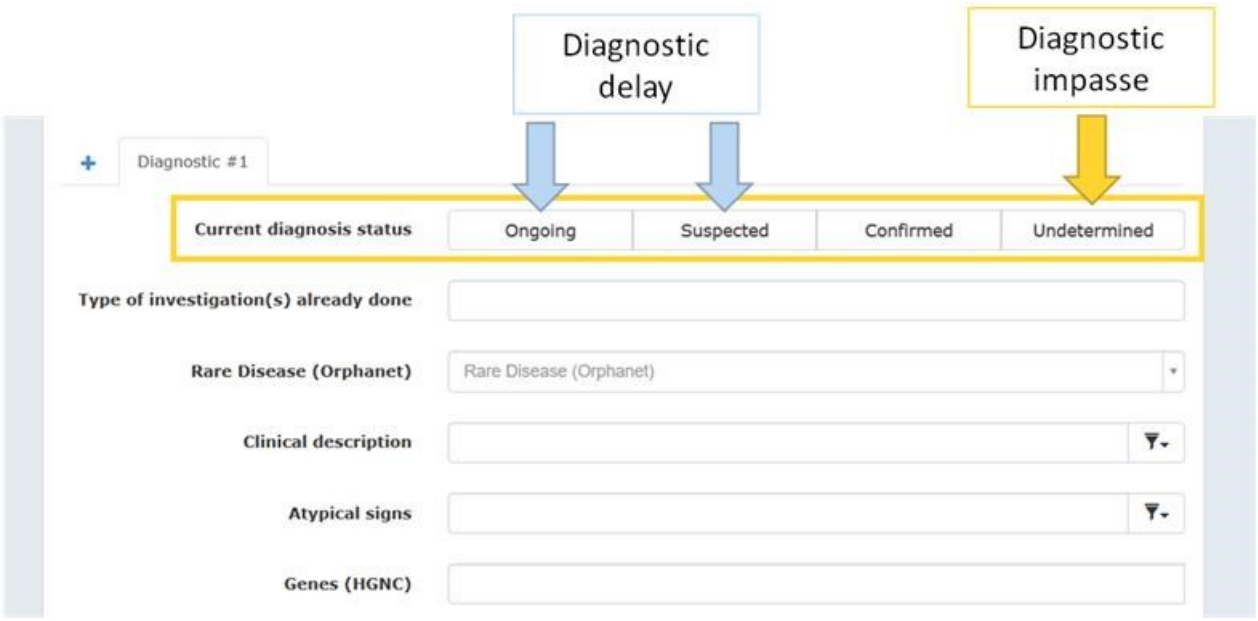
2.1.1. Diagnostic assessment

This global system was thought to include undiagnosed patients from the very beginning. The item Number 9.1 of the French MDS is about the diagnostic assertion and is mandatory.

Diagnostic assertion	Definition
Ongoing (initial)	Early investigative phase, diagnosis is in progress. No test result is available yet.
Suspected (likely)	This is a tentative diagnosis - still a candidate that is under consideration.
Confirmed	There is sufficient diagnostic and/or clinical evidence to treat this as a confirmed condition.
Undetermined (unknown)	The physician cannot determine the clinical diagnosis; it may be due to the absence of tests or to non-contributory tests. The investigation is completed or impossible to perform.

Important: Please note that in France, the data is captured by rare disease expert centers, assuming that the undetermined assertion is used on purpose by experts and not applied within the general healthcare system.

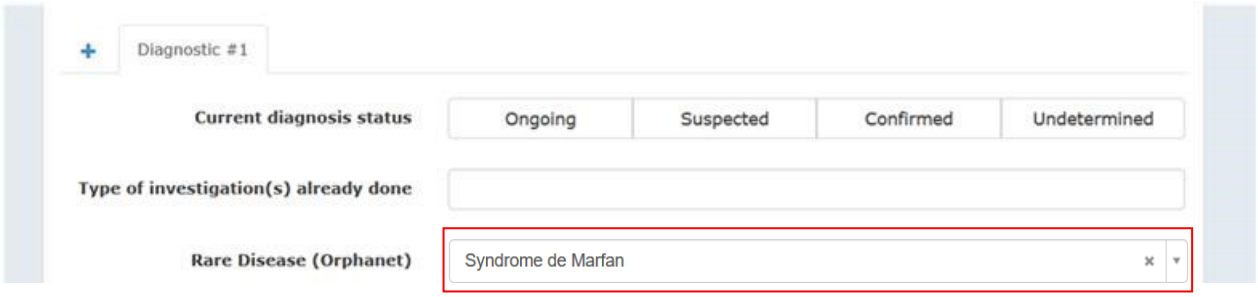
The use of such an assertion mechanism should be carefully done. When used, we recommend that it should be accompanied with clear instructions directed towards rare disease experts.



