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Current concepts in fracture healing: temporal dynamization and applications for additive manufacturing

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Abstract

Objectives: Current surgical fracture treatment paradigms, which use rigid metallic constructs to heal bones, provide reasonable clinical outcomes; however, they do not leverage recent advances in our understanding of bone healing and mechanotransduction throughout bone healing. The objective of this review was to investigate the efficacy and potential clinical applicability of surgical techniques and implants that deliberately introduce interfragmentary motion throughout the healing process.

Methods: The authors searched PubMed and Google Scholar databases for articles reporting on fracture repair using dynamic locking plates, dynamized surgical techniques, and reverse dynamization. Data collection also included assessment of additively manufactured (AM) implants that provide dynamic mechanical behaviors.

Results: Forty articles were included for final review. It was found that accelerated rates of fracture healing can be achieved with staged 2-part surgeries or dynamic implant designs. Temporal dynamization, where static fixation of bones is followed by the introduction of micromotion and controlled loading, has been shown to improve callus volume and accelerate the healing response. Reverse dynamization, where micromotion is encouraged during early callus formation and arrested later, may represent a significant advance for the treatment of critical defect injuries. Advances in AM techniques will likely provide the ability to create high-resolution implants capable of dynamized and reverse dynamized modalities.

Conclusions: There is no one-size-fits-all approach to optimization of fracture healing. However, it has been clearly demonstrated that fracture treatment can be enhanced by systematically altering the construct stiffness throughout the different phases of healing, which may be achieved with AM implant designs.

Keywords: bone mechanotransduction, far cortical locking, fracture dynamization, interfragmentary motion

1. Introduction

Bone healing is a physiologically complex and multifactorial process, where the healing response and callus formation is intimately regulated by the external mechanical environment. Parameters that can influence the transfer of loads to the callus tissue include geometry of the fracture, gap size, type of fixation, stability of the fixation, and the magnitude and direction of interfragmentary motion (IFM) (Fig. 1). These global factors directly impact the local stresses and strains that occur at the fracture site, which influences a broad and cascading series of biological healing pathways.

It is difficult to optimize the speed and strength of fracture healing. Modulation of implant mechanical parameters can promote bone healing and reduce stress-shielding, which has led
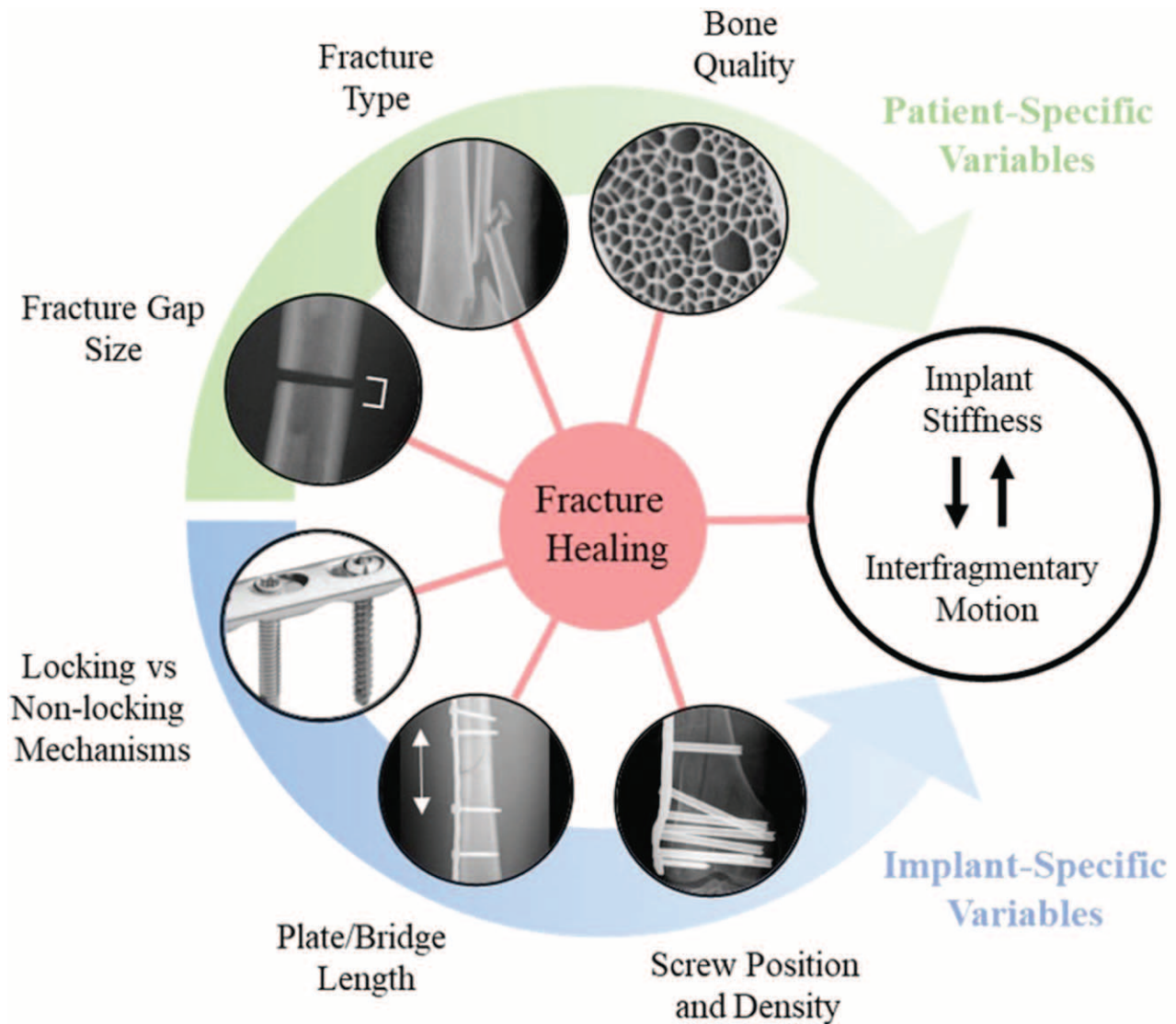
Figure 1. A diagram demonstrating some of the variables that must be considered for fracture care. Patient-specific variables are shown on the green arrow while implant and surgical technique variables are shown on the blue arrow. All of these can be important considerations in the context of bone healing, and all lead to changes in stiffness of the reconstruction and interfragmentary motion.

