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HEALTH SERVICES RESEARCH

BELGIAN NEUROMUSCULAR DISEASES REGISTRY (BNMDR)

Annual report 2017

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Belgian Neuromuscular Diseases Registry

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The Belgian neuromuscular diseases registry (BNMDR) is the result of several collaborations without which the project would not be possible. First of all, we would like to thank the patients and their families, who entrust us with their data, as well as the patient organizations, who stood at the cradle of this registry. Secondly, it should be noted that the specialist doctors and data managers of the neuromuscular reference centers perform remarkable work every year to complete the data collection in time, despite their already busy clinical schedule. We express our deep appreciation for their commitment to this work, repeated each year. Our thanks also go to our partners from the Healthdata.be platform, for their collaboration and support when facing the many technical challenges embedded in the project. Our colleagues from the Health Services Research department were also instrumental to the conception of this report. In particular, we would like to thank Kris Doggen and Hadrien Maloux who implemented and executed the data validation process. Finally, our thanks go to the INAMI which grants us its confidence by financing the project.

The year of the 2017 data collection will be remembered as a transition year. We said goodbye to Corinne Bleyenheuft, who left to pursue other opportunities, and Marjan Cosyns took on the role of project manager. In addition, in 2019, we welcomed Marlène Jagut as a new team member. Her training as a geneticist and previous experience as communication manager for the International Rare Diseases Research Consortium will be valuable for the project. Together with the changes in team composition, we decided to give the report a make-over. Modifications were made to both the lay-out and content. All of this combined with setting up the BNMDR-SMA sub-registry caused a delay in reporting. Nevertheless, we hope you enjoy reading this new report.

The BNMDR team

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LIST OF ACRONYMS AND ABBREVIATIONS

ACTIVLIM	ACTIVLIM is a measure of activity limitations for patients with upper and/or lower limb impairments. It has been validated in children (age 6-15) and in adults (age 16-80) with neuromuscular disorders.
ALS	Amyotrophic Lateral Sclerosis
BMD	Becker Muscular Dystrophy
BNMDR	Belgian Neuromuscular Disease Registry
CIDP	Chronic Inflammatory Demyelinating Polyradiculoneuropathy
CRAMP	Computer Registry of All Myopathies and Polyneuropathies
DM1	Myotonic Dystrophy type 1
DM2	Myotonic Dystrophy type 2
DMD	Duchenne Muscular Dystrophy
ES	Effect size
FVC	Forced Vital Capacity
FSHD	FacioScapuloHumeral Dystrophy
HMSN	Hereditary Motor and Sensory Neuropathy (or Charcot-Marie-Tooth disease, CMT)
HSP	Hereditary Spastic Paraplegia
ICD-10	International Classification of Diseases – 10
LGMD	Limb Girdle Muscular Dystrophy
NMRC	Neuromuscular Reference Centre
NIHDI	National Institute for Health and Disability Insurance (FR: Institut National d'Assurance Maladie Invalidité, INAMI; NL: National IRijksinstituut voor Ziekte- en Invaliditeitsverzekering, RIZIV)
NISS	National register number (FR: Numéro d'Identification à la Sécurité Sociale; NL: Identificatienummer van de sociale zekerheid)
OMIM	Online Mendelian Inheritance in Man (online catalogue of human genes and genetic disorders)
PPS	Post-Poliomyelitis Syndrome
RD-Connect	Rare Diseases-Connect is an integrated platform connecting databases, registries, bio-banks and clinical bioinformatics for rare diseases research
SAS	Statistical Analysis Software
SCA	SpinoCerebellar Ataxias
SMA	Spinal Muscular Atrophy
TREAT-NMD	Translational Research in Europe – Assessment and Treatment of Neuromuscular Diseases

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SUMMARY

The goals of the Belgian Neuromuscular Diseases Registry (BNMDR) are: to enable epidemiological research aimed at evaluating the importance of neuromuscular diseases and patient characteristics, to promote health services for patients with a neuromuscular disease, to provide information to public health authorities for planning of health care in Belgium, and to improve patient recruitment for clinical trials.

Patients' enrollment increases every year since the registry's creation in 2008. In 2017, a total number of 5,765 patients were registered, resulting in a Belgian prevalence estimate of 50.8 neuromuscular patients per 100,000 population. Patients' recruitment was better in the north than in the south of the country. This is presumably due to the geographical distribution of the reference centers collecting the data. Although the gap between those two regions tends to decrease year after year, an under-registration of patients coming from the southwest remains evident. This continuous observation highlights the need of the recognition of an expert center in this area.

The particularity of a general registry dedicated to neuromuscular diseases (compared to other health care registries) is that the patient population is diverse. Neuromuscular diseases indeed comprise various rare disorders affecting the anterior horn cells, peripheral nerves, muscles or neuromuscular junctions. Some disorders are genetic, while others are not. The vast majority of them are degenerative, sometimes with a fatal outcome in the short or long term. Some occur during childhood, and others occur during adulthood. In consequence, patients constitute a heterogeneous group making the extraction of global trends difficult.

For 2017, General demographic data showed a slightly higher number of males than females with a neuromuscular disease (N = 3,145 versus N = 2,620 respectively). The age range varied between 2 months and 97 years, with a median of 48 years (pc25 = 27 years and pc75 = 62 years). The vast majority of registered patients (75.3%) were ambulant, a significant proportion (19.7%) were wheelchair-bound and life support was needed in 2.0%. Diagnosis was considered final (with or without genetic confirmation) in about three quarters of patients (74.6%). Further, 220 deaths were reported, of which 135 (61.4%) occurred in patients suffering from Amyotrophic Lateral Sclerosis (ALS).

The ten most prevalent diseases of 2017 were, in order of significance: Hereditary Motor and Sensory Neuropathy, Myotonic Dystrophy type 1, ALS, Hereditary Spastic Paraplegia, Duchenne Muscular Dystrophy (DMD), Chronic Inflammatory Demyelinating Polyneuropathy, Facioscapulohumeral Dystrophy, Limb Girdle Muscular Dystrophy, Spinocerebellar Ataxias, and Postpolio Syndrome. Those ten diseases, accounting for 63.2% of all registrations, are analyzed in detail in the present report. It should be noted that this hierarchy is based on the NIHDI classification in which the four sub-types of Spinal Muscular Atrophy (SMA) are divided in four distinct disease groups. When pooled together, SMA was ranked 9th in the list.

For two defined groups of diseases, i.e. DMD/Becker Muscular Dystrophy (BMD) and SMA, the registry also collects additional data within the international TREAT-NMD network (Translational Research in Europe – Assessment and Treatment of NeuroMuscular Diseases). Those specific data are also analyzed in the present report. TREAT-NMD aims to advance diagnosis, care and treatment for neuromuscular patients. A total of 302 DMD patients, 109 BMD patients and 212 SMA patients were registered in 2017, making them eligible for feasibility studies and recruitment enquiries.

To optimize the quality of care in the reference centers, each center received a feedback report with benchmarking information. In addition, the quality of the 2017 data entry was subjected to a 5% verification of the files encoded within each reference center. The average percentage of mistakes was 12.7%, with a minimum of 0% and a maximum of 33.3%. It should be mentioned that the number of verified files was rather low in some centers, resulting in a artificially high error percentage. In the future, we will rethink our methodology to avoid such bias.

1. BACKGROUND

1.1. NEUROMUSCULAR DISEASES: GENERALITIES

1.1.1. DEFINITION

Neuromuscular diseases are not a single disease but several hundreds of different diseases that affect the peripheral nervous system, including muscles. Neuromuscular diseases can be classified depending on the functional subunits they are affecting (**Figure 1**):

- **Anterior horn cell disorders** where anterior horn cells of the spinal cord or motor neurons are affected (e.g. spinal muscular atrophy and amyotrophic lateral sclerosis)
- **Peripheral nerve disorders** where the nerves of the limbs are affected (e.g. peripheral neuropathies, such as hereditary motor and sensory neuropathy and Guillain-Baré syndrome)
- **Disorders of neuromuscular junction** where the junction between the nerve and the muscle is affected (e.g. myasthenia)
- **Muscle disorders** where the muscles are affected (e.g. myopathies such as Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy (BMD))

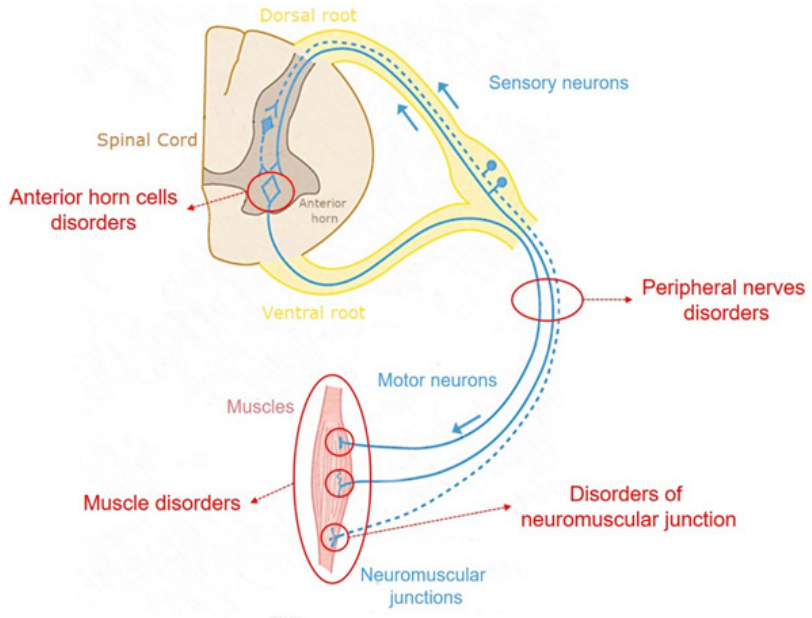


Figure 1. A schematic representation of the neuromuscular system

Adapted from Clinical Neuroanatomy 27th edition (1)
Red circles highlight the type of neuromuscular disorders associated with the impairment of the different parts of the peripheral neuromuscular system.

Neuromuscular diseases differ in their age of appearance (from the newborn to the elderly), their severity and their evolutionary consequences, their therapeutic management (which depends on the cause). They can affect the motor skills of the legs and/or arms but also other organs and functions that depend on the muscles (motor skills of the eyes, speech, swallowing, digestion, breathing, heart function). Each of these diseases is uncommon and therefore classified as a rare disease. However, all neuromuscular diseases together affect more than 5.500 people in Belgium (BNMDR, 2017).

1.1.2. CAUSES OF NEUROMUSCULAR DISEASES

Neuromuscular diseases have very different causes. For most of them, the cause is genetic, meaning that a mutation in a gene appears spontaneously or is transmitted by one or the two parents. This genetic mutation will impair the function of cells at the level of motor neurons, peripheral nerves or muscles and will then be responsible for the disease. In other cases, it is an autoimmune disease that will cause damage to the nerves (ie. chronic inflammatory demyelinating neuropathy), neuromuscular junction (ie. myasthenia) or inflammation of the muscles (ie. myositis). There are many other possible causes such as drug or environmental toxicity, vitamin deficiency, endocrine or general diseases, infections.

1.1.3. NEUROMUSCULAR DISEASES MANIFESTATIONS

Most often patients experience loss of muscle strength due either to defective muscle control or to muscle atrophy. This can cause difficulties in walking or using one's arms or hands. It can also be muscle pain that appears during efforts. Other manifestations include muscle cramps as well as disorders of balance or abnormal sensations such as tingling. If other muscles of the body are affected, the disease may manifest as double vision, eyelid drop, difficulty speaking, swallowing, breathing. These manifestations may be transient or permanent depending on the disease. Regardless of the disease, symptoms associated with neuromuscular diseases have a major impact on patients' life quality.

1.1.4. NEUROMUSCULAR DISEASES MANAGEMENT

The diagnosis is based on a set of findings, among which the clinical examination of the specialized neurologist is the main element. It is then crucial for patients to be interviewed and examined by a neurologist who knows these diseases and will correctly determine tests to be performed to clarify the diagnosis. After diagnosis, neuromuscular diseases management consists of the evaluation of the consequences of the disease and their correction. It can include motility disorders of the limbs, breathing, swallowing, cardiac function that need to be addressed medically to increase the patient's life quality. This support is optimized in specialized centers with good knowledge of these diseases.

1.2. CARE TO PATIENTS WITH NEUROMUSCULAR DISEASES IN BELGIUM

In 1999, a rehabilitation agreement (2–5) was created by the National Institute of Health and Disability Insurance (NIHDI) at the request of neuromuscular patient associations. Six reference centers for neuromuscular diseases (NMRCs) were accredited at the time the agreement was put in place, and have been joined by a new center in 2014.

The rehabilitation agreement clearly states in its first article (§2) the mission of the NMRC:

> *"The ultimate goal of the NMRC is to ensure all aspects of diagnosis and treatment (both must be integrated) of neuromuscular diseases in a broad context of expertise, accurate registration and patient-oriented scientific research. Thus, their mission is to significantly improve the prognosis in terms of human functioning, life expectancy and quality of life for the patients concerned and their families (...). "*

The rehabilitation agreement also defines the criteria required for a medical center to be accredited as an expert center or NMRC. In particular, the NIHDI puts a strong emphasis on the expertise as well as the multidisciplinarity required to manage patients with neuromuscular diseases (article1, §3):

> *By NMRC, (...), is meant a center perceived as such by both patients and referrers, led by a medical specialist with widely recognized expertise and ample experience in the diagnosis and treatment of patients with neuromuscular diseases; and with a team of medical experts in diagnosis having at their disposal all the necessary diagnostic techniques, including those for carrier detection and prenatal diagnosis (...), together with a team of various medical and non-medical specialists in neuromuscular diseases treatment and rehabilitation. The NMRC must have all the infrastructure and equipment necessary to achieve its content goal and adapted to the specificities of the patients concerned.*

1.3. BELGIAN NEUROMUSCULAR DISEASES REGISTRY (BNMDR)

1.3.1. DESCRIPTION

The Belgian Neuromuscular Diseases Registry (BNMDR) exists since 2008 and is financed by the NIHDI. The main missions of the BNMDR are to:

- Facilitate clinical, epidemiological and etiologic research in the field of neuromuscular diseases
- Support and promote the quality of care in the NMRCs
- Provide information to the public health authorities for the management of the convention and the planning of care
- Facilitate the recruitment of patients for research on new treatments.

The content of the registry is managed by Sciensano in collaboration with the seven NMRCs. More precisely, the NMRCs annually collect, in the BNMDR, data from their patients that are later on analyzed by Sciensano. The information collected in the registry concerns, for most diseases, basic data such as age, sex, geographical origin (district), diagnosis, functional status of the person, reference center where the patient is followed. For two disease groups, DMD/BMD and Spinal muscular atrophy, more specific additional clinical data (6,7) are collected within the registry for sharing with the international network called TREAT-NMD (8). All patients are also completing a questionnaire, the ACTIVLIM scale, that measures activity limitation in daily life activities for children and adults with neuromuscular diseases (9,10). The addition of this patient reported outcome measure (PROM) is extremely valuable to better understand the impact of the disease on patient quality of life.

The registry and its contents are supervised by a steering committee, minimally consisting of one specialist doctor from each reference center, two doctor from the College of Physicians Directors of the NIHDI, two members of Sciensano and a representative of patients organisations. A small scientific council, composed of specialists from the reference centers and two Sciensano members, also meets on a need basis to discuss more specific scientific issues.

The BNMDR registry is finally listed on the international platform RD-connect (11), an integrated platform that links databases, registries, biobanks and clinical bioinformatics data for research in the framework of rare diseases.

1.3.2. CHALLENGES

Because of the intrinsic variety within the neuromuscular diseases family, the BNMDR is confronted with several challenges, while collecting or analyzing the patients data. In particular, the classification and the epidemiology of neuromuscular diseases will be presented here.

1.3.2.1. Classification of neuromuscular diseases

Various systems exist to classify diseases, rare diseases and/or neuromuscular diseases at national and international levels. As a consequence, the total number of neuromuscular diseases described greatly differs depending on the classification system considered: e.g. 62 disease groups according to the NIHDI classification (**see Annex 1**) compared to 371 diseases according to Orphanet in 2017 (12).

The following classifications have different characteristics and can be used to organized neuromuscular diseases:

- The NIHDI classification is the official classification used by the Public Health Authorities in Belgium. It is based on the organization of diseases depending on affected functional subnit in the peripheral nervous system as well as the cause of the disease: ie. neuropathies, myopathies... hereditary or inflammatory...

- The Computer Registry of All Myopathies and Polyneuropathies (CRAMP) initiative was developed in 2004 by the Dutch Neuromuscular Research Support Centre. This registry aimed to store information on patient characteristics and diagnoses (13) in a uniform and easily retrievable manner. It gave rise to the CRAMP classification (14) that was later adapted to the needs of the BNMDR.
- The Orphanet classification (12) is an international classification for rare diseases based on scientific articles published and reviewed by experts. Diseases are included in as many classifications as needed, depending on their clinical presentation. For example, DMD is classified under "rare cardiac diseases", "rare genetic diseases" and "rare neurological diseases".
- The International Classification of Diseases – 10 (ICD-10) (15) is an international classification not specific for rare diseases. The classification aims to permit systematic recording analysis, interpretation and comparison of mortality and morbidity data collected in different countries or areas and at different times. The updated version ICD-11 has been released in June 2018 (16).
- The Online Mendelian Inheritance in Man (OMIM) (17) is an international classification based on genetics. It is defined as a continuously updated catalog of human genes and genetic disorders and traits, with particular focus on the molecular relationship between genetic variation and phenotypic expression.

At the time of the 2017 data collection, only the INAMI and CRAMP[1] classifications were used in the BNMDR. In 2018, the three international classifications were added and are automatically fed from the CRAMP classification. This allows us to communicate accurately on the international level. Moreover, in 2020, we are considering to completely re-think our classification system and base it on one of the international systems as the CRAMP classification has not been updated since the start of the registry. It should also further simplify our communication with third parties.

1.3.2.2. Epidemiology of neuromuscular diseases

The BNMDR is a project specific to Belgium. It means that only consented patients living in Belgium and suffering from a neuromuscular disease are included in the registry. With the information collected in the BNMDR, it is possible to estimate the prevalence (i.e. proportion of persons affected at or during a particular time period) and the incidence (i.e. proportion or rate of persons who develop the condition during a particular time period) of neuromuscular diseases in Belgium. However, it would be extremely informative to be able to set side by side these values with international data.

The scientific literature reports estimates of prevalence/incidence for some specific neuromuscular diseases. However, to our knowledge, it is difficult to find estimates of prevalence/incidence for all neuromuscular diseases together. In 1991, a world survey of mostly inheritable neuromuscular disorders was published for the first time in a peer reviewed journal (18). In 2010, a report from the Great Britain's patient association Muscular Dystrophy Campaign included thirteen groups of neuromuscular diseases (19). Since 2013, Orphanet yearly publishes prevalence and incidence data for a great number of rare disorders (20).

Since the 1990s, the neuromuscular diseases field has made tremendous progress thanks to major advances in the genetic field. As a consequence, diagnosis for numerous neuromuscular disorder largely improved. A study of Deenen *et al.* aimed to expand the scope of the first world survey by analyzing the literature between 1990 and 2014 for epidemiological data for 30 neuromuscular disorders (21). Among the 30 diseases, only 8 had a complete set of data (information about incidence, prevalence, age distribution and sex). For 17 diseases, the data set was incomplete and for the remaining 5, no data were found. When the authors added up the 25 prevalence estimates they found, they reached a total of 160 patients per 100,000 population highlighting that neuromuscular diseases are rare as individual diseases but not as a group.

[1] The CRAMP classification has been adapted to the needs for the BNMDR.

2. METHODOLOGY

2.1. POPULATION

The target population are all persons suffering from a neuromuscular disease and living in Belgium. Theoretically, all the patients in consultation with a NMRC are included in the registry, whether or not they benefit from the rehabilitation agreement financed by the NIHDI. Prior to registration, patients receive information about the objectives and the functioning of the registry and can only be included after signing an informed consent form. Patients are identified by their Social Security Identification Number (SSIN) which is pseudonomized before sending the data. Patient names never appear in the registry. Patients are therefore not identifiable by the researcher. Although the majority of patients participate, some of them refuse to be registered (according to physicians estimate, between 0% and 5% depending on the NMRC).

2.2. DATA COLLECTION

In addition to administrative data (year of data collection, treating physician, SSIN, inclusion or not in the rehabilitation agreement and start date of the agreement or date of its extension), the following variables are collected and studied:

- For all patients :
  - Demographic data : birth date, sex, geographic origin (district), living status
  - Clinical data :
    - Diagnosis (NIHDI classification and CRAMP classification (14)
    - Date of appearance of the first symptoms
    - Status of diagnosis: definitive or not (+ date where appropriate)
    - Genetic confirmation of the diagnosis (+ date where appropriate)
    - Stage of the disease : pre-symptomatic, symptomatic but not ambulant (only for patients < 2.5 years), ambulant, wheelchair dependent, or dependent on life support
    - "ACTIVLIM" questionnaire completed by the patient. It measures activity limitations in everyday life (22)
- For patients suffering from Duchenne muscular dystrophy (DMD) or spinal muscular atrophy (SMA), NMRCs are requested to record additional data based on the datasets published by the international "TREAT-NMD" network (6,7). The list of these variables is given in **Annex 2**.

The definition of all the variables can be found on the Healthdata.be website (23).

2.3. SOFTWARE

In 2008, the first collection was made from an Access application installed locally at the NMRCs. Regarding the classification of diseases, this collection was inspired by the Dutch CRAMP model (14). Anonymity was not ensured as the patient's SSIN number was visible in the registry.

Since 2010, data are collected on an annual basis, and a web application is used to centralize the data. Each patient receives a unique identification number, based on the recoding of their SSIN number through the e-Health platform, ensuring anonymity. Regarding the classification of diseases,

the system was revised by cross-referencing the NIHDI and CRAMP system. The ACTIVLIM scale, measuring activity limitations in everyday life, was added to the data collected, as well as TREAT-NMD-specific data for patients with DMD or SMA.

