

# Fuchs endothelial corneal dystrophy: current perspectives

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**Abstract:** Fuchs endothelial corneal dystrophy (FECD) is the most common corneal dystrophy and frequently results in vision loss. Hallmarks of the disease include loss of corneal endothelial cells and formation of excrescences of Descemet's membrane. Later stages involve all layers of the cornea. Impairment of endothelial barrier and pump function and cell death from oxidative and unfolded protein stress contribute to disease progression. The genetic basis of FECD includes numerous genes and chromosomal loci, although alterations in the transcription factor 4 gene are associated with the majority of cases. Definitive treatment of FECD is corneal transplantation. In this paper, we highlight advances that have been made in understanding FECD's clinical features, pathophysiology, and genetics. We also discuss recent advances in endothelial keratoplasty and potential future treatments.

**Keywords:** Fuchs endothelial corneal dystrophy, corneal endothelial cell, corneal transplantation, Descemet's stripping automated endothelial keratoplasty, Descemet's membrane endothelial keratoplasty, endothelial keratoplasty

## Introduction

Fuchs endothelial corneal dystrophy (FECD) was first described by Professor Ernst Fuchs as "Dystrophia epithelialis" more than 100 years ago, when he noticed a pattern of slowly progressive corneal clouding with greater involvement of the inferior cornea, reduced corneal sensation, and diurnal variation in symptoms affecting primarily the epithelium in elderly patients.<sup>1</sup> Six years later with the development of the slit lamp biomicroscope, Koeppe observed the classic finding of guttae in the corneal endothelium of patients with the corneal edema described by Fuchs.<sup>2</sup> Subsequent authors found different clinical signs associated with the dystrophy including progression of endothelial changes to corneal edema,<sup>2</sup> reduced corneal endothelial cell (CEC) density with abnormal size and shape, formation of a markedly thickened Descemet's membrane (DM) containing guttae excrescences, spindle-shaped bundles of wide-spaced collagen, and the hereditary nature of the disease.<sup>2,3</sup>

During the past 100 years, studies of pathophysiology have increased our understanding of this disease, and improved treatments have been developed. The aim of this paper was to review relevant information about FECD and provide current perspectives on this disorder.

## Anatomic changes Descemet's membrane and endothelium Descemet's membrane

Deposits of collagen type VIII (COL8) perpendicular to the plane of DM are found at 4 months of gestation and at 8 months form the anterior banded layer (ABL) of DM.<sup>4,5</sup>

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After birth, DM components assemble in a nonlamellar fashion giving rise to the posterior nonbanded layer (PNBL), which expands throughout postnatal life.<sup>6–8</sup> In normal DM, the alpha 1 and alpha 2 subunits of COL8 (COL8A1 and COL8A2) are equally and regularly organized within the ABL. In contrast, corneas with COL8A2 mutations from patients with early-onset FECD have this regularly spaced distribution disrupted, a PNBL with wide-spaced collagen, and an irregular mosaic deposition of different amounts of COL8A1 and COL8A2 in a noncoordinated fashion.<sup>7,9</sup> In addition, early-onset FECD corneas have thickened ABL that indicate a prenatal onset of its pathologic process. On the other hand, in late-onset FECD corneas the ABL is normal and an abnormal postnatal layer is formed posterior to the PNBL, resulting in thickening of DM and guttae.<sup>5,7,10,11</sup> Guttae formation is associated with increased expression of two proteins: clusterin (CLU) and transforming growth factor-beta-induced protein (TGFBIP).<sup>12–14</sup> CLU is a protein that promotes aggregation and is associated with oxidative stress. The secretory form of the protein plays a prosurvival function and the nuclear form induces cellular apoptosis. Both forms are upregulated in FECD corneas, especially the secretory form that is more evident around guttae, suggesting its role in cell survival.<sup>15–17</sup> TGFBIP is an extracellular matrix adhesion molecule that interacts with collagens, integrins, and fibronectins<sup>18</sup> and appears to have a protective role against pro-apoptotic stimuli. Both TGFBIP and CLU colocalize in the middle of guttae.<sup>13</sup> Son et al<sup>19</sup> suggested that guttae could originate from expanded rough endoplasmic reticulum (RER) that becomes closely approximated and possibly fuses to the basal cell membrane, enabling attachment between DM and RER contents by extrusion or cellular death, rather than the localized cellular secretion of DM material.

