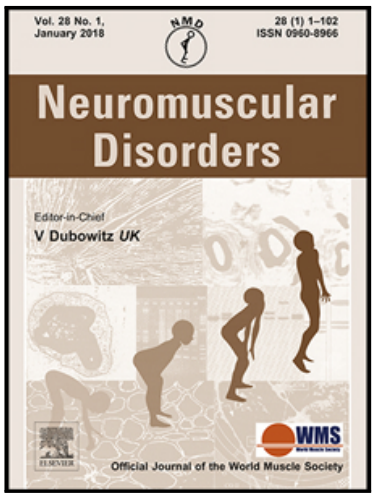


# An integrated modelling methodology for estimating the prevalence of centronuclear myopathy

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**Highlights**

- There is a lack of comprehensive data on CNM prevalence by age and disease subtype
- There is a need for an integrated model enhancing current epidemiologic data
- The CNM incidence can be stratified by causative gene, severity and geographic region
- The CNM prevalence is estimated by causative gene, severity and geographic region
- The current data provide insight into CNM outcomes, e.g. severity and life years lost

# An integrated modelling methodology for estimating the prevalence of centronuclear myopathy

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## Abstract

Centronuclear myopathies (CNM) are a group of rare inherited muscular disorders leading to a significantly reduced quality of life and lifespan. To date, CNM epidemiologic reports provide limited incidence and prevalence data. Here, an integrated model utilizing available literature is proposed to obtain a better estimate of overall CNM patient numbers by age, causative gene, severity and geographic region. This model combines published epidemiology data and extrapolates limited data over CNM subtypes, resulting in patient numbers related to age and disease subtype. Further, the model calculates a CNM incidence

twofold the current estimates. The estimated incidence of 17 per million births for severe X-linked myotubular myopathy (XLMTM), the main subtype of CNM, corresponds to an estimated prevalence of 2715 in the US, 1204 in the EU, 688 in Japan and 72 in Australia. In conclusion, the model provides an estimate of the CNM incidence, prevalence and survival, and indicates that the current estimates do not fully capture the true incidence and prevalence. With rapid advances in genetic therapies, robust epidemiologic data are needed to further quantify the reliability of incidence, prevalence and survival rates for the different CNM subtypes.

**Key words**

Centronuclear myopathy, causative gene, severity, incidence, prevalence, geographic region

**Highlights**

- There is a lack of comprehensive data on CNM prevalence by age and disease subtype
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## 1. Introduction

Centronuclear myopathies (CNM) are a group of rare inherited congenital myopathies. CNM is associated with a large heterogeneity in clinical presentation, ranging from severe, infantile onset to more moderate and mild phenotypes presenting in adolescence or adulthood [1]. Clinical symptoms include profound muscle weakness (that includes the facial musculature),

muscle atrophy, and respiratory and feeding difficulties. Typical muscle histopathological features include centralization of the nuclei, disorganization of perinuclear organelles and myofiber hypotrophy. The main subtypes of CNM include X-linked myotubular myopathy (XLMTM), caused by myotubularin 1 (*MTM1*) mutations [2], autosomal dominant forms caused by dynamin 2 (*DNM2*) mutations [3] and amphiphysin 2 (*BIN1*) mutations [4], and autosomal recessive forms caused by amphiphysin 2 (*BIN1*) mutations [5] and ryanodine receptor 1 (*RYR1*) mutations [6]. Other causal genes that affect a small number of the CNM patient population have been identified (e.g. *SPEG* [7] and *TTN* [8]). XLMTM is the most severe form, typically associated with congenital onset, profound muscle weakness and high mortality rates. XLMTM presents mainly in male patients due to its X-linked nature, although an increasing number of cases are described where female carriers show clinical symptoms as well. Classification of XLMTM into mild, moderate and severe phenotypes is based on respiratory status and motor development [2,9].

Describing and characterizing disease epidemiology helps to better appreciate social burden of CNM. Disease epidemiological data can direct drug development by targeting potential unmet needs and allowing the assessment of the societal value of potential novel therapies that target the identified unmet need. The quantification of disease burden also facilitates planning for health care services. For many rare diseases, validated estimates of stratified incidence and prevalence are lacking, often due to limited availability and heterogeneity of available data. Currently, for severe, male XLMTM, an incidence of 20 per million (mln) male births (1 in 50,000) has been reported [10–12]. The pediatric point prevalence (age <18 years) is estimated to be <10 in 1,000,000 in the US [13]. It is likely that these data underestimate the true incidence and prevalence across all phenotypes [12,14,15].

The model described here estimates the current CNM patient numbers according to disease gene (*MTM1, DNM2, BIN1*, *RYR1* and other) and severity in the EU, US, Australia and Japan and is based on an analysis of the current limited available CNM epidemiologic data. Sample sizes from the published studies are often small and assumptions had to be made to generate the estimates. Additional epidemiological data are hence needed to reduce the uncertainties resulting from these assumptions.