In 2015, a new web application was created by Healthdata.be and is still currently used for data collection. The unique identification numbers remained identical to the ones used in the previous data collections between 2010 and 2014. This number is still based on the recoding of the SSIN by the e-Health platform. This allows a longitudinal follow-up of the patients and a comparison of the data collected from 2010 onwards.

2.4. DATA FLOW

The data flow is illustrated in **Figure 2**. NMRCs enter the data into a secure local application called "HD4DP" (HealthData for Data Providers). The data is then encrypted and securely transferred (via the e-Health platform) to another secure application called "HD4RES" (HealthData for Researchers). This application allows to exchange information with the NMRCs.

The data is validated and stored in the "Data WareHouse" (DWH), which uses the SAS computing environment. When errors are detected during the validation process, requests for corrections are sent to the NMRCs via HD4RES to HD4DP. Upon final receipt of corrected data, the data are stored in the DWH and prepared for analysis. The analysis environment is also a SAS environment.

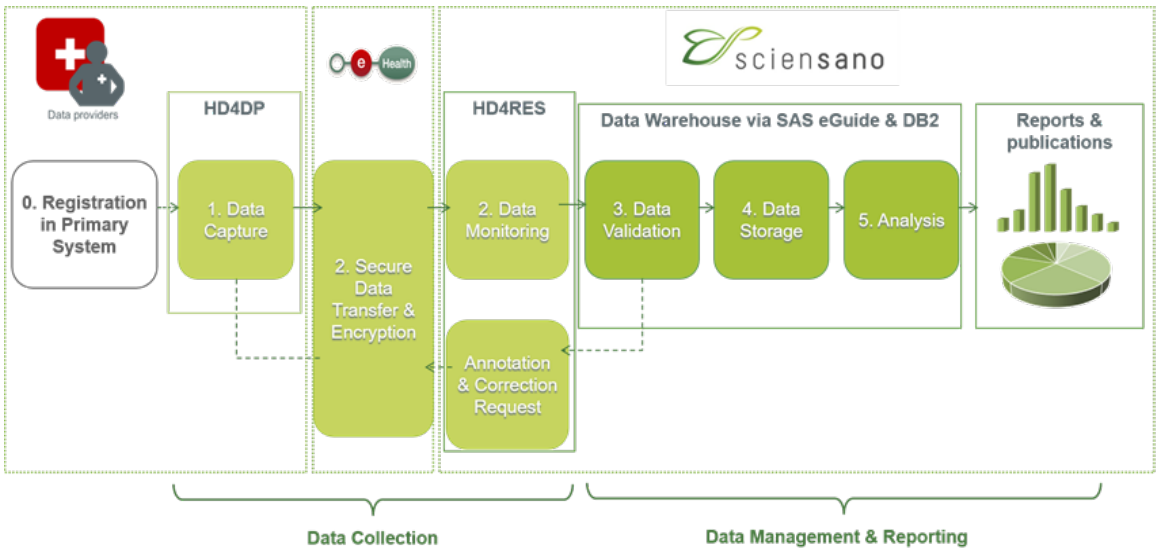


Figure 2. Illustration of the data flow in the BNMDR registry

2.5. DUPLICATES MANAGEMENT

As mentioned above, each patient is uniquely identified via his SSIN. However, duplicates may still occur within the database. They can be of two kinds:

- Duplicate within the same NMRC (the same patient was erroneously encoded twice)
- Duplicated patients registered in several NMRCs during the same year

For duplicates within the same NMRC, only the most recent record is taken into account for data analysis. Duplicated patients registered in multiple NMRCs are not eliminated for statistical analysis related to each NMRC. However, they are eliminated for the analysis concerning all the patients included in the registry.

It was chosen to keep in priority the most complete record, meaning records having a final diagnosis and convention data completed. If all records are complete, then the choice is random.

2.6. FEEDBACK

Each of the 7 NMRCs (9 hospitals) receives a feedback report that compares the results of the NMRC in question with the other NMRCs. This method is called benchmarking and aims to optimize the quality of care.

3. DEMOGRAPHIC DATA

This chapter presents the following demographic data :

- total number of registrations
- age data by 5-years categories
- gender data
- data on geographic origin (district) in the form of a map with an estimate of the general prevalence of neuromuscular diseases among the Belgian population according to their district of residence

The total number of patients in the registry is increasing every year, as shown in **Figure 3**. This increase reflects continuous recruitment of new patients into NMRCs. In 2017, the total number of registrations amounted to 5765. They were 3145 males (54.6%) and 2620 females (45.4%), ranging in age between 2 months and 97 years. The median age was 48 years (p25= 27 years and p75= 62 years).

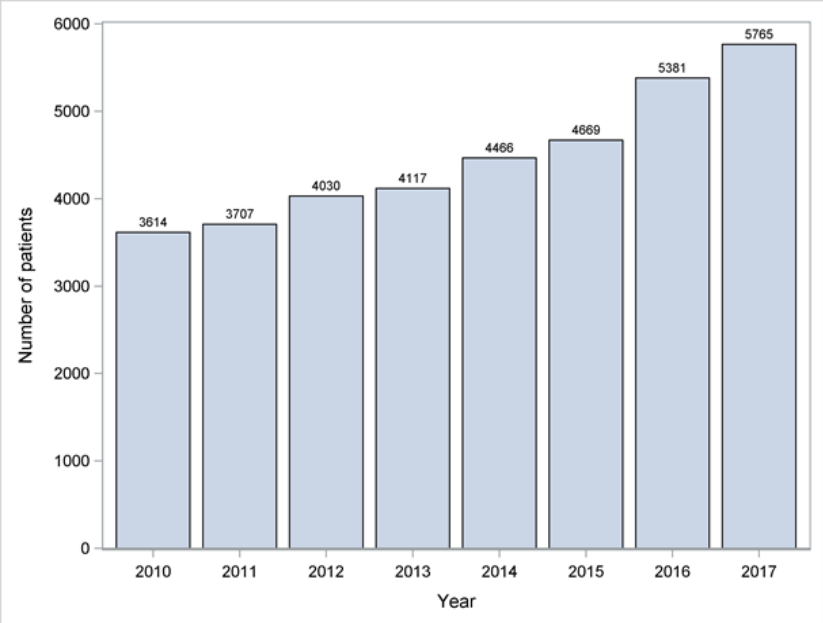
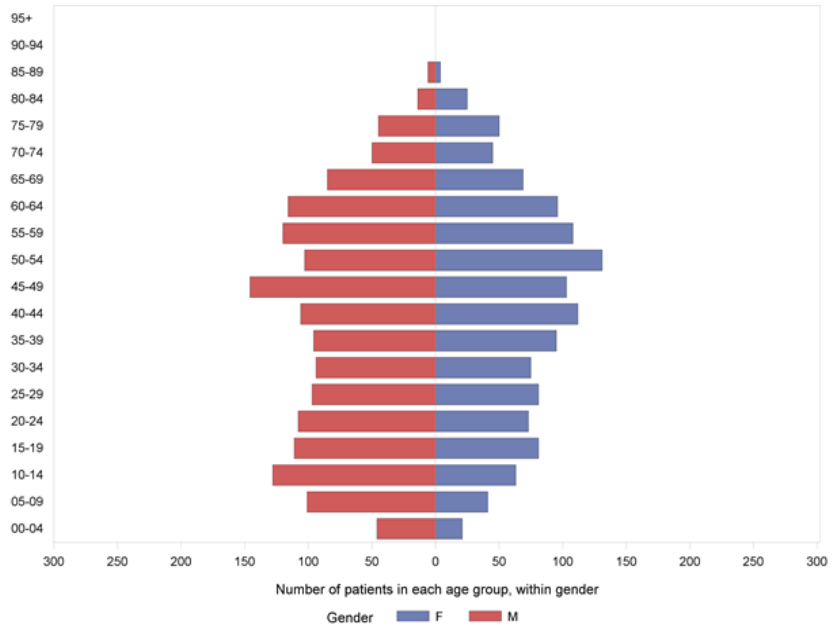


Figure 3. Total number of patients in the BNMDR registry – evolution since 2010

The distribution of patients by age and gender is shown **Figure 4**, which also compares the current age pyramid to the one of 2010. The distribution is bimodal in males and unimodal in females. In females, there is no second peak at 10-14 years. The second peak in males at 10-14 years is possibly due to an important number of young DMD patients. Over the years, it is clear that the shape of the distribution did not change but only the numbers increased.

2010



2017

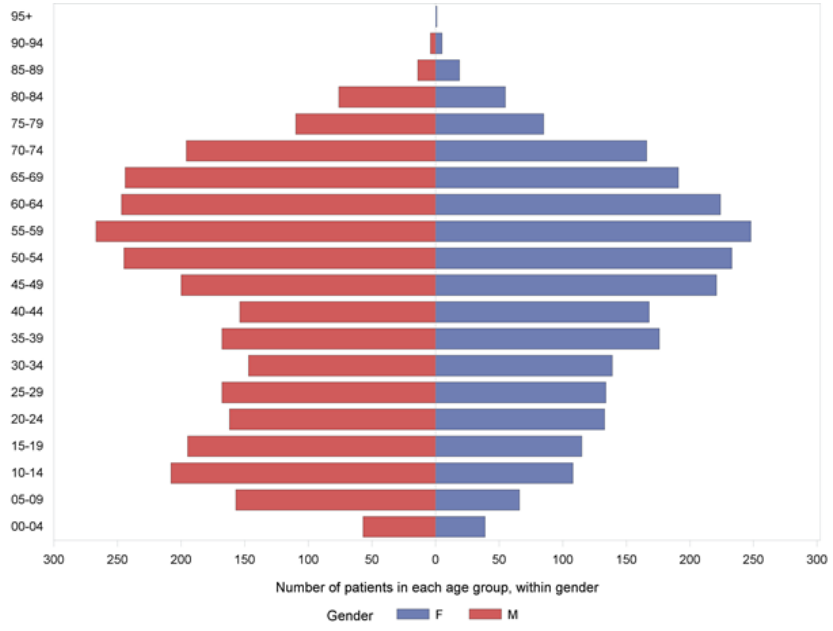


Figure 4. Age distribution by gender in 2010 (top) and in 2017 (bottom)

For 2017, the overall prevalence of neuromuscular diseases in Belgium is estimated at 50.8 for 100,000 inhabitants (BNMDR, 2017). **Figure 5** shows the overall prevalence of neuromuscular diseases in Belgium represented by patients' place of residence (district) in 2017.

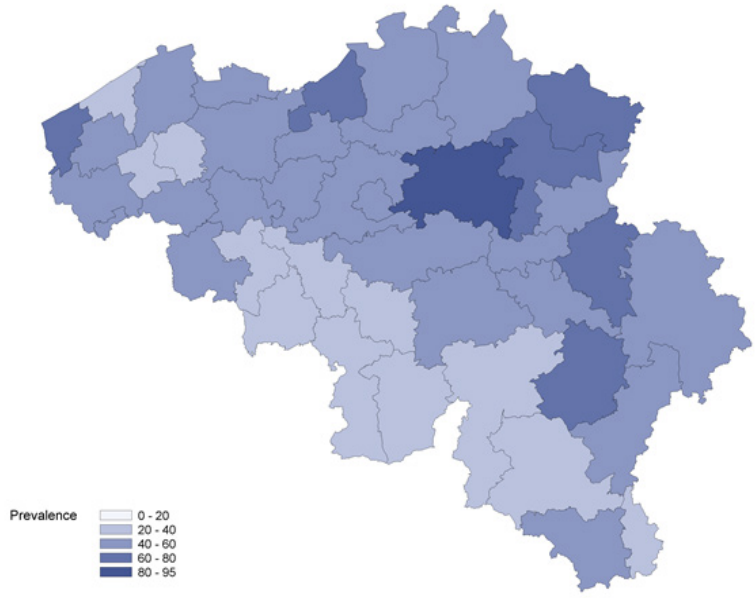


Figure 5. Prevalence of neuromuscular diseases per 100,000 inhabitants and by district of residence in Belgium, estimated by the BNMDR registry in 2017

In general, the prevalence estimated by the registry in Flanders and in Brussels-Capital region is higher than the one estimated in Wallonia, with a maximum for the district of Leuven. This uneven distribution may be partly explained by the geographic location of the NMRCs, as shown in **Figure 6**.

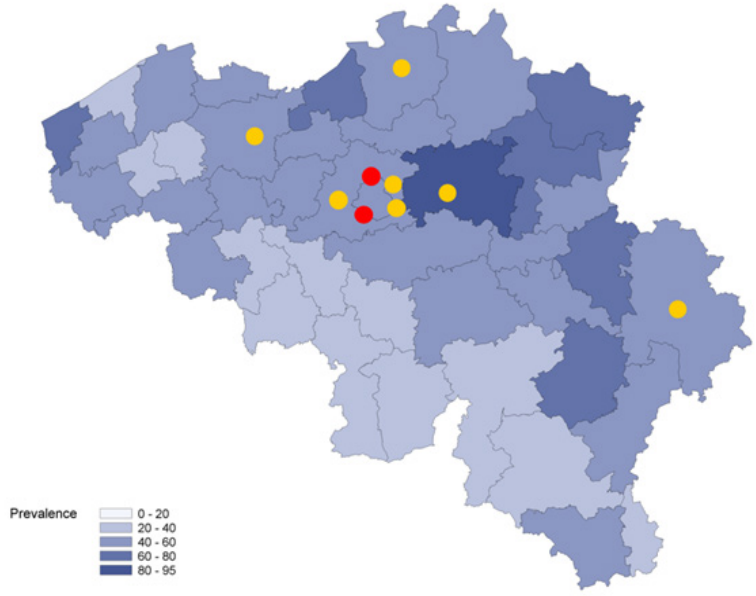


Figure 6. Geographic location of the NMRCs reported on the map estimating the prevalence of neuromuscular diseases in Belgium in 2017

At the begining of the project, in 2010, there was a clear difference in term of patients recruitment between the North and South of Belgium. When observing the evolution of the estimated prevalence since 2010 (**Figure 7**), it seems that patient recruitment is improving each year in the south of the country. In 2014, a seventh NMRC has joined the convention: it is NMRC of the Université Libre de Bruxelles (ULB) and is spread over two sites, Hôpital Erasme for adults and HUDERF for children (red spots on **Figure 6**). At the beginning, this NMRC was only authorized to integrate within the convention a limited number of patients, which corresponds to a small fraction of the patients actually followed in the center. In 2017, this NMRC was able to integrate all of its patients into the convention – which reflects in the registry. This allows us to have a better idea of the geographical distribution of patients attending the NMRCs. We can clearly observe an increase in patient recruitment from 2015 onwards in the South of the country. This is most likely due to the opening of this 7th NMRC but it also correlates with an increase in patient's recruitment for the center of Liège.

Despite this important improvement, the gradient North-South is still clear. We can conclude that access to the NMRCs remains problematic for some patients in the South of Belgium. This key information is to be taken into account ensure equal care and access for all patients with neuromuscular diseases in Belgium. An option to circumvent this issue would be the opening of a new NMRC in the Southwest of the country or to consider the opening, in that region, of a satellite hospital run by the current NMRC(s).

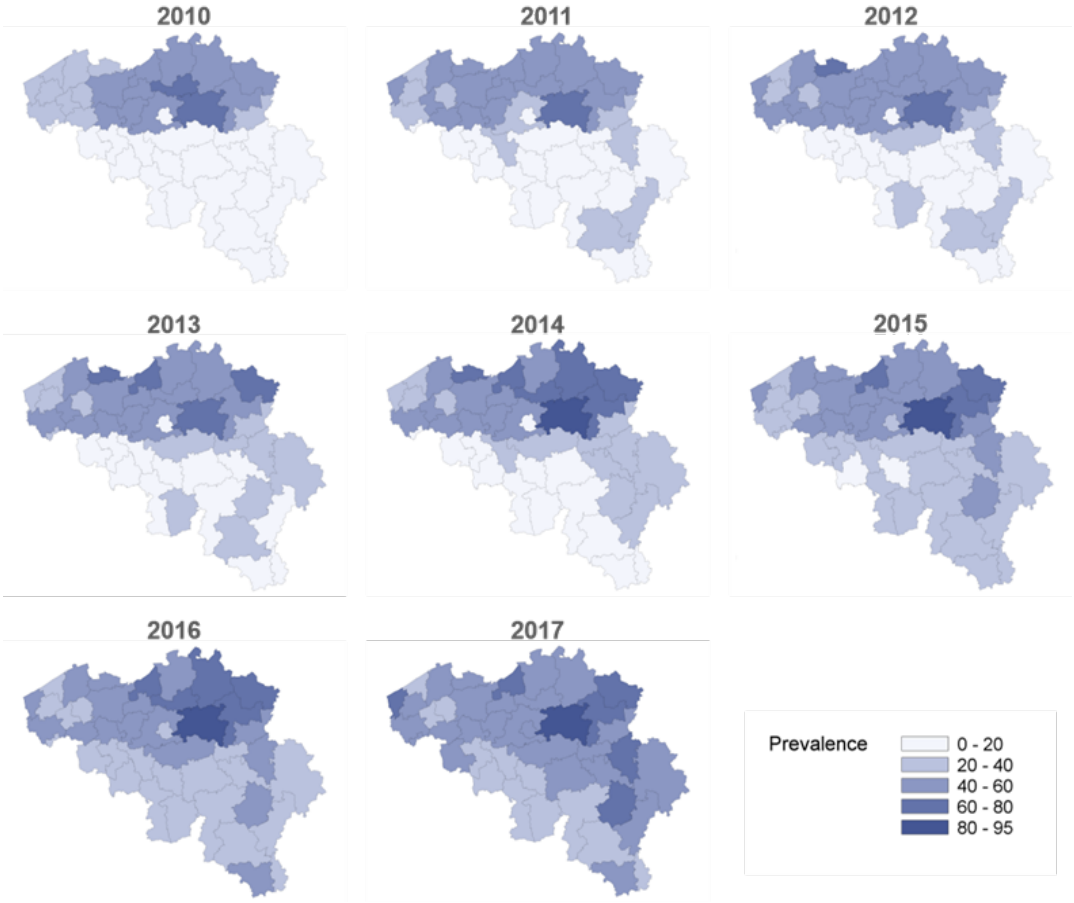


Figure 7. Evolution of the prevalence of neuromuscular diseases in Belgium, estimated by the BNMDR registry between 2010 and 2017

4. DIAGNOSIS

4.1. GENERALITIES

As presented in introduction, different classification systems can be used to describe neuromuscular diseases: the NIHDI classification, the CRAMP classification (14), Orphanet (12), ICD-10 (15) and OMIM (17). The first two classifications were developed in the context of the BNMDR; while the last three are international classification systems not specific for neurosmuscular diseases. For the 2017 data collection, only the NIHDI and CRAMP classifications were used in the registry. The NIHDI classification distinguishes between 62 disease groups, while the CRAMP classification is more complex with an 8-level tree structure. This allows the disease to be described in more detail.

In 2018, the three international classifications (i.e., Orphanet, ICD-10 and OMIM) will be automatically added based on the CRAMP classification. This will allow us to communicate accurately on the international level. Moreover, in 2022, we will consider to completely re-think our classification system to base it on one of the international systems. It should simplify our communication with third parties.

The distribution of patients according to the NIHDI diagnosis is shown in **Table 1**.

Table 1. Distribution of the NIHDI diagnosis in descending order of prevalence in Belgium for 2017

Neuromuscular diseases (NIHDI classification)	Number of patients	% of BNMDR population
Hereditary Motor and Sensory Neuropathy	773	13.4
Myotonic Dystrophy type 1	582	10.1
Amyotrophic Lateral Sclerosis	520	9.0
Hereditary Spastic Paraplegia	306	5.3
Duchenne Muscular Dystrophy	302	5.2
Chronic Inflammatory Demyelinating Polyneuropathy	288	5.0
Other Neuropathies	256	4.4
Facioscapulohumeral Dystrophy	252	4.4
Limb girdle Muscular Dystrophy	251	4.4
Other Myopathies	226	3.9
Spinocerebellar Ataxias	201	3.5
Related to Polio Virus Infection	169	2.9
Mitochondrial Myopathy	117	2.0
Congenital Muscular Dystrophy	109	1.9
Becker Muscular Dystrophy	109	1.9
Myasthenia Gravis	97	1.7
Intermediate Spinal Muscular Atrophy	94	1.6
Kugelberg – Welander Spinal Muscular Atrophy	83	1.4
Friedreich Ataxia	68	1.2
Muscle Glycogenoses	67	1.2
Guillain-Barré Syndrome	56	1.0
Multifocal Motor Neuropathy	56	1.0

Neuromuscular diseases (NIHDI classification)	Number of patients	% of BNMDR population
Distal Spinal Muscular Atrophy	53	0.9
Primary Lateral Sclerosis	51	0.9
Distal Myopathy	48	0.8
Inclusion body myositis	45	0.8
Other disorders of Motor Neurons	43	0.7
Polymyositis	39	0.7
Congenital Myasthenia	38	0.7
Hereditary Neuropathy with Liability to Pressure Palsies	38	0.7
Other disorders of neuromuscular transmission	37	0.6
Arthrogryposis Multiplex Congenita	27	0.5
Central Core Disease	26	0.5
Neuropathy associated with Plasma Cell Dyscrasia	26	0.5
X-linked Bulbo-Spinal Muscular Atrophy or Kennedy's disease	25	0.4
Dystrophinopathy	24	0.4
Myotonic Dystrophy type 2	22	0.4
Becker type Myotonia Congenita	22	0.4
Primary Muscular Atrophy	20	0.3
Oculopharyngeal Muscular Atrophy	19	0.3
Adult Spinal Muscular Atrophy	18	0.3
Werdnig-Hoffman Spinal Muscular Atrophy	17	0.3
Dermatomyositis	15	0.3
Nemaline Myopathy	14	0.2
Hereditary Sensory and Autonomous Neuropathy	14	0.2
Emery-Dreifuss Muscular Dystrophy	14	0.2
Fibre type Disproportion Myopathy	12	0.2
Familial Periodic Paralysis	11	0.2
Thomsen type Myotonia Congenita	10	0.2
Paramyotonia Congenita	10	0.2
Multiminicore Disease	9	0.2
Disorders of Fatty Acid Metabolism	7	0.1
Amyloidosis	7	0.1
Other Myotonic Disorders	6	0.1
Myotubular Myopathy	6	0.1
Centronuclear Myopathy	4	0.1
Lambert-Eaton Syndrome	3	0.1
Vasculitis	3	0.1
Other Muscular Dystrophies	0	0
Neuropathy associated with Paraproteinemia	0	0
Neuropathy in Systemic Disease	0	0
Other Hereditary Ataxias	0	0
Total	**5765**	**100**

The status of the diagnosis (definitive or not) and the stage of the disease are illustrated in **Table 2** and **Table 3**. Given the diversity of diseases represented in the registry, the interpretation of these global descriptive data is quite limited. It is nevertheless interesting to be able to evaluate the importance of the missing data for these variables. The table shows that the majority of patients (74.6%) in the BNMDR have received a final diagnosis (**Table 2**). Regarding the stage of the disease, the majority of patients (75.3%) in the BNMDR are ambulant and a significant proportion (19.7%) are wheelchair-bound (**Table 3**). Only 2.0% of patients are on life support.