In addition, several means to describe the patient, even though the diagnosis has not been made yet, are provided. It includes the possibility to **describe the phenotype and the genotype of the undiagnosed patient**. The use of those complementary descriptors is not mandatory but highly recommended so that patients with close similar phenotypes or genotypes profiles can be grouped as well as for population-based studies.

2.1.2. Nosological descriptors

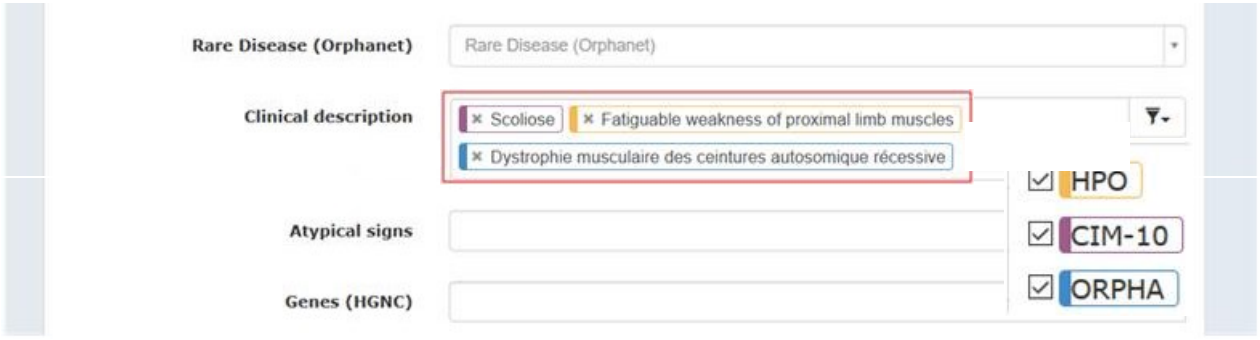
The use of the most precise terms of the Orpha nomenclature, i.e. disorder and subtypes levels, has been made possible to allow the description of the suspected diagnosis. More than 17.000 terms are available, representing more than 7.300 ORPHAcodes (as terms include synonyms), and are used as a flat list i.e. without classification levels. ORPHAcodes are recommended by the EC to code the diagnosis of rare disease patients. Only one term can be indicated in the field ("rare disease (Orphanet)").



2.1.3. Phenotypic descriptors

Phenotypes can be indicated using the HPO nomenclature. This nomenclature providing more than 10.000 terms is promoted by the European Commission and already in use in a lot of databases and cohorts/registries through Europe. In addition, groups of disorders of the Orpha nomenclature are also available, as well as the ICD-10 terms (that include a few rare disease names but are mainly general terms).

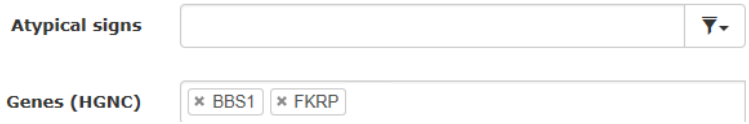
Several codes from those nomenclatures can be used to describe as precisely as possible the patients' phenotype.



ORPHA = Groups of Diseases

2.1.4. Genetics descriptors

Genotypes can be described using HGNC list of genes. Several genes can be coded.



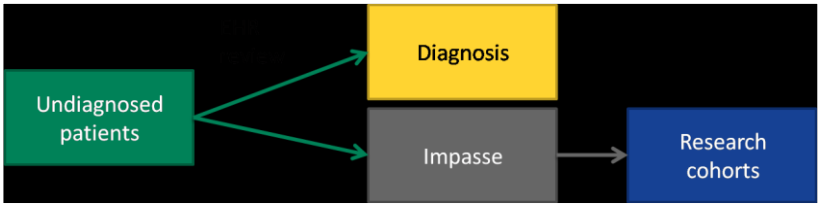
The mutation can be collected in free text format but following the HGVS structure is recommended.

2.2. Current national project on diagnosis delay and impasse (PNMR3 action 1.7)

This project aims to populate the observatory of diagnosis (to be created soon) with precise elements on the number of patients concerned and their "distance" to the diagnosis. This will be possible by using the BNDMR data, and might require additional field for the data collection to be more focused on the diagnostic journey and to reducing the loss of chances to be diagnosed.

It should help standardize, at national level, by medical field (filières de santé maladies rares), a homogeneous data collection for patients without diagnosis, allowing to detect, at the national level, non-diagnosed patients with similar pictures; create alert algorithms for patients who have been out of the healthcare system for a given period of time and for whom a new exploration would have a good chance to provide a diagnosis. Review of patient records is necessary as knowledge and technologies evolve quickly.

This project will also facilitate the inclusion of patients who can be recruited as part of the research program on diagnostic impasses or that would be good candidates for Whole Exome Sequencing/Whole genome Sequencing (WES/WGS).



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