

Col VI Day Summary – 2nd Edition (EN)

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On June 6, 2026, the second edition of Col VI Day took place. This initiative is the result of a global network of patients and institutions seeking to raise awareness of the conditions affecting patients with collagen VI abnormalities. Research presented at the event covered treatments under development, assessment and management of clinical symptoms, population statistics on the prevalence of collagen VI-related muscular dystrophies, and personal accounts from patients and families living with these conditions.

The presentations covered a wide range of topics. Some focused on research that might one day contribute to new therapies. Others addressed diagnosis, registries, orthopedic management, rehabilitation, outcome measures, and related conditions that can resemble COL6-related disease. In short, the meeting demonstrated that progress in COL6 depends on several interconnected elements: understanding disease biology, accurately identifying patients, monitoring them over time, improving everyday care, and preparing reliable tools for future clinical trials.

We congratulate all the organizers, facilitators, moderators, speakers, and attendees. This collective effort encourages us to envision a near future full of possibilities and demonstrates the power of working together—patients, families, and researchers—to go further and contribute to the well-being and improved quality of life of everyone affected by collagen VI-related muscular dystrophies.

A Potential Future Cell Therapy for COL6-Related Myopathies

The first speaker, Professor Hidetoshi Sakurai of the Center for iPS Cell Research and Application at Kyoto University, Japan, presented research into a potential cell therapy strategy for collagen VI-related myopathies. His group is investigating whether cells derived from induced pluripotent stem cells (iPSCs) can help restore collagen VI support in affected muscle tissue. This matters because collagen VI forms part of the structure surrounding muscle cells and, when it is absent or defective/altered, muscle regeneration becomes less effective and fibrosis can develop (rather than

regenerating muscle with elastic fibers, fibrosis involves excessive collagen production that creates rigid, noncontractile tissue, causing pain, stiffness, and loss of mobility).

Professor Sakurai's team tested several types of mesenchymal stromal cells in collagen VI-deficient mice. The most promising results came from iPSC-derived mesenchymal stromal cells. Following transplantation, treated mice showed evidence of collagen VI supplementation, larger regenerating muscle fibers, less fibrosis, and improved performance in functional tests such as grip strength and physical activity. The summary also states that these iPSC-derived cells outperformed mesenchymal cells derived from bone marrow or adipose tissue, and that bone marrow-derived cells showed fibrosis during long-term observation. His team also worked on a xeno-free induction system using HLA-edited universal iPSCs (somatic cells, such as skin cells, are converted into induced pluripotent stem cells/iPSCs and then differentiated into mesenchymal stem cells. These cells are ideal for cell therapy because they have a high capacity for tissue regeneration and immune-system modulation; *xeno-free* means they are derived from human tissues rather than other animals), with the aim of reducing the risk of immune rejection in future clinical applications.

For Families:

This is early-stage research in disease models, not a treatment currently available to patients. The encouraging point is that researchers are testing ways to rebuild the muscle environment affected by collagen VI deficiency, rather than simply treating symptoms. In mice, this approach improved muscle structure, scarring, and strength, which is a positive result, but further safety testing, refinement, and clinical development are needed before we can know whether it may help people with COL6-related conditions. Clinical trials at this research center are expected to begin in 2029.

The National Registry for Understanding COL6 Disease in Russia

The second speaker was Diana Abramova, co-founder of the Russian Registry of Patients with Collagen Disorders and leader of the Russian Association of Patients with Collagen VI Disorders. She presented the development and findings of the Russian registry of patients with collagen VI-related myopathies. The registry was established to collect clinical and genetic information from patients affected by

collagen VI-related disorders and associated conditions, helping build a clearer picture of the disease in Russia.

The number of patients in the registry grew from 71 to 203 over two years. Most patients had genetic confirmation, and the largest group carried variants in the COL6A1 gene. The registry also included data on walking ability, respiratory status, contractures, scoliosis, and relationships between genotype (genetic characteristics) and phenotype (clinical characteristics). The study notes that some patients lost the ability to walk during follow-up, while others remained stable, and that respiratory support was generally initiated between ages 5 and 15 when needed. It was also reported that the registry had joined the **Global Registry Network**.