### Endothelium

Human corneal endothelium is in a postmitotic state and postnatal cell loss is permanent. In FECD, dying cells leave spaces that are filled through the expansion of adjacent cells resulting in loss of cellular hexagonal morphology (pleomorphism) and variation in cell size (polymegathism). Extracellular matrix excrescences (guttae) appear as round dark areas within the cellular monolayer on specular microscopy.<sup>8,11,20</sup> In early-onset FECD, endothelial cells were highly active in producing more COL8 protein than normal and displayed an abundant, unusual RER. In late-onset FECD, melanin was found intracellularly and extracellularly, together with expanded RER, dilated mitochondria, and epithelial markers. These findings suggest that endothelial cells

undergo metaplasia becoming more similar to fibroblasts and epithelial cells in FECD.<sup>9,11,21–24</sup>

### Epithelium, nerves, and stroma

Tissue fluid accumulation (edema) leads to pathologic alterations including subepithelial fibrosis, haze, and decreased numbers of keratocytes.<sup>25–28</sup> These changes make the anterior corneal surface irregular and cause visual distortions, which may persist even after endothelial keratoplasty.<sup>29</sup> In advanced cases of FECD, less than 48% of keratocytes remained by *in vivo* confocal microscopy (IVCM), leaving a hypocellular region in the anterior cornea.<sup>25</sup> On histology, subepithelial fibrosis occurs through fibroblastic cells that are presumably modified keratocytes, separated from Bowman's layer (BL) by an accumulation of collagen "scar tissue" septae. On electron microscopy, BL was thickened and irregular, containing a layer of horizontally oriented scar tissue.<sup>25,30</sup> These subepithelial cells are easily distinguished from stromal cells on IVCM by their morphology and their location between the BL and the basal epithelium, which corresponds to the location of subepithelial fibroblasts. Anterior stromal cells can be sparse, brightly reflective, and fragmented, possibly representing degenerating cells or cell remnants with the surrounding extracellular matrix also brightly reflective by IVCM. These alterations remain 3 years after endothelial keratoplasty together with the same stromal cell density which is 20% lower at the anterior 10% of the stroma compared with normals.<sup>31,32</sup>

Supporting Fuchs's findings from 1910,<sup>1</sup> patients with FECD had decreased corneal sensitivity before corneal transplantation compared with controls. Their preoperative sensitivity was regained 6 months after deep lamellar endothelial keratoplasty and 2 years after Descemet's stripping automated endothelial keratoplasty (DSAEK), but never reached levels of normal corneas.<sup>33</sup> Moreover, branches of the trigeminal nerve on ICVM showed reduced density and increased tortuosity.<sup>33</sup> These alterations are likely to decrease the neurotrophic stimulus essential for maintaining epithelial cell function.<sup>34,35</sup>

It has been observed in three-dimensional Orbscan maps that the anterior cornea becomes less prolate due to edema and that this alteration is counterbalanced by the posterior cornea that becomes flatter and more oblate with disease progression. These changes occur because of posterior corneal biomechanical properties of preferential expansion with corneal edema.<sup>36</sup> This pattern of edema leads to a myopic shift prior to transplant that with reversal of stromal edema can

induce the hyperopic shift seen after Descemet's membrane endothelial keratoplasty (DMEK).<sup>37</sup>

## Pathophysiology

### Endothelial function

Endothelial cells contain various junctional complexes, including tight junctions, macula occludens, macula adherens, and gap junctions. The maintenance of a transparent cornea depends upon the endothelium producing a state of relative stromal dehydration. Tight junctions between epithelial cells form a barrier to reduce the flow of water from the tear film into the stroma, but the absence of a continuous tight junction barrier between endothelial cells provides a leaky barrier for aqueous humor from the anterior chamber. Endothelial cells actively transport ions by Na<sup>+</sup>/K<sup>+</sup>-ATPase pumps in the opposite direction of the inward water movement maintaining a dynamic equilibrium between deturgescence and the tendency of the stroma to swell.<sup>38</sup> The number of ionic pump sites per endothelial cell can be increased in early stages of FECD, but with disease progression they are markedly reduced and coincide with the onset of corneal edema.<sup>14,39</sup> Burns et al<sup>40</sup> demonstrated that despite CECs forming a leaky barrier, their absence leads to increased corneal permeability and could be the earliest physiologic defect in FECD. Evidence suggests that progressive loss of ion pumps is more important than loss of CEC barrier function in the progression of FECD.<sup>40-43</sup>