Table 2. Diagnosis status (source: BNMDR 2017)

Final diagnosis?	Number of patients	% of BNMDR population
Yes	4299	**74.6**
No	766	13.3
Missing	700	12.1
TOTAL	**5765**	**100**

Table 3. Stage of the disease (source: BNMDR 2017)

Stage of the disease	Number of patients	% of BNMDR population
Pre-symptomatic	34	0.6
Symptomatic - not ambulant (only for patients < 2.5 years)	0	0.0
Ambulant	4340	**75.3**
Loss of ambulation wheelchair	1136	19.7
On life support	114	2.0
Missing	141	2.4
TOTAL	**5765**	**100**

Additionally, the number of patients on life support per diagnostic is presented in **Table 4**. The majority of patients placed on life support are suffering either from Duchenne Muscular Dystrophy or Amyotrophic Lateral Sclerosis (respectively representing 36.0% and 31.5% of all patients on life support). However, it is important to note that 41.2% of patients with Werdnig-Hofman Spinal Muscular Atrophy are placed on life support.

Table 4. Number of patients on life support per diagnostic (source: BNMDR 2017)

Neuromuscular diseases (NIDHI classification)	Number of patients on life support	% of patients on life support	Number of patients in this disease group	% of patients on life support among the disease group
Duchenne Muscular Dystrophy	41	**36.0**	302	13.6
Amyotrophic Lateral Sclerosis	36	**31.5**	520	6.9
Werdnig-Hofman Spinal Muscular Atrophy	7	6.1	17	**41.2**
Intermediate Spinal Muscular Atrophy	4	3.5	94	4.3
Limb Girdle Muscular Dystrophy	4	3.5	250	1.6
Congenital Muscular Dystrophy	3	2.6	109	2.8
Muscle Glycogenoses	2	1.7	67	3.0
Other myopathies	2	1.7	226	0.9
Chronic Inflammatory Demyelinating Polyneuropathy	2	1.7	288	0.7
Myotonic Dystrophy type 1	1	0.9	582	0.2
Central Core Disease	1	0.9	26	3.9
Becker Muscular Dystrophy	1	0.9	109	0.9
Primary Muscular Dystrophy	1	0.9	20	5.0
Dystrophinopathy	1	0.9	24	4.2
Kugelberg-Welander Spinal Muscular Atrophy	1	0.9	83	1.2
Hereditary Spastic Paraplegia	1	0.9	305	0.33
Other disorders of motor neurons	1	0.9	43	2.3
Hereditary Motor and Sensory Neuropathy	1	0.9	773	0.1
Facioscapulohumeral Dystrophy	1	0.9	252	0.4
Other neuropathies	1	0.9	255	0.4
Friedreich ataxia	1	0.9	68	1.5
Spinocerebellar ataxias	1	0.9	201	0.5
TOTAL	**114**	**100**	-	-

Finally, the number of deceased patients per diagnostic is presented in **Table 5**. For 2017, 220 patients were reported as deceased being 3.8% of all registered patients. The majority of deaths occur among patients with Amyotrophic Lateral Sclerosis (representing 61.4% of total deaths). Equally, the majority of deceased patients per disease group is the highest for patients with Amyotrophic Lateral Sclerosis (i.e., 26.0%). Other disease groups with a high death rate are Werdnig-Hofman Spinal Muscular Atrophy and Primary Muscular Atrophy (representing respectively 23.5% and 10.0% of patients in their disease group).

Table 5. Deaths by diagnosis (source: BNMDR 2017)

Neuromuscular diseases (NIDHI classification)	Number of deceased patients	% of deceased patients	Number of patients in this disease group	% of deceased patients among the disease group
Amyotrophic Lateral Sclerosis	135	**61.4**	520	**26.0**
Myotonic Dystrophy type 1	11	5.0	582	1.9
Duchenne Muscular Dystrophy	10	4.5	302	3.3
Related to Polio Virus Infection	6	2.7	169	3.5
Other neuropathies	6	2.7	255	2.3
Facioscapulohumeral Dystrophy	5	2.3	252	2.0
Chronic Inflammatory Demyelinating Polyneuropathy	5	2.3	288	1.7
Limb Girdle Muscular Dystrophy	5	2.3	250	2.0
Werdnig-Hofman Spinal Muscular Atrophy	4	1.8	17	**23.5**
Spinocerebellar ataxias	4	1.8	201	2.0
Other myopathies	3	1.4	226	1.3
Hereditary Spastic Paraplegia	3	1.4	305	1.0
Hereditary Motor and Sensory Neuropathy	3	1.4	773	0.4
Congenital Muscular Dystrophy	2	0.9	109	1.8
Mitochondrial Myopathy	2	0.9	117	1.7
Polymyositis	2	0.9	39	5.1
Primary Muscular Atrophy	2	0.9	20	**10.0**
Guillain-Barré Syndrome	2	0.9	56	3.6
Becker Muscular Dystrophy	1	0.4	109	0.9
Fibre type Disproportion Myopathy	1	0.4	12	8.3
Dermatomyositis	1	0.4	15	6.7
Inclusion Body Myositis	1	0.4	45	2.2
Myasthenia Gravis	1	0.4	96	1.0
Primary Lateral Sclerosis	1	0.4	51	2.0
Kugelberg-Welander Spinal Muscular Atrophy	1	0.4	83	1.2
Other disorders of motor neurons	1	0.4	43	2.3
Friedreich ataxia	1	0.4	68	1.5
Oculopharyngeal Muscular Atrophy	1	0.4	19	5.3
TOTAL	**220**	**100**	-	-

4.2. ANALYSIS OF THE TEN MOST PREVALENT DISEASES WITHIN THE REGISTRY

This report contains a specific section for each of the ten most prevalent diseases in the registry (see **Table 6**). Together, they represent 63.2% of the 2017 BNDMR population.

Importantly, according to the NIHDI classification, the four sub-types of Spinal Muscular Atrophy (SMA) are dividied in four distincts disease groups. For this reason, none of the SMA sub-types appear in the ten most prevalent diseases. However, when the four sub-types are pooled together, SMA is ranked 9th in the list. Because additional data are already collected on SMA via the TREAT-NMD project, the detailed section on SMA is to be found in chapter 5 on TREAT-NMD and not in chapter 4 on the ten most prevalent diseases.

Each disease specific section of the report contains a brief general description of the disease as well as the following analyses performed for the disease of interest:

- Demographic data
- Diagnosis status (definitive or not)
- Genetic confirmation (if appropriate)
- Stage of the disease

For maps showing the prevalence data for each disease for Belgium, particular attention should be paid to the scale. In fact, the scale of each card has been chosen to reflect as accurately as possible the prevalence data of an individual disease. Each district can therefore be compared to another one for the same disease (within the same card), but the color nuances of the different cards (and thus the different diseases between themselves) can not be compared with each other because the scales might be different.

Table 6. Ten most prevalent neuromuscular diseases (source: BNMDR 2017)

Ranking	Neuromuscular diseases (NIHDI classification)	Number of patients	% of BNMDR population
1	Hereditary Motor and Sensory Neuropathy	773	13.4
2	Myotonic Dystrophy type 1	582	10.1
3	Amyotrophic Lateral Sclerosis	520	9.0
4	Hereditary Spastic Paraplegia	306	5.3
5	Duchenne Muscular Dystrophy	302	5.2
6	Chronic Inflammatory Demyelinating Polyneuropathy	288	5.0
7	Facioscapulohumeral Dystrophy	252	4.4
8	Limb girdle Muscular Dystrophy	251	4.4
*	**Spinal Muscular Atrophy (all types)**	**212**	**3.6**
	- Werdnig-Hofman Spinal Muscular Atrophy	17	0.3
	- Intermediate Spinal Muscular Atrophy	94	1.6
	- Kugelberg-Welander Spinal Muscular Dystrophy	83	1.4
	- Adult Spinal Muscular Atrophy	18	0.3
9	Spinocerebellar Ataxias	201	3.5
10	Related to Polio Virus Infection	169	2.9

4.2.1. HEREDITARY MOTOR AND SENSORY NEUROPATHY

Hereditary Sensory and Motor Neuropathy (HMSN), also known as Charcot-Marie-Tooth disease, is characterized by progressive distal weakness and muscle atrophy, deformity of the feet, distal sensory deficit, and decreased osteotendinous reflexes (24). The disease has different subtypes classified according to the pathophysiology (axonal or demyelinating), the mode of transmission (autosomal dominant, autosomal recessive or X-linked), the age of onset (during childhood or at adulthood), and the genetic mutation in question (25).

HMSN accounted for 13.4% of the total population of the registry in 2017; it is therefore the most frequent neuromuscular disease. The prevalence of the disease for Belgium is estimated at 6.8 / 100,000 inhabitants (7.6 / 100,000 inhabitants in Flanders, 5.3 in Brussels-Capital Region and 5.8 in Wallonia). Although probably significantly underestimated, this prevalence assessment falls within the range found in the international literature (from 3.1 to 82.3 / 100,000 population, with a median of 10/100, 000 population) (21). Orphanet published a prevalence of 25.0/ 100,000 population in Europe for HMSN (20). As with most of the diseases described in this report, the observed north-south gradient for Belgium is likely related to under-representation of patients from the south of the country in NMRCs.

Demographic data for sensory and motor neuropathy are presented in **Figure 8** and **Figure 9**.

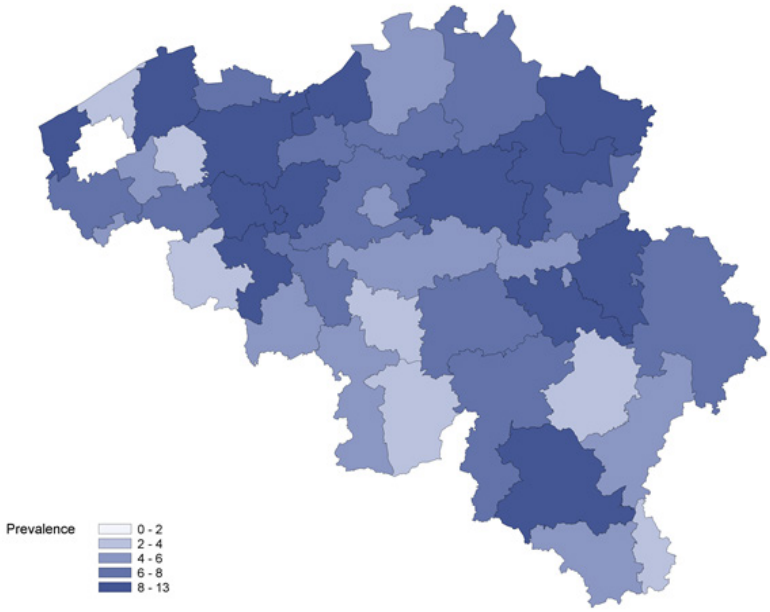


Figure 8. Hereditary motor and sensory neuropathy: Prevalence / 100,000 inhabitants (BNMDR, 2017)

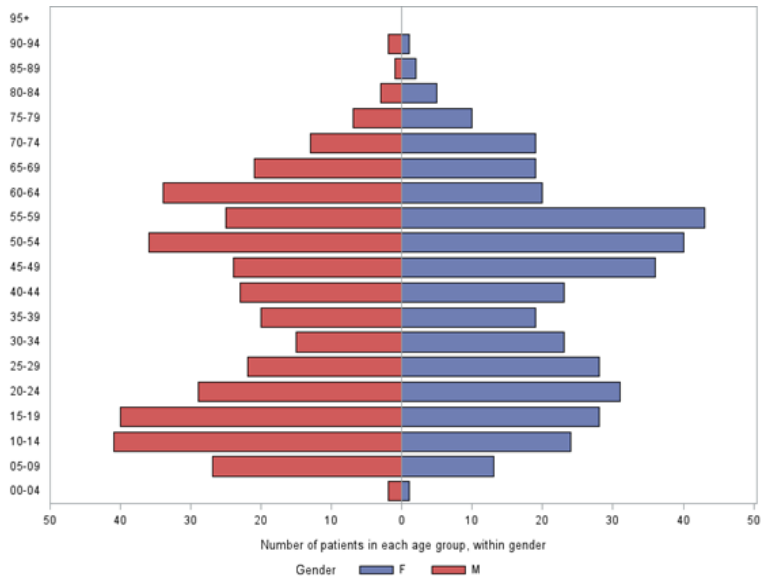


Figure 9. Hereditary motor and sensory neuropathy: Age distribution by gender (BNMDR, 2017)

The status of the diagnosis (definitive or not) is illustrated in **Table 7**. More than three quarters of patients with HMSN in the BNMDR (76.9%) have received a final diagnosis.

Table 7. Hereditary motor and sensory neuropathy: diagnosis status (Belgium, 2017)

Final diagnosis?	Number of patients	% of the disease group population
Yes	594	**76.9**
No	99	12.8
Missing	80	10.3
TOTAL	**773**	**100**

The status of the genetic confirmation of the disease is illustrated in **Table 8**. Less than half of patients with HMSN in the BNMDR (44%) have genetic confirmation of their disease reflecting the variety in subtypes of this disease. It is important to note that the information on genetic confirmation is missing for 28.6% of the patients.

Table 8. Hereditary motor and sensory neuropathy: genetic confirmation of the diagnosis (BNMDR, 2017)

Genetically confirmed diagnosis?	Number of patients	% of the disease group population
Yes	340	**44.0**
No	212	27.4
Missing	221	28.6
TOTAL	**773**	**100**

The status of the stage of the disease is illustrated in **Table 9**. Most patients with HMSN in the BNMDR (89.1%) are ambulant and 8.2% are wheelchair-bound.

Table 9. Hereditary motor and sensory neuropathy: stage of the disease (BNMDR, 2017)

Stage of the disease	Number of patients	% of the disease group population
Pre-symptomatic	2	0.2
Symptomatic - not ambulant (only for patients < 2.5 years)	0	0.0
Ambulant	693	**89.7**
Loss of ambulation wheelchair	63	8.2
On life support	1	0.1
Missing	14	1.8
TOTAL	**773**	**100**

4.2.2. MYOTONIC DYSTROPHY TYPE 1

Myotonic dystrophy type 1 (DM1), or Steinert's disease, is an autosomal dominantly transmitted genetic disorder. It is characterized by delayed muscle relaxation and muscle weakness in the limbs, which begins at the extremities and can progress slowly to affect the proximal muscles. There are also associated systemic manifestations, affecting the gastrointestinal tract, the uterus, the respiratory and cardiac muscles, the lens and the endocrine system. The disease may appear at any age, including early childhood (26).

Steinert's disease represents 10.1% of the total population of the registry in 2017. The prevalence estimated by the BNMDR registry in Belgium is 5.1 / 100,000 inhabitants (6.1 in Flanders, 3.9 in Brussels-Capital Region and 3.8 in Wallonia). In the international literature, prevalence data for Europe are between 1.2 and 14.3 / 100,000 inhabitants (27,28). Similarly, Orphanet published a prevalence of 12.5/ 100,000 population in Europe for DM1 (20). In other parts of the world, the disease is either absent as in the Bantu population of South Africa, or much more important, as in some regions of Quebec where the prevalence is estimated at 189 per 100,000 inhabitants (28).

A second disease called myotonic dystrophy type 2 (DM2) also exists. It has a milder phenotype and is less prevalent. DM2 represents 0.4% of the total population of the registry in 2017. The prevalence estimated by the BNMDR registry in Belgium is 0.19 / 100,000 inhabitants.

The demographic data for DM1 are shown in **Figure 10** and **Figure 11**. We can note a lack of patients recruitment in the Southwest region of Belgium (see figure below). In addition, few patients older than 70 years old are registered, probably due to reduced life expectancy because of cardiac and respiratory problems.

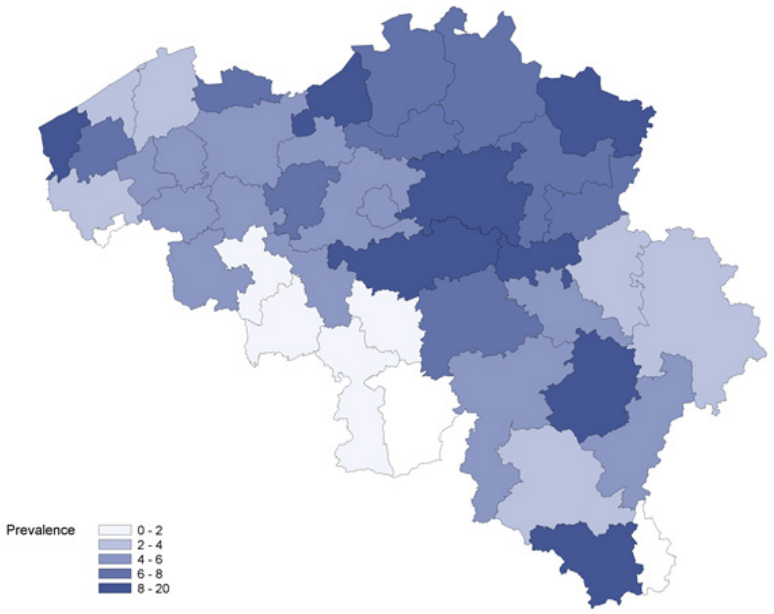


Figure 10. Myotonic dystrophy type 1: Prevalence / 100,000 inhabitants (BNMDR, 2017)

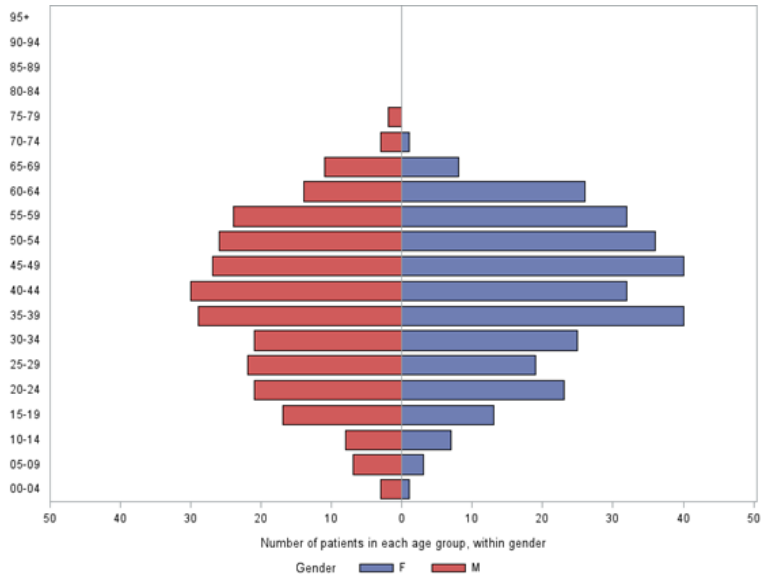


Figure 11. Myotonic dystrophy type 1: Age distribution by gender (BNMDR, 2017)

The status of the diagnosis (definitive or not) is illustrated in **Table 10**. Most patients with DM1 in the BNMDR (89.6%) have received a final diagnosis.

Table 10. Myotonic dystrophy type 1: diagnosis status (BNMDR, 2017)

Final diagnosis?	Number of patients	% of the disease group population
Yes	521	**89.6**
No	2	0.3
Missing	59	10.1
TOTAL	**582**	**100**

The status of the genetic confirmation of the disease is illustrated in **Table 11**. The majority of patients (63.4%) with DM1 in the BNMDR have genetic confirmation of their disease. It is important to note that the information on genetic confirmation is missing for more than a third of the patients (34.4%).

Table 11. Myotonic dystrophy type 1: genetic confirmation of the diagnosis (BNMDR, 2017)

Genetically confirmed diagnosis?	Number of patients	% of the disease group population
Yes	369	**63.4**
No	13	2.2
Missing	200	34.4
TOTAL	**582**	**100**

The status of the stage of the disease is illustrated in **Table 12**. The majority of patients with DM1 in the BNMDR (87.4%) are ambulant and 9.3% are wheelchair-bound.

Table 12. Myotonic dystrophy type 1: stage of the disease (BNMDR, 2017)

Stage of the disease	Number of patients	% of the disease group population
Pre-symptomatic	6	1.0
Symptomatic - not ambulant (only for patients < 2.5 years)	0	0.0
Ambulant	509	87.4
Loss of ambulation wheelchair	54	9.3
On life support	1	0.2
Missing	12	2.1
TOTAL	**582**	**100**

4.2.3. AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS), also known as "Charcot's disease" in French and "Lou Gehrig disease" in English, is the most well-known motor neuron disease. It is characterized by progressive degeneration of the motor neurons of the anterior horn of the spinal cord and of the nuclei of certain motor cranial nerves and the corticospinal / bulbar tracts. As a result, progressive paralysis develops throughout the skeletal musculature of the limbs, trunk and cephalic extremity. For most patients, life expectancy is less than 5 years (from the moment the disease starts). In the vast majority of cases, the disease is sporadic. However, 5% to 10% of cases are familial, mostly autosomal dominant but also in rare cases autosomal recessive or X-linked (29).

