

**PW 36:  
Muscle assessment,  
scales and  
patients' registries**

PW36-447	<p><b><u>SPARSE SHAPE MODELS WITH OPTIMAL IMAGE SUPPORT FOR MRI CALF MUSCLE SEGMENTATION</u></b></p> <p>ESSAFI S<sup>1</sup>, LANGS G<sup>1</sup>, BASSEZ G<sup>2</sup>, DEUX JF<sup>2</sup>, VIGNAUD A<sup>3</sup>, RAHMOUNI A<sup>2</sup>, PARAGIOS N<sup>1</sup></p> <p>(1) GALEN Group, Laboratoire MAS, Ecole Centrale Paris/ INRIA Saclay - Île-de-France, Parc Orsay Université, Chatenay-Malabry, FRANCE. (2) Centre Hospitalier Universitaire Henri Mondor, Créteil, FRANCE. (3) Siemens Medical Solutions, Saint Denis, FRANCE.</p>
To contact the author:: salma.essafi@ecp.fr.	<p>The aim of this study is to evaluate a model based method for the automatic segmentation of human calf muscles in T1-MRI data. Recent advances in biomedical imaging have made possible the in-vivo non invasive visualization of anatomical and functional information on the muscle state. These modalities offer new means to assess the state of the muscle and the performance of different therapeutic strategies. A crucial pre-requisite is the accurate segmentation of individual muscles, a challenging task due to the lack of contrast between different regions.</p> <p>Sparse shape models (SSM) learn a statistical model of shape and local textures from an annotated training set and derive a sparse representation and reconstruction mechanism for individual muscles. SSMs take the heterogeneous distribution of salient features in the muscle MRI data that causes standard segmentation methods to fail. During application, SSMs use the sparse model to automatically and accurately segment the muscle in a T1-MRI volume. The evaluation of the accuracy of SSM segmentation was performed on 4 T1-MRI data sets with a spatial resolution of 0.5859x0.5859x7 mm. For all data sets a manual expert annotation of the medial gastrocnemius served as standard-of-reference. In addition SSM accuracy is compared to a standard approach that does not take the heterogeneous data into account. The segmentation error was found to be sufficient for further processing of the data. The mean segmentation error of SSMs is 9.53, while standard segmentation achieves 37.78. On all examples, SSM outperform the standard approach.</p> <p>Thus, SSMs provide for an accurate segmentation of human calf muscles in T1-MRI data. Their performance is superior to standard methods. The work aims at a non-invasive analysis of the structure of muscles affected by myopathies.</p>

PW36-448	<p><b>NON INVASIVE ASSESSMENT OF MOUSE MUSCLE VOLUME USING 3D <math>\mu</math>-ECHOGRAPHY</b></p> <p>NEJJARI M<sup>1</sup>, JANIER M<sup>1</sup>, GOURDON G<sup>2</sup>, PUYMIRAT J<sup>3</sup>, HIBA B<sup>1</sup>  (1) Université Lyon1, ANIMAGE, Lyon, FRANCE. (2) INSERM UR 383, Necker Hospital, Paris, FRANCE. (3) Human Genetics Unit, Laval CHU, Québec, CANADA.</p>
To contact the author:: bassem.hiba@cermep.fr.	<p>Introduction: Mouse models are now widely used for drug discovery and muscle disorder studies (e.g. myopathy). Therefore a quantitative method to determine muscle volume in vivo will help us for the follow-up of the muscle disease. In the present work, we report a method based on 3D ultrasound (3D-US) imaging to quantify Tibialis Anterior muscle (TA) volume with high accuracy and precision.</p> <p>Methods: Mice were anesthetized and the lower leg was scanned along the TA muscle (over a 20 mm, 0.2 mm steps) using a 3D-US high-resolution probe (spatial lateral resolution 40<math>\mu</math>m). A semi-automated segmentation algorithm was used to delineate the TA muscle in the acquired images and assess its volume.</p> <p>Validation and reproducibility of the measurement was investigated in 5 mice (C57bl6 of 10 months) examined 4 times and Intra-reader was also investigated.</p> <p>Results: Mean muscle volume measured by 3D-US was <math>40.4 \pm 1.1 \text{ mm}^3</math> in control mice. Statistical analysis showed an intra-reader deviation equal to or less than 2%. In addition, a high correlation between TA muscle ex vivo weights and the volumes obtained using 3D-US was found for the investigated mice (<math>R &gt; 0.95</math>).</p> <p>The proposed method was used to follow-up TA volume evolution in 7 normal mice from age 2 to age 7 months. We observed a mean muscle volume increase from <math>17.6 \pm 1.3 \text{ mm}^3</math> to <math>22.5 \pm 1.4 \text{ mm}^3</math>, which correspond to an increase of 28%.</p> <p>Conclusion: 3-D US imaging provided a good precision and accuracy in the measurements of muscle volume in small animal models (e.g. TA muscle). This method could be very useful for the quantification of disease progression and for evaluation of the efficacy of new therapies.</p>