### Cellular stress

Oxidative stress plays an important role in the pathogenesis of FECD. A common pathway with the unbalanced production/clearing rate of reactive oxygen species and reactive nitrogen species and their harmful effects to the cell has been proposed.<sup>44-46</sup> Moreover, proteomic and polymerase chain reaction array analyses detected generalized downregulation of antioxidants and oxidative stress-related genes.<sup>44,47,48</sup> This pro-oxidative environment could lead to mitochondrial and nuclear DNA damage, changes in cell morphology, and apoptosis. Supporting this hypothesis is the finding of a lower number of mitochondria<sup>44,49,50</sup> and apoptotic cell death by terminal deoxynucleotidyl transferase-dUTP nick-end labeling and DNA fragmentation assays.<sup>51,52</sup>

Matthaei et al<sup>53</sup> showed that a reactive oxygen species-generating enzyme NOX4<sup>54</sup> and a cellular senescence marker CDKN2A<sup>55</sup> were overexpressed in FECD CECs collected from transplanted patients. Also, they found that the CDKN2A pathway could further contribute to senescence of CECs in FECD, since its transcriptional activators ETS1 and

ARHGAP18 (SENEX) were increased and a transcriptional repressor of CDKN2A, ID1, was decreased.

Protein folding is vital for a functional cell.<sup>56</sup> Misfolded protein accumulation can lead to endoplasmic reticulum (ER) stress, which induces cell toxicity and apoptosis.<sup>57</sup> A mechanism called the unfolded protein response (UPR) reduces misfolded protein accumulation to relieve cell stress, but for severe and prolonged levels of ER stress the UPR can also produce apoptosis. FECD corneas showed evidence of increased UPR by transmission electron microscopy and immunohistochemistry.<sup>58</sup>

## Genetics

Two clinical subtypes of FECD have been identified. The early onset, which is rare and presents within the first decade progressing through the second to third decades, and the typical late onset that starts at the second to third decades and evolves with symptoms at the fifth to sixth decades.<sup>2,8,59-62</sup> Both subtypes appear to have similar time of progression from onset of the disease until corneal decompensation.<sup>63</sup>

Autosomal dominant transmission of FECD occurs, although sporadic cases are most common.<sup>64</sup> The genetic basis of FECD is complex and heterogeneous, demonstrating variable expressivity and incomplete penetrance.<sup>64,65</sup> Mutations in a variety of genes have been proven or suggested to play a pathogenic role in FECD. The International Committee for Classification of Corneal Dystrophies (IC3D)<sup>64</sup> classifies FECD in three categories:

- Category 1: A well-defined corneal dystrophy in which the gene has been mapped and identified and the specific mutations are known.
- Category 2: A well-defined corneal dystrophy that has been mapped to one or more specific chromosomal loci, but the gene(s) remain(s) to be identified.
- Category 3: A well-defined corneal dystrophy in which the disorder has not yet been mapped to a chromosomal locus.

At the time of IC3D, Edition 2, published in 2015,<sup>64</sup> only early-onset FECD was listed as category 1. All other genetic associations with FECD were listed as categories 2 and 3. Due to emerging evidence, some of the genetic associations listed below undoubtedly will be changed to category 1 in the next edition of IC3D.

### Category I

#### Alpha 2 collagen VIII

The endothelium secretes type VIII collagen, which is the principal component of the ABL. This collagen has

two isoforms, alpha 1 (COL8A1) and alpha 2 (COL8A2), which associate to form trimeric molecules organized into a highly ordered three-dimensional structure.<sup>66</sup> Two causal mutations (Gln455Lys and Leu450Trp)<sup>63,67</sup> in COL8A2 result in abnormal intracellular accumulation of mutant collagen VIII peptides and affect triple helical stability.<sup>68,69</sup> These mutations were also seen in patients with posterior polymorphous dystrophy, a different phenotype with distinct clinical presentation. Meng et al<sup>70</sup> and Jun et al<sup>71</sup> showed consistent pathology with human early-onset FECD patients in knock-in mouse models of both the Gln455Lys and Leu450Trp mutations in COL8A2. They found that both models exhibited upregulation of the UPR together with its associated genes and proteins. Furthermore, they noted upregulation of the autophagy marker DRAM1, suggesting a role for altered autophagy in the disease.

