Current and emerging management options for patients with Morquio A syndrome

Mohamed F Algahim
G Hossein Almassi
Division of Cardiothoracic Surgery, Medical College of Wisconsin, Milwaukee, WI, USA

Abstract: Morquio A syndrome is a lysosomal storage disease associated with mucopolysacchari
dosis. It is caused by a deficiency of the lysosomal enzyme, N-acetylgalactosamine-6-
sulfate sulfatase, which leads to accumulation of keratan sulfate and condroitin-6
sulfate in multiple organs. Patients present with multisystemic complications involving the musculoskeletal,
respiratory, cardiovascular, and digestive systems. Presently, there is no definitive cure, and current
management options are palliative. Enzyme replacement therapy and hematopoietic stem cell
therapy have been proven effective in certain lysosomal storage diseases, and current investiga-
tions are underway to evaluate the effectiveness of these therapies and others for the treatment
of Morquio A syndrome. This review discusses the current and emerging treatment options for
Morquio A syndrome, citing examples of the treatment of other mucopolysaccharidoses.

Keywords: lysosomal, storage disease, mucopolysaccharidosis

Introduction
Mucopolysaccharidoses (MPSs) are inherited lysosomal storage disorders caused by
enzymatic defects in the catabolism of glycosaminoglycans (GAGs). Presently, there
are eleven different enzymatic defects associated with seven different types of MPS.
The lack of enzymatic activity leads to tissue-specific intracellular accumulation of
substrates. Clinically, patients present with multisystemic complications associated with
organ-specific dysfunction secondary to the intracellular substrate accumulation.

In 1929, Luis Morquio, of Uruguay, described four family members with features
of dysostosis multiplex, corneal clouding, aortic valve disease, and urinary excretion
of keratan sulfate.1 MPS type IV, also known as Morquio syndrome, is an autosomal
recessive disorder and is subclassified into type IV-A (MPS IV-A, Morquio A) and
type IV-B (MPS IV-B). Morquio type IV-A is caused by a defect in N-acetylglacto-
samine-6-sulfate sulfatase (GALNS; EC 3.1.6.4) – a lysosomal enzyme essential
catabolism of keratan sulfate (KS) and condroitin-6-sulfate (C6S); MPS IV-B is
caused by β-galactosidase-1 deficiency essential for the catabolism of glyconjugates
with terminal β-galactosyl residues. Recent molecular analysis demonstrated that most
of MPS IV-A cases result from misfolding of GALNS.2 The inability to catabolize
GAGs, such as KS and C6S, results in their accumulation within the lysosomes and
subsequent cellular and organ dysfunction. As a consequence, patients with Morquio
syndrome present with progressive complications specific to cellular involvement of
ossseous, corneal, valvular, and other organ-specific tissue.

The incidence of MPS IV-A in the United States has not been established. In
British Columbia, Canada, the estimates are 1 per 200,000 live births, and in Europe,
the incidence varies from 1 per 76,000 in Northern Ireland to 1 in 450,000 live births in The Netherlands and Portugal.\textsuperscript{3-5} Neonatal screening for lysosomal storage diseases will allow for better quantification of the incidence of MPS IV-A.

Patients with MPS IV-A appear normal at birth, but initial presenting symptoms often manifest after 1 year of age.\textsuperscript{6} Musculoskeletal complications are the most common presenting features of MPS IV-A; patients may also develop complications involving the cardiac, respiratory, and digestive systems. Unlike most other MPS conditions, MPS IV-A does not affect neurologic function, and patients maintain normal intellect, although behavioral problems with anxiety, depression, and attention have been associated with MPS IV-A.\textsuperscript{7} Morbidity can vary from mild to severe disease – those with severe disease present at an earlier age and have more pronounced and rapidly progressive comorbidities, while patients with the attenuated form have a slower rate of progression. Yet the cumulative effect of the disease progression in the mild cases leads to debilitating comorbidities by adulthood. Patients with severe disease die in the second or third decade, while mild disease allows for life into the seventh decade; most patients die of pulmonary infections, cervical instability, and valvular heart disease.\textsuperscript{8}