## 2. Methodology to estimate patient prevalence

In order to capture CNM prevalence, estimates of both incidence and survival data are required for the different patient subtypes. The incidence can be determined by combining available prevalence data, subtype distribution data and survival curves (based on severity) [16]. Registry data can be used to estimate incidence rates for CNM subtypes, but one should be aware that data might be scarce, for example due to the lack of diagnosis at birth. In case of subtypes for which survival data are unavailable, prevalence data are based on survival curves of other subtypes with similar severity.

To define the CNM prevalence, a non-systematic, targeted review was conducted of current available CNM data on key epidemiological measures - incidence, prevalence and survival by disease gene and severity in the US, EU, Australia and Japan. In the orphan disease context, data are often limited to case reports, special populations studies and registry data with variable sample sizes and different subtypes. Because of the limited data availability, heterogeneity and variability, it was necessary to address associated uncertainties related to each patient subtype. Therefore, the source data were collected and structured hierarchically

according to data reliability and grouped into the following levels from high to low reliability:

1. Published direct evidence in representative patient populations
2. Published indirect evidence in representative patient populations (*e.g.* patient distribution according to disease severity)
3. Data with limited published supportive evidence or limited patient numbers (*e.g.* case reports)

When epidemiologic data on a subtype were limited, more reliable existing data were used as an assumption to derive an estimation for this subtype. Data not directly incorporated in the integrated prevalence model, were subsequently used to calibrate and validate model parameters. The model was then used to identify the prevalence by geographic region according to the causative gene and severity, resulting in an overall insight into the CNM prevalence components and dynamics.

## 3. Available epidemiologic data

### *3.1 Incidence and prevalence*

XLMTM is subdivided into 3 types: severe, moderate and mild. XLMTM usually occurs in the severe form (79% of the patients) and is characterized by generalized hypotonia and weakness, chronic ventilatory support and severe motor disability [17]. The moderate (6% of the patients) and mild (15% of the patients) phenotypes are commonly associated with reduced ventilatory dependence and delayed motor milestones [9,17]. This predicted distribution of XLMTM forms is in line with the UMD-MTM1 registry data on the worldwide male XLMTM population [18]. Incidence data are limited to the severe form of

XLMTM, which is repeatedly reported to affect 20 per mln male births [10–12]. Also symptomatic female carrier cases due to skewed X-inactivation or other epigenetic factors have been described and are considered to be underestimated [19].

The CNM paediatric (age <18 years) point prevalence across all subtypes has been estimated to be <10 per mln people in the US [13]. The patient distribution according to disease gene subtypes is estimated to be 45% *MTM1* (XLMTM), 15% *DNM2*, 10-15% *RYR1*, <5% *BIN1* and 20% unidentified mutations (non-XLMTM) [20]. A genotype-phenotype correlation in an Italian CNM patient cohort reported a similar distribution of 48% XLMTM and 52% non-XLMTM patients. The latter population includes CNM subtypes caused by mutations other than the *MTM1* gene [21] .

*3.2 Survival curves by disease severity and geographic region*

McEntagart *et al.* reported a median overall XLMTM survival of 29 months (n=123) [17]. There was a large spread in median survival age by disease severity, with a 13-year survival of 22%, 80% and 100% for severe, moderate and mild phenotypes, respectively. In addition, the survival rate varied according to geographic region with a greatly increased chance of survival in the US or Japan with a 1-year survival of 84% compared to a 1-year survival rate of 41% in the EU. These numbers are consistent with UMD-MTM1 registry data demonstrating a EU 1-year survival of 30% in 106 male French patients. Another study by Herman *et al.* (n=55), reported a 64% 1-year US survival [9], confirming the higher US survival compared to the EU. Treatment policies in the US and Japan were considered similar [17]. The geographic discrepancy may be attributed to divergent treatment policies with a higher ventilatory support use of 87% in the US compared to 36% in the EU [17,22]. However, it should not be excluded that differences in diagnostic rate, due to variable health

care systems, may also impact the survival rate. This is in line with a recent report discussing the rare neuromuscular disorder Spinal Muscular Atrophy (SMA), where it was found that not all patients may have access to optimal care and research opportunities [14]. In addition, the authors attribute differences in genetic testing availability and screening practices, along with genetic confirmation of prevalent cases that previously only had clinical diagnosis also to regional variability. Raised awareness of CNM and additional data may provide more insight into the matter, as it did for Pompe Disease [23].

For non-XLMTM *(e.g. DNM2 BIN1, RYR1,* etc.), survival data have not been reported. Patients with a *DNM2* mutation present with a large variability in clinical phenotype, ranging from a severe, infantile onset to milder phenotypes with disease presentation at later age [3,24,25]. Patients with *DNM2* mutations have been enumerated in 3 small, non-infantile patient populations - patients older than 5 years (n=16), an adult population (n=14), and in an Italian CNM patient cohort (n=38), as the most common prevalent form of non-XLMTM [21,26,27]. *BIN1* and *RYR1* mutations have been associated with a disease severity intermediate between *MTM1* and *DNM2* [4–6].

