Frozen versus fresh corneal graft carriers in Boston keratoprosthesis surgery

The Boston keratoprosthesis type 1 (KPro), one of the most commonly used artificial corneas, is a surgical option when the success of traditional penetrating keratoplasty is expected to be limited. Indications include multiple graft failures, aniridia, chemical burns, and autoimmune diseases such as Stevens-Johnson Syndrome. The Boston KPro is made of polymethyl methacrylate (PMMA) but still requires a corneal allograft button to anchor it in place. Unlike traditional corneal transplants, the endothelial status of the donor is not a factor in device suitability since it is the PMMA that provides optical clarity. This suggests that alternatives to fresh corneal donors may be considered, which is especially attractive given the limited availability of fresh tissue and the resources required in its acquisition.

Frozen or cryopreserved tissue is one such alternative. In the current issue, Sabeti and colleagues report on the 10-year clinical outcomes of Boston KPro type 1 implants using fresh versus frozen graft carriers. This is an extension of the group’s previous work reporting outcomes at 2 years and 5 years.

In this prospective, non-masked, randomized controlled trial, 37 eyes of 37 patients were initially enrolled and randomized to receive KPro type 1 implants with either fresh or frozen grafts. Of the 37 participants, 26 consented to the 60- and 120-month extension phases. 7 of these were lost to follow-up and ultimately, 19 eyes were included in the current 120-month extension study. 11/19 (57.8%) had received a fresh corneal graft carrier and 8/19 (42.1%) a frozen graft carrier. There was no difference in baseline demographics in terms of age, gender, or disease category between these groups. Ocular diseases were categorized into aniridia, autoimmune, chemical burn, infectious and other.

The primary outcome of the study was device retention. There was no reported statistically significant difference between device retention at 10 years in patients receiving fresh vs. frozen carriers (90.9% vs. 75.0% respectively, p = 0.546). Mean 10-year best correct visual acuity (BCVA) between groups also showed no statistically significant difference, with BCVAs of 20/300 and 20/125 respectively, p = 0.135. In both groups, there was a significant improvement in BCVA from baseline. The study also reported complication rates, which was similar in both groups; in the fresh carrier group, the complication rate was 2.36 per patient and in the frozen carrier group, 2.37 per patient (p = 0.988).

Though the sample size is small at 19 patients, the long-term results presented in this study are promising for Boston KPros using frozen graft carriers. Other alternatives to fresh corneal carrier grafts have also been studied, including gamma-irradiated donors and xenografts. Sabeti and colleagues acknowledge that there are a relatively small number of KPros performed each year, but conclude that substituting fresh tissue for frozen can be particularly beneficial in less fortunate populations. However, the lack of fresh cornea grafts is just one part of the problem in developing nations. Resources are lacking not only in graft procurement, transportation, and storage of fresh tissue but for the transplant surgeries and transplant centres themselves. Furthermore, additional research and developments are needed to address common KPro complications, such as glaucoma, which require close monitoring — access to regular and timely follow-up may be challenging in these developing countries. Nevertheless, while there are various factors limiting regular usage of KPros in such populations, studies such as the current one presented by Sabeti and colleagues and continued improvements in device design can hopefully begin to address these limitations.

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Article being referenced: https://www.canadianjournaloophthalmology.ca/article/S0008-4182(21)00082-X/fulltext

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The coronavirus disease 2019 (COVID-19) has been the focus of many studies since the start of the ongoing pandemic in December 2019. Since then, over 3.04 million Canadians have been infected by the SARS CoV-2 virus.1 Its sequelae and complications have been studied in many organ systems including the ocular system.2 Viral ribonucleic acid (RNA) of SARS-CoV-2 has been found in retinal tissues of deceased patients.3 There are several possible mechanisms for COVID-19 related retinopathy discussed in current literature. Angiotensin-converting enzyme 2 (ACE2) is expressed throughout the respiratory, cardiovascular, GI, renal, nervous system, and retina that is also the target receptor for SARS CoV-2.4 The destruction of ACE2 receptors and resultant inflammation and oxidative stress could be one mechanism by which the virus causes retinal disease.5 Alternatively, systemic viral infections can produce immune-mediated inflammatory responses such as the interferon γ (IFN-γ)-mediated migration of microglial cells from the inner retina to the outer retina and subretinal space, causing outer retinal thickening.6 Finally, COVID-19 is associated with increased arterial and venous ischemic events secondary to endotheliitis. As such, retinal ischemic changes such as cotton wool spots, flame-shaped hemorrhages, and retinal pallor have also been reported in post-COVID-19 patients suggesting another possible etiology.4,7