There is no definitive cure for Morquio syndrome; the current standard of care is medical and surgical management of the involved systems with the goal of palliation, prevention, and slowing of the progression of complications.\textsuperscript{9,8} Once diagnosed, treatment of Morquio syndrome requires a system-specific and multidisciplinary approach, often involving primary care physicians, orthopedists, pulmonologist, cardiologists, and anesthesiologists. Other MPS and lysosomal storage diseases – Hurler syndrome (MPS I), Hunter syndrome (MPS II), Maroteaux-Lamy syndrome (MPS VI), Gaucher disease, Fabry disease, and Pompe disease – are currently being treated with enzyme replacement therapy (ERT). Hematopoietic stem cell therapy (HSCT) has played an important role in the treatment of Hurler syndrome and is currently under intensive study for the treatment of other MPSs. The role of ERT and HSCT for the treatment of MPS IV-A is also under investigation.

The present review discusses the complications of MPS IV-A and reviews the current and emerging treatment options.

**Complications and current management options**

The musculoskeletal system is often first to be afflicted and involves the appendicular and axial skeletons. Radiologic evidence of osseous involvement can be diagnostic as early as 6 months of age and often precedes physical manifestation of MPS IV-A.\textsuperscript{8,9} Obvious orthopedic involvement often becomes evident between 2 and 3 years of age, and most patients are diagnosed by 5 years of age.\textsuperscript{6} Patients often present with weakness, stunted growth, dwarfism, pectus carinatum, and genu valgum. Ligamentous laxity and direct bone involvement lead to a delay in ability to walk, limb instability, and a waddling gait. These findings result from accumulation of KS within bone, cartilage, and ligaments that lead to defects in tissue formation. As the disease progresses, patients develop more serious orthopedic complications. The most serious musculoskeletal manifestation of MPS IV-A is odontoid dysplasia and C1-2 instability, which is found in all patients with MPS IV-A. This predisposes to atlantoaxial subluxation with cervical cord compression and progressive myelopathy that leads to gradual or abrupt neurologic deficits, such as muscle weakness, cervical myelopathy, bowel and bladder dysfunction, hemiplegia, quadriparesis, and death.\textsuperscript{10} The risk of cervical spinal cord compression poses a dilemma when the need for intubation arises in patients with cervical instability, as there is a significant risk of iatrogenic damage to the cervical cord at the time of intubation. The risk is further compounded as most patients require multiple surgeries and undergo major surgical interventions by the age of 10, with the neck being the most common musculoskeletal surgical site.\textsuperscript{6,11} Magnetic resonance imaging is used to screen for involvement of the cervical spine and prophylactic occipito-cervical fusion has been recommended to prevent the associated complications.\textsuperscript{12-14}

Difficulty in perioperative airway control is further compounded by previous cervical fusion, chest habitus, short neck, and GAG deposition in the tissues of the airway.\textsuperscript{15} These factors may also delay extubation and predispose patients to tracheostomy. A thorough preoperative evaluation and plan, involving an anesthesiologist experienced with MPS, are essential ahead of surgical intervention requiring intubation.\textsuperscript{15-17} In our experience with an adult MPS IV-A patient requiring intubation for surgery, awake oral fiberoptic intubation was necessary due to diffuse abnormalities of the vertebral bodies and disc spaces, and thoracolumbar kyphosis and dextroscoliosis.\textsuperscript{18} Aside from the aforementioned issues involving operative airway management, involvement of the respiratory system in MPS IV-A predisposes patients to serious complications. Excessive KS deposition in the airway tissue, along with kyphoscoliosis, leads to progressive and debilitating restrictive and obstructive lung processes.\textsuperscript{8} Patients with MPS IV-A develop airway obstruction and sleep
apnea and are prone to frequent upper respiratory tract infections and pneumonia, which can be a source of significant morbidity.\(^6,8\) Formal sleep studies should be undertaken to evaluate the severity of sleep apnea; some patients require continuous positive airway pressure devices for obstructive sleep apnea, and home oxygen may be necessary in severe disease. Breathing exercises should also be encouraged. In patients with frequent respiratory infections, seasonal influenza vaccine may be offered, and a low threshold for starting antibiotic regimen when infection is evident is justified; tonsillectomy and adenoidectomy are often indicated in most patients to further prevent infections.\(^6,8,19\)