## 4. Estimation of CNM incidence and survival

### *4.1 Approach*

Incidence data for male, severe XLMTM are publicly available (Table 1). The combination of the incidence data with information on distribution according to disease severity allows us to estimate epidemiologic data for currently underreported subtypes (mild and moderate phenotypes) (Figure 1, step A). Secondly, the combination of epidemiologic data on XLMTM incidence with reported XLMTM survival curves according to disease severity and

geographic region independently allow generation of prevalence data according to disease severity and geographical region (Figure 1, step B). Finally, combining the reported pediatric point prevalence distribution with survival data, estimated based on survival curves of XLMTM patients with similar severity, allows us to estimate the incidence rates (Figure 1, step C).

*4.2 Estimation of XLMTM incidence*

For the male population, the reported patient distribution over the XLMTM forms (79.3% severe, 6.0% moderate and 14.7% mild) (Table 2) can be reasonably accepted to represent the entire population [17]. For severe XLMTM, the incidence was found to be 20.0 per mln births and is used as a basis to estimate the incidence of moderate and mild cases. If 20.0 per mln male births accounts for 79.3% of severe XLMTM incidence, 6.0% and 14.7% moderate and mild proportions, respectively, imply an incidence for moderate XLMTM of 1.5 per mln male births (20/0.793*0.06) and 3.7 per mln births for mild XLMTM (20/0.793*0.147). The overall XLMTM incidence is hence estimated to be 25.2 per mln male births (Figure 2).

The currently available data are based on the traditional diagnostic approach, whereby gene-specific tests were conducted based upon clinical and histological findings [28]. Patients with less profound clinical presentations could thus be easily misdiagnosed or not diagnosed at all. The implementation of Next Generation Sequencing (NGS) is transforming genetic diagnosis and its unbiased assessment is expected to lead to a higher CNM diagnostic rate [19,28,29]. The impact of NGS implementation on XLMTM diagnosis rate is reasonably assumed to double the diagnosis rates for patients with mild and moderate phenotypes. This assumption led to a total incidence of 30.4 XLMTM cases per mln male births (1 in 32 857) (Figure 2).

In addition, female XLMTM incidence is inferred to be 10% of all male XLMTM cases, which is in line with the recently reported proportion of XLMTM females compared with all diagnosed patients around 6% to 13% [19,28]. These numbers may be an underestimation as well [22]. Following this reasoning, the resulting incidence estimate is 3.0 XLMTM cases per mln female births (30.4x0.1=3). Female XLMTM patients were hypothesized to have moderate or mild phenotypes with the same distribution over these phenotypes as male XLMTM patients (e.g. % moderate female distribution 29.2% = 10.0% / (10.0% + 24.3%)) (Figure 2).

The resulting overall XLMTM incidence for male and female population is, based on the above plausible hypotheses, estimated at 16.7 cases per mln (male and female) births (1 in 59 740), distributed over 59.7% severe, 11.7% moderate and 28.5% mild XLMTM phenotypes (Figure 2). The epidemiologic incidence estimates are representative for the worldwide population as various forms of CNM have been reported with roughly equal frequencies in all studied ethnic groups [20].

*4.3 Estimation of XLMTM survival curves according to geographical region and disease severity*

McEntagart *et al.* reported overall XLMTM survival rates separately for the US and the EU and described the general survival according to disease severity for the US and EU combined (Table 3). [17]. Based on these data, the survival categorized per disease severity could be calculated and optimally fitted for each geographical region. The resulting US and EU survival curves are depicted in Figure 3. The survival curves were validated based on 2 independent 1-year survival data points for both the US [9,17] and EU populations [13, UMD-MTM1 registry data] and 13-year survival data points for the US and EU [17].

*4.4 Estimation of non-XLMTM incidence and survival curves*

For the non-XLMTM CNM population, data on incidence and survival are not available. By combining the reported pediatric point prevalence distribution (45% XLMTM and 55% non-XLMTM patients) [20,21] with estimated XLMTM prevalence and non-XLMTM survival assumptions, the non-XLMTM incidence can be estimated. Here, it was assumed that the non-XLMTM cohort had a survival curve similar to the mild XLMTM population to generate a conservative incidence estimation. Applying this survival, an incidence distribution estimation of 30% non-XLMTM compared to 70% XLMTM results in a pediatric point prevalence corresponding to the reported XLMTM/non-XLMTM prevalence distribution. Since the XLMTM incidence distribution of 69.7% corresponds to 16.7 per mln of all births, the 30.3% non-XLMTM proportion corresponds to an overall non-XLMTM incidence estimate of 7.3 per mln births (Figure 4). This can be used as input for the integrated prevalence model and extrapolated worldwide based on roughly equal frequencies reported in all studied ethnic groups [20].

Non-XLMTM patients appear to have a higher overall survival than XLMTM patients. Although different clinical presentations between and within the non-XLMTM subtypes (*DNM2*, *BIN1*, *RYR1* and unidentified) have been described, no quantitative data are available describing survival by disease gene. In the integrated prevalence model, the same survival curve was hypothesized for all etiologic subtypes of non-XLMTM, namely the same survival as for moderate and mild XLMTM forms (Figure 3). Also for non-XLMTM incidence regarding to disease severity, the distribution of moderate and mild XLMTM was presumed resulting in a non-XLMTM distribution of 29.2% moderate and 70.8% mild phenotypes (*e.g.* 70.8% = 28.5% / (11.7%+28.5%)).

