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Preliminary data for the cost-effectiveness assessment of the newborn screening for SMA in Belgium

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Neonatal screening is becoming increasingly important in the spinal muscular atrophy (SMA) landscape. Yet there is a growing set of evidences that early pre-symptomatic management is much more efficient than post-symptomatic treatment, there is however no information available on the cost-effectiveness of SMA newborn screening (NBS). Such health economic analysis is nevertheless very important to convince policy makers to allocate funds for NBS. We will present the health-economic data of pre-symptomatic and post-symptomatic treated patients in Belgium that will further be used to assess the cost-effectiveness of NBS. Between March 2018 and February 2020, screening was conducted among 71,000 newborns, among which 9 were detected with SMA. All but one identified patients were treated before the onset of symptoms: 5 with nusinersen (one was mildly symptomatic at the time of treatment), 2 with Zolgensma, 1 with Risdiplam and the last one to be determined. Survival, costs and quality of life of these 9 patients (aged between 10 days and 18 months) are currently prospectively collected. In addition, data from 3 additional asymptomatic patients who were siblings of affected children are also collected. Survival, health care resources consumption and quality of life data have also been collected on symptomatic treated and untreated patients. For untreated patients, we collected prospectively the data during two years in 81 patients (53 patients with SMA Type 2, 9 non-ambulant with SMA Type 3 and 19 ambulant with SMA Type 3). We are also collecting similar data prospectively in 30 symptomatic patients treated with nusinersen and 2 untreated patients, aged between 4 months and 60 years (9 patients with SMA 1, 14 patients with SMA 2, and 9 patients with SMA 3). Two-thirds of these patients already have at least 2 years of follow-up. Using these three sets of data, we are currently developing a model to assess the cost-effectiveness of newborn screening for SMA. We will present the preliminary results issued from this model.

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CONGENITAL MUSCULAR DYSTROPHIES

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Gene therapy approach for *LAMA2*-related muscular dystrophy using linker proteins

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LAMA2-related muscular dystrophy (*LAMA2* MD or MDC1A) is the most frequent form of congenital muscular dystrophies. It is caused by mutations in *LAMA2*, the gene encoding laminin-α2, the long arm of the heterotrimeric (α2, β1, γ1) basement membrane protein laminin-211 (Lm-211). Patients with the early-onset form lack Lm-211 due to biallelic loss-of-function mutations in *LAMA2*. The large size of the cDNA encoding laminin-α2 and the heterotrimeric structure of Lm-211 present a challenge for gene replacement or gene editing strategies. To overcome this, we have designed two rather small linker proteins that qualify for adeno-associated virus (AAV)-mediated gene delivery. This strategy takes advantage of the compensatory expression of laminin-α4, giving rise to Lm-411 (α4, β1, γ1), present in *LAMA2* MD biopsies and laminin-α2-deficient mice. Lm-411 only forms a labile muscle basement membrane and thus is unable to functionally compensate for the loss of Lm-211. To overcome the functional deficit of Lm-411, one linker protein, called mini-agrin (mag), mediates binding of Lm-411 to the sarcolemmal Lm-211 receptor α-dystroglycan. The second linker, called αLNNd, consisting of the N-terminal part of laminin-α1 and the laminin-binding site of nidogen-1, allows polymerization of Lm-411. When added together, Lm-411 and the linkers form a functional muscle basement membrane *in vitro* and upon transgenic expression in *dyW/dyW* mice, a mouse model for *LAMA2* MD. Consequently, the muscular dystrophy in *dyW/dyW* mice is largely improved, overall body weight is increased and median survival is drastically extended from 15 weeks to 81 weeks (Reinhard et al., Science Transl. Med., 2017). We will present data from our ongoing efforts to evaluate the therapeutic potential of the linker proteins by targeting different tissues at different time points and by testing the possibility to use AAV9-mediated delivery of the linkers to *dyW/dyW* mice.

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Collagen VI-related myopathy. Clinical and genetic findings in a large Chilean cohort

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Collagen VI related myopathy is one of the more prevalent inherited neuromuscular myopathies. Determining the genetic and clinical features in our population is relevant to improve patients care and develop a platform for collaborative studies and future clinical trials. We describe the phenotype, genotype and muscle MRI (WBMRI) in a series of patients with Collagen VI-Related Myopathy (COLVI-RM). A retrospective study of patients with a genetic diagnosis of Collagen-VI-RM, IRB-approved. Demographic data and patients' characteristics were obtained from medical records. Eighteen patients (9 families) with COL6 mutation from twenty-one patients suspected of COLVI-RM. 12/6 (female/male), age range 1-54 years and (average: 25 years). All patients present an autosomal dominant COL6-related condition; 4/9 were *de novo* mutations. 5/9 families carry a COL6A1 mutation, 3/9 families a COL6A3 and one family a COL6A2 mutation. Age of disease onset was before the age of two in 9/18. (motor delay, frequent falls, hip dislocation), followed by neonatal onset (5/18) (hypotonia, congenital torticollis, hip dislocation). A one-year-old patient was diagnosed at pre-symptomatic state. Most patients presented typical COLVI-RM skin lesions (16/18) and distal hyperlaxity. Most showed a slight elevation of total CK (261-500). Muscle biopsies from 9 patients showed a dystrophic pattern in 5, nonspecific myopathic pattern in 4 patients. Seven patients had a WBMRI previous to genetic diagnose; all of them showed the characteristic involvement of muscles described in COLVI-RM. 16/18 patients developed a Bethlem phenotype, maintaining ambulation. Two patients presented an Ullrich dystrophy phenotype and ventilatory failure. COLVI-RM dominant conditions and Bethlem myopathy phenotype are prevalent in our cohort. WBMRI is a useful tool that guides the diagnostic process. The use of NGS helps to shorten the diagnostic odyssey and perform a better clinical follow-up and genetic counselling.

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Diet, motor activity & daily activity limitations in individuals with *SELENON* (*SEPN1*) related myopathy

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SELENON (SEPN1) related myopathies (SELENON-RM) are a group of rare congenital myopathies caused by mutations in the *SELENON* gene. SELENON-RM patients typically present with axial weakness, spinal rigidity, scoliosis, decreased stamina, low body mass, and respiratory insufficiency; however, there is a wide range of symptom severity in these patients,