In this issue, Yildiz and colleagues conducted a retrospective cross-sectional study to evaluate the presence of microstructural changes in the macula and the peripapillary retinal nerve fibre layer (RNFL) in post-COVID-19 patients between April and October 2020.8 A total of 236 eyes of 122 participants were included in this study. Group 1 consisted of 119 eyes who were positive for COVID-19 confirmed by polymerase chain reaction (PCR) testing 2-8 weeks prior to their participation in the study. Group 2 consisted of 117 eyes of 59 normal controls, determined as those without any signs or symptoms of COVID-19 by interview. These two groups were age- and sex-matched with no significant difference in best corrected visual acuity (BCVA), lens status (phakic/pseudophakic), axial length, and spherical equivalent refractive error. Spectral-domain optic coherence tomography (SD-OCT) scans of the macular and peripapillary RNFL were performed. Only those images with quality index >15 and no artifacts were included. Central foveal thickness (CFT), thickness of single layers of the retina, peripapillary RNFL thickness, and choroidal thickness were obtained.

The primary outcome was the presence of any microstructural differences between Groups 1 and 2. Yildiz and colleagues found that the CFT was significantly higher in Group 1 (271.0 ± 26.8 μm) compared with Group 2 (263.2 ± 22.0 μm) (p=0.015). The mean outer nuclear layer (ONL) thickness was also significantly higher in group 1 (85.4 ± 13.3 μm) than in Group 2 (81.4 ± 15.2 μm) (p=0.035). The mean peripapillary RNFL thickness and thickness of the other retinal and choroid layers of Group 1 and Group 2 were not significantly different.

A secondary outcome of this study found the incidence of co-existing comorbidities to be higher in Group 1 (n=26/62, 41.3%) compared with Group 2 (n=12/59, 20.3%) (p=0.013). Further subanalysis of those participants in Group 1 who recovered from hospitalization for COVID-19 showed that the mean thickness of the ONL was significantly greater in those who were hospitalized (89.0 ± 13.6 μm) compared to those who were not (82.1 ± 12.3 μm, p=0.003). This suggests that there may be a direct correlation between ONL thickness and presence and severity of COVID-19 infection.

There are a few limitations to this study including lack of confirmatory negative PCR test in control group participants. As the authors mention, about 17.9% of positive patients show no symptoms which could lead to skewed results if asymptomatic participants were actually COVID-19 positive.8 Yildiz and colleagues also declare lack of

SD-OCT imaging of post-COVID-19 patients

The coronavirus disease 2019 (COVID-19) has been the focus of many studies since the start of the ongoing pandemic in December 2019. Since then, over 3.04 million Canadians have been infected by the SARS CoV-2 virus.1 Its sequelae and complications have been studied in many organ systems including the ocular system.2 Viral ribonucleic acid (RNA) of SARS-CoV-2 has been found in retinal tissues of deceased patients.3 There are several possible mechanisms for COVID-19 related retinopathy discussed in current literature. Angiotensin-converting enzyme 2 (ACE2) is expressed throughout the respiratory, cardiovascular, GI, renal, nervous system, and retina that is also the target receptor for SARS CoV-2.4 The destruction of ACE2 receptors and resultant inflammation and oxidative stress could be one mechanism by which the virus causes retinal disease.5 Alternatively, systemic viral infections can produce immune-mediated inflammatory responses such as the interferon γ (IFN-γ)-mediated migration of microglial cells from the inner retina to the outer retina and subretinal space, causing outer retinal thickening.6 Finally, COVID-19 is associated with increased arterial and venous ischemic events secondary to endotheliitis. As such, retinal ischemic changes such as cotton wool spots, flame-shaped hemorrhages, and retinal pallor have also been reported in post-COVID-19 patients suggesting another possible etiology.4,7

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longitudinal observation and lack of multi-modal imaging as additional limitations.