To determine the prevalence of *BIN1*, *DNM2*, *RYR1* and other causative mutations, distributions were based on the published paediatric point prevalence distribution [20]. Based on the identical survival curve hypothesis, the non-XLMTM subtype prevalence distributions are equal to the paediatric point prevalence: 15% *DNM2*, 10-15% *RYR1*, <5% *BIN1* and 20% unidentified mutations.,

## 5. CNM prevalence per geography and disease gene

During the following calculations, the CNM incidence and prevalence in Japan and Australia were determined by using the US and EU patient survival, respectively. This rationale was based on similar CNM treatment policies reported for Japan and the US [17] and comparable treatment regimens for SMA in Australia and the EU [30,31].

### *5.1 CNM incidence estimation*

Based on the combined XLMTM and non-XLMTM CNM incidence of 16.7 per mln and 7.3 per mln births, respectively, the yearly number of newborn cases was determined. The overall CNM incidence for the EU, US, Japan and Australia was thus estimated to be 24.0 per mln births (Figure 5). This implies approximately 250 global CNM births per year, subdivided in 123 yearly newborns in the EU, 96 in the US, 24 in Japan and 7 in Australia (Figure 6A, Table 4).

The incidence according to disease gene was estimated earlier to be 69.7% patients with MTM1 mutations, which corresponds to 174 patients (Figure 6B). Within this population, 104 patients are classified with severe, 20 with moderate and 50 with mild phenotypes. For

the non-XLMTM gene mutations, 30.3% overall yearly incidence estimates comes down to 2.8% *BIN1*, 8.3% *DNM2*, 8.3% *RYR1* and 11.0% unidentified causal mutations. Expressed in numbers, 7 newborns per year are carriers of mutations in the *BIN1* gene, 21 have *DNM2* mutations, 21 with CNM-associated *RYR1* mutations and 28 have unidentified gene mutations leading to *CNM*.

*5.2 Comprehensive CNM prevalence estimation*

To assess the CNM prevalence as a function of age and per subtype, the survival curve accounting for disease gene, severity and geographic region (Figure 3) was applied to the number of incident patients (Figure 5). As such, the global prevalence was estimated to be 4679 patients (Table 4). Classified per geographic region, it was estimated that there are 2715 CNM patients in the US and 1204 EU patients (Figure 6C).

Taking the disease gene into account, the prevalence is estimated at 56.7% with *MTM1*, 3.9% with *BIN1*, 11.8% with *DNM2*, 11.8% with *RYR1* mutations and 15.8% with unidentified causal mutations, corresponding to 2652, 184, 553, 553 and 737 global patients, respectively (Figure 6D). The XLMTM patients can be divided into subtypes according to disease severity, resulting in 16.6% (776) severe, 7.1% (334) moderate and 33.0% (1542) mild phenotypes.

Analysis of the CNM patient survival according to disease gene and severity over time demonstrates the impact of the subtype-specific survival rate to the prevalence. The number of surviving patients with severe phenotypic clinical manifestations decreases significantly after 1 year compared to moderate and mild XLMTM and non-XLMTM patients (Supplemental Figure 1A). Analyzing patient numbers according to geographic region, the

higher US patient survival results in a corresponding higher number of patients in the US compared to the EU (Supplemental Figure 1B-C).

*5.3 Limitations*

The published raw data sources on CNM incidence, prevalence and survival were not verified for validity and exactitude. The prevalence and incidence data presented in this review have to be considered as estimates of which the reliability depends on the quality of the available data, the degree to which assumptions are substantiated, and the uncertainty related to the often small sample sizes.

## 6. Sensitivity analysis

The prevalence model generates an estimate of the current CNM prevalence through integration of all available key epidemiological CNM data with estimates based on plausible hypotheses in case of limited or unavailable data. To estimate the impact of new data or altered assumptions, two sensitivity analyses were conducted.

*7.1. CNM incidence estimation based on reduced diagnostic rate assumptions*

The overall CNM incidence estimate of 24 per mln births (Figure 2), includes the assumption of a doubled moderate and mild XLMTM rate upon the implementation of NGS. As the impact of NGS on current reported incidence numbers is however difficult to estimate, the impact of a presumed 50% increase in moderate and mild XLMTM diagnosis rate is assessed. The resulting overall CNM incidence estimate is 9% (22 per mln births) lower compared to the base case of 24 per mln births (Supplemental Figure 2). This relates to a total estimated number of incident patients in the EU, US,

Australia and Japan combined of 228. This leads to a 12% lower total CNM prevalence estimate (4106 patients) as calculated by the prevalence model (Table 4).