PW36-449	<p><b><u>ASSESSING NEUROMUSCULAR FUNCTION FOR PATIENT FOLLOW-UP USING VARIOUS METHODOLOGIES: CORRELATIONS AND VARIABILITIES</u></b>  HOGREL JY<sup>1</sup>, OLLIVIER G<sup>1</sup>, CANAL A<sup>1</sup>, CALPAÏN STUDY GROUP T<sup>1</sup>  (1) Institut de Myologie, Paris, FRANCE.</p>
To contact the author:: <a href="mailto: jy.hogrel@institut-myologie.org">jy.hogrel@institut-myologie.org</a> .	<p>Assessment of the neuromuscular function during the time course of neuromuscular disorders is much informative for patient follow-up either during the natural history of his disease or during a therapeutic intervention. Within this last frame, the choice of the evaluation criteria is crucial for many reasons. Many methods exist to assess the various aspects of the neuromuscular function. This was the aim of this study to perform and to analyze a selection of different tests for the follow-up of patients during the natural history of their disease.</p> <p>This study is a small part of a larger multicentric study about a multi-parametric approach to natural history knowledge of calpainopathies for efficacy assessment of therapies. Twenty one patients suffering from LGMD 2A (calpainopathy) were followed every six months during two years. Each patient visit included Manuel Muscle Testing (MMT), Quantified Muscle Testing (QMT), Muscle Function Measure (MFM), isometric dynamometry (Biodex) and timed functional tests. Elbow and knee flexion and extension were particularly analyzed. Their reproducibility and variability were assessed. Correlations between the measurements obtained using different methods were analysed.</p> <p>This study revealed that the results obtained with QMT or Biodex were not always highly correlated and may differ depending on the muscle function studied. For instance, the evaluation of elbow and knee extensions seems to be much more reliable than the evaluation of elbow and knee flexions for this patient population. Moreover, both QMT and Biodex were unsuitable to detect small strengths in very weak patients. From longitudinal data, it was possible to compute percentage of variations to be considered significant of true strength changes.</p> <p>Natural history of disorders may help to identify the muscle function to be studied in further therapeutic trials and to provide the amount of change significant of a true evolution.</p>