In Belgium, ALS represents 9.0% of the total population of the registry in 2017. The prevalence estimated by the BNMDR is 4.6 / 100,000 inhabitants (5.7 in Flanders, 3.4 in Brussels-Capital Region and 2.9 in Wallonia). In the literature, there is a prevalence range of 1.07 to 11.31 / 100,000 population (21). Orphanet published a prevalence of 3.85 / 100,000 population for ALS worldwide (20).

The demographic data for ALS are shown in **Figure 12** and **Figure 13**. As expected based on the disease's natural history, no patient younger than 20 years old are registered in the BNMDR.

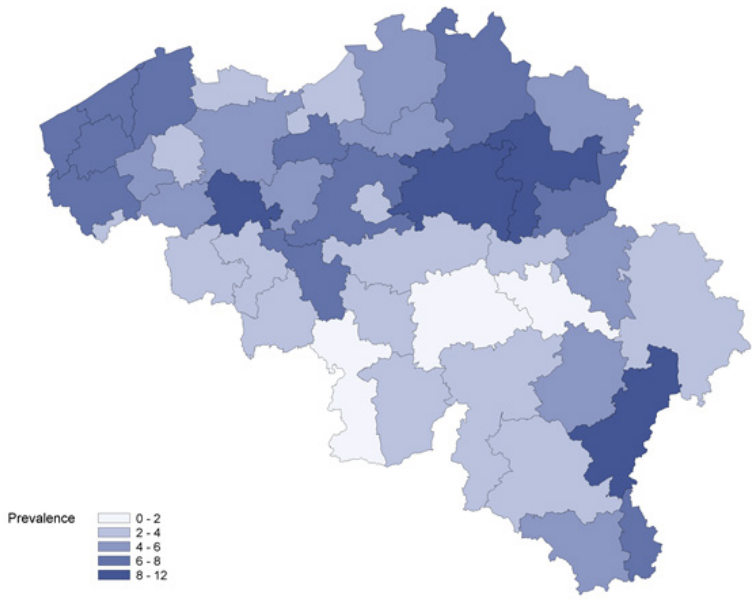


Figure 12. Amyotrophic lateral sclerosis: Prevalence / 100,000 inhabitants (BNMDR, 2017)

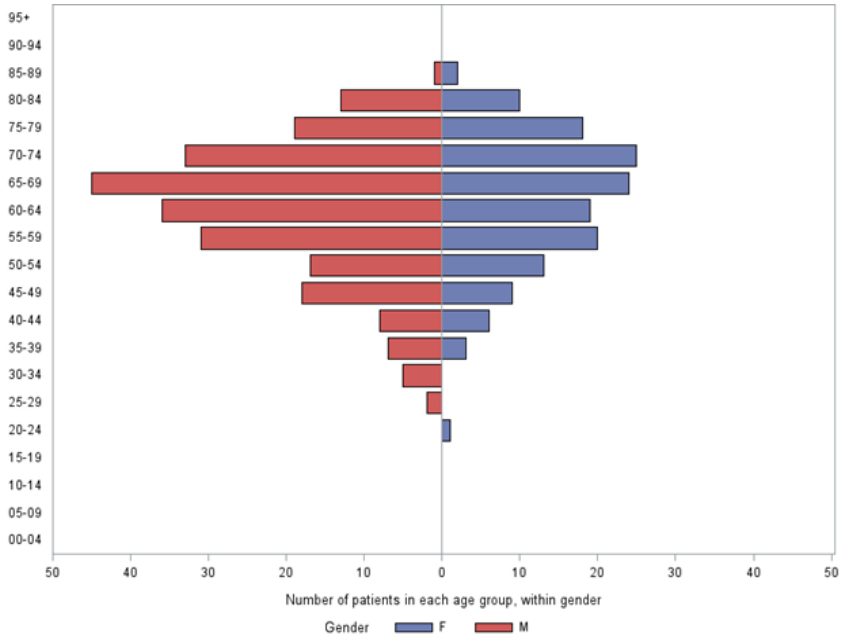


Figure 13. Amyotrophic lateral sclerosis: Age distribution by gender (BNMDR, 2017)

The status of the diagnosis (definitive or not) is illustrated in **Table 13**. The vast majority of patients with ALS in the BNMDR (79.0%) have received a final diagnosis.

Table 13. Amyotrophic lateral sclerosis: diagnosis status (BNMDR, 2017)

Final diagnosis?	Number of patients	% of the disease group population
Yes	411	**79.0**
No	26	5.0
Missing	83	16.0
TOTAL	**520**	**100**

The status of the genetic confirmation of the disease is illustrated in **Table 14**. The majority of patients with ALS in the BNMDR (67.9%) have not a genetic confirmation of their disease reflecting the sporadic apparition of this disease. It is important to note that the information on genetic confirmation is also missing for about a quarter of the patients (24.0%.)

Table 14. Amyotrophic lateral sclerosis: genetic confirmation of the diagnosis (BNMDR, 2017)

Genetically confirmed diagnosis?	Number of patients	% of the disease group population
Yes	42	8.1
No	353	**67.9**
Missing	125	24.0
TOTAL	**520**	**100**

The status of the stage of the disease is illustrated in **Table 15**. The more than half of the patients with ALS in the BNMDR (56.9%) are ambulant and almost one third of the patients are wheelchair-bound (32.9%).

Table 15. Amyotrophic lateral sclerosis: stage of the disease (BNMDR, 2017)

Stage of the disease	Number of patients	% of the disease group population
Pre-symptomatic	2	0.4
Symptomatic - not ambulant (only for patients < 2.5 years)	0	0.0
Ambulant	296	**56.9**
Loss of ambulation wheelchair	171	32.9
On life support	36	6.9
Missing	15	2.9
TOTAL	**520**	**100**

4.2.4. HEREDITARY SPASTIC PARAPLEGIA

Hereditary Spastic Paraplegia (HSP) (Strumpell-Lorrain Disease) is a predominantly retrograde, bilateral neurodegenerative disease that occurs predominantly in crossed and direct corticospinal bundles, affecting mainly the lumbosacral and thoracic segments and characterized by slowly progressive symmetrical spastic paraparesis. To date, more than 80 HSP-related gene variants (loci) have been defined by genetic linkage analysis (30). The mode of transmission may be autosomal dominant, autosomal recessive or X-linked. The onset of symptoms typically occurs during the 2nd or 3rd decades of life, but these may also manifest sooner (in the 1st decade) or much later (until the 7th decade) (31).

In Belgium, hereditary spastic paraplegia represents 5.3% of the total population of the BNMDR registry in 2017. It estimates the prevalence of HSP at 2.7 / 100,000 inhabitants (3.5 in Flanders, 1.9 in Brussels-Capital Region and 1.5 in Wallonia). In the international literature, the prevalence is estimated between 0.1 and 10 / 100,000 inhabitants (31–33). Orphanet published a prevalence of 5.2 / 100,000 population for HSP worldwide (20).

The demographic data for HSP are shown in **Figure 14** and **Figure 15**. We can note an important gap in patients recruitment in the South of Belgium.

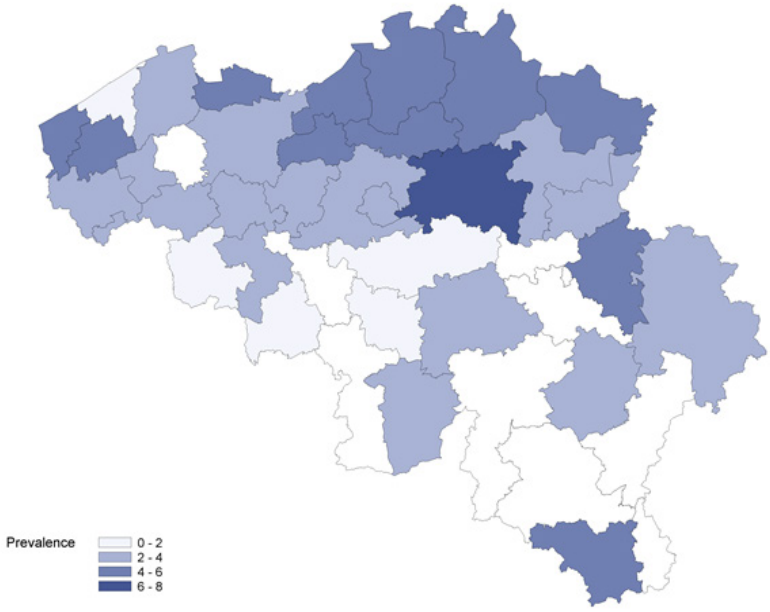


Figure 14. Hereditary spastic paraplegia: Prevalence / 100,000 inhabitants (BNMDR, 2017)

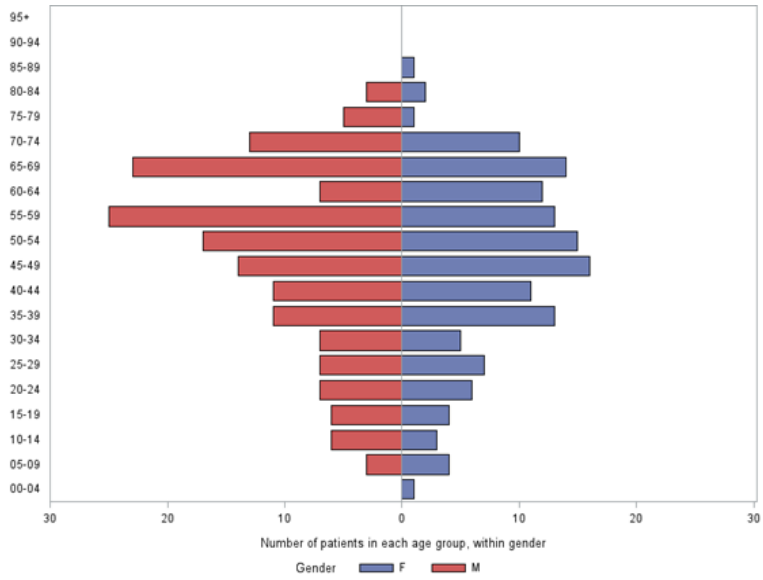


Figure 15. Hereditary spastic paraplegia: Age distribution by gender (BNMDR, 2017)

The status of the diagnosis (definitive or not) is illustrated in **Table 16**. The majority of patients with HSP in the BNMDR (69.3%) have received a final diagnosis.

Table 16. Hereditary spastic paraplegia: diagnosis status (BNMDR, 2017)

Final diagnosis?	Number of patients	% of the disease group population
Yes	212	**69.3**
No	51	16.7
Missing	43	14.0
TOTAL	**306**	**100**

The status of the genetic confirmation of the disease is illustrated in **Table 17**. About one third of patients with HSP in the BNMDR (35.3%) have a genetic confirmation of their disease and one third of patients (33%) have a missing diagnosis. This reflects the variety of genetic mutations causing the disease.

Table 17. Hereditary spastic paraplegia: genetic confirmation of the diagnosis (BNMDR, 2017)

Genetically confirmed diagnosis?	Number of patients	% of the disease group population
Yes	108	**35.3**
No	97	31.7
Missing	101	33.0
TOTAL	**306**	**100**

The status of the stage of the disease is illustrated in **Table 18**. The vast majority of patients with HSP in the BNMDR (72.2%) are ambulant and a quarter of the patients (25.2%) are wheelchair-bound.

Table 18. Hereditary spastic paraplegia: stage of the disease (BNMDR, 2017)

Stage of the disease	Number of patients	% of the disease group population
Pre-symptomatic	0	0.0
Symptomatic - not ambulant (only for patients < 2.5 years)	0	0.0
Ambulant	221	**72.2**
Loss of ambulation wheelchair	77	25.2
On life support	1	0.3
Missing	7	2.3
TOTAL	**306**	**100**

4.2.5. DUCHENNE MUSCULAR DYSTROPHY

Duchenne muscular dystrophy (DMD) is an X-linked recessive genetic disease, but about one-third of patients are affected by spontaneous mutation. The natural history of the disease is, between the age of 2 and 6 years old, marked by a progressive weakness in the muscles of the lower limbs leading to more frequent falls. Between the ages of 6 and 12, muscle weakness is accentuated until the upper limbs and trunk muscles are also significantly impacted. Walking becomes difficult and the child is dependent on a wheelchair between the ages of 9.5 and 13 years old. Respiratory function deteriorates due to weakness of the respiratory muscles and alteration of the thoracic anatomy (kyphoscoliosis). There is also cardiomyopathy. It is usually cardiorespiratory failure that leads to the death of the patient in late adolescence. Patient survival is currently much longer, as corticosteroid treatment, scoliosis surgery and non-invasive ventilation have changed the natural course of the disease. There are also new drugs targeting certain specific mutations (34–36).

In Belgium, DMD represents 5.2% of the total population of the registry in 2017. The prevalence estimated by the BNMDR is 2.7 / 100,000 inhabitants (2.6 in Flanders, 1.7 in Brussels and 3.0 in Wallonia). This estimate is consistent with international literature assessments, estimating the prevalence of the disease between 0.7 and 4.7 / 100,000 inhabitants (21,37,38). Orphanet published a prevalence of 4.78 / 100,000 population for DMD worldwide (20).

Demographic data for DMD are shown in **Figure 16** and **Figure 17**. As illustrated on Figure 17, few female carriers are also registered in BNMDR.

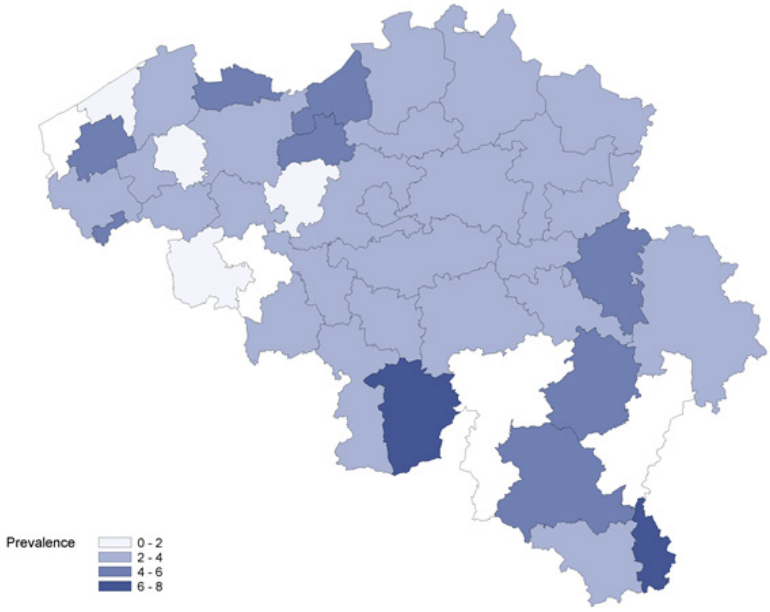


Figure 16. Duchenne muscular dystrophy: Prevalence / 100,000 inhabitants (BNMDR, 2017)

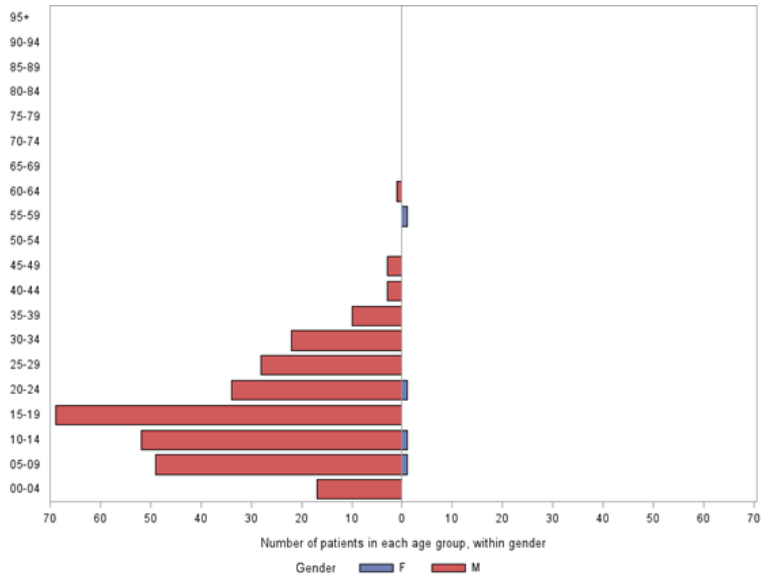


Figure 17. Duchenne muscular dystrophy: Age distribution by gender (BNMDR, 2017)

The status of the diagnosis (definitive or not) is illustrated in **Table 19**. Almost all patients with DMD in the BNMDR (97.0%) have received a final diagnosis.

Table 19. Duchenne muscular dystrophy: diagnosis status (BNMDR, 2017)

Final diagnosis?	Number of patients	% of the disease group population
Yes	293	**97.0**
No	2	0.7
Missing	7	2.3
TOTAL	**302**	**100**

The status of the genetic confirmation of the disease is illustrated in **Table 20**. Most patients with DMD in the BNMDR (88.7%) have a genetic confirmation of their disease.

Table 20. Duchenne muscular dystrophy: genetic confirmation of the diagnosis (BNMDR, 2017)

Genetically confirmed diagnosis?	Number of patients	% of the disease group population
Yes	268	**88.7**
No	9	3.0
Missing	25	8.3
TOTAL	**302**	**100**

The status of the stage of the disease is illustrated in **Table 21**. About the same proportion of patients with DMD in the BNMDR are ambulant or wheelchair-bound (42.7% and 40.7% respectively). It is important to note that 13.6% of the patients are on life support.

Table 21. Duchenne muscular dystrophy: stage of the disease (BNMDR, 2017)

Stage of the disease	Number of patients	% of the disease group population
Pre-symptomatic	5	1.7
Symptomatic - not ambulant (only for patients < 2.5 years)	0	0.0
Ambulant	129	**42.7**
Loss of ambulation wheelchair	123	**40.7**
On life support	41	13.6
Missing	4	1.3
TOTAL	**302**	**100**

The data specifically collected in the framework of the international "TREAT-NMD" network for DMD are presented in Chapter 5.

4.2.6. CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a chronic and progressive sensory-motor disease of the peripheral nerves. Clinically, it manifests as generalized and symmetrical weakness, areflexia, and sensory disturbances. The etiology is unknown, but the disease may start as a result of infection, vaccination, surgery, trauma or pregnancy. The disease usually occurs in adults between 30 and 60 years of age, but can occur at any age, including young children (39).

In 2017, CIDP represented 5.0% of the total population of the BNMDR registry. The estimated prevalence for Belgium is 2.5 / 100,000 inhabitants (1.8 in Flanders, 1.4 in Brussels-Capital Region and 4.2 in Wallonia). These figures are included in the range found in the international literature, which is 0.7 to 8.9 / 100,000 inhabitants (21). Orphanet published a prevalence of 3.7 / 100,000 population for CIDP in Europe (20).

Demographic data on CIDP are presented in **Figure 18** and **Figure 19**. We can note an important recruitment of patients in the South east of the country.

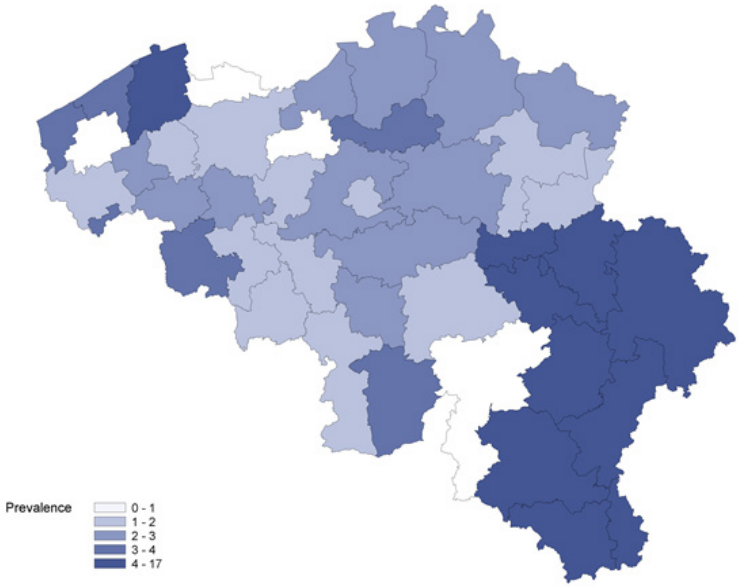


Figure 18. Chronic inflammatory demyelinating polyradiculoneuropathy: Prevalence / 100,000 inhabitants (BNMDR, 2017)

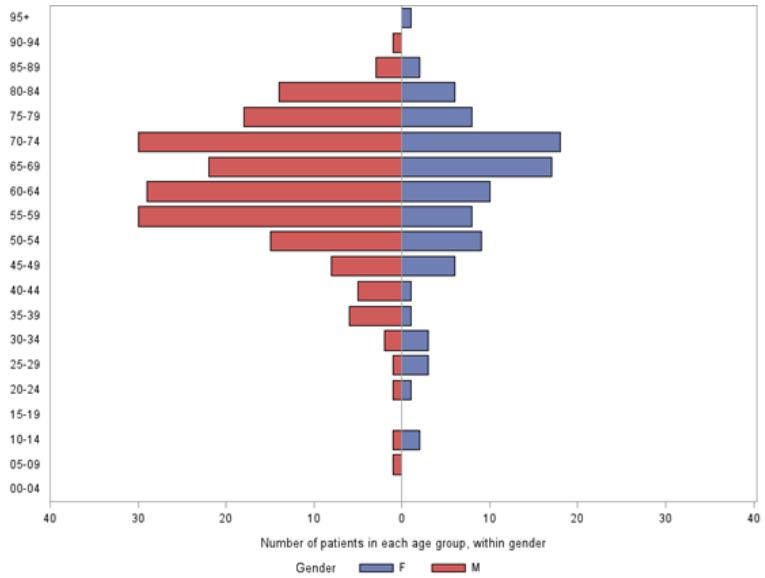


Figure 19. Chronic inflammatory demyelinating polyradiculoneuropathy: Age distribution by gender (BNMDR, 2017)

The status of the diagnosis (definitive or not) is illustrated in **Table 22**. The vast majority of patients with CIDP in the BNMDR (72.2%) have received a final diagnosis. It is important to note that the information on definitive diagnosis is missing for almost a quarter of the patients (23.3%).