*7.2 CNM prevalence estimation based on higher severe and moderate XLMTM survival*

Recently, Amburgey *et al*. reported US survival data in 50 severe and moderate XLMTM patients, with an average age of death of 6 years and 10 months [32]. This survival rate is higher in comparison with the data reported by McEntagart *et al*. 15 years earlier [17]. In order to determine the impact of changes on survival, the CNM prevalence of the McEntagart *et al*. survival data was compared with the data from Amburgey *et al*. (Supplemental Figure 3). Incorporation of the updated survival data from Amburgey *et al*. for severe and moderate XLMTM resulted in an increase of the total CNM prevalence with 31.6%, which corresponds with an increase from 2715 to 3572 patients in the US (Supplemental Figure 3). The new survival data implementation yielded a 2.1- and 1.4-fold increased severe and moderate CNM prevalence, respectively.

## 7. Discussion

The limited availability and high variability of epidemiologic CNM data, which is inherent to rare diseases, impede an exact determination of incidence, prevalence and survival. However, these epidemiologic data are indispensable for determining the disease burden and for related treatment development. For the 3 defined subtypes of XLMTM, namely severe, moderate and mild XLMTM, only incidence data for severe XLMTM were available [10–12]. Via the reported subtype distributions, calculations could be performed to determine the moderate and mild XLMTM incidence as well [9,17,19]. The number of incident cases in combination with an integrated survival curve per geographic region and disease severity allowed us to

establish a reliable CNM prevalence estimate [9,17]. For the non-XLMTM subtypes however, limited epidemiologic data are available. To estimate the current non-XLMTM prevalence, the paediatric point prevalence extrapolation from XLMTM and survival curve assumptions were required [20,21]. The current model thus focuses on XLMTM as a starting point and provided a first estimate of non-XLMTM patient numbers. This estimation may deviate from true data and will be more reliable as additional data of further (quantitative) research becomes available. In addition, it was necessary to integrate data gathered from different populations at different time points within the same model, due to the paucity of available data. Notwithstanding these limitations, the provided prevalence overview allows an approximation of the overall CNM patient distribution according to disease gene, severity and geographic region, including its dynamics. This integrated dataset enables drug developers to take decisions with additional insights on the natural course of disease over time and the impact of demographic, genetic and other factors hereon. Further, a more comprehensive quantification and evaluation presents the magnitude of the true burden of illness across the spectrum of this disease, enhancing the societal benefit of developing novel therapies targeted towards unmet needs. In addition, a comprehensive view on burden of disease facilitates planning for health care services for those impacted by this disease.

The integrated actual CNM incidence estimate of 24 per mln births, as reported here, is twice the number published for male, severe XLMTM [11,12]. This might be an overestimation of the clinical real-life situation, as the incidence number of 1 in 50 000 severe XLMTM patients includes prenatal diagnosis [12]. This estimate also includes patient subtypes with limited case reporting or patients who are currently under diagnosis based on traditional gene-specific test implementation. The integrated total prevalence estimate of 4679 patients in the EU, US, Australia and Japan provides an indication for the worldwide disease impact.

The data analysis highlights how different geographic regions impact CNM epidemiology. The survival rate, for example, depends on the geographic region, which might be due to divergent treatment policies, variable diagnostic rates, potential limited access of patients to health care and research opportunities, and differences in genetic testing standardization. Also, the geographic region affects the number of patients surviving (prevalence) and, accordingly, the disease outcomes across regions. While the predicted US incidence (96 cases) is 20% lower compared to the EU (123 cases), the higher patient survival in the US compared to the EU results in a more than doubled prevalence with 2715 patients in the US compared to 1204 in the EU. Likewise, the impact of XLMTM survival according to disease severity strongly affects patient prevalence; e.g. while there are only 50 mild compared to 104 severe phenotypic incident XLMTM cases, a much higher proportion of mild prevalent phenotypes is present (1542 compared to 776 severe phenotypes). A limitation of the study resides in the paucity of available survival data, as the survival curves reported by McEntagart *et al*. were confined to 13 years. The US survival curves are based on data from patients recruited via family meetings and through registries. Further, the data were extrapolated to the entire US territory, although it is likely that the survival across the different states is not homogenous. The same rationale applies in the EU to a certain extent.

The reported new data on the survival rates of severe and moderate XLMTM patients by Amburgey *et al.* demonstrated that improved neuromuscular respiratory care resulted in a 32% increase of the patients prevalence in the US in comparison with the data published in 2002 [17]. For the EU, a substantial improvement in medical care and thereby patient survival could also be expected. In addition, the advances in neuromuscular respiratory care compared with 2002 confirm that differences in care decisions between continents impact survival curves. These simulations underline that the caveats in current available data and

assumptions preclude a true determination of the CNM prevalence, however through hierarchical implementation a best estimate was obtained. Further research and data collection on moderate and mild XLMTM incident and prevalent patient numbers and non-XLMTM patient numbers and survival per gene are required to validate and finetune current prevalence estimates. As a result, the prevalence estimate will become more accurate as will the insights in the CNM disease course and the impact of CNM on the quality of life and survival.