PW36-450	<p><b><u>THE 6-MINUTE WALK TEST AS A CLINICAL TRIAL OUTCOME MEASURE IN DUCHENNE MUSCULAR DYSTROPHY: RELIABILITY AND CORRELATION WITH OTHER MEASURES OF DISEASE SEVERITY</u></b></p> <p>MCDONALD CM<sup>1</sup>, HENRICSON EK<sup>1</sup>, HAN JJ<sup>1</sup>, NICORICI AR<sup>1</sup>, ABRESCH RT<sup>1</sup>, ATKINSON LA<sup>2</sup>, REHA AL<sup>2</sup>, ELFRING GL<sup>2</sup>, MILLER LL<sup>2</sup></p> <p>(1) University of California, Davis Medical Center, Sacramento CA, USA. (2) PTC Therapeutics, South Plainfield NJ, USA.</p>
To contact the author:: cmmcdonald@ucdavis.edu.	<p><b>Background:</b> The 6-minute walk test (6MWT) is a commonly used measure of cardiorespiratory endurance. Researchers have begun to use it as a strength-related outcome measure in clinical trials in neuromuscular disease. We evaluated the 6MWT differentiation between boys with Duchenne muscular dystrophy (DMD) and healthy controls, test-retest variability in boys with DMD, and correlation of the 6MWT with timed functional measures.</p> <p><b>Methods:</b> We enrolled ambulatory boys 5-12 years old with DMD (n=15) and without (n=20). Boys with DMD were tested 7 days apart using a modified American Thoracic Society 6MWT and standard clinical timed function testing. Healthy controls underwent testing at a single time point.</p> <p><b>Results:</b> Across all ages, distance traveled differed between boys with DMD and healthy controls. In boys aged 5-6, those with DMD averaged 367 ± 74 m compared to 574 ± 35 m (p&lt;.01) for the healthy controls. In boys aged 7-9, those with DMD averaged 354 +/- 31 m compared to 622 ± 50 m (p&lt;.001) for the healthy controls. In boys aged 10-12, those with DMD averaged 265 ± 146 m compared to 646 ± 49 m (p&lt;.001) for the healthy controls. As age increased in the DMD group, percent predicted scores decreased from 82% at age 5 to 56% at age 12. 6MWT test-retest correlation was high (r=.92). In the DMD group, the 6MWT correlated well with time to walk 10 m (r=.80), time to walk 25 m (r=.80), time to climb 4 standard stairs (r=.77), and time to stand (r=.64).</p> <p><b>Conclusion:</b> A modified 6MWT in ambulatory boys with DMD is reproducible, differentiates boys with DMD from healthy controls at all ages, and correlates with other measures of disease severity.</p>

PW36-451	<p><b><u>QUALITY OF LIFE OF ADOLESCENTS WITH NEUROMUSCULAR DISEASES: HERE'S WHAT THEY SAY</u></b>  VUILLEROT C<sup>1</sup>, HODGKINSON I<sup>1</sup>, BERARD C<sup>1</sup>, ECOCHARD R<sup>2</sup>, D'ANJOU MC<sup>3</sup>, COMMARE MC<sup>4</sup>  (1) Hospices Civils de Lyon, CHU Lyon Sud, L'Escale, Service de Médecine Physique et de Réadaptation Pédiatrique, Pierre Benite, FRANCE. (2) Hospices Civils de Lyon, Service de Biostatistique, LYON, FRANCE. (3) CHU St Etienne, Service de MPR pédiatrique, St Etienne, FRANCE. (4) CHU Grenoble, service MPR Pédiatrique, Grenoble, FRANCE.</p>
To contact the author:: carole.vuillerot@chu-lyon.fr.	<p>Little is known about quality of life of adolescents with neuromuscular diseases or the factors that influence it. We searched whether physical impairment, physical disability, and medical complications were predictors of low quality of life. Motor function, health, orthopaedic status, and rehabilitation were assessed in 43 adolescents with neuromuscular diseases (age: 13.8±1.7; sex ratio 2.9/1). Quality of life was measured with the VSP-A (Vécu Santé Perçu par l'Adolescent), a validated health-related quality of life self-perception test. A multiple linear mixed regression related quality of life to impairment, disability, and respiratory status. Comparisons were made with data from an age/sex-matched healthy population. On the average, the VSP-A scores in diseased adolescents were: i) similar to those of the healthy population as regards vitality, body image, relationships with parents and friends, and physical and psychological well-being ; ii) higher as regards school performance (68 vs. 52.8%) and relationships with teachers (67.4 vs. 43.2%); iii) lower as regards leisure activities (43.9 vs. 60.9%). Physical disability and physical impairment were not significantly associated with seven out of the nine domains but scores for leisure activities and vitality were significantly associated with physical impairment (p=0,001 and p=0,006 respectively). Adolescents with ventilatory support did not express lower scores than non-ventilated ones (67.7% +/- 11 vs. 62.9%+/-15, p=0.39). These surprising results should question our medical, educational, and rehabilitation practices. Already well-managed disabled adolescents should benefit from a less compassionate and more daring and dynamic interpersonal contacts.</p> <p><i>Conclusions</i> - These surprising results should question our medical, educational, and rehabilitation practices. Already well-managed disabled adolescents should benefit from a less compassionate and more daring and dynamic interpersonal contacts.</p>