In summary, Yildez and colleagues performed a very comprehensive study with the largest sample size to date to describe retinal microstructural changes related to SARS CoV-2 infection and were the first to analyze single layers of the retina. They found that the central foveal thickness and outer nuclear layers are significantly thicker in post-COVID-19 patients and discovered a positive correlation between ONL thickness and severity of infection. Further studies with longitudinal follow up are required to investigate long-term complications.

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References


Ocular manifestations of Mycobacterium chimaera after cardiothoracic surgery

Within the last decade, there have been several reports of disseminated Mycobacterium chimaera infection after cardiothoracic surgery; these outbreaks have been linked to contaminated heater-cooler units used during extracorporeal circulation. In addition to producing non-specific systemic manifestations, these infections tend to involve the eye. In this issue, Ma and colleagues describe ocular findings and multimodal ophthalmic imaging in patients with disseminated M. chimaera infection.

The authors include 7 patients who developed M. chimaera infection following cardiothoracic surgery. Patients presented with, or developed, systemic findings including constitutional symptoms, end organ dysfunction, and laboratory abnormalities. As is typical for this infection, there was a long delay between index surgery and diagnosis of M. chimaera infection, ranging from 19 to 36 months. Ocular manifestations were prevalent in all patients. Bilateral, wide-spread, white-yellowish choroidal lesions were observed in 6 patients. One patient presented with a solitary white granular choroidal lesion. In two patients, fundus abnormalities were detected incidentally before systemic manifestations were present. No patient experienced visual/ocular symptoms. Mild uveitis and optic nerve edema have been reported, although these were absent in this series.

All patients received systemic multi-agent anti-mycobacterial therapy and had ongoing ophthalmologic surveillance. One patient with progressive choroiditis was treated with intravitreal antibiotic and steroid; however, this was ineffective at halting progression. Six patients experienced...
progression of systemic illness and choroidal disease, and later passed away from disseminated infection. The only surviving patient experienced no progression of ocular involvement. The authors describe the appearance of choroidal lesions on multimodal imaging. As in other reports, the lesions were appreciated with fundus autofluorescence as hyper- and hypo-autofluorescent lesions representing active and inactive lesions, respectively. Fluorescein angiography demonstrated hyperfluorescent lesions in late frames, and OCT showed choroidal thickening with irregular overlying retinal pigment epithelium. Findings on indocyanine green angiography are not presented, although this modality may disclose clinically apparent lesions.

This study will be of interest to ophthalmology trainees for several reasons. First, ophthalmological consultation may be sought when a diagnosis of *M. chimaera* is suspected. Given non-specific systemic findings and delay between index surgery and development of systemic illness, we may have a unique opportunity to provide critical input to assist diagnosis. Second, routine ophthalmological follow up is indicated once a diagnosis of disseminated *M. chimaera* has been made. As in this, and other series, progression of ocular findings may correlate with systemic disease, and therefore may inform systemic management. Third, although the differential for multifocal choroiditis is broad, a history of cardiothoracic surgery may be pertinent to elicit when such a clinical picture is encountered. Indeed, this series demonstrates that the ophthalmologist might be the first provider to identify signs of *M. chimaera* infection.

The authors point out that limitations of their study include the small number of patients included. Nevertheless, Ma and colleagues report is among the largest published series describing ocular findings in *M. chimaera* infection and should serve as a useful reference for ophthalmologists who might participate in the care of patients with this rare and life-threatening condition.