The estimated CNM prevalence likely includes a high number of CNM patients who are either not diagnosed, not reported in registries (*e.g.* neonatal deaths) or not followed in a neuromuscular center (*e.g.* adults and patients with milder clinical presentations). This results in significant differences between the estimates reported here and data from other sources. Accordingly, the implementation of NGS will enable firmer data generation on the birth incidence of CNM by gene mutation. A natural history study in the EU including XLMTM patients from France, Germany, Spain, Italy, Belgium and UK recruited 40 patients [33]. Fitting of this number into the current model results in an estimate of 17 severe, 38 moderate and 296 mild XLMTM patients. The 40 recruited patients likely reflect the severe and moderate XLMTM populations, while XLMTM patients with a mild phenotype are probably significantly underestimated to date. Based on the Belgian demographics, the model estimates a total of 14 XLMTM – 1 severe, 1 moderate and 12 mild XLMTM patients – and 15 non-XLMTM cases. The Belgian registry for neuromuscular disorders (BNMDR), that exhaustively collects cases from the national reference center, reports 4 CNM patients [34]. The reported patients likely match the 2 severe or moderate XLMTM cases estimated in the model, but do not reflect the expected 12 mild XLMTM and 15 non-XLMTM cases. Given the current absence of treatment and the rarity of the disease, it is possible that several cases,

especially if not typical, are undiagnosed. A similar situation has occurred with Pompe disease, where availability of a treatment led to an increased awareness of the disease. This, in turn, resulted in more widespread screening in patients with elevated CPK with or without weakness and an increased diagnosis of 7% in this population [23].

Verhaart *et al*. found how true prevalence of SMA was underestimated by patient registries [14,15]. This was partly due to divergent patient participation in registries between countries, limited access of some patients to health care services, differences in health care infrastructure, genetic testing and patient care. Further, patient registry information is based on clinical trial participation or voluntary registration. Lack of interest or presence of severe forms of the disease, leading to infant death and a reduced likelihood of the parents to register their child, results in reduced reporting of the patients. It is thus highly likely that especially the severe forms of rare diseases are underreported. These limitations should be considered here as well.

Lastly, although different CNM subtypes are theoretically defined, the high heterogeneity of clinical symptoms, variation in disease onset and differences in standard of care and diagnosis standardization adds to the complexity for the determination of representative epidemiological data [22].

As rapid advances and progress is made in the development of new medicines for rare diseases, it is increasingly important to understand the epidemiologic burden of disease and the impact potential new medicines. This integrated CNM prevalence model allows to assess the potential impact of new treatment paradigms on the disease outcomes in different subtypes.

In conclusion, although the model provides a detailed estimate of the overall incidence of CNM the current estimates do not fully capture the true incidence. Further data generation (e.g. through registries and screening) will increase the reliability of incidence, prevalence and survival rates for the different CNM subtypes.

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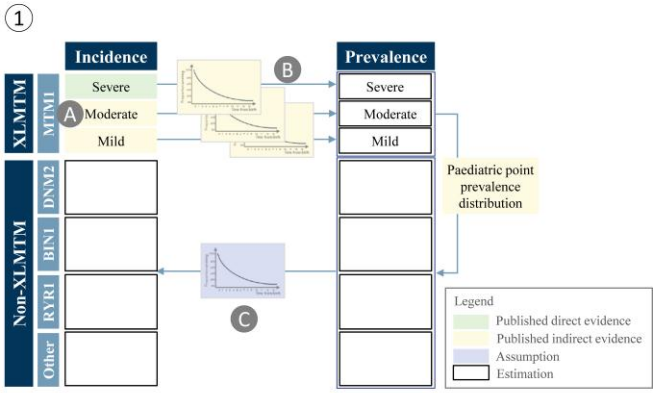


Figure 1. **Schematic overview of the methodology to estimate key epidemiologic measures.** Step A: Published incidence data for severe XLMTM in combination with subtype distribution data results in an estimation of epidemiologic subtype data. Step B: Combination of epidemiologic XLMTM data with subtype survival data and corresponding geographical regions allows generation of prevalence data per subtype and per geographical region. Step C: the non-XLMTM subtype incidence can be estimated from the combination of the paediatric point prevalence distribution and subtype survival curve assumptions.