For Families:

Registries may seem purely administrative, but they are one of the foundations of progress in rare diseases. They help answer basic but crucial questions: how many patients there are, which genetic variants are present, how symptoms generally progress, when respiratory or orthopedic problems emerge, and which patients may be eligible for future studies or clinical trials. For families, participation in well-structured registries can increase disease visibility and support better care and research planning. The main message is that rare diseases cannot be properly understood without careful collection of patient data and long-term follow-up.

The Interplay Between MRI and Needle Electromyography in COL VI Diagnosis

Dr. Sergey Kurbatov's presentation addressed the challenges and tools involved in diagnosing collagen VI-related myopathies, focusing on how these conditions can mimic spinal muscular atrophy (SMA). He noted that patients on the Ullrich–Bethlem spectrum often experience diagnostic delays exceeding six years and consult multiple specialists before receiving an accurate diagnosis. He emphasized that although muscle magnetic resonance imaging (MRI), with its “tiger-skin” pattern, and needle electromyography are essential tools, they are not entirely specific and can show neurogenic patterns that lead to misdiagnosis and delay access to appropriate therapies.

Kurbatov presented detailed case studies, including patients initially diagnosed with SMA or Duchenne muscular dystrophy because of conflicting electrophysiological findings. The research shows that recessive variants in the COL6A3 gene, especially the 7447A>G mutation, are strongly associated with this phenotype mimicking SMA type 4, often without the classic contractures of collagen-related disease. The presentation summary concluded that diagnosing inherited muscle diseases is a multistage process in which clinical exome sequencing becomes essential for distinguishing these conditions and avoiding inappropriate treatments.

For Families:

Dr. Kurbatov emphasized that the journey toward a diagnosis of collagen VI-related muscular dystrophy is often marked by many years of uncertainty and possible confusion with other conditions, such as SMA. For families, the central point is clear: investing in an accurate genetic diagnosis does more than give the disease a name; it is the decisive step toward ending this distressing wait and ensuring access to the most appropriate care possible.

COL12A1-Related Myopathy as a Differential Diagnosis for COL6 Disorders

Dr. Evgenia Melnik, a neurologist and geneticist at a referral center in Moscow, presented COL12A1-related myopathy as a crucial differential diagnosis for COL6-associated conditions. Her presentation highlighted that some diseases can be clinically very similar to COL6 myopathy despite having different genetic causes.

She explained that although there is significant overlap between COL12A1 and COL6 myopathies, certain clinical features help distinguish them. These include gingival hypertrophy, earlier and more severe respiratory involvement in severe recessive cases, and distinct patterns on muscle MRI. While COL6 myopathy is classically associated with a “tiger-skin” or “outside-in” pattern, COL12A1 disease may show diffuse reduction in muscle volume with thickening of the epimysium on MRI. Dr. Melnik presented data from a Russian cohort of seven patients from five families identified through whole-exome sequencing, with several previously unreported genetic variants discovered.

For Families:

The practical message is that diagnosis in rare neuromuscular diseases is complex. Two patients may have very similar symptoms but entirely different genetic causes. This rigor is essential because prognosis, family counseling, research eligibility, and treatment strategies depend directly on a correct diagnosis. The presentation reinforces the crucial importance of genetic testing—especially whole-exome or whole-genome sequencing—when the diagnosis is unclear. For families, an accurate diagnosis is not just a “name” for the disease; it is the necessary foundation for more appropriate care, a better understanding of the clinical journey, and access to future treatment and research opportunities.

Orthopedic Management in Collagen VI-Related Muscular Dystrophies

Dr. Dmitry Feklistov shared his clinical experience in orthopedic management of patients with collagen VI-related muscular dystrophies, addressing complications that profoundly affect everyday life, such as contractures, scoliosis, and hip instability. He explained that these are not isolated events but part of a self-reinforcing cycle: collagen VI deficiency triggers muscle weakness and mitochondrial dysfunction, which in turn activate fibroblasts and promote fibrosis (tissue stiffening). Dr. Feklistov stressed that although conservative strategies, such as orthoses, can delay progression, surgical interventions become necessary at specific times, particularly to protect respiratory function and ensure appropriate posture.