Cardiovascular complications are common in MPS and can affect the cardiac valves, the coronary arteries, and the aorta.\(^20–22\) Excessive GAG accumulation in valve, coronary, and aortic tissue leads to thickening of the tissue and subsequent valvular dysfunction, coronary artery intimal sclerosis, and weakening of the aortic wall. Specifically, the accumulation of GAG within tissue is associated with activation of toll-like receptors and inflammatory pathways that likely contribute to the associated cardiovascular complications that predispose patients to valvular stenosis or insufficiency, ischemic heart disease, and aortic aneurysms.\(^20–23\) These processes are progressive and patients present with symptomatic disease in adulthood. Valvular disease is a common complication in MPS; the left-sided heart valves are affected more than right-sided heart valves, and the mitral valve is most often involved.\(^20,24\) Surgical correction of symptomatic valvular disease is warranted but can be complicated, and at times avoided because the severe comorbidities associated with the late presentation impart significant and cumulative surgical risks. In MPS IV-A, the aortic valve is most often involved, although the mitral valve is also frequently involved; the pathophysiology is similar to that of other MPSs and is secondary to excessive KS deposition in the valve tissue and likely activation of inflammatory processes.\(^23,25,26\) We, amongst others, were successful in aortic valve replacement in a patient with Morquio syndrome.\(^18,27,28\)

Involvement of other organ systems in patients with MPS IV-A predisposes to non–life-threatening, but significant, morbidities. Patients develop visual disturbances from excessive GAG deposition in corneal tissue. This leads to corneal clouding with increased light scatter and photophobia; wearing darkened glasses and peaked cap are recommended to alleviate the symptoms.\(^8\) Hearing loss is common in MPS IV-A. Several factors contribute to the severity of hearing loss, which is due to both conductive and neurosensory deficits. Symptoms of hearing loss are associated dysostosis of the auditory bones and recurring middle ear infections that cause scarring and abnormalities in the inner and middle ears.\(^8,19\) Patients with severe recurring ear infections may benefit from early placement of ventilating tubes, although many patients ultimately require hearing aids.\(^8,19\) Patients are also predisposed to dental problems. MPS IV-A patients have unique dental features with small and wide-spaced teeth, spade-shaped incisors, and thin and weak enamel. Patients are predisposed to frequent caries and require meticulous hygiene; prophylactic antibiotics for bacterial endocarditis are necessary in patients requiring dental treatment.

**Emerging treatment options**

**ERT**

The concept of ERT was first described in 1964 by Christian de Duve when he speculated, “… any substance which is taken up intracellularly in an endocytic process is likely to end up within lysosomes. This obviously opens up many possibilities for interaction, including replacement therapy.”\(^29,30\) In-vivo and in-vitro studies have demonstrated hydrolysis of sucrose in acid-maltase deficient cells of Pompe disease treated with the enzyme interlase.\(^29,31\) This corroborated the idea of de Duve and led to other important studies in the early development of ERT. The concept of lysosomal storage diseases was new at the time of these studies, and significant progress was made after the identification and purification of the deficient enzymes of several lysosomal storage diseases.\(^29\) Aside from Pompe disease, many of the early studies were of Hurler syndrome, Hunter syndrome, inclusion cell disease, and Gaucher type 1. Further progress was made after successful identification of the recognition signal essential for intracellular uptake of the deficient enzymes. This was demonstrated with glucocerebrosidase deficiency in Gaucher type I, which became the first lysosomal storage disease to be treated with ERT. Of the MPSs, the first to be treated with ERT was Hurler syndrome (MPS I) using recombinant human \(\alpha\)-L-iduronidase. Presently, ERT is being used to treat patients with MPS I, MPS II, MPS VI, Fabry, Gaucher, and Pompe disease. ERT for the treatment of MPS IV-A is currently under investigation.

ERT is a lifetime therapy that involves regular intravenous infusions of the recombinant enzyme. Therapy is often associated with infusion reactions that vary from headache, flushing, fever, and/or urticaria to potentially life threatening anaphylactic reactions. Such reactions are due to the development of antibodies against the recombinant enzyme; the incidence may increase concomitantly with the increase in dosage.\(^32–36\) If such reactions become limiting, patients may...
require pretreatment with anti-pyretics and/or anti-histamines in order to prevent severe anaphylactoid reactions; patients may be able to be desensitized over time as well. Therapy is therefore given in a controlled hospital setting, although a home infusion regimen has been described as a feasible and safe alternative for some patients.