## Categories 2 and 3

### Transcription factor 4

Transcription factor 4 (TCF4) is a transcription factor encoded by the *TCF4* gene localized on chromosome 18. Wieben et al<sup>72</sup> demonstrated an association between an intronic thymine–guanine–cytosine trinucleotide repeat in the *TCF4* gene of FECD patients. They found that 79% of FECD patients had more than 50 repeats in the third intron of the *TCF4* gene compared with 3% of control individuals. They hypothesized that the repeat expansion could alter transcription start or expression levels of specific *TCF4* isoforms, or gain-of-function RNA aggregation and toxicity as the basis for endothelial cell death. The role of RNA toxicity in the pathogenesis of FECD was confirmed by the work of Du et al<sup>73</sup> and Mootha et al.<sup>74</sup>

### Transcription factor 8

Five mutations linked to late-onset FECD were identified in the transcription factor 8 (*TCF8*) gene located on chromosome 9.<sup>75</sup> *TCF8* encodes the ZEB1 protein and is upregulated by the E2-2 protein encoded by *TCF4*. Despite *TCF8* mutations being sufficient for the development of late-onset FECD, they are not necessary.<sup>76–78</sup> The precise role of the *TCF8* gene is not completely clear, but *TCF4* and *TCF8* genes have similar biologic functions and their mutations may be linked to the same pathway in the development of late-onset FECD.<sup>77,78</sup>

### Lipoxygenase homology domain-containing 1 gene

Lipoxygenase homology domain-containing 1 gene (*LOXHD1*) is a protein found in the plasma membrane. Two causal mutations in *LOXHD1* gene have been associated

with progressive, autosomal, recessive nonsyndromic hearing loss. Riazuddin et al<sup>79</sup> found at least 15 heterozygous missense mutations in the *LOXHD1* gene in >200 sporadic affected FECD patients that were absent from >800 control chromosomes. They hypothesized that these mutations in *LOXHD1* were associated with overexpressed proteins, which form aggregates that could be cytotoxic and lead to CEC death.

### Solute carrier family 4 sodium borate transporter member 11

Solute carrier family 4 sodium borate transporter member 11 (*SLC4A11*) encodes the protein NaBC1, a cotransporter normally located on the cell surface.<sup>80</sup> Heterozygous mutations were found not only in patients with late-onset FECD, but also in congenital hereditary endothelial dystrophy type 2 and resulted in NaBC1 failing to migrate to the cell surface. These mutated proteins are retained at the ER and are targeted for intracellular degradation.<sup>81–84</sup>

Despite being reported to be a HCO<sub>3</sub><sup>-</sup> independent sodium borate cotransporter,<sup>80</sup> the exact role of *SLC4A11*/NaBC1 in the corneal endothelium is yet unclear, as is biological relevance of borate to the cornea. An *SLC4A11* knockout mouse was developed to investigate the absence of the NaBC1 protein, but the primary phenotypic change observed in the cornea was an increase in absolute height of corneal basal epithelial cells with no dystrophic phenotype of FECD or congenital hereditary endothelial dystrophy type 2.<sup>85</sup>

### Chromosomal loci

Several chromosomal loci have been associated with FECD. The first discovered was Fuchs corneal dystrophy (FCD) locus 1 localized on chromosome 13 with a typical autosomal dominant inheritance pattern, containing 44 protein-encoding genes.<sup>86</sup> FCD2 on chromosome 18 is also associated with autosomal dominant inheritance and 28 protein-encoding genes.<sup>87</sup> FCD3 is found on chromosome 5, has 95 protein-encoding genes, and is phenotypically subtler than FCD1 and 2.<sup>88</sup> FCD4 is on chromosome 9, interacts with the *TCF8* mutation, and has a severe phenotype.<sup>75</sup> A linkage study including many small FECD families revealed chromosomes 1, 7, 15, 17, and X as potentially being involved in FECD.<sup>89</sup> Afshari et al<sup>89</sup> concluded that FECD could be inherited in both an autosomal dominant and complex fashion.