PW36-452	<p><b><u>THE MOTOR FUNCTION MEASURE (MFM) SCALE WAS USED TO EVALUATE PATIENTS WITH DUCHENNE MUSCULAR DYSTROPHY (DMD).</u></b>  BERARD C<sup>1</sup>, VUILLEROT C<sup>1</sup>, PAYAN C<sup>2</sup>, GIRARDOT F<sup>1</sup>  (1) Hospices Civils de Lyon, CHU Lyon Sud, L'Escale, Service de Médecine Physique et de Réadaptation Pédiatrique, Pierre Benite, FRANCE. (2) Institut de myologie, Paris, FRANCE.</p>
To contact the author:: carole.berard@chu-lyon.fr.	<p><i>Study participants and setting:</i> Patients without medication were evaluated at 3 months for 13 patients (mean age 11y 7 mo; SD 1y 10mo) and at one year for 41 patients (mean age 14y 1 mo; SD 5y 5mo) in a referral center. Twelve patients treated with steroids (mean age 10 y 2 mo; SD 2y 2 mo) were evaluated after one year of treatment and compared with 12 age-matched DMD controls.</p> <p><i>Results:</i> In a 3-month period, subscore D1 showed a significant average decrease of 4.7% (p&lt;0,01). In a 1-year period, all scores showed significant decreases: D1 4.9% (p&lt;0,01), D2 7.7% (p&lt;0,01), D3 4.3% (p&lt;0,03) and Total Score 5.8% (p&lt;0,01). For the 11 walking patients at the beginning of the study, the average value of D1 annual decrease is 26.1%. For the non-ambulant patients, the annual average decrease was 11.8% for D2 and 6.3% for Total Score. A sensitive threshold value for the loss of the ability to walk and a predictive value a year before loss of ambulation could be estimated. In the group of patients treated with steroids, compared to controls, it was evidenced a stabilization of the total score (-0.59 vs. -5.87, p&lt;0,02 ) and dimension D2 (0.98 vs. -8.50, p&lt;0,01).</p> <p><i>Conclusions:</i> Our preliminary results are promising for the use of the MFM in clinical trials to evidence either deterioration of disease or lack of deterioration induced by therapeutics.</p>

PW36-453	<p><b><u>THE ONLINE WEB VERSION OF THE NMD GENE TABLE OF NEUROMUSCULAR DISORDERS</u></b>  HAMROUN D<sup>1</sup>, BEROUD C<sup>1</sup>, CLAUSTRES M<sup>1</sup>, KAPLAN JC<sup>2</sup>  (1) INSERM, U827, Montpellier, FRANCE. (2) Université Paris Descartes/CNRS, Institut Cochin, et Laboratoire de Biochimie et Génétique Moléculaire, Hôpital Cochin, PARIS, FRANCE.</p>
To contact the author:: dalil.hamroun@inserm.fr.	<p>The first gene table of neuromuscular disorders (<i>Neuromuscular Disorders, 1991, Vol 1, N<sup>o</sup>, 75-76</i>) was a list of seven identified genes and sixteen mapped loci awaiting identification of the causative gene. In the January 2008 printed version of the table there are 213 identified genes, 103 mapped but not yet identified loci, 536 phenotypes and 742 key references (<i>ibid, 2008, Vol 18, N<sup>o</sup>, 101-129</i>). This increase has generated a high degree of complexity, because mutations in a given gene may produce a large number of patho-phenotypes, such as in laminopathies; and because, conversely, a given patho-phenotype may be caused by mutations affecting one among several possible genes, such as in CMT. Thus the printed updated table, now published once a year, has reached a size making it difficult to maintain and to consult. In order to help find one's way through this chaos we started in 2005 a computerized online version of the NMD gene table (see <a href="http://194.167.35.195">http://194.167.35.195</a>), which is regularly updated and implemented. The main advantage of the web version is its interactivity facilitated by : (i) cross-referencing the different items pertaining to each entry (<i>name of disease, mode of inheritance, locus symbol with OMIM number, chromosomal localization, approved gene symbol with OMIM number; approved protein name, key references, other allelic disease phenotypes</i>); (ii) introducing outward links providing instantaneous connection to the following databases: <i>Leiden Muscular Dystrophy, OMIM, NCBI, Genatlas</i>. A query tool allows one to ask many kinds of questions. In the future other external links will be added, in particular to Locus Specific Databases giving access to the mutational spectrum of each gene. The online NMD gene table should allow clinicians to obtain molecular diagnosis far more easily.</p>