For Families:

The essential message is that orthopedic follow-up should not be viewed as optional or as something to consider only when a serious problem arises; it is an indispensable pillar of daily care. Complications such as contractures or spinal deformities affect not only mobility but also breathing, sleep, comfort, and independence. Prevention should always be the focus: regular monitoring of range of motion, ongoing assessment of the spine and hips, and timely use of supportive devices (such as orthoses or standing frames) are powerful tools for preserving function over time. Orthopedic care should be seen as an ally in achieving the best possible quality of life, through a preventive, continuous process integrated with each patient's functional goals.

Rehabilitation and Assistive Devices in Collagen VI-Related Muscular Dystrophies

Physiotherapist Alexander Stevanovich addressed one of the greatest everyday challenges: the delicate balance between keeping patients active and avoiding excessive strain. He explained that in collagen VI-related conditions there is a practical paradox: both inactivity and intense physical exertion can be harmful. Rehabilitation should therefore focus not only on therapy sessions but also on integrating stretching, aquatic physiotherapy, occupational therapy, and proper positioning throughout the daily routine. The presentation emphasized that orthopedic support and devices—from wheelchairs to standing systems—are essential for protecting the body and maintaining function.

For Families:

The central message is that rehabilitation is not about “pushing the limits” or demanding more than the body can give; it is about discovering how to use existing strength to maintain independence. It is essential to dispel misconceptions about assistive devices: a wheelchair or orthosis is not a sign of surrender or “loss,” but a powerful tool for conserving energy and quality of life. Care also extends far beyond the clinic: how patients are positioned when sitting or lying down during the rest of the day is just as important as exercise itself. Successful rehabilitation becomes an integral part of the routine while respecting each person's actual needs and pace.

Outcome Measures in Patients with Collagen VI-Related Muscular Dystrophy

Dr. Numan Bulut discussed the critical need for standardized *outcome measures*, used by clinicians and researchers to assess muscle function, mobility (such as the six-minute walk test or functional scales), and overall health status (including scoliosis and respiratory function). The main message was clear: to advance treatment of rare diseases, we need a common language. Reliably and consistently assessing progression is the only way to understand whether a patient is stable, improving, or losing function; it is also the essential foundation for future clinical trials to determine whether a drug truly works.

For Families:

Measuring outcomes may seem bureaucratic and removed from real life, but for families it means reassurance and preparedness. These assessments allow us to understand the natural history of the disease accurately and how each patient's care is progressing. More than just data, these tools translate clinical reality into scientific evidence; without them, it is impossible to rigorously test therapies or know what truly affects the lives of people with the condition. Participating in standardized assessments is an active step toward the future, helping build the evidence base needed to develop effective treatments later on.

Understanding Why Muscles Weaken in Collagen VI Disease

Dr. Payam Mohassel presented research into the molecular mechanisms that lead to muscle weakness in collagen VI-related conditions. His work investigates how the absence of collagen VI disrupts the environment around muscle cells, focusing specifically on the TGF-beta signaling pathway. In healthy tissues, collagen VI helps keep this pathway under control; when it is absent, the system fails, allowing excessive TGF-beta activation that directly contributes to muscle damage and fibrosis (tissue stiffening). Dr. Mohassel also presented preliminary data on losartan—a well-known blood-pressure medication—which showed the ability to reduce this excessive signaling in mouse models, resulting in less fibrosis and improved muscle regeneration.

For Families:

This presentation helps clarify one of the reasons behind disease progression: collagen VI is not merely a supporting structure; it also regulates signals vital to muscle health. When it is missing, inflammation- and fibrosis-related signals become overactive. Although the idea of using losartan may attract interest because it is an existing medication, caution is essential: these results are preliminary and have only been tested in animal models. Much more research is needed to determine whether this approach could be safe and effective for people with COL6-related conditions. This is not an encouragement to use medication, a recommendation to self-medicate, or medical advice; it is solely a description of the research presented.