## Risk factors and associated conditions

Zhang et al<sup>90</sup> studied smoking, sex, diabetes, and age in 2,044 FECD patients and association with central corneal

thickness (CCT). They found that patients who smoke had more guttae and that smoking in female FECD patients increased the risk of developing advanced disease, possibly due to increased oxidative stress. They also showed that diabetes was associated with an independent increase in CCT unrelated to the severity of the disease. Orlin et al<sup>91</sup> described five patients who had FECD and keratoconus and Lipman et al<sup>92</sup> demonstrated that two distinct familial corneal diseases (keratoconus and FECD) could occur in the same patient. Age-related macular degeneration was significantly more prevalent in a group of 50 patients with central guttae compared with controls.<sup>93</sup> Olsen<sup>94</sup> retrospectively analyzed 27 FECD patients regarding the presence of cardiovascular disease. He found that history of myocardial infarction, angina pectoris, or cardiac insufficiency treated by medication was found in 44% compared with 11% of the control group. He hypothesized the existence of a common endothelial factor for the development of corneal endothelial dystrophy and atherosclerotic lesions.

## Clinical staging

The Krachmer grading scale<sup>95</sup> is used to subjectively evaluate disease progression as follows: grade 0 (G0) negative; 0–12 central guttae (G1); greater than 12 central nonconfluent guttae (G2); 1–2 mm of confluent central guttae (G3); 2–5 mm of confluent central guttae (G4); greater than 5 mm of confluent central guttae or G4 with stromal or epithelial edema (G5). Despite being used since 1978, this method has some limitations concerning its reproducibility, variance between observers, and grading mild corneal edema. Objectively measuring CCT is sometimes used as a parameter of endothelial failure and disease progression.<sup>96</sup> However, patients without FECD can have a CCT of 640  $\mu\text{m}$  or more free from edema. The inverse also occurs, and patients with advanced FECD can have a CCT with less than 600  $\mu\text{m}$  with or without edema. The difficulty of using CCT to grade FECD severity is that baseline CCT in patients with FECD is usually unavailable.<sup>96–99</sup> Repp et al<sup>100</sup> proposed that the peripheral corneal thickness could serve as an internal reference when measuring central thickness in the same cornea of patients with early FECD. They found that the corneal central-to-peripheral thickness ratio was an objective measure more sensitive in diagnosing early and moderate stages of FECD compared with the subjective classification. They also described a linear relationship between central-to-peripheral thickness ratio and disease progression in which the ratio was increased in the early and moderate cases compared with controls.

Fujimoto et al<sup>101</sup> mapped the endothelial characteristics through 15 different points on FECD corneas looking for

abnormal areas (guttae). They quantitatively confirmed that the central part was earliest and more severely damaged followed by the inferotemporal area when the disease reached the periphery. They also found that the degree of guttae formation in the central endothelium was not markedly different in moderate-to-severe cases, whereas in the periphery the degree of abnormality was statistically different between mild, moderate, and severe cases. They propose that progression of the disease could be objectively described by the degree of peripheral guttae formation.

## Treatment

Palliative treatment for FECD involves improving quality of life when visual acuity is not a priority. Techniques include conjunctival flaps, anterior stromal puncture, phototherapeutic keratectomy, amniotic membrane transplantation, bandage contact lens, collagen cross-linking, and hyperosmotic solutions.<sup>102</sup> Definitive treatment involves corneal transplant with the main goal of restoring vision by two different approaches: full-thickness and lamellar transplant.

### Full-thickness transplant

Penetrating keratoplasty (PK) has traditionally been used for treating FECD.<sup>103</sup> In most cases, transplant was delayed until corneal edema ensued. No tissue from the patient cornea remained within the margins of the graft.<sup>104</sup>

### Lamellar transplant

This approach has gained popularity over the past decade,<sup>105</sup> and it involves preservation of healthy tissue from the recipient cornea with replacement of its pathologic portions. This method has the best results, if performed before irreversible changes occur on the host anterior cornea. Two major techniques include:

- DSAEK: The recipient endothelium and DM are replaced by a donor graft consisting of a layer of deep stroma of variable thickness, DM, and healthy CECs.<sup>106–112</sup> Donor stroma is added to the host cornea. Ultrathin DSAEK is a variant in which the maximum thickness of the graft is 100  $\mu\text{m}$ .<sup>113</sup>
- DMEK: Pathologic CECs and DM are substituted by an equivalent healthy donor tissue without additional stroma.<sup>114</sup>

## Comparison between techniques for corneal transplantation

### Penetrating keratoplasty

This technique has the highest rejection rate, intraoperative and postoperative complications, and postoperative

astigmatism compared with the others. It takes up to 2 years for vision recovery, but after 18 months of follow-up more patients will have 20/20 best-corrected visual acuity than DSAEK patients.<sup>115,116</sup> PK may be preferable when there are complex anterior segment pathologies.<sup>117</sup> CEC survival in the early postoperative period appears to be higher compared with lamellar transplant,<sup>118,119</sup> but that difference is lost in 2 years when the percentage of endothelial cells lost equalizes with the other techniques.<sup>120,121</sup>

### Descemet's stripping automated endothelial keratoplasty

This method has been the treatment choice in the past decade for patients with endothelial failure. It has decreased rejection rate, intraoperative and postoperative complications, astigmatism, and faster visual recovery with more consistent results compared with PK.<sup>122–125</sup> However, substantial numbers of patients do not achieve 20/20 vision postoperatively, possibly due to the interface between donor and recipient stroma and the higher-order aberrations associated with the transplanted tissue.<sup>126–128</sup> Furthermore, a hyperopic shift of ~1.5 D is expected due to the surgery.<sup>107,129–131</sup> Evidence also supports that younger patients with FECD have better visual recovery when compared with older patients.<sup>113,132</sup> Ultrathin DSAEK has the advantage of quicker visual recovery that at 1 year reaches equivalency with DMEK.<sup>133,134</sup>

### Descemet's membrane endothelial keratoplasty

This technique has improved outcomes over DSAEK in rejection rates and visual recovery.<sup>135–137</sup> However, it is not currently the technique of choice due to its learning curve. It is not recommended in eyes with complicated anatomy, and the learning process may lead to higher rates of intraoperative and postoperative complications like graft dislocation requiring rebubbling and primary graft failure when compared with DSAEK.<sup>104,138,139</sup> It is less expensive because it does not require a microkeratome, but it is more surgeon-dependent than DSAEK. Studies have shown the highest rates of patient satisfaction.<sup>140,141</sup>

### Long-term survival

Long-term follow-up studies for lamellar transplant techniques are limited. According to Nanavaty and Shortt,<sup>103</sup> randomized controlled trials are required to decide which operation is best for each individual patient in the long term. Furthermore, Hjortdal et al<sup>142</sup> showed that despite having a low rate of rejection, lamellar grafts failed more often than with PK. This finding could be related to the

learning curve and the traumatic manipulation of donor tissue intraoperatively, which would be expected to decrease with surgeon's experience.

## Future treatments

New modalities for treating CEC dysfunction have been reported. These include use of Y-27632 eye drops, a selective Rho-associated kinase (ROCK) inhibitor, after transcorneal freezing.<sup>143</sup> Y-27632 promoted cell proliferation and wound healing both in vitro and in vivo.<sup>144</sup> It had demonstrated efficacy in treating a small group of patients with central corneal edema caused by FECD.<sup>143</sup> The second approach is transplantation of cultured CECs as a sheet or by injection of a cell suspension into the anterior chamber. Both techniques have been effective in animal models.<sup>145–148</sup> Injection of cultured CECs with a ROCK inhibitor regenerated healthy corneal endothelium and restored corneal transparency in monkeys and rabbit models and could be a new cell-based regenerative therapy.<sup>149</sup>

Such future minimally invasive approaches promise to have advantages over current surgical procedures potentially including earlier vision recovery, decreased rejection, reduced costs and donor cornea needs, and broader availability.

## Conclusion

Despite the complexity of FECD, continuous steps to clarify its causes and treatments have been made in the past century. Intellectual curiosity to fully understand the underlying disease processes, motivation to improve treatments, and advances in technology have enabled us to evolve from disease observers to care providers. Thus, we have reduced the burden of vision loss in FECD patients with effective therapeutic options, and an even more promising future lies ahead for our understanding and treatment of this disease.

## Disclosure

The authors report no conflicts of interest in this work.

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