ERT has demonstrated substantial improvements in disease-related comorbidities of MPSs, but ERT does not cross the blood–brain barrier, and the effects on neuropsychological and developmental deterioration have been suboptimal. In patients with Hurler syndrome, treatment with recombinant human α-L-iduronidase results in decreased lysosomal storage in the liver and significant improvement in hepatosplenomegaly; improvement in maximal range of shoulder flexion and elbow extension as well as improvement in ambulation, and improvement in sleep apnea. In Hunter syndrome, compared with placebo, patients treated with recombinant human iduronate-2-sulfatase were able to walk greater distances on the 6-minute walk test, had an increase in the percentage of predicted forced vital capacity, and an increase in absolute vital capacity. ERT was approved for Hunter syndrome in the United States and Europe in 2006 and in Japan in 2007. Similar improvements have also been demonstrated in patients treated with human recombinant arylsulphatase B for Maroteaux-Lamy syndrome. These patients experienced clinical improvement in walking and stair climbing, and improved joint range of motion; patients also demonstrated improvement in pulmonary function. ERT in the treatment of these MPSs demonstrated a notable decrease in urinary GAG levels. ERT has not demonstrated significant improvements in neurologic deterioration in MPS patients. In all three MPSs treated with ERT, patients developed some degree of infusion-associated reaction and antibody formation to the recombinant enzyme; although, patients with severe Maroteaux-Lamy syndrome tolerated higher doses of recombinant enzyme therapy and had greater clinical gains. Furthermore, in sibling case studies of all three of the above MPSs treated with ERT, improved response and benefits in clinical outcomes were demonstrated in the younger siblings diagnosed at birth and started on ERT in the first 6 months of life. These findings highlight the importance of early diagnosis and associated positive response to early treatment of MPS.

Continued understanding of ERT and the disease process of the lysosomal storage diseases has set the stage for further application of the treatment in other MPSs. ERT for MPS IV-A is ideal given the lack of neurologic deterioration in these patients. Current investigations to isolate a suitable recombinant GALNS for replacement therapy in humans are underway, and preliminary results in animal models are promising. A knockout mouse model of MPS IV-A has been successful; and GALNS enzyme has been produced and purified using Chinese hamster ovary (CHO) cells and is a source of selectively secreted human recombinant enzyme. Another potential source of purified recombinant GALNS enzyme under investigation is that derived from *Escherichia coli*. These findings have allowed for in-vivo studies of ERT and have set the stage for clinical studies in humans. In an in-vivo study of an MPS IV-A mouse model, with 12 weeks of intravenous treatments with two recombinant human GALNSs produced in CHO cell lines, there was improved lysosomal storage in visceral organs, heart valves, ligaments, and connective tissue; there was also a dose-dependent clearance of storage tissue in the brain, and normalization of blood KS levels. Although ERT is considered unable to cross the blood–brain barrier, the dose-dependent improvement in neurologic response to ERT in the mouse model has been observed by others and is associated with longer duration of treatment. In humans, much of the studies of ERT are early in the investigatory process, and data are yet to be published. A human recombinant enzyme, BMN 110 (BioMarin Pharmaceuticals Inc, Novato, CA, USA), is currently under investigation for use in humans. A Phase I/II human multicenter, open-label, dose-escalation study to evaluate safety, tolerability, and efficacy of BMN 110 in patients with MPS IV-A has been completed, and results have yet to be published (NCT00884949). Presently, there are several ongoing multicenter and multinational studies to investigate the effects of BMN 110 on MPS IV-A patients, and include: a Phase II study specific to patients with limited ambulation (NCT01697139); a randomized, double-blind, pilot study assessing the safety and physiologic effects of BMN 110 (NCT01609062); and several studies to assess long-term effects and safety of BMN 110 (NCT01242111, NCT01415427, NCT01275066), including those less than 5 years of age (NCT01515956). Furthermore, the response to BMN 110 therapy, and potentially other recombinant enzymes, was evaluated in a study of biomarkers of MPS IV-A; alpha-1-antitrypsin, lipoprotein(a), and serum amyloid P were reported as suitable candidate biomarkers, in addition to KS. While much work has yet to be done assessing ERT for the treatment of MPS IV-A, substantial progress has been made. The outcomes of the aforementioned clinical trials will dictate the role of ERT as a treatment option for MPS IV-A in the near future.
HSCT