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Article being referenced: https://www.canadianjournalofophthalmology.ca/article/S0008-4182(21)00081-8/fulltext

**References**


**Dry eye disease in children with blepharokeratoconjunctivitis**

Pediatric blepharokeratoconjunctivitis (BKC) is a chronic inflammatory disease of the eyelid margin with secondary conjunctival and corneal involvement. The wide spectrum of clinical presentations include meibomian gland dysfunction (MGD), recurrent chalazion, chronic blepharitis, punctate keratitis, and phlyctenules. BKC is a common disease as it accounts for up to 15% of all pediatric referrals and the severity of the disease is greater in Asian and Middle Eastern population. However, due to the varying clinical presentation the diagnosis is often delayed. Early recognition is important for starting treatment especially if there is corneal involvement that can compromise visual acuity. While the pathophysiology remains unclear, it is hypothesized that the bacteria colonizing the eyelids can trigger inflammation (Type IV hypersensitivity) and alter the lipid composition of meibomian glands. In addition to ocular surface inflammation, dry eye disease (DED) manifests as a result of meibomian gland dysfunction (evaporative dry eye disease), aqueous tear deficiency or both. Unlike in adults, DED in the pediatric BKC population is poorly characterized. Exploring DED in this unique pediatric BKC population will help ophthalmologists to monitor disease severity and guide management in a timely fashion.

In this issue, Elbaz and colleagues report on a prospective case-control study to evaluate signs and symptoms of DED in pediatric BKC patients. They recruited patients with...
quiescent BKC to isolate the effects of DED in BKC corneas while eliminating confounding signs and symptoms related to active inflammation. The control group had no history of ocular surface disease while the mean age and gender distribution was similar between groups. Patients underwent a comprehensive dry eye assessment which included the Canadian Dry Eye Assessment (CDEA) questionnaire, measuring tear film osmolality, Schirmer’s test, tear break-up time (TBUT), corneal fluorescence staining (CFS), and conjunctival lissamine green staining. Results showed higher CFS in patients with BKC but all other DED tests were similar between the two groups. Given that the Schirmer’s test was within normal limits, the authors proposed that differences in CFS was likely from ongoing subclinical inflammation rather than aqueous tear deficiency. Interestingly, the TBUT (an indicator for MGD), was similar between the groups suggesting that children may have robust mechanisms to compensate for evaporative DED. Overall, this study showed that patients with BKC did not express significant signs and symptoms of DED but CFS can be a useful test to help monitor DED in pediatric BKC.

Small sample size (25 patients), variability of findings among BKC patients, and examiners not being blinded to testing are some of the limitations of this study. In addition, normal cut-off values for DED tests were based on adult literature and may not be directly applicable to the pediatric population. Nonetheless, this pilot study is first to provide a comprehensive assessment of DED in pediatric BKC and highlights the need for large scale studies to investigate the efficacy of DED tests in children. Furthermore, future studies are needed to investigate the utility of a multimodal DED testing in patient with both stable and active BKC while eliciting how these findings can guide management.

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Article being referenced: https://www.canadianjournalofophthalmology.ca/article/S0008-4182(21)00066-1/fulltext

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**Sunlamp use is a risk factor for uveal melanoma**

Uveal melanoma can be a visually devastating diagnosis and remains one of few intraocular pathologies that can be fatal. A great deal of work has been done to improve treatment modalities, with increased rates of radiation compared to surgery allowing for fewer enucleations; unfortunately, these advances have not yet translated to longer survival times.1 Given the morbidity and mortality surrounding uveal melanoma, identification and avoidance of modifiable risk factors is essential. Known risk factors in the literature include light skin and eye colour, atypical and common cutaneous nevi, welding, occupational cooking, propensity to burn in the sun, intense sun exposure, iris nevi, and cutaneous freckles.1,2,3 Many of these risk factors overlap with those known to be associated with cutaneous malignant melanoma, which suggests that there may be other commonalities to be explored. In this issue, Weis and colleagues set out to determine if sunlamp usage was a risk factor for the development of uveal melanoma,4 as sunlamps are known to be carcinogenic with regard to cutaneous melanomas and other skin cancers.