PW36-454	<p><b><u>FRENCH DATABASE FOR MYOTONIC DYSTROPHIES (DM1-DM2): GENERAL PRINCIPLES AND DESCRIPTION</u></b>  BASSEZ G<sup>1</sup>, GUIRAUD-DOGAN C<sup>1</sup>, HAMROUN D<sup>2</sup>, BEROUD C<sup>2</sup>  (1) Reference center for neuromuscular diseases, CHU Henri Mondor, Créteil, FRANCE. (2) Institut Universitaire de Recherche Clinique, CHU de Montpellier, Montpellier, FRANCE.</p>
To contact the author:: guillaume.bassez@hmn.aphp.fr.	<p>Myotonic dystrophy is the commonest muscular dystrophy in adults and the most variable neuromuscular disorder. This high variability of the multisystemic involvement creates particular challenges for both management and the design of optimal therapeutic trial. Therefore, a database specifically dedicated to myotonic dystrophies may be a valuable tool for promoting clinical research and optimizing the management of the patients. This database will contain clinical and paramedical data collected during the medical consultations of DM patients in several French neuromuscular centres and sent to the Henri Mondor hospital for recording. Basic informations will be first reported in an inclusion document (identification, expansion size of the mutation, clinical history, clinical evaluation of neuromuscular and systemic signs, and professional and social consequences of the disease) and next completed by an annual follow-up section reporting the recent clinical events and an actualised clinical evaluation. The database may then allow us: 1) to identify prognostic factors (muscle weakness, cardiac and respiratory involvement, swallowing disturbances, intellectual impairment) and to study their potential interrelations; 2) to compare the main features of both diseases in patients from two different countries. In particular, the study will compare the DM1 genetically homogenous population of Quebec to the genetically heterogeneous French patients 3) to study mortality and morbidity; 4) to search for genotype/phenotype correlations; and 5) to compare DM1 and DM2 features. Furthermore, recent research has provided more information on the underlying molecular pathomechanisms involved in myotonic dystrophies that creates new opportunities for more specific therapy. The database will be of great interest to select patients for future therapeutic trials.</p>

PW36-455	<p><b><u>UMD-DMD FRANCE: A NATIONAL KNOWLEDGEBASE OF MOLECULAR DEFECTS IN THE DYSTROPHIN GENE</u></b></p> <p>TUFFERY-GIRAUD S<sup>1</sup>, BÉROUD C<sup>2</sup>, LETURCQ F<sup>3</sup>, BEN YAOU R<sup>4</sup>, HAMROUN D<sup>5</sup>, DESMET FO<sup>2</sup>, MICHEL-CALEMARD L<sup>6</sup>, KHAU VAN KIEN P<sup>5</sup>, HUMBERTCLAUDE V<sup>5</sup>, KAPLAN JC<sup>3</sup>, CHELLY J<sup>3</sup>, CLAUSTRES M<sup>2</sup></p> <p>(1) Université Montpellier 1, UFR Médecine, Montpellier, F-34000, FRANCE. (2) Inserm U827, Montpellier, F-34000, FRANCE. (3) CHU Hôpital Cochin, Laboratoire de Biochimie et Génétique Moléculaire, Paris, FRANCE. (4) INSERM, U582, IFR14, Institut de Myologie, Paris, FRANCE. (5) CHU Montpellier, Laboratoire de Génétique Moléculaire, Montpellier, F-34000, FRANCE. (6) French Collaborative Network of molecular diagnostic laboratories, Lyon, FRANCE.</p>
To contact the author:: sylvie.tuffery@montp.ins erm.fr.	<p>UMD-<i>DMD</i> France is a national locus-specific database (LSDB) dedicated to dystrophinopathies. It has been developed through a multi-center academic effort to provide an up-to-date resource of curated information covering all identified and fully validated mutations in patients with dystrophinopathies in France. Whenever necessary, mutations have been reevaluated at the light of the currently available techniques. The database includes 2270 entries corresponding to 2070 independent mutational events identified in either male patients (2034) or symptomatic female carriers (36). These mutations consist in 1420 deletions, 261 duplications, and 449 small rearrangements of which 39.1% are nonsense. Experts in the <i>DMD</i> gene and related diseases are responsible for data quality and accuracy. In addition to gather mutations, the UMD-<i>DMD</i> France includes available data on dystrophin and RNA analysis, phenotypic groups, and transmission. The database aims at further including extensive description of phenotypes associated with the reported mutations to better delineate the clinical spectrum of dystrophinopathies and to allow genotype/phenotype correlations. New tools have been specifically developed in the UMD software to facilitate large-scale mutation analyses of the <i>DMD</i> gene. UMD-<i>DMD</i> will benefit to all the scientific community interested in dystrophinopathies including geneticists, clinicians, and researchers involved in the design of therapeutic strategies. Also it will prove useful to implement forthcoming global registries of patients for clinical trials as ultimate goal within the European Network of Excellence for treatment of neuromuscular disorders (TREAT-NMD). <b>Network of French Laboratories:</b> R. Bernard (Marseille), E Bieth (Toulouse), M. Blayau (Rennes), P Boisseau (Nantes), L Calemard (Lyon), M Cossée (Strasbourg), I Creveau (Clermont-Ferrand), B De Martinville (Lille), A Guiochon (Kremlin Bicêtre), P Khau van Kien (Montpellier). F Leturcq (Cochin), MP Moizard (Tours), N Monnier (Grenoble), C Philippe (Nancy).</p>