Building Human Muscle Models in the Laboratory

Dr. Malte Tiburcy shared his tissue-engineering work using human pluripotent stem cells to create functional muscle rings in the laboratory. These models make it possible to simulate collagen VI-related muscular dystrophy realistically. By introducing specific mutations into these cells, the team can observe reduced contractile function and abnormal regenerative responses compared with healthy cells. This drug-screening system enables researchers to test different therapies in parallel, accelerating the identification of promising compounds more safely and efficiently before any human testing.

For Families:

This presentation focuses on creating essential tools to accelerate scientific progress. Before any treatment reaches patients, researchers need reliable systems to test the safety and effectiveness of new therapies. The positive point is that these laboratory muscle models can already demonstrate clear signs of the disease (such as weakness and impaired regeneration), making the search for new drugs much more robust and faster. This is a fundamental technical step toward ensuring future therapies are well understood before they are offered to patients.

Why Tendons May Be Directly Affected in Collagen VI Diseases

Researcher Vittoria Cenni, PhD, offered a crucial perspective by focusing specifically on the role of collagen VI in tendons. She explained that tendon problems are not merely indirect consequences of muscle weakness but a primary part of disease biology. Collagen VI is essential for organizing tendon structure and for how cells sense and respond to physical tension (a process called mechanotransduction). Patient samples showed changes in tendon dimensions and irregularities, as well as difficulties in cell migration during injury repair, helping explain why tendon function is compromised at the level of the tissue's underlying structure.

For Families:

This explanation is illuminating: contractures and joint problems are not simply the result of “insufficient physiotherapy” or inactivity; they are part of the condition's own biology. This reinforces the need for careful orthopedic follow-up (as discussed earlier)

and adapted rehabilitation that respects these biological characteristics of tendons. Understanding that the problem affects the whole system—muscle, tendon, and muscle matrix—helps us set more realistic expectations for contracture management and plan care that considers the patient as a whole, rather than only muscle strength or its absence.

Addressing Mitochondrial Dysfunction in Collagen VI Myopathies

Professor Paolo Bernardi presented treatment strategies focused on what happens inside muscle cells. Although the genetic defect manifests outside the cell (in the extracellular matrix), it triggers severe internal problems, especially in calcium regulation, mitochondrial function (mitochondria are the cells' energy *powerhouses*), and muscle fiber survival. The absence of collagen VI causes calcium overload, which damages mitochondria and leads to cell death. The team developed new compounds, such as ProteRO1, designed to protect these mitochondria. In mouse studies, treatment quickly showed promising results: reduced damage, less cell death, and improved muscle strength.

For Families:

This section focused on events at the cellular level: how a collagen VI defect outside the cell ultimately “steals energy” and damages structures inside muscle. The encouraging point is that compounds are already being studied to protect these “energy powerhouses” (mitochondria), with positive results in animal models. It is important to remember that ProteRO1 remains experimental and requires further studies before use in humans. The broader message is that future COL6 treatments will be varied: some will seek to replace collagen, while others, like this one, will seek to protect cells from the consequences of its absence.

Orthopedic Surgical Outcomes in Patients with Collagen VI Disorders

Melania Gianotta's presentation focused on optimizing surgical outcomes for patients with collagen VI myopathy, with particular emphasis on scoliosis surgery. The specialist explained that scoliosis is a common complication that progresses rapidly, often by more than 26 degrees per year, and can severely affect respiratory function by reducing chest-wall compliance. Preoperative respiratory management is crucial,

involving cough-assist machines and noninvasive ventilation (NIV), especially when vital capacity falls below 50%. She mentioned the experimental use of salbutamol to try to improve muscle strength and delay disease progression before major interventions.

Regarding the surgical approach, Gianotta explained that the optimal timing of surgery is key, with surgery generally indicated when the Cobb angle exceeds 40 degrees or when there is sitting imbalance and pain. Anesthetic management is particularly complex because of the risks of difficult airway management, hyperkalemia, and postoperative respiratory complications. The presentation highlighted the need for a multidisciplinary team to prepare patients psychologically, optimize their nutritional status, and ensure early postoperative mobilization to preserve residual mobility and improve quality of life.