The authors’ meta-analysis was conducted by reviewing literature obtained through the MEDLINE, EMBASE, MD Consult, and Web of Science databases, covering the years 1966 to 2019. A sunlamp was considered any device that uses UV light for the purpose of tanning skin. Only articles that looked at the relationship between sunlamps and uveal melanomas were included in the study. A total of 5 studies including 1753 uveal melanoma cases and 3399 controls were assessed in the meta-analysis. The studies demonstrated excellent quality in terms of selection and
comparability, with lower scores for assessment of exposure (given that this is inherently self-reported data). Location of the studies varied in latitude from 33.87 degrees south to 51.49 degrees north of the equator, and were conducted in the United States, Australia, and Germany. Four of the five studies included uveal melanomas from all sites (i.e., the choroid, ciliary body, and/or iris) and one study included only choroid and ciliary body tumours. The different studies calculated odds ratios and frequently adjusted for factors such as age, eye colour, skin colour, and sun exposure. A random effects model in this meta-analysis showed a positive association between sunlamps and uveal melanoma, with an odds ratio of 2.15 (95% confidence interval 1.26–3.64).

This meta-analysis is limited by the small number of studies that met inclusion criteria, and consequently the small sample size. This is likely due to the low incidence of uveal melanoma in the general population. The study also cannot comment on the role of eye protection at the time of using the sunlamp, as four of the five studies included either did not mention this or did not provide raw data from which results could be calculated. Nonetheless, this study provides data demonstrating that sunlamp exposure is an important modifiable risk factor for the development of uveal melanoma. When appropriate, ophthalmology residents and staff should advise their patients regarding the dangers of sunlamp usage.

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Article being referenced: https://www.canadianjournalofophthalmology.ca/article/S0008-4182(21)00090-9/fulltext

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Selective laser trabeculoplasty and excisional goniotomy outcomes in glaucomatous eyes

Eyes with primary open-angle glaucoma (POAG) have progressive trabecular meshwork (TM) dysfunction with reduced aqueous humor outflow facility leading to elevated IOP. While the trabecular meshwork appears to be the main contributor to aqueous conventional outflow, this outflow is also regulated distally by the collecting channels that have a capacity for contraction and flow resistance.1 Kahook Dual Blade (KDB) goniotomy is a minimally invasive glaucoma surgery (MIGS) performed using a single-use dual blade to excise a full en-bloc strip of the trabecular meshwork, allowing the aqueous to drain directly to the distal outflow pathways in eyes with open-angle glaucoma.2 Despite the superior safety of KDB compared to conventional filtering surgery, the IOP-lowering capacity of KDB is limited and unpredictable.3 Thus, a predictive tool for the success of KDB would have substantial clinical value. In this issue, King and colleagues evaluated the use of poor response to selective laser trabeculoplasty (SLT) to identify eyes with potential post-trabecular outflow impairment, and thus predict poor IOP responses to trabecular-bypassing procedures.4 The authors hypothesized a relationship between the IOP-lowering response to SLT and subsequent excisional goniotomy with combined Kahook Dual Blade (KDB) goniotomy and phacoemulsification in eyes with glaucoma.

The study was a single-surgeon, single-site retrospective review of 30 eyes of 24 patients who underwent SLT and then subsequently underwent phacoemulsification combined with a KDB excisional goniotomy in the same eye. The mean age of the cohort was 69.7±9.8, was mostly female (66.7%), and was predominantly white (91.7%). Inclusion criteria were patients with early to advanced primary or secondary open-angle glaucoma, a minimum of 2 months of follow-up after SLT, and 6 months of follow-up after KDB. The indications for both SLT and KDB
goniotomy were the need for IOP reduction, the desire to reduce the medication burden, or both. SLT was considered successful if IOP was reduced ≥20% from baseline or if medication use was reduced with no further IOP-lowering interventions at 2 months. On the other hand, KDB was considered successful by the same criteria at 6 months. Failures were defined as those that required additional IOP-lowering procedures after KDB.

Although their results on the effects of SLT and KDB reproduced the expected outcomes of previously published studies regarding mean IOP reduction and medication reductions;5,6 no relationship was found between the outcomes of the 2 interventions. Poor response to SLT failed to predict eyes that would exhibit poor IOP responses to KDB goniotomy. However, KDB success rates were unexpectedly higher in eyes with failed prior SLT (69.2%) than in eyes with successful SLT (52.9%). These results suggest that KDB may still be beneficial in patients with previously failed SLT treatment.