Table 22. Chronic inflammatory demyelinating polyneuropathy: diagnosis status (BNMDR, 2017)

Final diagnosis?	Number of patients	% of the disease group population
Yes	208	**72.2**
No	13	4.5
Missing	67	23.3
TOTAL	**288**	**100**

The status of the stage of the disease is illustrated in **Table 23**. Most patients with CIDP in the BNMDR (91.0%) are ambulant.

Table 23. Chronic inflammatory demyelinating polyradiculoneuropathy: stage of the disease (BNMDR, 2017)

Stage of the disease	Number of patients	% of the disease group population
Pre-symptomatic	1	0.3
Symptomatic - not ambulant (only for patients < 2.5 years)	0	0.0
Ambulant	262	**91.0**
Loss of ambulation wheelchair	17	5.9
On life support	2	0.7
Missing	6	2.1
TOTAL	**288**	**100**

4.2.7. FACIOSCAPULOHUMERAL DYSTROPHY

Facioscapulohumeral dystrophy (FSHD) is a genetic disorder with autosomal dominant inheritance. It is initially characterized by muscle weakness in the face and shoulders. The muscles of the upper and lower limbs, as well as the abdominals can also be involved in the course of the disease. The symptom onset usually occurs between the ages of 3 and 44, but a later age of onset (up to 75 years) has also been described in literature (40).

In 2017, FSHD accounted for 4.4% of the total population of the BNMDR registry. It estimates the prevalence of the disease at 2.2 / 100,000 inhabitants (2.1 in Flanders, 2.7 in Brussels-Capital Region and 2.3 in Wallonia). Data from the international literature estimate the prevalence of the disease between 0.5 and 6.8 / 100,000 inhabitants (21). Orphanet published a prevalence of 4.5 / 100,000 population for FSHD in Europe (20).

Demographic data for FSHD are shown in **Figure 20** and **Figure 21**.

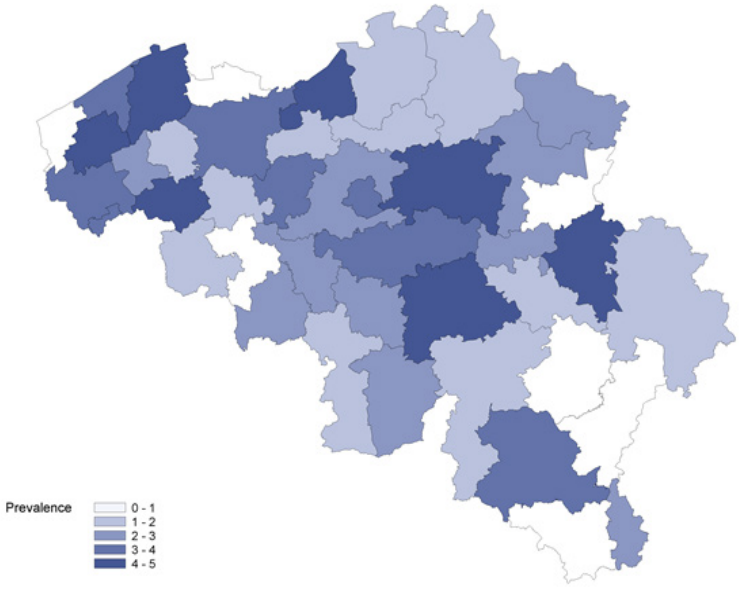


Figure 20. Facioscapulohumeral dystrophy: Prevalence / 100,000 inhabitants (BNMDR, 2017)

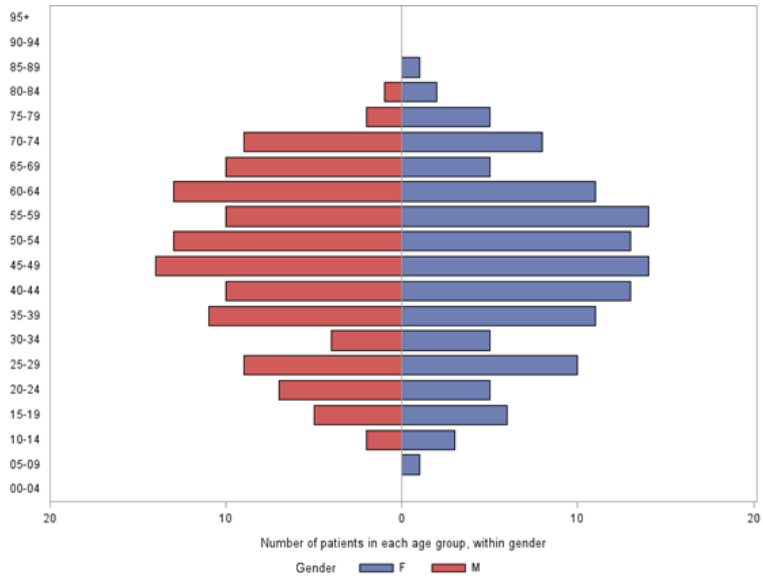


Figure 21. Facioscapulohumeral dystrophy: Age distribution by gender (BNMDR, 2017)

The status of the diagnosis (definitive or not) is illustrated in **Table 24**. Most BNMDR patients with FSHD (80.5%) have received a final diagnosis.

Table 24. Facioscapulohumeral dystrophy: diagnosis status (BNMDR, 2017)

Final diagnosis?	Number of patients	% of the disease group population
Yes	203	**80.5**
No	20	8.0
Missing	29	11.5
TOTAL	**252**	**100**

The status of the genetic confirmation of the disease is illustrated in **Table 25**. Almost half of the patients with FSHD in the BNMDR (49.2%) have a genetic confirmation of their disease. It is important to note that the information on genetic confirmation is also missing for more than a third of the patients (36.5%).

Table 25. Facioscapulohumeral dystrophy: genetic confirmation of the diagnosis (BNMDR, 2017)

Genetically confirmed diagnosis?	Number of patients	% of the disease group population
Yes	124	**49.2**
No	36	14.3
Missing	92	36.5
TOTAL	**252**	**100**

The status of the stage of the disease is illustrated in **Table 26**. The vast majority patients (79.8%) with FSHD in the BNMDR are ambulant and 15.8% are wheelchair-bound.

Table 26. Facioscapulohumeral dystrophy: stage of the disease (BNMDR, 2017)

Stage of the disease	Number of patients	% of the disease group population
Pre-symptomatic	4	1.6
Symptomatic - not ambulant (only for patients < 2.5 years)	0	0.0
Ambulant	201	**79.8**
Loss of ambulation wheelchair	40	15.8
On life support	1	0.4
Missing	6	2.4
TOTAL	**252**	**100**

4.2.8. LIMB GIRDLE MUSCULAR DYSTROPHY

Limb girdle muscular dystrophy (LGMD) is a heterogeneous group of hereditary diseases with autosomal dominant (type 1) or recessive (type 2) inheritance. Clinically, these diseases resemble Duchenne muscular dystrophy, except that the occurrence is the same in men and women (41).

In 2017, LGMD accounted for 4.4% of the total population of the BNMDR registry. It evaluates the prevalence in Belgium at 2.2 / 100,000 inhabitants (2.5 in Flanders, 1.7 in Brussels-Capital Region and 1.9 in Wallonia). In the international literature, the prevalence is estimated at 0.8 - 6.9 / 100,000 inhabitants (21,37). In agreement, Orphanet published a prevalence of 2.3 / 100,000 population for LGMD worldwide (20).

Demographic data for LGMD are shown in **Figure 22** and **Figure 23**.

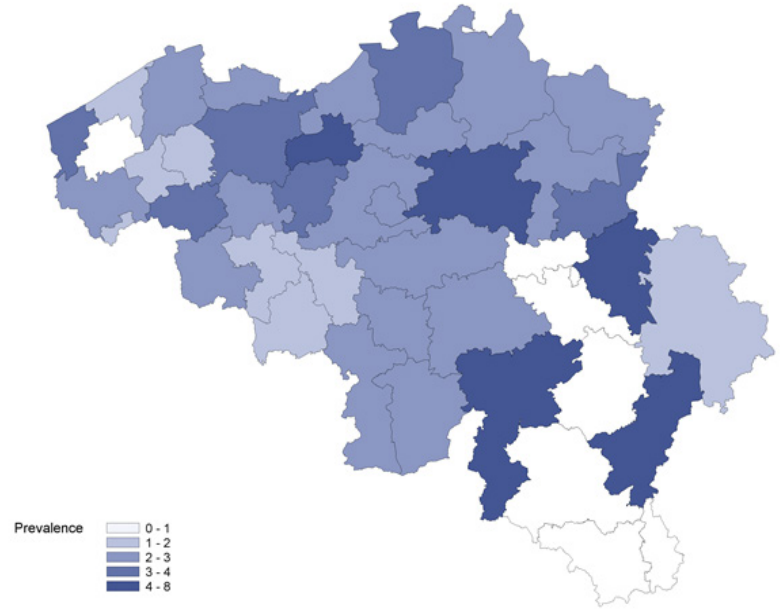


Figure 22. Limb girdle muscular dystrophy: Prevalence / 100,000 inhabitants (BNMDR, 2017)

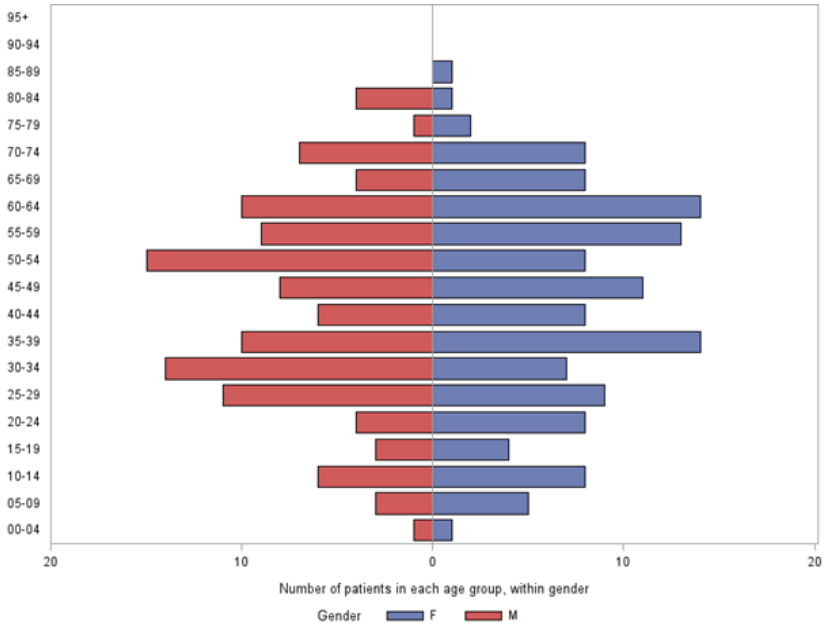


Figure 23. Limb girdle muscular dystrophy: Age distribution by gender (BNMDR, 2017)

The status of the diagnosis (definitive or not) is illustrated in **Table 27**. About two third of BNMDR patients with LGMD (63.3%) have received a final diagnosis..

Table 27. Limb girdle muscular dystrophy: diagnosis status (BNMDR, 2017)

Final diagnosis?	Number of patients	% of the disease group population
Yes	159	**63.3**
No	45	18.0
Missing	47	18.7
TOTAL	**251**	**100**

The status of the genetic confirmation of the disease is illustrated in **Table 28**. One third of patients with LGMD in the BNMDR (33.1%) have a genetic confirmation of their disease. About the same proportion of patients (32.2%) do not have a genetic confirmation of their disease, reflecting the variety in subtypes of this disease. It is important to note that the information on genetic confirmation is also missing for 34.7% of the patients.

Table 28. Limb girdle muscular dystrophy: genetic confirmation of the diagnosis (BNMDR, 2017)

Genetically confirmed diagnosis?	Number of patients	% of the disease group population
Yes	83	**33.1**
No	81	32.2
Missing	87	34.7
TOTAL	**251**	**100**

The status of the stage of the disease is illustrated in **Table 29**. The majority of patients with LGMD in the BNMDR (68.5%) are ambulant and about a quarter of the patients (28.3%) are wheelchair-bound.

Table 29. Limb girdle muscular dystrophy: stage of the disease (BNMDR, 2017)

Stage of the disease	Number of patients	% of the disease group population
Pre-symptomatic	0	0.0
Symptomatic - not ambulant (only for patients < 2.5 years)	0	0.0
Ambulant	172	**68.5**
Loss of ambulation wheelchair	71	28.3
On life support	4	1.6
Missing	4	1.6
TOTAL	**251**	**100**

4.2.9. SPINOCEREBELLAR ATAXIAS

Spinocerebellar ataxias (SCAs) are a group of heterogeneous inherited diseases whose common phenotype is progressive ataxia. In the past, several classification attempts have been made to organize these diseases on a physiopathological or clinical basis. With the advancement in molecular genetic methods, genetic classification is more commonly used. The mode of transmission may be autosomal dominant, autosomal recessive, X-linked or mitochondrial (32,42).

In 2017, SCAs accounted for 3.5% of the total population of the BNMDR registry. The prevalence is estimated at 1.8 / 100,000 inhabitants (2.8 in Flanders, 0.8 in Brussels-Capital Region and 0.2 in Wallonia).In the

international literature, the prevalence of these diseases is estimated to be between 1.1 and 11.2 / 100,000 inhabitants (32). Orphanet did not publish prevalence for all SCAs together but provides an estimation for the most frequent forms: ie, SCA1, SCA2 and SCA3, with a published prevalence of of 1.5 / 100,000 population worldwide respectively for each of these subtypes (20).

Demographic data for SCAs are shown in **Figure 24** and **Figure 25**. We can note a massive gap in patient recruitment in the South of Belgium.

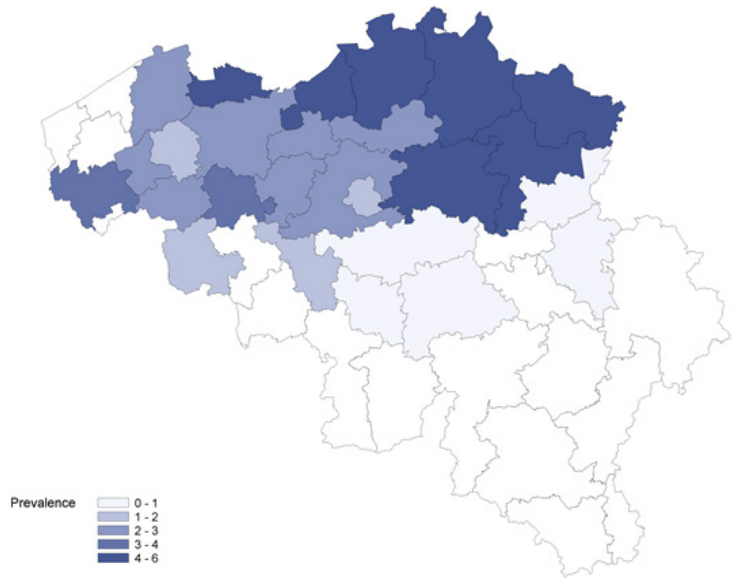


Figure 24. Spinocerebellar ataxias: Prevalence / 100,000 inhabitants (BNMDR, 2017)

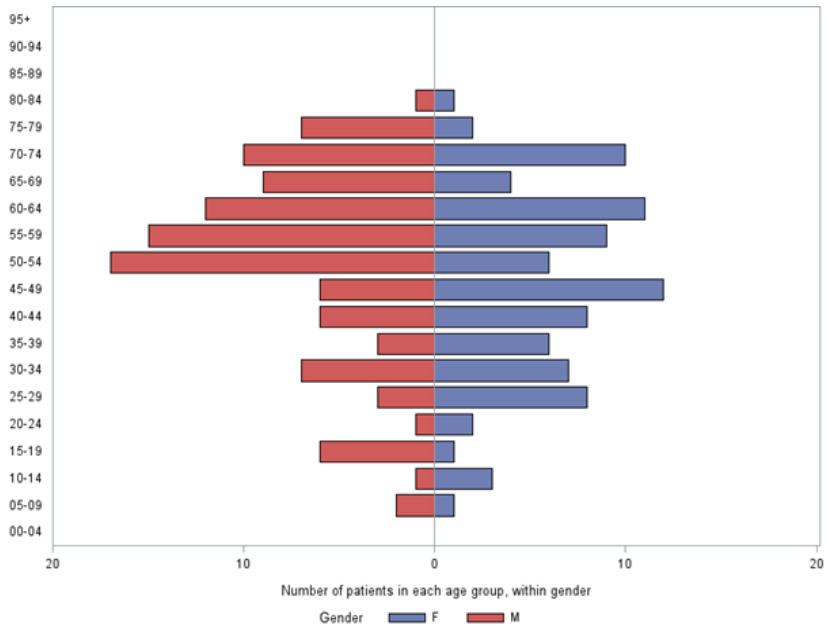


Figure 25. Spinocerebellar ataxias: Age distribution by gender (BNMDR, 2017)

The status of the diagnosis (definitive or not) is illustrated in **Table 30**. About two third of patients with SCAs in the BNMDR (63.7%) have received a final diagnosis. It is important to note that a significant proportion of patients (25.9%) does not have a final diagnosis, highlighting the variety of disease's subtypes.

Table 30. Spinocerebellar ataxias: diagnosis status (BNMDR, 2017)

Final diagnosis?	Number of patients	% of the disease group population
Yes	128	**63.7**
No	52	25.9
Missing	21	10.4
TOTAL	**201**	**100**

The status of the genetic confirmation of the disease is illustrated in **Table 31**. About a quarter of the BNMDR patients with SCAs (25.9%) have a genetic confirmation of their disease. More than a third of the patients (36.8%) do not have a genetic confirmation of their disease, reflecting again the variety in subtypes of this disease. It is important to note that the information on genetic confirmation is also missing for 37.3% of patients.

Table 31. Spinocerebellar ataxias: genetic confirmation of the diagnosis (BNMDR, 2017)

Genetically confirmed diagnosis?	Number of patients	% of the disease group population
Yes	52	**25.9**
No	74	36.8
Missing	75	37.3
TOTAL	**201**	**100**

The status of the stage of the disease is illustrated in **Table 32**. The majority of the patients (67.7%) with SCAs in the BNMDR are ambulant and about a third of patients (31.3%) are wheelchair-bound.

Table 32. Spinocerebellar ataxias: stage of the disease (BNMDR, 2017)

Stage of the disease	Number of patients	% of the disease group population
Pre-symptomatic	0	0.0
Symptomatic - not ambulant (only for patients < 2.5 years)	0	0.0
Ambulant	136	**67.7**
Loss of ambulation wheelchair	63	31.3
On life support	1	0.5
Missing	1	0.5
TOTAL	**201**	**100**

4.2.10. POSTPOLIOMYELITIS SYNDROME

Postpoliomyelitis syndrome (PPS) is described as the appearance of new neuromuscular symptoms (progressive muscle weakness, fatigue, arthralgia, myalgia) occurring many years after acute poliomyelitis. Several authors have proposed different diagnostic criteria. Boyer et al. (43) propose to retain those of Halstead *et al.*, which have been validated by a panel of international experts:

- Confirmed primary infection by poliovirus with an initial motor impairment
- Partial or complete motor function recovery (may extend over several years)
- Rapid or gradual loss of endurance and / or muscle strength with or without muscle atrophy in areas previously healthy. This is associated with widespread muscle and joint fatigue and intolerance to cold
- This clinical picture is characeterized by its unusual duration (evolving for more than a year).
- Other rarer symptoms may be present (abnormal sleep, breathing difficulties, dysphagia, dysarthria, fasciculations, joint deformity).

The etiology of this syndrome remains unknown to this day. Most authors believe that it is related to the death or structural and functional dysfunction of surviving primary motor units after the primary infection. Among the mechanisms at the origin of these dysfunctions, several hypotheses are evoked (43):

- Presence of viral genetic residues capable of stimulating and disrupting the inflammatory and immunological response in the central or peripheral nervous system
- Occurrence of an imbalance between the degenerative and regenerative physiological phenomena within the giant motor units
- Architectural abnormalities, functional muscle fibers and / or cerebral integration disorders of movement

Between 22% and 85% of individuals with polio sequelae develop PPS. The delay between acute illness and the onset of PPS may vary between 8 and 71 years (44,32).

In 2017, PPS represented 2.9% of the total population of the BNMDR registry. The prevalence is evaluated in Belgium at 1.5 / 100,000 inhabitants (1.1 in Flanders, 2.7 in Brussels-Capital Region and 1.8 in Wallonia). This estimate is very different from the figures in the international literature, which estimates the prevalence of PPS at 18 /100 000 in Japan and 92 /100 000 in Sweden (21,45,46). However, there are great disparities between countries concerning the prevalence of poliomyelitis and poliomyelitis vaccination policies. No case of poliomyelitis was recorded in Belgium in 2017. The last indigenous case occurred in 1979 and the last case imported in 1989. The risk of an epidemic in Belgium remains negligible thanks to high vaccination coverage (> 95%; vaccination is compulsory for children since 1967) (47,48).

Demographic data for PPS are shown in **Figure 26** and **Figure 27**.