PW36-456	<p><b><u>TREAT-NMD UMD PATIENTS' REGISTRIES: FROM PATIENTS TO THERAPY</u></b>  HUMBERTCLAUDE V<sup>2</sup>, TUFFERY-GIRAUD S<sup>3</sup>, HAMROUN D<sup>2</sup>, DESMET FO<sup>1</sup>, LALANDE M<sup>1</sup>, COLLOD-BÉROUD G<sup>1</sup>, LOCHMÜLLER H<sup>4</sup>, CLAUSTRES M<sup>1</sup>, BÉROUD C<sup>1</sup>  (1) INSERM U827 F-34000, Montpellier, FRANCE. (2) CHU Montpellier, Laboratoire de Génétique Moléculaire, Montpellier, FRANCE. (3) Université Montpellier 1, UFR Médecine, Montpellier, FRANCE. (4) TREAT-NMD network, Newcastle upon Tyne, UNITED-KINGDOM.</p>
<p>To contact the author::  humbertclaude@montp.inserm.fr.</p>	<p>The TREAT-NMD (Translational Research in Europe for the Assessment and Treatment of Neuromuscular Diseases) 'network of excellence' is funded by the European Union and aimed at improving treatment and finding cures for patients with neuromuscular disorders. The development of the TREAT-NMD UMD patients' registries will allow identifying patients with respect to their genetic defect and clinical status. Duchenne-Becker muscular dystrophies and spinal muscular atrophy will be specifically targeted. The primary objective of these European patients' registries is to facilitate the planning of appropriate clinical trials and supports the recruitment of patients. Data collection is performed either from a "patient report" filled out directly by the patient (or his legal representative) or from a "professional report" filled out by a clinician and/or a geneticist. Three levels of data have been defined: (1) mandatory items (requested for patients' inclusion into the database), (2) highly encouraged items (very important items but not requested for patient's inclusion) and finally (3) optional items (useful for secondary purposes of the registries). The mandatory items contain patient's personal data (encrypted), mutation name (reported according to the international nomenclature system) and clinical data (motor function, scoliosis surgery, steroid therapy (DMD only) and feeding function (SMA only)). In each national registry, curators validate the data in order to maintain high-quality data and to insure the respect of both national and European legislations. Authorized medical experts and researchers will have access to encrypted data if their research project fits the goals of TREAT-NMD and after approval by the TREAT-NMD global registry oversight committee.</p> <p>To our knowledge, this is the first example of such a large international initiative to build patients' registries. In the next years, we will need to convert this try to speed up clinical trials development and a rapid enrollment of patients.</p>