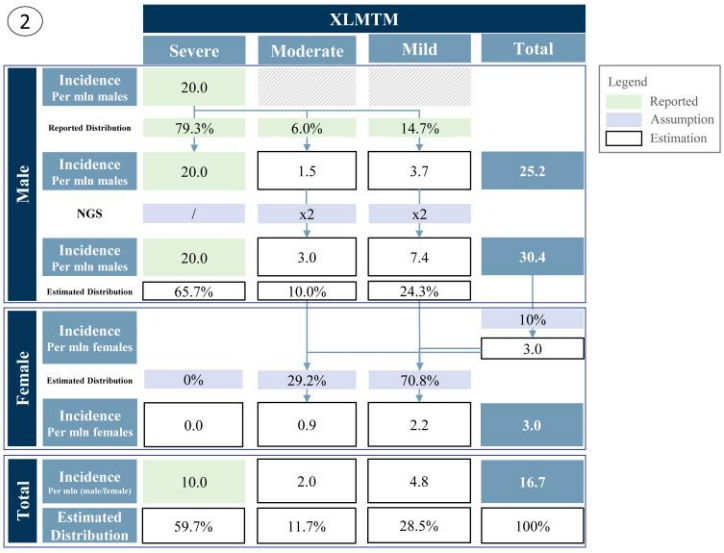


Figure 2. **XLMTM incidence estimation.** Starting from the reported severe XLMTM incidence, moderate and mild XLMTM incidences could be estimated based on reported subtype distributions. The assumptions accounted for a doubling of diagnoses for mild and moderate XLMTM, resulting from the use of NGS. In addition, female XLMTM patients were included, reported to be approximately 10% of the XLMTM population and assumed to present with a moderate or mild phenotype. The resulting overall XLMTM incidence for male and female population is estimated at 16.7 cases per mln births. *NGS; Next Generation Sequencing.*

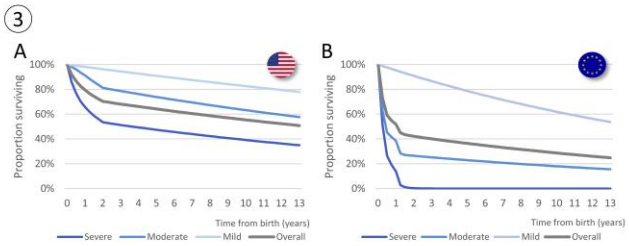


Figure 3. **XLMTM survival in function of age for the overall population and the disease severity subgroups in the US (A) and the EU (B).** The survival curves are based on McEntagart *et al*. [17], who reported XLMTM survival rates separately for the US and the EU. Taking the survival rate of each subtype into account, survival curves for severe, moderate and mild XLMTM according to geographical region could be calculated.


Figure 4. **Non-XLMTM incidence estimation.** The estimation of non-XLMTM prevalence was based on the reported prevalence distribution of XLMTM and non-XLMTM combined with non-XLMTM survival curves. It was assumed that the non-XLMTM population had a similar survival curve to the mild phenotype of XLMTM. Applying this survival rate to the non-XLMTM prevalence, the incidence distribution could be estimated. Earlier calculations determined that the XLMTM incidence distribution corresponds to 16.7 per mln of all births, resulting in and overall non-XLMTM incidence estimate of 7.3 per mln births.

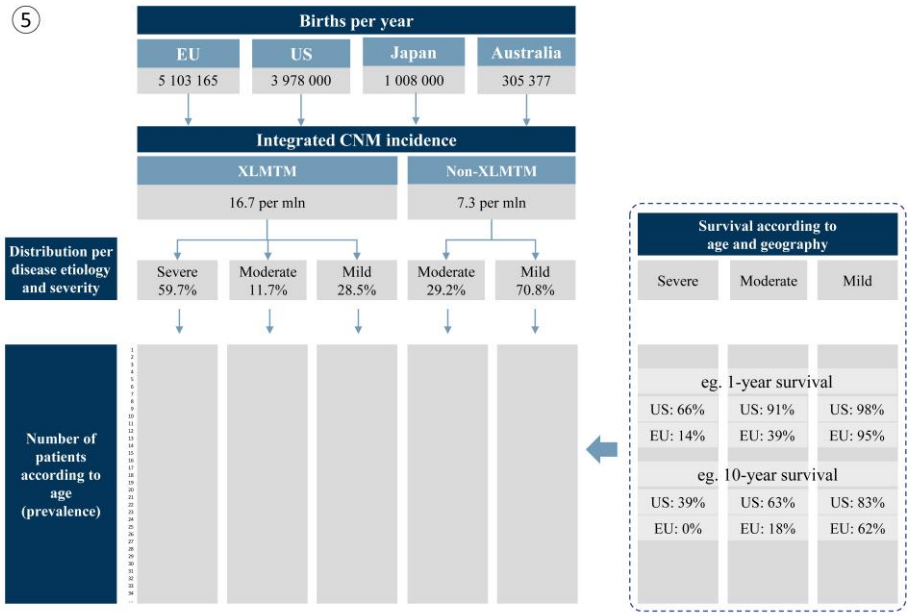


Figure 5. **Integration of estimated epidemiologic input data on incidence and survival according to disease etiology, severity and geography in CNM patient prevalence model.** Based on the births per year per geographical region and the integrated overall CNM incidence, the yearly number of newborns per geographical region could be determined. The survival per subtype is depicted in the US and the EU based on 1-year and 13-year survival reported by McEntagart *et al.* [17]. Combination of these data allow to estimate CNM incidence and prevalence according to geographical region and disease severity.