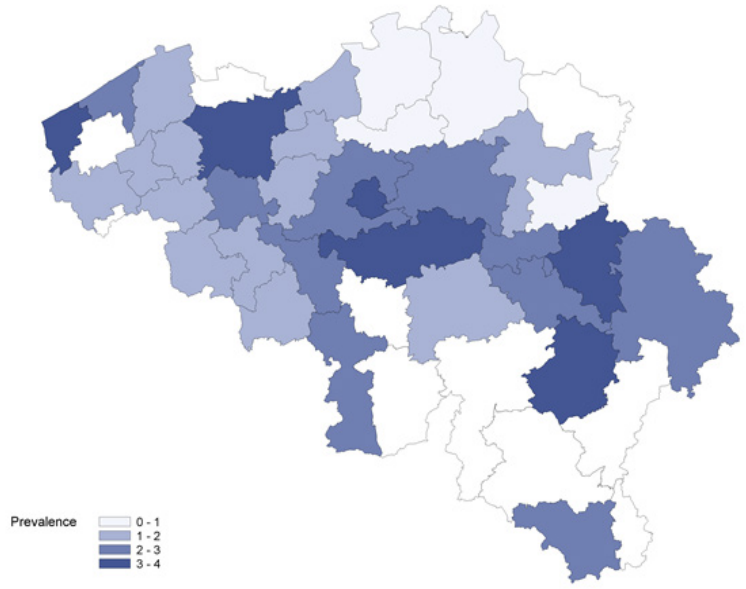


Figure 26. Postpoliomyelitis syndrome: Prevalence / 100,000 inhabitants (BNMDR, 2017)

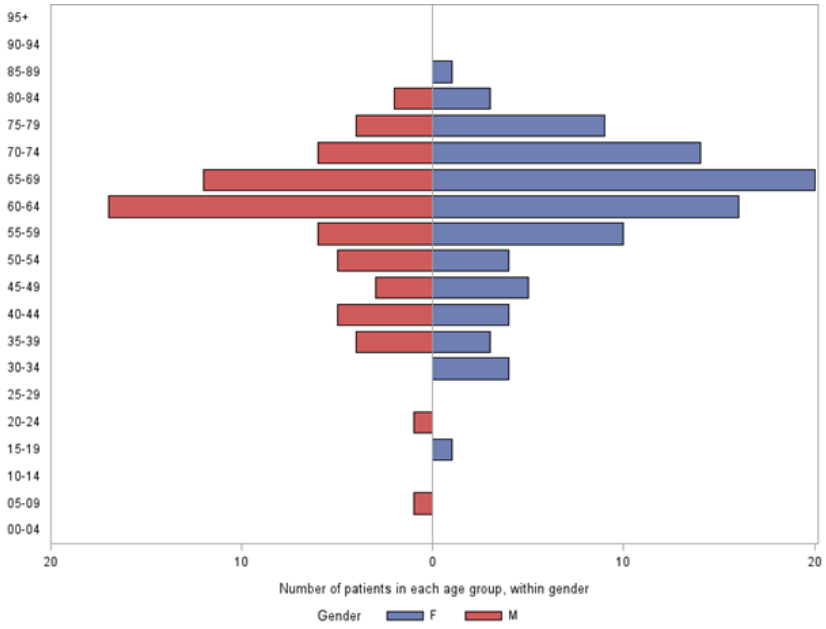


Figure 27. Postpoliomyelitis syndrome: Age distribution by gender (BNMDR, 2017)

The status of the diagnosis (definitive or not) is illustrated in **Table 33**. Most BNMDR patients with PPS (85.2%) have received a final diagnosis.

Table 33. Postpoliomyelitis syndrome: diagnosis status (BNMDR, 2017)

Final diagnosis?	Number of patients	% of the disease group population
Yes	144	**85.2**
No	2	1.2
Missing	23	13.6
TOTAL	**169**	**100**

The status of the stage of the disease is illustrated in **Table 34**. The vast majority of patients with PPS in the BNMDR (75.7%) are ambulant and 14.8% are wheelchair-bound.

Table 34. Postpoliomyelitis syndrome: stage of the disease (BNMDR, 2017)

Stage of the disease	Number of patients	% of the disease group population
Pre-symptomatic	0	0.0
Symptomatic - not ambulant (only for patients < 2.5 years)	0	0.0
Ambulant	128	**75.7**
Loss of ambulation wheelchair	25	14.8
On life support	-	-
Missing	16	9.5
TOTAL	**169**	**100**

5. TREAT-NMD

TREAT-NMD data are specifically collected for Duchenne and Becker muscular dystrophies, as well as for spinal muscular atrophy. These data are collected in addition to those already collected in the framework of the BNMDR registry. They allow the collaboration with the TREAT-NMD international network that aims to advance diagnosis, care and treatment for patients with neuromuscular diseases. The completion of these data is not mandatory; a reference center can choose to only send the basic data required for the proper functioning of the registry. Nevertheless, we strongly encourage the centers to send us as much data as possible because the collaboration with international network represents a clear added value, especially in term of potential participation in clinical trials. Despite a high number of missing data in 2010 - 2015 (49,50), the reference centers have made important efforts to complete these data. Since 2016, virtually all patients within the TREAT-NMD scope have at least some of the specific data completed.

5.1. DUCHENNE & BECKER MUSCULAR DYSTROPHIES

Both Duchenne (DMD) and Becker muscular dystrophies (BMD) are caused by mutations in the DMD gene, which encodes a protein called dystrophin. The DMD gene is the largest gene in the human genome; it covers 79 exons. The severity of the clinical phenotype depends on the maintenance or disappearance of reading frames. When dystrophin is completely absent or produced at very low levels (due to deletion suppressing the reading frame), the patient has DMD. When the patient presents with a mutation maintaining the reading frame ("in-frame mutations"), it allows the production of a dystrophin of abnormally low molecular weight, resulting in a less aggressive phenotype of the disease: BMD (51).

5.1.1. GENERAL RESULTS OF THE DATA COLLECTION

According to the NIHDI classification, there was 302 DMD patients and 109 BMD patients registered in the registry in 2017. Among those patients, there are 4 female carriers patients: 1 is pre-symtomatic and 3 are manifesting symptoms. The results by reference center are shown in **Figure 29** for DMD and in **Figure 30** for BMD. Patients for whom the TREAT-NMD data have been completed have a "Yes" answer. This concerns the vast majority of patients in 2017. However the percentage of data completion is better for DMD than for BMD patients. Indeed, the percentage of patients with TREAT-NMD missing data is 1.3% and 13.8% for DMD and BMD patients respectively.

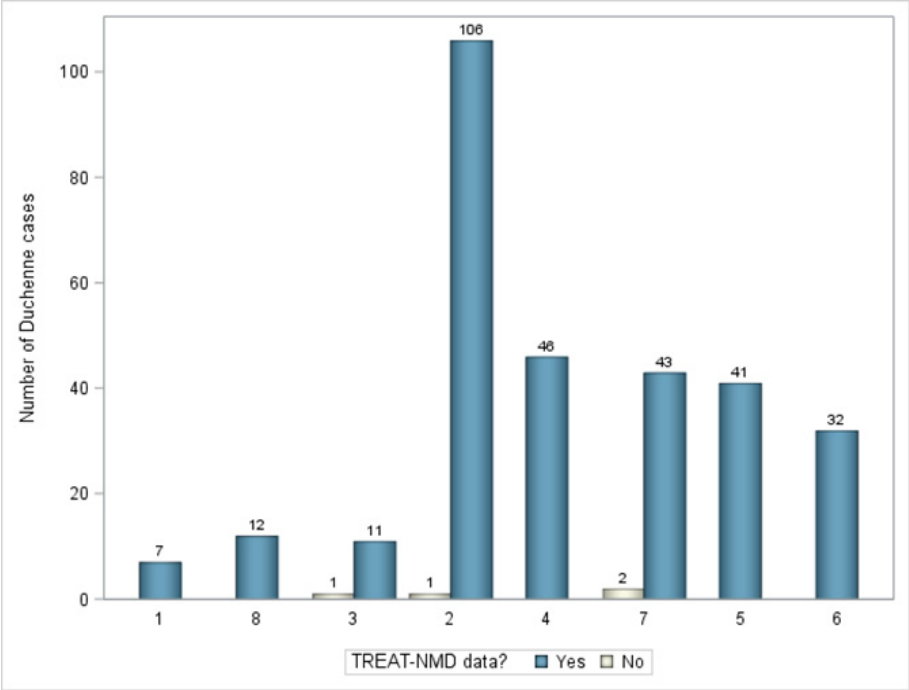


Figure 28. TREAT-NMD data for Duchenne muscular dystrophy, by NMRC (Belgium, 2017)

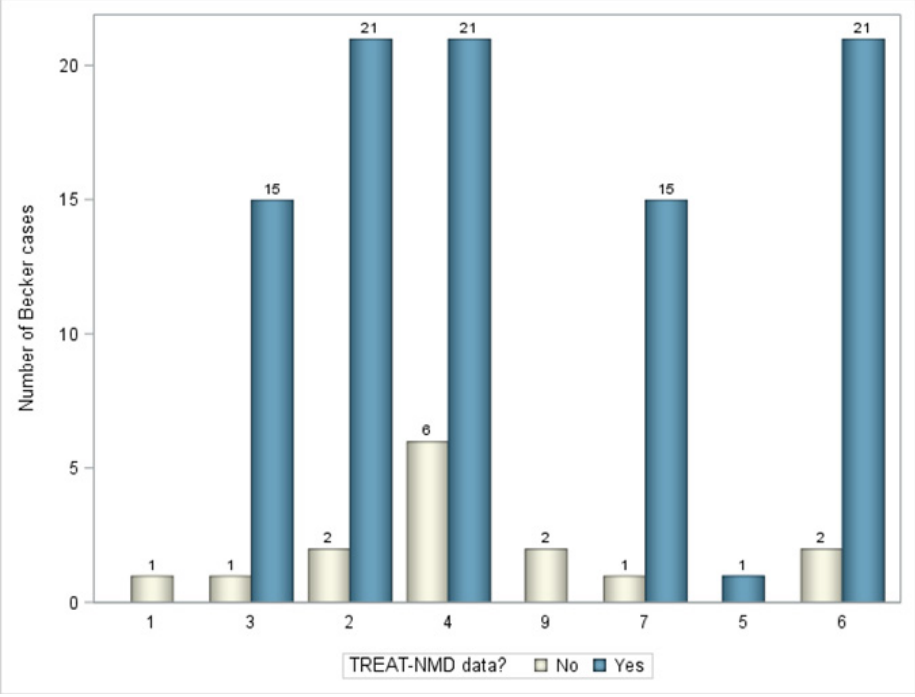


Figure 29. TREAT-NMD data for Becker muscular dystrophy, by NMRC (Belgium, 2017)

5.1.2. DATA FOR DUCHENNE PATIENTS IN BELGIUM

According to the NIHDI classification, there was 302 DMD patients registered in the BNMDR in 2017. The age of those patients is between 2 and 62 years old, with an average age of 18.1 years old ± 10.3 years. At the moment, patients are generally receiving symptomatic treatments. However, disease modifying therapies are in the pipeline and clinical trials are ongoing to evaluate their safety and efficacy.

The use of steroid therapy is illustrated in **Table 35**. Half of DMD patients (50.0%) are currently receiving a steroid therapy while one third (33.4%) never received such therapy.

Table 35. Duchenne Muscular Dystrophy: steroid therapy (BNMDR, 2017)

Steroid therapy?	Number of patients	% of the disease group population
Currently	151	**50.0**
Previously	28	9.3
Never	101	**33.4**
Unknown	18	6.0
Missing	4	1.3
TOTAL	**302**	**100**

The inclusion in a clinical trial is illustrated in **Table 36**. At the moment, 4.9% of DMD patients are involved in a clinical trial. More than two third of DMD patients (69.3%) never participated in a such study.

Table 36. Duchenne Muscular Dystrophy: inclusion in a clinical trial (BNMDR, 2017)

Clinical trial?	Number of patients	% of the disease group population
Currently	15	**4.9**
Previously	55	18.2
Never	209	**69.3**
Unknown	19	6.3
Missing	4	1.3
TOTAL	**302**	**100**

In 2017, 10 patients were reported as deceased: 8 patients died in 2017 and the date of death for the 2 remaining patients is unknown. Among the 8 deceased patients in 2017, the age of death was in average 29.5 years old ± 11.9 years.

5.1.2.1. Motor function in Duchenne patients in Belgium

The status of ambulation is illustrated in **Table 37**. More than half of DMD patients (55.0%) are currently unable to walk.

Table 37. Duchenne Muscular Dystrophy: ambulation status (BNMDR, 2017)

Currently able to walk?	Number of patients	% of the disease group population
Yes	132	43.7
No	166	**55.0**
Missing	4	1.3
TOTAL	**302**	**100**

Physicians also evaluated the ability of patients to sit without support. This variable is illustrated in **Table 38**. The majority of DMD patients (62.5%) are currently able to sit without support.

Table 38. Duchenne Muscular Dystrophy: sitting without support status (BNMDR, 2017)

Able to sit without support?	Number of patients	% of the disease group population
Yes	189	**62.5**
No	98	32.4
Missing	15	5.0
TOTAL	**302**	**100**

In addition, the use of a wheelchair is also assessed. Please note that the use of wheelchair is different than the ability to walk for a patient. Some patients use the wheelchair intermittently. The status wheelchair use is illustrated in **Table 39**. More than half of DMD patients (54.6%) are currently using a wheelchair permanently.

Table 39. Duchenne Muscular Dystrophy: wheelchair use (BNMDR, 2017)

Wheelchair use	Number of patients	% of the disease group population
Permanent	165	**54.6**
Intermittent	41	13.6
Never	85	28.1
Unknown	2	0.7
Missing	9	3.0
TOTAL	**302**	**100**

Therefore the loss of ambulation is defined by the moment a patient has to use the wheelchair permantly. **Figure 30** shows a frequency distribution of age at loss of ambulation for the 2017 BNMDR data. "0" means that the patient has never walked, "99" means that the information is unknown.

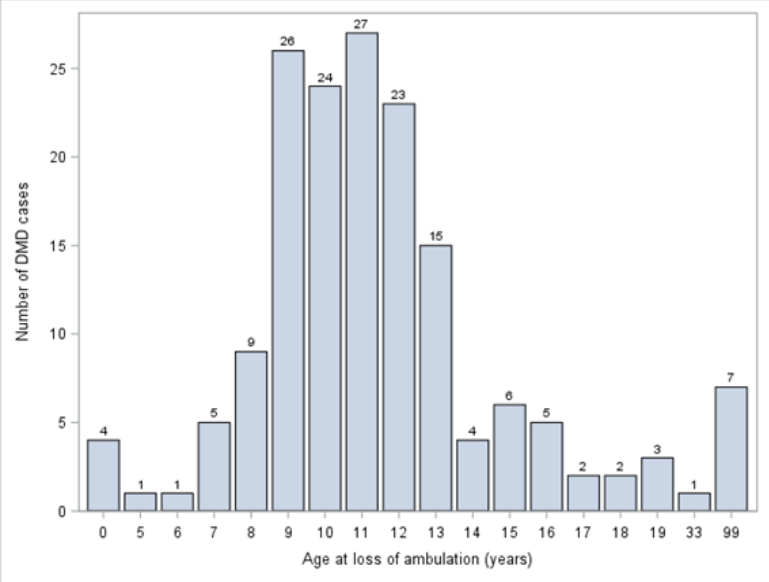


Figure 30. Age of ambulation loss for Duchenne patients (BNMDR, 2017)

For the 158 patients for whom information was provided, the average age of walking loss is 11.0 ± 3.6 years. In the natural history of the disease, the average age of ambulation loss is 9.5 to 13 years of age (34–36). The age at loss of ambulation was compared according to the treatments received by the patient (previously on steroids, previously in a clinical trial or no treatment). A Kruskal-Wallis H test showed that the difference between the different treatment groups was marginally significant (X2(2) = 5.010, p = 0.082), with a trend of a higher age at loss of ambulation for patients who were in a clinical trial.This analysis is illustrated in the **Table 40**. It is expected that the number of patients participating in a clinical trial will increase. Hence, it will be interesting to follow whether this trend will continue.

Table 40. Duchenne Muscular Dystrophy: loss of ambulation depending on treatment (BNMDR, 2017)

Population	Number of patients	Age at loss of ambulation (years) Median (P25 – P75)
Non ambulant patients who **never received a treatment***	56	10 (9 – 12)
Non ambulant patients who previously had a **steroid therapy**	27	10 (9 – 11)
Non ambulant patients who previously were in a **clinical trial**	34	12 (11 – 13)

* Non ambulant patients who never received a treatment means non ambulant patients who never reciede steroid therapy nor were included in a clinical trial.

5.1.2.2. Respiratory function in Duchenne patients in Belgium

In Duchenne patients, respiratory function is impaired due to the weakness of the respiratory muscles and the alteration of the thoracic anatomy (kyphoscoliosis). In the course of the natural history of the disease, it is usually the cardiorespiratory failure that leads to the death of the patient at the end of adolescence. Patient survival is currently longer, as corticosteroid treatment, scoliosis surgery and non-invasive ventilation have changed the natural course of the disease (34,36,52).

The use of non-invasive ventilation for all DMD patients is illustrated in **Table 41**. A quarter of DMD patients (25.5%) had non-invasive ventilation (part-time or full-time) in 2017.

Table 41. Duchenne Muscular Dystrophy: non-invasive ventilation (BNMDR, 2017)

Non-invasive ventilation?	Number of patients	% of the disease group population
No	216	71.5
Part-time	40	**13.2**
All day	37	**12.3**
Unknown	5	1.7
Missing	4	1.3
TOTAL	**302**	**100**

The use of invasive ventilation for all DMD patients is illustrated in **Table 42**. Only 1.9 % of DMD patients had invasive ventilation (part-time or full-time) in 2017.

Table 42. Duchenne Muscular Dystrophy: invasive ventilation (BNMDR, 2017)

Invasive ventilation?	Number of patients	% of the disease group population
No	285	94.5
Part-time	1	**0.3**
All day	5	**1.6**
Unknown	7	2.3
Missing	4	1.3
TOTAL	**302**	**100**

Figures 31 show all Duchenne patients between 2010 and 2017: they are categorized according to treatment (ie: no treatment, on steroids (previously or currently) or in a clinical trials (previously or currently)). The median Forced Vital Capacity (FVC, %), is indicated according to the age of the patients. In the patients who have no treatment (blue), a general trend of gradual decrease in FVC can be observed during adolescence. This is generally consistent with data from the international literature (52,53). This trend of gradual decrease seems slowed down when patients are on steroids (red) or participate to a clinical trial (green).

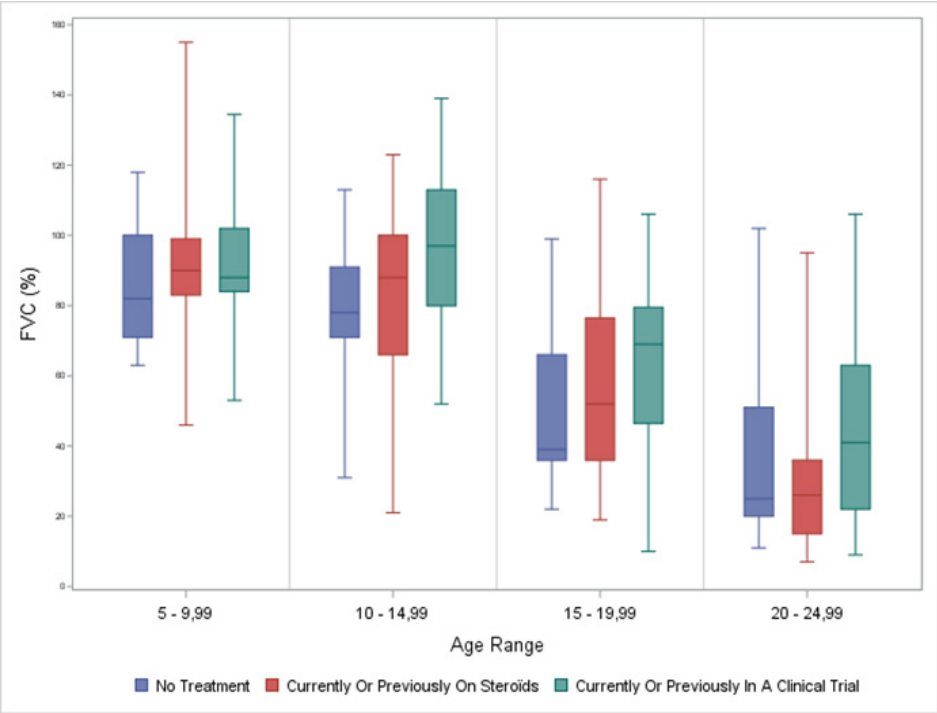


Figure 31. Box plot of the median FVC in function of age and treatment for Duchenne patients (2010 - 2017)

N = 1650, missing = 1183. Patients are categorized as follows: no treatment (blue), previously or currently on steroids (red) and previously or currently in a clinical trial (green). The horizontal line represents the median value, the length of the box the interquartile space (the distance between the 25th and the 75th percentile), and the vertical lines ("whiskers") represent the minimum and maximum values.*

** a single patient is included multiple times: one time for each data collection, for all the years he has been registred in the BMDR*

5.1.2.3. Cardiac function in Duchenne patients in Belgium

Without medical intervention, Duchenne patients die from respiratory or cardiac insufficiency at the end of adolescence. Treatment with corticosteroids and non-invasive ventilation have prolonged patients' life expectancy up to their forties. Improvement in respiratory management has revealed the significant morbidity and mortality caused by the underlying cardiomyopathy. Due to the abnormalities of dystrophin, fibrotic degeneration of cardiomyocytes leads to dilated cardiomyopathy with consequent heart failure and arrhythmia (35).

The presence of cardiomyopathy/heart failure is illustrated in **Table 43**. A bit more than a quarter (27.5%) of DMD patients have already suffered from a cardiomyopathy or heart failure in 2017.