The basis of HSCT for the treatment of MPS and other inherited metabolic disorders was established in 1968 when Fratantoni, Hall, and Neufeld demonstrated correction of biochemical defects of skin fibroblasts from patients with Hunter and Hurler syndromes when these cells were mixed with each other or normal cells.53 Later studies with transfection of plasma and leukocytes demonstrated improvement in degradation of GAGs in patients with Hurler and Hunter syndromes.56,57 In 1980, bone marrow transplant was successfully performed in a 1-year-old boy with Hurler syndrome (described below).58

HSCT entails transplantation of multipotent hematopoietic stem cells derived from bone marrow, peripheral blood, or umbilical cord blood from a healthy donor to a patient with innate cellular dysfunction to correct the dysfunctional cell line and the associated disease process. Appropriate human leukocyte antigen matching is essential for allogeneic graft transplantation, and complete ablation of the recipient’s immune system is necessary. This predisposes patients to complications of immune deficiency and serious graft-versus-host disease reactions. In spite of improved methods of stem-cell matching, HSCT remains a high risk procedure with substantial morbidity and mortality; therapy is generally reserved for patients with severe phenotype. When considering HSCT, established practice guidelines should be followed and a multidisciplinary approach should be undertaken to ensure optimal benefit and minimal risk of therapy, with the goal of long-term survival and improved quality of life.59,60

HSCT is an evolving alternative for the treatment of MPS. Ongoing replacement of the deficient lysosomal enzymes is achieved by transplanting the enzyme-deficient cell line with enzyme-competent donor cells capable of gaining access to the affected tissue, including the central nervous system. When compared with ERT, HSCT demonstrated superior reduction in substrate burden, and has been shown to prevent and/or cure associated musculoskeletal and organ-specific complications; unlike ERT, HSCT’s ability to access the central nervous system allows for treatment of neurocognitive degeneration.61 In the first successful bone marrow transplant of a patient with MPS, a 1-year-old boy with Hurler syndrome, the patient developed acute graft-versus-host disease, but 13 months after transplant, there was reversal of hepatosplenomegaly and corneal clouding, leukocyte iduronidase activity increased to that of a heterozygote, and arrest in neurocognitive and developmental deterioration was notable.58,62 The preservation of neurocognitive and intellectual development in patients with Hurler syndrome treated with HSCT has been established with more recent studies, and is considered one of the most important benefits of HSCT.52-64 Other benefits of HSCT in Hurler syndrome include: improvement in hearing, joint mobility, respiratory function, and cardiac function.62 Given the associated high risk of morbidity and mortality of HSCT, the current guideline recommendations of the International Consensus Panel on the Management and Treatment of Mucopolysaccharidoses I indicate a multidisciplinary approach on the decision to pursue HSCT; and HSCT must be performed early in the disease course – less than 2 years of age and before developmental deterioration begins – and is limited to patients with an intelligence quotient of ≥70%.62

While the effects of HSCT on Hurler syndrome are well established, HSCT for the treatment of other MPSs, particularly the effect on the neurologic deficits, has yet to be fully elucidated. The delayed presentation of other MPSs and the subsequent late initiation of therapy have been associated with the suboptimal effects of HSCT on neurologic function in certain MPSs. In patients with Hunter syndrome, HSCT demonstrated improvement in visceral and soft tissue involvement, but the effects on neurologic symptoms has not been substantial. Although, in a retrospective study of 21 patients with Hunter syndrome who received HSCT, 9.6 years after treatment, activities of daily living were maintained, improvements in cribriform changes and brain ventricular dilatation were noted, and stabilization of brain atrophy was also noted.63 Consistent with the idea that early diagnosis and initiation of treatment are important, the authors conclude that the effect of HSCT on the brain is optimized by treatment prior to clinical manifestations of developmental delay; and the poor response to HSCT is associated with severity of the syndrome. Investigational data of HSCT for the other MPSs are few, and results for neurocognitive benefits are mixed.52 In patients with Sanfilippo syndrome, HSCT has stabilized disease but with less impact on cognition; in two patients transplanted under the age of 2 years, modest cognitive gains were noted with improvement in behavior and sleeping patterns 3–5 years post transplant.59,66 Patients with Maroteaux-Lamy syndrome have reduced life expectancy and are candidates for HSCT; therapy has demonstrated improvements in hepatosplenomegaly, cardiopulmonary function, visual acuity, and mobility.59,67