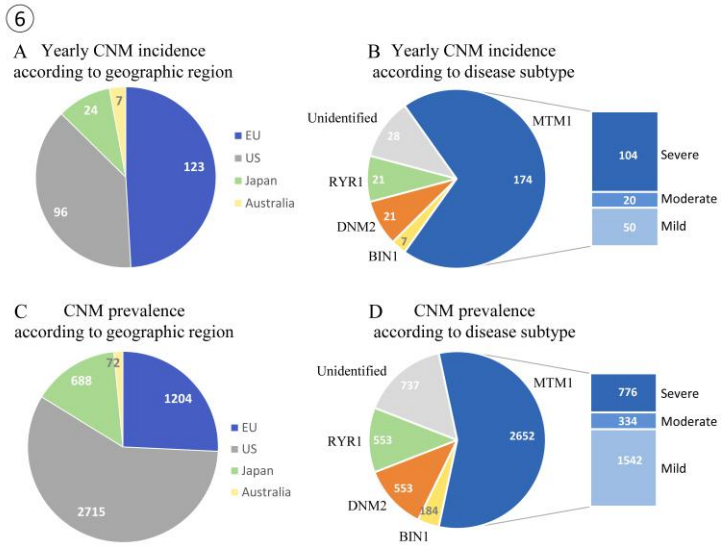


Figure 6. **CMN incidence and prevalence estimate according to geography (A,C), disease etiology and severity (B,D).** A. Estimation of the yearly CNM incidence according to geographic region based on the estimated XLMTM incidence. B. Estimation of the yearly CNM incidence according to disease subtype based on estimated CNM subtype distributions. C. Estimation of the CNM prevalence according to geographic region based on the number of patients in combination with the survival curves. D. Estimation of the CNM prevalence according to disease subtype based on the subtype distribution.

Table 1. Epidemiologic data structured according to incidence, prevalence and survival, and level of reliability.

| | XLMTM | | | | Non-XLMTM |
|---|---|---|---|---|---|
| | Male | | | Female | |
| | Severe | Moderate | Mild | | |
| **Incidence** | **A** Bertini et al., 2004; McEntagart et al., 2002 | **B** McEntagart et al., 2002; Herman et al., 1999; Jungbluth et al., 2013 | | **C** Savarese et al., 2016; Biancalana et al., 2017 | |
| **Survival rates** | **A** McEntagart et al., 2002* **B** Herman et al., 1999 | | | | **C** Werlauff et al., 2015; Echaniz-Laguna, 2013 |
| **Prevalence** | | | | | **B** Amburgey et al., 2011 |

**survival rates according to disease severity and geography are reported separately*

**Legend**

**A** Published direct evidence in significant patient populations
**B** Published related data in significant patient populations
**C** Data with limited published supportive evidence
No data available

Table 2. XLMTM patient distribution according to disease severity

| | XLMTM subtype | | | n | Reference |
|---|---|---|---|---|---|
| | Severe | Moderate | Mild | | |
| **Worldwide retrospective physician and clinical scientist questionnaire** | 79% | 6% | 15% | 116 | McEntagart et al., 2002 |
| **Epidemiologic follow-up study in North-American population** | 75% | 9% | 13% | 55 | Herman et al., 1999 |
| **UMD-MTM1 data on worldwide XLMTM population** | 82% | 18% | | 478 | This study |

Table 3. Published XLMTM survival in function of age according to geography and disease severity (reconstructed from McEntagart *et al*. [17]).

| Time from birth (years) | proportion surviving | | | | |
|---|---|---|---|---|---|
| | geography | | disease severity | | |
| | US or japan | EU | severe | moderate | mild |
| **1** | 85% | 42% | 47% | 100% | 100% |
| **2** | 83% | 32% | 37% | 100% | 100% |
| **3** | 79% | 29% | 36% | 91% | 100% |
| **4** | 79% | 27% | 35% | 85% | 100% |
| **5** | 73% | 27% | 32% | 80% | 100% |
| **6** | 65% | 27% | 29% | 80% | 100% |
| **7** | 65% | 27% | 29% | 80% | 100% |
| **8** | 65% | 27% | 29% | 80% | 100% |
| **9** | 65% | 25% | 27% | 80% | 100% |
| **10** | 59% | 25% | 25% | 80% | 100% |
| **11** | 55% | 25% | 25% | 80% | 100% |
| **12** | 55% | 25% | 23% | 80% | 100% |
| **13** | 51% | 25% | 21% | 80% | 100% |

Table 4. Integrated incident and prevalent patient pool estimate in the EU, US, Australia and Japan based on the base case doubled or alternative 50% moderate and mild rate assumption.

| | | XLMTM | | | non-XLMTM | Total |
|---|---|---|---|---|---|---|
| | | Severe | Moderate | Mild | | |
| Incidence | Base case | 104 | 20 | 50 | 76 | 250 |
| | Diagnose rate mod/mild 50% | 104 | 16 | 39 | 69 | 228 |
| Prevalence | Base case | 776 | 334 | 1542 | 2027 | 4679 |
| | Diagnose rate mod/mild 50% | 776 | 263 | 1214 | 1853 | 4106 |

Table 5. The US prevalent patient pool estimate in function of disease etiology and severity based on the McEntagart [17] data or updated Amburgey [31] data.

| | XLMTM | | | non-XLMTM | Total |
|---|---|---|---|---|---|
| **Implemented survival data** | **Severe** | **Moderate** | **Mild** | | |
| **McEntagart et al. (2002)** | 596 | 212 | 806 | 1100 | 2715 |
| **Amburgey et al. (2017)** | 1256 | 308 | 806 | 1203 | 3572 |