Table 43. Duchenne Muscular Dystrophy: cardiomyopathy/heart failure (BNMDR, 2017)

Cardiomyopathy/ Heart failure?	Number of patients	% of the disease group population
Yes	83	**27.5**
No	173	57.3
Unknown	37	12.2
Missing	9	3.0
TOTAL	**302**	**100**

The use of cardiac medication is illustrated in **Table 44**. More than a third (36.1%) of DMD patients had a cardiac medication in 2017.

Table 44. Duchenne Muscular Dystrophy: cardiac medication (BNMDR, 2017)

Cardiac medication?	Number of patients	% of the disease group population
Yes	109	**36.1**
No	166	55.0
Unknown	23	7.6
Missing	4	1.3
TOTAL	**302**	**100**

Data on the type of cardiac medication prescribed to Duchenne patients are shown in **Table 45**. As one can see, cardiac medication is very different from one patient to the other, with the exception of angiotensin converting enzyme inhibitors prescribed to 56.8% of Duchenne patients known to be treated with cardiac medication respectively.

In a recent systematic review of the literature (35), El-Aloul *et al.* described the benefits of angiotensin converting enzyme inhibitors, angiotensin antagonists, beta-blockers and aldosterone antagonists. However, there is no data in the literature about the best treatment to offer, nor the ideal starting age.

Table 45. For 2017, treatments prescribed for the 109 Duchenne patients known to be on cardiac medication

Prescribed medication	Number of patients
Alendronate	1
Bêtabloquant, ACE	1
Bêtabloquant, bisoprolol	1
Bisoprolol	1
Bisoprolol, Lisinopril	1
Bisoprolol, Lisinopril, Spironolactone	1
Bisoprolol, Zestril	1
Coversyl	**13**
Enalapril	5
Enalapril, Lasix	1
Kredex	2
Lisinopril, Carvedilol, Lanoxin	1
Lisinopril	**36**
Lisinopril, Carvedilol	6
Lisinopril, Spironolactone	1
Nadolol	1
Perindopril	1
Ramipril	1
Sotolol	1
Zestril	13
Bisoprolol, Aldactone, Zestril	1
Carvedilol	2
Coveram	1
Coversyl, Bisoprolol	1
Coversyl, Kredex	1
Coversyl, Seloken	1
Coversyl, Bisoprolol, Laxido	1
Enalapril, Aldactone, Carvedilol	1
Enalapril, Amlodipine	1
Enalapril, Carvedilol	1
Kredex, Coversyl, Spirololactone	1
Tritace, Emconcor	1
Zestril, Emconcor	1
Zestril, Seloken	5
Zestril, Bisoprolol, Lanoxin, Aldactone, Burinex, Tamsulosine	1
Valsatran	1
Total	**109**

5.1.2.4. Scoliosis surgery in Duchenne patients in Belgium

The reasons why Duchenne patients develop scoliosis are currently poorly understood. Trunk muscle weakness associated with reduced mobility is generally considered to be the factor that ultimately leads to the development of rapidly evolving scoliosis (increased angulation between 16° and 24° per year that most often occurs at the time of pubertal growth spurt). Making the decision of proposing a surgical procedure is complex because not all patients develop scoliosis at the same time, and do not show the same rate of progression. On one hand, early surgery is recommended in patients whose scoliosis progresses rapidly, or whose evolution of cardiorespiratory function makes it necessary to anticipate surgery. On the other hand, there are some patients for whom surgery is not needed, when scoliosis is stabilized at the end of growth (36).

The status of scoliosis surgery is illustrated in **Table 46**. A bit more than a quarter (26.5%) of DMD patients had already underwent a scoliosis surgery in 2017.

Table 46. Duchenne Muscular Dystrophy: scoliosis surgery (BNMDR, 2017)

Scoliosis surgery?	Number of patients	% of the disease group population
Yes	80	**26.5**
No	206	68.2
Unknown	11	3.6
Missing	5	1.7
TOTAL	**302**	**100**

5.1.3. DATA FOR BECKER PATIENTS IN BELGIUM

According to the NIHDI classification, there was 109 BMD patients registered in the BNMDR in 2017. The age of those patients is between 3 and 76 years old, with an average age of 32.6 years old ± 17.6 years.

The use of steroid therapy is illustrated in **Table 47**. Only 4.6% of BMD patients are currently receiving a steroid therapy while 60.5% of BMD patients never received such therapy.

Table 47. Becker Muscular Dystrophy: steroid therapy (BNMDR, 2017)

Steroid therapy?	Number of patients	% of the disease group population
Currently	5	**4.6**
Previously	4	3.7
Never	66	**60.5**
Unknown	19	17.4
Missing	15	13.8
TOTAL	**109**	**100**

The inclusion in a clinical trials is illustrated in **Table 48**. The majority of BMD patients (77.0%) never participated in a clinical trial. Indeed, as far as we know, there is not clinical trial for BMD patients.

Table 48. Becker Muscular Dystrophy: inclusion in a clinical trial (BNMDR, 2017)

Clinical trial?	Number of patients	% of the disease group population
Currently	0	0.0
Previously	0	0.0
Never	84	**77.0**
Unknown	10	9.2
Missing	15	13.8
TOTAL	109	100

In 2017, no BMD patient were reported as deceased.

5.1.3.1. Motor function in Becker patients in Belgium

As mentioned previously, Becker dystrophy has a slower disease progression than Duchenne dystrophy. Most Becker patients develop difficulty in walking, however, by definition, they remain ambulatory past the age of 15 years. Approximately 50% of affected individuals lose the ability to ambulate by the fourth decade. (34).

The status of ambulation is illustrated in **Table 49**. More than two third of BMD patients (68.8%) are currently able to walk.

Table 49. Becker Muscular Dystrophy: ambulation status (BNMDR, 2017)

Currently able to walk?	Number of patients	% of the disease group population
Yes	75	**68.8**
No	19	17.4
Missing	15	13.8
TOTAL	109	100

Physicians also evaluated the ability of patients to sit without support. This variable is illustrated in **Table 50**. The vast majority of BMD patients (76.1%) are currently able to sit without support.

Table 50. Becker Muscular Dystrophy: sitting without support status (BNMDR, 2017)

Able to sit without support?	Number of patients	% of the disease group population
Yes	83	**76.1**
No	5	4.6
Missing	21	19.3
TOTAL	109	100

In addition, the use of a wheelchair is also assessed. Please note that the use of wheelchair is different than the ability to walk for a patient. Some patients use the wheelchair intermittently. The status wheelchair use is illustrated in **Table 51**. Less than a third of BMD patients are currently using a wheelchair, either permanently (15.5%) or by intermittence (13.8%).

Table 51. Becker Muscular Dystrophy: wheelchair use (BNMDR, 2017)

Wheelchair use	Number of patients	% of the disease group population
Permanent	17	**15.5**
Intermittent	15	**13.8**
Never	58	53.2
Unknown	4	3.7
Missing	15	13.8
TOTAL	109	100

The loss of ambulation is defined by the moment a patient has to use the wheelchair permantly. **Figure 32** shows a frequency distribution of age at loss of ambulation for the 2017 BNMDR data. "99" means that the information is unknown.

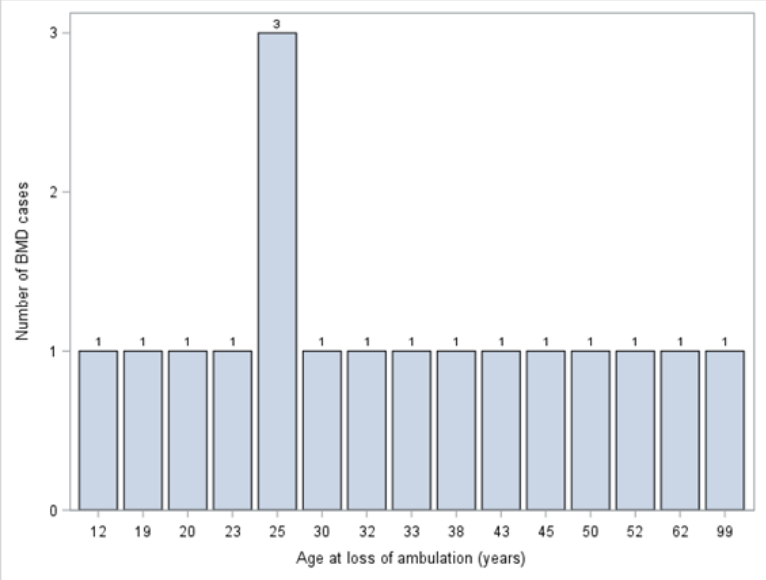


Figure 32. Age of ambulation loss for Becker patients (BNMDR, 2017)

For the 16 patients for whom information was provided, the average age of walking loss is 33.4 ± 13.8 years.

5.1.3.2. Respiratory function in Becker patients in Belgium

As in Duchenne patients, the respiratory function of Becker patients is impaired due to the weakness of the respiratory muscles and the alteration of the thoracic anatomy (kyphoscoliosis). However, disease progression is slower. In the course of the natural history of the disease, it is usually the cardiorespiratory failure that leads to the death of the patient. Patient survival is currently longer, as corticosteroid treatment, scoliosis surgery and non-invasive ventilation have changed the natural course of the disease (34,54,55).

The use of non-invasive ventilation is illustrated in **Table 52**. Only 3.7% of BMD patients had part-time non-invasive ventilation in 2017.

Table 52. Becker Muscular Dystrophy: non-invasive ventilation (BNMDR, 2017)

Non-invasive ventilation?	Number of patients	% of the disease group population
No	81	74.3
Part-time	4	**3.7**
All day	0	**0.0**
Unknown	9	8.2
Missing	15	13.8
TOTAL	**109**	**100**

The use of invasive ventilation for all DMD patients is illustrated in **Table 53**. No BMD patient had invasive ventilation (part-time or full-time) in 2017.

Table 53. Becker Muscular Dystrophy: invasive ventilation (BNMDR, 2017)

Invasive ventilation?	Number of patients	% of the disease group population
No	85	78.0
Part-time	0	**0.0**
All day	0	**0.0**
Unknown	9	8.2
Missing	15	13.8
TOTAL	**109**	**100**

Physicians also assess the Forced Vital Capacity (FVC). For this variable, the high number of missing data makes the interpretation of the results very delicate (information known only for 17/109 patients). For these 17 BMD patients, the median FVC, expressed in ml, was 3610 ± 1438. As an information, the average age of these 17 patients was 41.0 ± 20.2 years.

5.1.3.3. Cardiac medication for Becker patients in Belgium

Without medical intervention, the frequency of cardiac involvement in patients with Becker dystrophy is 60% to 75% (56). There are different cardiac manifestations in Becker patients ranging from very subtle signs to severe cardiomyopathy requiring cardiac transplant (57). Most of Becker patients have asymptomatic cardiac involvement. Only up to one third develops severe dilated cardiomyopathy with symptoms of heart failure (58). Due to the abnormalities of dystrophin, the primary pathology of cardiomyopathy in Becker patients is thought to be due to diffuse degeneration and fibrosis in the ventricles (56).

The presence of cardiomyopathy/heart failure is illustrated in **Table 54**. A fifth of BMD patients (19.2%) suffered from a cardiomyopathy or heart failure in 2017.

Table 54. Becker Muscular Dystrophy: cardiomyopathy/heart failure (BNMDR, 2017)

Cardiomyopathy/ Heart failure?	Number of patients	% of the disease group population
Yes	21	**19.2**
No	62	56.9
Unknown	11	10.1
Missing	15	13.8
TOTAL	**109**	**100**

The use of cardiac medication is illustrated in **Table 55**. A quarter of BMD patients (24.8%) had a cardiac medication in 2017.

Table 55. Becker Muscular Dystrophy: cardiac medication (BNMDR, 2017)

Cardiac medication?	Number of patients	% of the disease group population
Yes	27	**24.8**
No	56	51.4
Unknown	11	10.0
Missing	15	13.8
TOTAL	**109**	**100**

Data on the type of cardiac medication prescribed to Becker patients are shown in **Table 56**. As for Duchenne patients, there is no consensus regarding the management of cardiomyopathy in Becker patients. Cardiac medication seems different from one patient to the other, with the exception of Coversyl, an angiotensin converting enzyme inhibitor, that was prescribed to 29.6% of the Becker patients known to be treated with cardiac medication.

Table 56. For 2017, treatments prescribed for the 27 Becker patients known to be on cardiac medication

Prescribed medication	Number of patients
Atacand, Carvedilol	1
Atacand, Isoten minor	1
Atacand, Nobiten	1
Bisoprolol	1
Candasartan, Kredex	1
Carvedilol	1
Coversyl	**8**
Coversyl, Burinex, Eliquis	1
Cozaar	1
Emconcor, Enalapril	1
Fosamax	1
Inderal	1
Kredex	1
Lanoxin, Nobiten, Coversyl	1
Lisinopril	1
Losartan	1
Ramipril	1
Tritace, Bisoprolol	1
Zestril	1
Zestril, Emconcor	1
Total	**27**

5.1.3.4. Scoliosis surgery in Becker patients in Belgium

The reasons why muscular dystrophy patients develop scoliosis are thought to be the same for Duchenne and Becker patients. However, for Becker patients, the progression of the disease is slower than for Duchenne patients. As a consequence, even if they develop scoliosis, it might not need surgery before it is stabilized at the end of growth.

The status of scoliosis surgery is illustrated in **Table 57**. No BMD patient was reported as having already underwent a scoliosis surgery in 2017.

Table 57. Becker Muscular Dystrophy: scoliosis surgery (BNMDR, 2017)

Scoliosis surgery?	Number of patients	% of the disease group population
Yes	0	**0.0**
No	80	73.4
Unknown	13	11.9
Missing	16	14.7
TOTAL	**109**	**100**

5.2. SPINAL MUSCULAR ATROPHY

Spinal Muscular Atrophy (SMA) is an inherited autosomal recessive genetic disorder characterized by degeneration of alpha motor neurons within the spinal cord. The disease presents as loss of muscle strength leading to progressive paralysis, including at the level of the respiratory muscles. The clinical phenotypes have been grouped into 4 different forms, depending on the severity of the disease and the age of onset. The most severe form, called type I or "Werdnig-Hoffmann disease" (SMA1), occurs during the first 6 months of life. Without respiratory support, a child with SMA1 generally dies during the first 2 years. Type II or "intermediate" SMA (SMA2) appears slightly later than type I, between the age of 6 and 18 months, and is associated with a lower life expectancy than the general population. Type III or "Kugelberg-Welander disease" (SMA3) shows symptoms after the age of 18 months. The life expectancy of SMA3 patients is usually similar to one of the general population. SMA type III can be further divided into type IIIa and type IIIb depending on whether a child was diagnosed before or after the age of three, respectively (59). Type IV, also called "adult form" SMA (SMA4), occurs during the twenties or thirties, and walking is preserved as an adult (60,61). The proportion of each SMA type compared to all SMA types has been described: authors described than type I SMA constitutes 60% of SMA births, type II SMA approximately 30% and another 10% for type III SMA. In those two publications, the authors do not distinguish between type III and type IV SMA (62–64).

5.2.1. GENERAL RESULTS OF THE DATA COLLECTION

The results of the 2017 data collection by reference centers are shown in **Figure 36**. TREAT-NMD data is not completed in 10.8% of SMA patients.

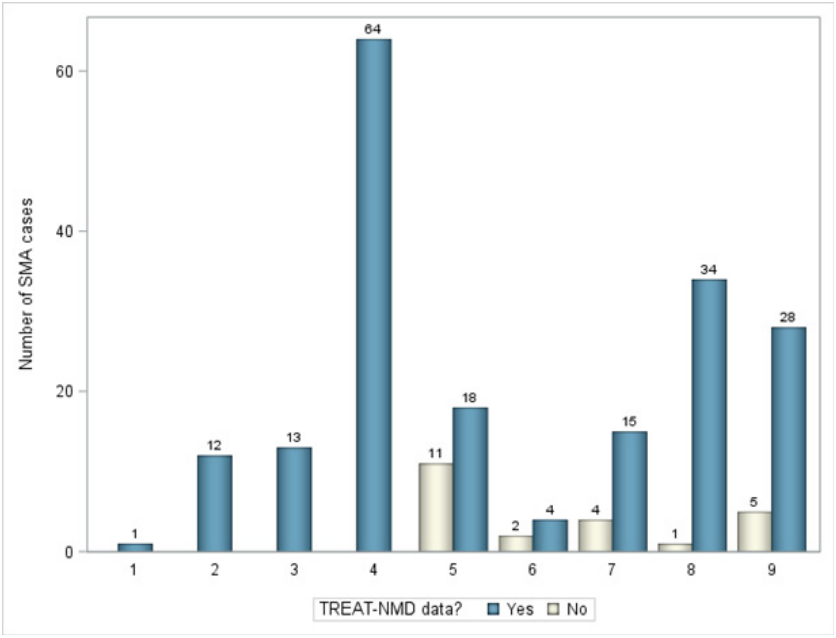


Figure 33. Spinal Muscular Atrophy: results of 2017 data collection by reference centers (N = 212)

In 2017, 212 SMA patients (all types together) were registered in the BNMDR. They were 104 males (49.1%) and 108 females (50.9%), ranging in age between <1 year and 76 years. The median age is 24.2 ± 17.6 years. However, it is important to also present the results of the data collection according to the SMA type of the patients.

The number of patients per SMA type is illustrated in **Table 58**. Among the 212 SMA patients registered in 2017, 8% are type I, 44,3% type II, 39.2% type III and 8.5% are type IV. This is very different than what is published in the literature, mainly due to the underregistration of SMA type I patients.

Table 58. Spinal Muscular Atrophy: SMA type (BNMDR, 2017)

SMA type	Number of patients	% of the disease group population
SMA I	17	**8.0**
SMA II	94	44.3
SMA III	83	39.2
SMA IV	18	8.5
All types	**212**	**100**

The gender distribution per SMA type is illustrated in **Table 59**.

Table 59. Spinal Muscular Atrophy: sex distribution per SMA type (BNMDR, 2017)

SMA type	Number of patients	Gender distribution
SMA I	17	35.3% (M) – 64.7% (F)
SMA II	94	52.1% (M) – 47.9% (F)
SMA III	83	47.0% (M) – 53.0% (F)
SMA IV	18	55.6% (M) – 44.4% (F)
All types	**212**	**49.1% (M) – 50.9% (F)**

The age distribution per SMA type for all SMA patients is illustrated in **Table 60**. The average age of patients is increasing according to the SMA type.

Table 60. Spinal Muscular Atrophy: age distribution per SMA type (BNMDR, 2017)

SMA type	Number of patients	Age range (years)	Median age (range)
SMA I	17	<1 - 16	5.5 ± 6.2
SMA II	94	1 - 51	17.7 ± 13.5
SMA III	83	3 - 64	29.1 ± 15.9
SMA IV	18	25 - 76	49.2 ± 15.7
All types	**212**	**<1 - 76**	**24.2 ± 17.6**

The participation to a clinical trial is illustrated in **Table 61**. Almost two third of SMA patients (64.6%) never participated in a clinical trial while only 9.9% are currently involved in such a trial. Among the 21 patients currently participating to a clinical trial, 23.8% are SMA type I, 52.4% SMA type II and 23.8% SMA type III.

Table 61. Spinal Muscular Atrophy: participation into clinical trial (BNMDR, 2017)

Clinical trial?	Number of patients	% of the disease group population
Currently	21	**9.9**
Previously	5	2.3
Never	137	**64.6**
Unknown	26	12.3
Missing	23	10.8
TOTAL	**212**	**100**

5.2.2. MOTOR FUNCTION OF SMA PATIENTS IN BELGIUM

As mentioned previously, the impact of SMA on the motor function of the patients is important and more severe depending on the SMA type. For instance SMAI patient usually never achieve the ability to sit independently while SMA IV patients will only have a mild motor impairement (62).

The status of ambulation is illustrated in **Table 62**. The vast majority of SMA patients (71.2%) are currently unable to walk.

Table 62. Spinal Muscular Atrophy: ambulation status (BNMDR, 2017)

Currently able to walk?	Number of patients	% of the disease group population
Yes	38	17.9
No	151	**71.2**
Missing	23	10.8
TOTAL	**212**	**100**

Physicians also evaluated the ability of patients to sit without support. This variable is illustrated in **Table 63**. Less than half of SMA patients (44.3%) are currently able to sit without support.

Table 63. Spinal Muscular Atrophy: sitting without support status (BNMDR, 2017)

Able to sit without support?	Number of patients	% of the disease group population
Yes	94	**44.3**
No	77	36.3
Missing	41	19.3
TOTAL	**212**	**100**

To better evaluate the impact of patients' motor function, physicians evaluate what was the best motor function achieved by the patient. This variable is illustrated in **Table 64**. For 36.8% of SMA patients the best motor function achieved is the walking ability and for 44.3% of them it is the sitting ability. For 8% of SMA patients, neither the ability of walking or sitting is achieved.

Table 64. Spinal Muscular Atrophy: best motor function achieved (BNMDR, 2017)

Best motor function achieved	Number of patients	% of the disease group population
Walking	78	36.8
Sitting	94	44.3
Neither	17	8.0
Missing	23	10.8
TOTAL	**212**	**100**

The age at which the best motor function is achieved is also assessed and is presented in the **Table 65**. For this variable the percentage of missing data is important and is presented in the table as well. For SMA patients, the average age at which is ability of sitting is achieved is 2.3 ± 2.0 years and of walk is 6.5 ± 5.3 years.

Table 65. Spinal Muscular Atrophy: age best motor function achieved (BNMDR, 2017)

Best motor function achieved	Number of patients	% of the disease group population	Average age at which the best motor function is achieved
Walking	78	36.8	6.5 ± 5.3
Sitting	94	44.3	2.3 ± 2.0
Neither	17	8.0	-
Missing	23	10.8	-
TOTAL	**212**	**100**	**-**

In addition, the use of a wheelchair is also assessed. Please note that the use of wheelchair is different than the ability to walk. Some patients use the wheelchair intermittently. The use of wheelchair is illustrated in **Table 66**. More than two third (68.4%) of SMA patients are currently using a wheelchair, either permanently (63.7%) or by intermittence (4.7%).