For Families:

The main message is that surgical safety comes from careful planning. Scoliosis surgery in collagen VI disease is a delicate step but can offer major benefits when carried out properly. Preparation is key: caring for lung health and nutrition before the procedure and having a medical team familiar with the condition's specific characteristics. This collective effort aims not only to correct the spine but, above all, to protect respiratory capacity and ensure greater comfort and quality of life over the long term.

Molecular Structure of Collagen VI Microfibrils

Clair Baldock's presentation focused on analyzing the molecular structure of collagen VI microfibrils using cryo-electron microscopy (cryo-EM). She explained that, unlike common fibrillar collagens (such as collagen I), collagen VI has a distinctive “beads-on-a-string” structure (beaded microfibrils). Using recent advances in microscopy technology, her team generated high-resolution maps revealing the precise positions of nearly all amino acids in the structure, making it possible to understand how the three alpha chains ($\alpha 1$, $\alpha 2$, and $\alpha 3$) join to form the initial heterotrimer.

Baldock described the discovery of a specific coiled-coil region and the presence of disulfide bonds that are essential for stabilizing heterotrimer formation. Through experiments with laboratory-produced “mini-collagens,” her team demonstrated that mutations altering this region or removing cysteines prevent proper protein assembly. The presentation also showed the complete structure of the assembled microfibril, revealing how N-terminal and C-terminal domains interact between adjacent tetramers, providing a valuable resource for locating pathogenic variants and understanding assembly defects in patients.

For Families

Although this may seem distant from everyday life, mapping the structure of collagen VI is essential for science. By understanding exactly where protein assembly fails, researchers can better identify the causes of the disease and design more effective therapies. This technical knowledge provides the foundation needed to act directly on the root of the problem in the future and help the body restore its function more effectively.

Optimized Cell Models: Advances in Diagnosis and Precision Medicine

Dr. Valérie Allamand's presentation focused on optimizing skin fibroblast models to improve diagnosis and treatment evaluation for collagen VI myopathies. She introduced the “Opti-MEC” method, which uses specific molecules and crowding agents to mimic the environment of human tissues in the laboratory, prompting cells to produce a much more robust and organized extracellular matrix network than with traditional methods. This technique reduces variability in results between donors and allows much clearer visualization of structural abnormalities in patients' microfibrils, helping confirm uncertain genetic diagnoses.

On the therapeutic side, Dr. Allamand demonstrated how these optimized models are used to test precision-medicine strategies. In cases of heterozygous mutations, small interfering RNAs (siRNAs) proved effective at silencing the disease-causing allele, allowing the cell to use only the healthy copy to rebuild the collagen network. Her team is also investigating suppressor tRNAs to treat severe homozygous mutations, seeking

ways to “bypass” genetic errors and restore production of the full-length protein, although this latter approach still faces challenges in delivery efficiency to cells.

For Families

Dr. Valérie Allamand's presentation highlights an important advance in how we study the disease in the laboratory. By creating models that more faithfully simulate the real environment of human tissues, researchers can better visualize the structural defects caused by collagen VI abnormalities and test “precision medicine” treatments. This means seeking personalized strategies—such as silencing the nonfunctional gene copy or attempting to correct genetic errors—so that the cell resumes production of the correct protein. This fundamental technical work brings science closer to future, more targeted and effective therapies.

Global Patient Registry: Connecting Data to Accelerate Solutions

Dr. Jessica Moraes of the John Walton Muscular Dystrophy Research Center (Newcastle University) focused on the importance and operation of the Global Registry for Collagen VI-Related Dystrophies. She explained that the registry is an organized database connecting patients, researchers, and industry, enabling faster and more efficient identification and recruitment of participants for studies and clinical trials, especially in rare diseases where patients are geographically dispersed. In addition to facilitating research, the registry generates real-world evidence from demographic data, genetic diagnoses, and functional outcomes reported by patients themselves or their doctors, directly contributing to better standards of care and preparation for future clinical trials.