Identifying a simple and safe predictive biomarker for the success of MIGS will indeed have significant clinical value in patient selection for the various MIGS procedures. Considering the study limitations, future exploration of multicenter, larger sample sizes, and more coherent subtypes of glaucoma are warranted to re-evaluate their original hypothesis. Also, further studies are required to elucidate the benefit of KDB in patients that failed initial SLT treatment.

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Article being referenced: https://www.canadianjournalofophthalmology.ca/article/S0008-4182(21)00089-2/fulltext

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Reversible HER2 antibody-drug conjugate-induced ocular toxicity

Targeted therapies have dramatically improved life expectancy for patients with breast cancers expressing Human Epidermal growth factor Receptors (HERs).1,2 Antibody-drug conjugates (ADCs) are one such medication. ADCs use cytotoxic drugs bound to monoclonal antibodies to specifically target HER2 receptors upregulated in otherwise unresponsive metastatic cancers.3 From an ophthalmic perspective, ADCs can cause ocular surface toxicity, including dry eye, punctate keratitis, corneal erosions, and limbal stem cell (LSC) dysfunction.4 Management of this toxicity currently includes ceasing drug exposure and optimizing the ocular surface with aggressive lubrication, anti-inflammatories, autologous serum tears (ASTs), and ocular surface protection.

In this issue, Sharma and colleagues examined ocular adverse drug reactions in patients enrolled in a phase I/II clinical trial of A116, a novel anti-HER2 ADC.5 Twenty-three patients with metastatic, unresectable HER2 tumours were enrolled. Patients were excluded if at baseline they had pre-existing moderate-to-severe corneal disease.

Six eyes of 3/23 patients ultimately developed toxicity from A166, 3–5 weeks after drug initiation. Toxicity initially manifested with dry eye symptoms and decreased contrast vision ranging from 20/100 to 20/300. On exam, patients exhibited a late fluorescein-staining whorl pattern epitheliopathy emanating from the superior limbus (4/6 eyes) and inferior limbus (2/6 eyes), consistent with LSC dysfunction.5

In all 3 patients, A166 was stopped, and ocular treatments coordinated at the discretion of treating ophthalmologists. Across all 3 cases, symptomatic epitheliopathy from A166 toxicity worsened over several weeks despite first-line measures including preservative-free artificial tears (PFATs, up to every 1-2 hours), lubricating ointment and topical steroids. Further measures, met with variable success, included...
bandage contact lenses, punctal plugs, lifitegrast, and amniotic membrane grafting. Patients with more challenging clinical courses had pre-existing risk factors for ocular surface disease, including laser in-situ keratomileusis, connective tissue disease, and previous dry eye treated with lifitegrast.

The authors implemented ASTs (20%) at late timeframes for all 3 patients, with epitheliopathy resolving completely in all 3 cases after several weeks. The lengthy delay (≥3 weeks after symptom onset) in starting ASTs ensured that most A166 had been cleared before ASTs were prepared to prevent ASTs from perpetuating A166 toxicity. It is therefore impossible to conclude whether resolution of epitheliopathy was due to treatment with ASTs or clearance of A166 from systemic circulation. Despite several clinical trials demonstrating efficacy of ASTs in dry eye disease, a recent Cochrane meta-analysis failed to show significant results due to low evidence.

After epitheliopathy resolved, 1 patient refused further treatment with A166; 1 patient resumed low-dose A166 treatment with maintenance PFATs, ASTs, lifitegrast, and scleral contact lenses; and 1 patient was deemed unsuitable for further A166 treatment due to cancer progression.

It is believed that ADCs cause ocular surface toxicity by binding to physiologic HER2 receptors on corneal epithelial cells, resulting in LSC cytotoxicity. Topical steroids were ineffective in this study, leading the authors to believe that the mechanism of epitheliopathy is toxic, not inflammatory. While A166-associated ocular surface toxicity was uncommon in this study, it required cessation of treatment and aggressive temporizing measures to reverse.

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Article being referenced: https://www.canadianjournalofophthalmology.ca/article/S0008-4182(21)00077-6/fulltext

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