Table 66. Spinal Muscular Atrophy: wheelchair use (BNMDR, 2017)

Wheelchair use	Number of patients	% of the disease group population
Permanent	135	**63.7**
Intermittent	10	**4.7**
Never	22	10.4
Unknown	7	3.3
Missing	38	17.9
TOTAL	**212**	**100**

Therefore the loss of ambulation is defined by the moment a patient has to use the wheelchair permantly. **Figure 34** shows a frequency distribution of age at loss of ambulation for the 2017 BNMDR data. "0" means that the patient has never walked. "99" means that the information is unknown.

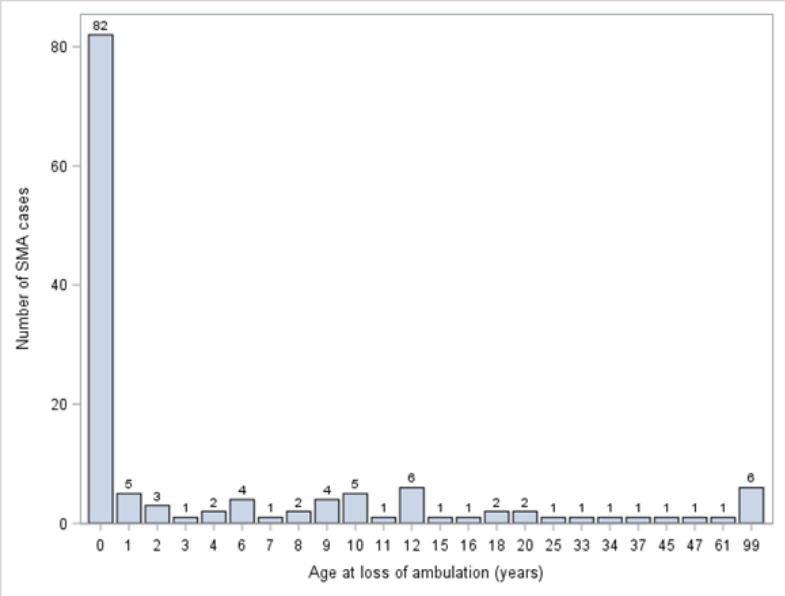


Figure 34. Age of ambulation loss for SMA patients (BNMDR, 2017)

5.2.3. RESPIRATORY FUNCTION OF SMA PATIENTS IN BELGIUM

Repiratory problems experienced by SMA patients are caused by weakness of the respiratory muscles, ineffective cough and night hypoventilation or sleep apnea syndrome. In SMA1 patients, the anticipated management of respiratory problems by assisted coughing techniques and non-invasive or invasive ventilation is associated with a longer survival time. For SMA2 patients, non-invasive ventilation should be provided during the night if there is nocturnal hypoventilation or apnea. Assisted coughing techniques should be used if it turns out that the cough is ineffective. For SMA3 patients, the management depends on subgroup stratification. If the patient belongs to subgroup IIIa, he / she should be evaluated and treated as an SMA2 patient. Patients belonging to subgroup IIIb and SMA4 patients have normal respiratory function at rest (65).

The use of non-invasive ventilation is illustrated in **Table 67**. A fifth of SMA patients (21.7%) had non-invasive ventilation, either part-time (20.8%) or full-time (0.9%) in 2017.

Table 67. Spinal Muscular Atrophy: non-invasive ventilation (BNMDR, 2017)

Non-invasive ventilation?	Number of patients	% of the disease group population
No	132	62.3
Part-time	44	**20.8**
All day	2	**0.9**
Unknown	11	5.2
Missing	23	10.8
TOTAL	**212**	**100**

The use of invasive ventilation is illustrated in **Table 68**. 3.8% of SMA patients had invasive ventilation, either part-time (2.8%) or full-time (0.9%) in 2017.

Table 68. Spinal Muscular Atrophy: invasive ventilation (BNMDR, 2017)

Invasive ventilation?	Number of patients	% of the disease group population
No	171	80.7
Part-time	6	**2.9**
All day	2	**0.9**
Unknown	10	4.7
Missing	23	10.8
TOTAL	**212**	**100**

5.2.4. FEEDING IN SMA PATIENTS IN BELGIUM

Infants with SMA type I usually require in addition to ventilation, a feeding support (66,67). Patients with with type II often later develop swallowing problems (59,63,64,68,69). For this reason, physicians assess the placement of nasal or gastric feeding tube.

The placement of a nasal or gatric feeding tube is illustrated in **Table 69**. Because only few SMA type I patients are registered in the BNMDR, only 12.7% of SMA patients have already had gastral or nasal tube placed in 2017.

Table 69. Spinal Muscular Atrophy: feeding use (BNMDR, 2017)

Feeding use?	Number of patients	% of the disease group population
Yes	27	**12.7**
No	149	70.3
Unknown	13	6.1
Missing	23	10.8
TOTAL	**212**	**100**

5.2.5. SCOLIOSIS SURGERY IN SMA PATIENTS IN BELGIUM

Virtually all patients with SMA2 and SMA3a have scoliosis, which is frequently associated with chest deformities and respiratory difficulties. Scoliosis can occur early in the patient's life (sometimes before the age of 4). In non-ambulatory patients, surgical correction of the scoliosis is the treatment of choice and is indicated when the Cobb angle is greater than 20°. The best age to intervene is around 10-12 years old, because at this age patients have exceeded 80% of their potential in terms of growth (70).

The status of scoliosis surgery is illustrated in **Table 70**. More than a third (35.4%) of SMA patients had already underwent a scoliosis surgery in 2017.

Table 70. Spinal Muscular Atrophy: scoliosis surgery (BNMDR, 2017)

Scoliosis surgery?	Number of patients	% of the disease group population
Yes	75	**35.4**
No	97	45.8
Unknown	16	7.5
Missing	24	11.3
TOTAL	**212**	**100**

6. ACTIVLIM

The ACTIVLIM scale is a validated patient report outcome measure (PROM) to evaluate limitations in daily life activities for children and adults with neuromuscular diseases (9,10). This questionnaire has 22 items, including 4 items specific for adults, 4 items specific for children, and 14 items common to adults and children. For each item, the answer is based on a 3-level scale: "easy", "difficult" or "impossible". The questionnaire was developed using the Rash model, which allows conversion of ordinal scores into linear measures located on a 1-dimensional scale. The list of different items used, as well as an online analysis module are available on the website rehab-scales.org (22).

The BNMDR registry collects ACTIVLIM data on an annual basis for all patients with neuromuscular disease between 6 and 80 years old. In 2016, Batcho et al. published a study based on the BNMDR ACTIVLIM data from 2011 and 2012. It highlighted the validity of the scale and the invariance of the hierarchy of items by age, sex, language, and over time (71).

In the course of 2017, a comparision analysis of the BNMDR ACTIVLIM data from 2011 and 2015 has been conducted to assess the overall evolution of the cohort of patients over a longer period of time. This study has been presented at conferences in 2018. This analysis showed that 64% of all neuromuscular patients of the sample experienced a deterioration of their activity ($P \leq 0.012$; effect size (ES) =−0.32). The magnitude of deterioration was the most important for Duchenne muscular dystrophy (74% of them deteriorated; $P < 0.001$; ES =−0.46), limb-girdle muscular dystrophy (74% deteriorated; $P < 0.001$; ES =−0.44), hereditary spastic paraplegia (66% deteriorated; $P < 0.001$, ES =−0.41), and amyotrophic lateral sclerosis (69% deteriorated; $P < 0.001$; ES =−0.40). Deterioration was significant but less important for myotonic dystrophy type 1 (63% deteriorated; $P < 0.001$; ES =−0.32), spinocerebellar ataxias (67% deteriorated; $P < 0.001$; ES =−0.31), facioscapulohumeral dystrophy (59% deteriorated; $P = 0.016$; ES =−0.23), and hereditary motor and sensory neuropathy (60% deteriorated; $P < 0.001$; ES =−0.22). For patients with chronic inflammatory demyelinating polyneuropathy (CIDP), no deterioration was observed ($P = 0.939$; ES =−0.01). In conclusion, this is the first study focusing on activity level of neuromuscular using ACTIVLIM across a 5-year period. As expected, most patients showed deterioration in their activity, except CIDP patients. Indeed CIDP is sensitive to efficient treatment such as corticosteroids, plasmapheresis, intravenous immunoglobulin (IVIg), at least for some patients. The results of this study will be the subject of a separate publication.

There is an improvement of the response rate to the ACTIVLIM questionnaire over the years (see **Figure 35**), especially considering that the number of patients registered each year is more important. However, since 2015, the absolute number of patients without a completed ACTIVLIM seems to increase again. We can only encourage the centers to invert this trend again as the data for the ACTIVLIM is particularly valuable if collected each year for a patient to allow longitudinal follow-up.

We wanted here to assess the response rate to the ACTVLIM over the years. This variable is illustrated in the **Figure 35**.

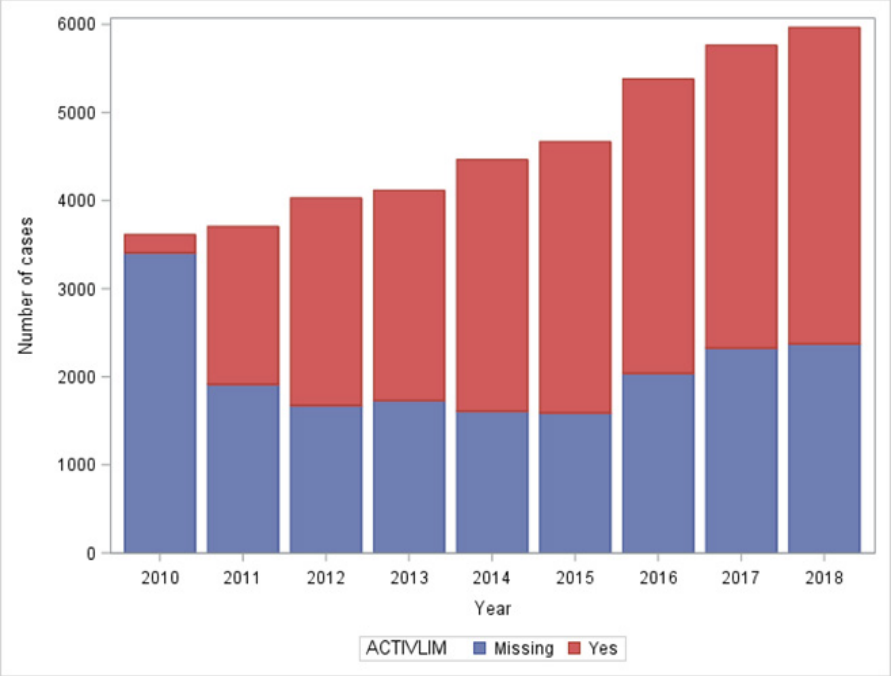


Figure 35. Status of ACTIVLIM response rate 2010-2017 (BNMDR, 2017)

9. OUTCOME AND CONCLUSION

The 2017 BNMDR data collection resulted in a total number of 5,765 registrations. They were 3,145 males and 2,620 females (male to female ratio of 1.2 to 1), ranging in age between 2 months and 97 years. The median age was 48 years (p25= 27 years and p75= 62 years).

The main positive point is the continued gradual increase in the number of registrations collected by the BNMDR, which reflects a better recruitment in the reference centers. In addition, there is better national coverage: in particular, more patients have been recruited in the south of the country compared to previous years. However, despite an improved recruitment of patients in the South East of the country, there is still an important lack of patient recruitment in the South West of the country. This result emphasizes the need for the recognition of an expert center in this area. It is likely that people in this region do not receive the specialized care they need if they do not have the means or possibility to travel to Liège or Brussels. It should be noted that the average income per inhabitant is the lowest in the province of Hainaut (72).

Based on the 2017 BNMDR data, the overall prevalence of neuromuscular diseases in Belgium is estimated at 50.8 per 100,000 inhabitants. This is about one third of the estimate reported by Deenen et al (21). This underestimation can only be partially explained by the observed north-south gradient. Although the BNMDR targets all neuromuscular patients living in Belgium independent of their convention status, in practice, especially patients who are in convention are registered as workload in the NMRC is very high. In addition, being tertiary care, it is possible that patients showing mild symptoms are not followed in a NMRC and thus are not registered in the BNMDR. Further, it should be remembered that, per center, 0-5% of patients do no give their consent to be registered in the BNMDR. Finally, it should be pointed out that the estimate of Deenen et al. was calculated by adding up 25 prevalence estimates found in literature, which is a very different methodology. In the future, we would like to reach out to other general neuromuscular diseases registries to compare prevalence estimates.

For the year 2017, the ten most prevalent diseases in the registry were: Hereditary Motor and Sensory Neuropathy, Myotonic Dystrophy type 1, Amyotrophic Lateral Sclerosis (ALS), Hereditary Spastic Paraplegia (HSP), Duchenne Muscular Dystrophy (DMD), Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Facioscapulohumeral Dystrophy, Limb Girdle Muscular Dystrophy, Spinocerebellar Ataxias (SCA), and Postpolio Syndrome (PPS). The patients suffering from those diseases accounted for 63.2% of all BNMDR registrations. This hierarchy is based on the NIHDI classification in which the four sub-types of Spinal Muscular Atrophy (SMA) are divided in four distinct disease groups. When pooled together, SMA was ranked 9th in the list.

The north-south gradient for patient recruitment was present for all diseases. However, it was particularly pronounced for HSP, SCA and PPS for which there was an important lack of patient recruitment in the South. Surprisingly, there was a high prevalence of CIDP in the South-East of the country. We do not yet understand what is reflected here. Longer-term follow-up is needed to elucidate this observation.

In 2017, the vast majority of patients registered in the BNMDR (75.3%) were ambulant and a significant proportion (19.7%) were wheelchair-bound. Life-support was needed in 2.0% of patients, mostly suffering either from DMD (36.0%) or ALS (31.5%). Interestingly, among all patients registered in the BNMDR in 2017, about three quarters (74.6%) had received a final diagnosis (with or without a genetic confirmation). It should be noted that there is a lot of variation depending on the disease, which makes it difficult to give a clear trend on the entire population of patients. In fact, being a general neuromuscular diseases registry, dealing with the heterogeneity of the neuromuscular diseases remains one of the main challenges faced by the BNMDR.

In 2017, 220 patients were reported as deceased among the BNMDR population, which represented 3.8% of all BNMDR patients. The majority of deaths occured among patients with ALS (representing 61.4% of total deaths). Equally, the majority of deceased patients per disease group was the highest for patients with ALS (i.e., 26.0%). Other disease groups with a high death rate were Werdnig-Hofman SMA (type 1) and Primary Muscular Atrophy (representing respectively 23.5% and 10.0% of patients in their disease group).

For DMD, Becker muscular dystrophy (BMD) and SMA, additional data are collected. Adhering to the TREAT-NMD core datasets for DMD/BMD and SMA allows collaboration with the TREAT-NMD international network that aims to advance diagnosis, care and treatment for patients with neuromuscular diseases. The collection of the TREAT-NMD data is not mandatory. However, we acknowledge the efforts made by the centers to complete this section as extensively as possible. Indeed, the decrease in missing data observed over the years is important for our communication with TREAT-NMD and gives these patients the opportunity to participate in clinical trials.

In 2017, 302 DMD patients, 109 BMD patients and 212 SMA patients were registered in the BNMDR, representing respectively 5.2%, 1.9% and 3.8% of all BNMDR patients. It should be noted that 23.1% of DMD patients and 12.2% of SMA patients had already participated or were currently participating in a clinical trial. Giving the research advancements in the field of disease modifying therapies for DMD and SMA, we expect this number to grow in the coming data collections. Therefore, TREAT-NMD decided in 2017 to expand their core datasets to be able to collect robust longitudinal data that not only captures natural history and informs standards of care for patients, but also measures the effectiveness of interventions. The implementation of the TREAT-NMD SMA expanded dataset in the BNMDR is foreseen for 2019.

In view of expanding a dataset, it should be kept in mind that the workload for the data providers to enter the data is already very important and is logically even more important each year with the increasing number of registrations. This is confirmed by an observed increase in the proportion of patients in convention but who did not visit the center during the current collection year. We are always looking for solutions to make the work of the data provider easier. Last year, we envisaged to allow the encoding of the ACTIVLIM scale by the patient, directly in HD4DP via a tablet computer. However, this solution was rejected by Healthdata for privacy reasons. Some centers are exploring an internal solution to this issue. In addition, Healthdata is working on a new API-based architecture which will allow automatic extraction of data out of the electronic patient file.

Another threat to this project is the technological infrastructure. We are indeed dependent on the well-functioning of the Healthdata infrastructure. Despite an improvement compared to the 2016 data collection, we still experience difficulties in receiving data which causes a delay in data analysis and data reporting.

ANNEX 1: NIHDI CLASSIFICATION OF NEUROMUSCULAR DISEASES

MUSCULAR DYSTROPHIES

1. Congenital Muscular Dystrophy
2. Duchenne Muscular Dystrophy
3. Becker Muscular Dystrophy
4. Dystrophinopathy
5. Facioscapulohumeral Dystrophy
6. Limb girdle Muscular Dystrophy
7. Emery-Dreifuss Muscular Dystrophy
8. Distal Myopathy
9. Oculopharyngeal Muscular Dystrophy
10. Myotonic Dystrophy type 1
11. Myotonic Dystrophy type 2
12. Other Muscular Dystrophies

MYOTONIC AND RELAXATION DISORDERS

13. Thomsen type Myotonia Congenita
14. Becker type Myotonia Congenita
15. Paramyotonia Congenita
16. Familial Periodic Paralysis
17. Other Myotonic Disorders

MYOPATHIES

Congenital Myopathies

18. Central Core Disease
19. Multiminicore Disease
20. Nemaline Myopathy
21. Myotubular Myopathy
22. Centronuclear Myopathy
23. Fibre type Disproportion Myopathy

Metabolic Myopathies

24. Muscle Glycogenoses
25. Disorders of Fatty Acid Metabolism
26. Mitochondrial Myopathy

Inflammatory Myopathies

27. Polymyositis
28. Dermatomyositis
29. Inclusion body myositis

Other myopathies

30. Other Myopathies

DISORDER OF THE NEUROMUSCULAR TRANSMISSION

31. Myasthenia Gravis
32. Congenital Myasthenia
33. Lambert-Eaton Syndrome
34. Other disorders of neuromuscular transmission

DISORDER OF THE MOTOR NEURONS

35. Amyotrophic Lateral Sclerosis
36. Primary Muscular Atrophy
37. Postpolio Syndrome
38. Primary Lateral Sclerosis
39. Werdnig-Hoffman Spinal Muscular Atrophy
40. Intermediate Spinal Muscular Atrophy
41. Kugelberg – Welander Spinal Muscular Atrophy
42. Adult Spinal Muscular Atrophy
43. X-linked Bulbo-Spinal Muscular Atrophy or Kennedy's disease
44. Distal Spinal Muscular Atrophy
45. Hereditary Spastic Paraplegia
46. Other disorders of Motor Neurons

NEUROPATHIES

Hereditary

47. Hereditary Motor and Sensory Neuropathy
48. Hereditary Neuropathy with Liability to Pressure Palsies
49. Hereditary Sensory & Autonomous Neuropathy

Inflammatory

50. Guillain-Barré Syndrome
51. Chronic Inflammatory Demyelinating Polyneuropathy
52. Multifocal Motor Neuropathy
53. Vasculitis
54. Neuropathy associated with Paraproteinemia
55. Neuropathy associated with Plasma Cell Dyscrasia
56. Amyloisdosis
57. Neuropathy in Systemic Disease
58. Other Neuropathies

HEREDITARY ATAXIAS

59. Friedreich Ataxia
60. Spinocerebellar Ataxias
61. Other Hereditary Ataxias

VARIOUS

62. Arthrogryposis Multiplex Congenita

ANNEX 2: TREAT-NMD SPECIFIC VARIABLES (DMD / SMA)

DMD-specific variables	Common variables DMD & SMA	SMA-specific variables
	Date of last follow-up	
• mutation name in gene (Human Genome Variation Society (HGVS) rules) • deletion: all exons tested (yes / no / unknown) • duplication: all exons tested (yes / no / unknown) • deletion/duplication: boundaries known (yes / no / unknown) • point mutation: all exons sequenced (yes / no / unknown) • targeted mutation testing in this patient but testing of all exons in an affected male relative (index patient) (yes / no / unknown)	Molecular data	• mutation name in gene (HGVS rules) • number of SNM2 copies
• DMD / BMD / IMD / female carrier / unknown	Diagnosis	• diagnosis SMA (SMA / other / unknown) • SMA classification (SMA1 / SMA2 / SMA3 / asymptotic / unknown)
• currently able to walk (yes / no) • currently able to sit without support (yes / no)	Motor function	• currently able to walk (yes / no) • currently able to sit without support (yes / no) • best motor function achieved (walking / sitting / neither) • age at which best motor function is achieved
	Current steroids therapy (Currently / Previously / Never / Unknown)	
	Scoliosis surgery (Yes / No / Unknown)	
		Feeding: gastric/nasal tube (Yes / No / Unknown)
Heart: • current cardiac medication (yes / no / unknown; if yes, please list medication) • heart failure/cardiomyopathy (yes / no / unknown) • last LVEF & date • last fractional shortening & date • was this measured by scintigraphy? (yes / no / unknown)		
	Is the patient included in a clinical trial? (Currently / Previously / Never / Unknown) Specify the name of the involved drug Respiratory function: • non-invasive ventilation (All-day / Part-time / No / Unknown) • invasive ventilation (All-day / Part-time / No / Unknown) • last FVC in % , last FVC in ml, date of last FVC	

DMD-specific variables	Common variables DMD & SMA	SMA-specific variables
Previous muscle biopsy (yes / no / unknown)		
Other registries (Yes / No; if yes: specify)		
Family history: other affected family members (Yes / No; if yes: specify)		

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