The registry currently has 501 participants from 57 countries, mostly from the United States and Great Britain, with the predominant age range being 0–12 years. The data show that the most commonly reported phenotype is Bethlem, followed by Ullrich, and that mutations in the *COL6A1* gene are the most prevalent among registered participants. Dr. Moraes emphasized that the registry is overseen by a steering committee including patients, association representatives, and specialist clinicians, ensuring that anonymized/non-identifiable data are used ethically and for the benefit of the community. She concluded by encouraging new patients to register and inviting

researchers to use this resource to strengthen the global collagen VI research ecosystem.

CollaBlot Technique: Assessing Collagen VI Organization

Dr. Virginia Arechavala-Gomez (a member of Fundación Noelia) presented CollaBlot, an innovative technique developed to quantify the structural organization of collagen VI in patient fibroblasts. Unlike traditional methods such as Western blotting, which only measure the amount of protein and destroy its structure, Col-Blot allows the intact extracellular matrix to be transferred onto a membrane, enabling analysis of microfibril length and connectivity using image algorithms.

This approach is fundamental for diagnosis and therapeutic development because it can distinguish mechanisms such as “haploinsufficiency” from “dominant-negative” effects, in which protein is produced but does not organize correctly. She also emphasized that the technique is already being used to assess the effectiveness of treatments such as antisense oligonucleotides (ASOs), checking whether they can restore the formation of functional, well-structured collagen networks.

For Families:

Dr. Virginia's presentation introduced CollaBlot, an innovative technique that changes how we assess the quality of the collagen produced. While traditional methods only count “how much” protein is present, this new approach examines whether collagen is actually well organized and connected. This is a crucial advance for the future, as it allows us to test much more precisely whether new treatments are genuinely restoring the collagen network in the body. It is a precision tool that helps us determine whether a therapy is working as intended.

3D Human Muscle Models: A Step Forward in Research

Yunsong (Cathy) Jiang, PhD, presented an innovative 3D human muscle platform developed in Professor Francesco Saverio Tedesco's laboratory. These “miniature muscles” combine muscle cells with fibroblasts, creating a much more realistic extracellular matrix environment than traditional 2D cultures. When healthy muscle cells were combined with fibroblasts from patients with UCMD or Bethlem, the tissues

developed macroscopic contracture-like changes. The disease models also exhibited fragmented collagen VI networks, increased TGF-beta signaling, and impaired contractility under electrical stimulation. This is the first platform to reproduce multiple key features of collagen VI myopathies in a human 3D system, making it a crucial tool for testing future therapies.

For Families:

This is an important technological leap: researchers can now observe, in miniature and outside the body, how the disease behaves and how tissues respond to it. By creating a model that “mimics” real contractures and muscle weakness, the research team gains a powerful tool for testing potential treatments before they even reach clinical trials. This significantly accelerates the search for solutions, allowing scientists to validate new therapies with much greater precision, speed, and safety.

Final Presentations

Caroline LeMay and Gustavo Dziewczaploski delivered the closing presentations. The first was a personal testimony sharing Caroline's life, education, and personal, family, and professional development as a patient living with the conditions and barriers imposed by collagen VI disease, while leading a full, complete, and successful life despite the obstacles posed by physical disability.

Gustavo concluded the event by reviewing the importance of investment in collagen VI research and the results it has produced in recent years, driving and developing clinical trials, accelerating scientific development, and highlighting the *seed funding* role played by foundations worldwide in raising the visibility of research.

Conclusion

The most important conclusion from this event is a balanced one: genuine scientific progress is underway, with various groups working on biological mechanisms and the development of new therapies. At the same time, many of these approaches are still in their early stages. The message for families is therefore one of hope combined with practical care: immediate priorities remain accurate diagnosis, regular monitoring, rehabilitation adapted to everyday routines, and participation in structured registries.

These elements not only support patients' well-being today but also provide the necessary foundation for science to advance toward tomorrow's therapies.

With this, we conclude an event of fundamental importance to the global collagen VI community. By bringing together patients, researchers, doctors, physiotherapists, and families, each discussion helped strengthen hope for a more promising tomorrow and broaden the horizons for new and varied therapeutic strategies for the benefit of all patients.