The role of HSCT in MPS IV-A is currently investigational. In a 2012 report by the Agency for Healthcare Research and Quality (Rockville, MD, USA) on the status of HSCT for Morquio syndrome and other childhood diseases, it was
concluded that “the strength of the body of evidence is insufficient to draw conclusions on the comparative benefit of single HSCT compared with symptom management and or disease natural history with respect to neurocognitive and neurodevelopmental outcomes for MPS IV-A.” As it relates to MPS IV-A, HSCT has not been shown to substantially treat the severe skeletal manifestation; this is likely due to lower vascularization of bone tissue. But, the improvement and reversal of the somatic complications of other MPSs treated with HSCT substantiate consideration of HSCT for the treatment of the hepatic, cardiovascular, respiratory, and digestive complications of MPS IV-A. The use of HSCT in MPS is limited to those with a severe phenotype with neurologic involvement. Although HSCT has demonstrated superiority to ERT, its use is limited by a poor safety profile. Consequently, clinical data of HSCT in milder phenotypes and in MPS where neurologic function is preserved – including MPS IV-A – are few and limited. Recent data have demonstrated improved survival with HSCT, making the case for the use of HSCT in milder phenotypes to allow for further investigations and understanding of treatment. While few data exist for HSCT in MPS IV-A, successful bone marrow transplantation was tolerated, with excellent survival, in patients with MPS IV-A transplanted for sickle cell anemia. In a recent description of a male patient with MPS IV-A treated with HSCT at an advanced age, 5 years after successful allogeneic bone marrow transplantation, the patient demonstrated recovery of GALNS activity in lymphocytes and improvements of motor function, respiratory function, and glaucoma; there was also an increase of bone mineral density and an overall improvement in quality of life. These findings suggest there is much to be learned about HSCT; as our understanding expands, HSCT may play a future role in the treatment of MPS IV-A. Further investigations are warranted to address the issues of safety of therapy, optimal time for transplantation, donor type, and other factors to ensure successful engraftment, and the role of HSCT in milder phenotypes of MPS.

**Gene therapy**

HSCT and ERT have shown promise for the treatment of MPS IV-A and other MPSs. Current alternative and potential adjunct therapies are under investigation to address the limitations of HSCT and ERT; particularly, the limited effects on the central and musculoskeletal systems. One such therapy includes gene therapy; we briefly discuss this treatment option for MPS IV-A.

The goal of gene therapy is to correct the genetic defect by direct insertion of normal DNA into the affected cells to institute endogenous production of the deficient enzyme by these cells. Current methods include using viral vectors to directly treat affected tissue or using inherent cellular properties for cross-correction. Direct administration involves targeted gene therapy vectors into isolated organ tissue, such as the brain, to target specific dysfunctional organ tissue. Cross-correction employs the same principles of ERT and that of the early studies of HSCT, as affected cells take up the target enzyme produced and leaked by cells of another organ system treated with gene therapy, eg, the liver. These methods have demonstrated promising results in animal models of lysosomal storage diseases. Directly administering gene therapy via recombinant adeno-associated virus vector into the diaphragm of a mouse model of Pompe disease has resulted in improved diaphragmatic muscle and respiratory function. In another murine model of Pompe disease, liver-directed recombinant adeno-associated virus vectors demonstrated cross-correction of skeletal and cardiac muscle with improved function and glycogen storage. Gene therapy may also play a role as an adjunct to HSCT, as autologous bone marrow or hematopoietic stem cells are treated with gene therapy to express the target enzyme prior to transplantation. These findings are promising, but much work is yet to be done to address the issues of immune reaction, choice of vector, and optimal route of administration of gene therapy.

**Conclusion**

Morquio A syndrome is a lysosomal storage disease with severe musculoskeletal complications. Symptoms are progressive and involve other organ systems, including the heart, respiratory, and visceral organs. Presently, treatment is palliative and focused on alleviation of organ-specific complications. While the role of HSCT and gene therapy for the treatment of MPS IV-A has yet to be fully defined with further animal and human studies, the current data of ERT are promising. These findings suggest ERT will likely play a key role in the future treatment of MPS IV-A.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**