to the development of less-stiff, dynamic, or functionally graded implants. Additionally, it has been shown that bone healing may be further optimized by creating dynamized constructs capable of changing behavior over the course of time. Recently, it has been demonstrated that three-dimensional (3D) printing of orthopaedic implants allows production of components that have different mechanical properties but maintain identical external geometries. Adjustments to parameters such as polymer/metal chemistry, fiber thickness, porosity, and infill patterns may effectively improve the congruency of mechanical properties between implants and native bone and even allow for programmatic degradation of the printed implant.

This review will summarize the current knowledge and research regarding biomechanical principles and the clinical approaches that are currently used to enhance bone healing through dynamization of the fracture site (Table 1). It will also highlight implant design philosophies and demonstrate how additive manufacturing (AM) will play a future role in controlling load transmission across fracture sites.

2. Rigid fixation

Internal fracture fixation typically relies upon metallic implants, where the mechanical properties of the construct remain relatively unchanged over its lifespan. Throughout most of the 20th century, plates with nonlocking screws were commonly used to reconstruct fractures. These constructs require high bone quality and rely upon friction between the plate, screws, and bone to inspire primary bone healing. In the 1990s, locked plating technology revolutionized fracture care by providing rigidity independent from bone quality, which is especially useful in osteoporotic patient populations and severely comminuted fractures. The high rigidity of locking plate reconstructions has led to unique failure mechanisms, such as screw cutout, which represents a common indication for revision surgery.[1] Notably, cutout typically occurs in elderly patients, which suggests that overly rigid constructs can be problematic in the setting of poor bone quality.

Overly stiff implants cause insufficient magnitude of IFM, which ultimately results in stress-shielding and adverse remod-

Table 1

Summary of 9 key experiments and outcomes included in this review

Author	Populaton/ model	Sample size	Anatomy	Type of fixation	Intervention	Timing of intervention	Outcome
Nontemporal Dynamization Bottlang et al 2010[4]	Ovine, 3.0 mm defect	12 (6 per group)	Tibia	Internal fixation plates	Locked plates vs far-cortical locking plates	N/A	Callus bone mineral content was asymmetric in locked plate group. In far cortical locking specimens, medial and lateral callus had similar bone mineral content and specimens healed to be stronger in torsion and sustained 156% greater energy to failure in torsion than locked plating specimens.
Richter et al 2015[12]	Ovine, 3.0 mm defect	12 (6 per group)	Tibia	Internal fixation plates	5.0 mm dynamic locking screws vs rigid construct with standard bicortical locking-head screws	N/A	There was more uniform callus formation, significantly more callus formation at the near cortex, and biomechanically more competent bone-healing in the dynamic locking screw group compared with use of rigid locking plate constructs with locking head screws.
Bottlang et al 2014[13]	Adult human	33	Distal Femur	Internal fixation plates	Prospective, observational; fractures stabilized with MotionLoc FCL	N/A	None of the 125 FCL screws used for fixation failed or lost fixation. There were only 2 instances of revisions. Dynamic plating of distal femur fractures with FCL screws appeared to provide safe and effective fixation in patients.
Forward Dynamization Kempf et al 1985[19]	Adult human	52	Femur	IM Nail	All patients were initially treated with static IM nail. 45/52 patients underwent conversion to dynamic locking, where locking pins were removed. Weight bearing was allowed only after dynamization.	12 weeks	Dynamization via surgical intervention showed many advantages: the risk of infection and nonunion was low, incidence and severity of malunion was reduced, hospital stay was shortened, and earlier mobilization was possible.
Claes et al 2011[17]	Rat, 1.0 mm defect	22 (11 per group)	Femur	Custom-made external unilateral fixator (dynamization achieved via removal of inner fixator bar)	Rats were randomized into 2 different dynamization groups: early vs late. Previously published data of control groups, constant rigid, and flexible fixation groups were included for comparison.	3 or 4 weeks	Late dynamization after both 3 and 4 weeks led to a stiffer callus with a smaller callus bone volume compared with the flexible group. The week 4 late dynamization group exhibited a significantly greater elastic modulus and significantly smaller callus bone volume compared with the rigid group suggesting increased remodeling and more advanced healing.

Table 1

(continued).

Author	Populaton/model	Sample size	Anatomy	Type of fixation	Intervention	Timing of intervention	Outcome
Boerckel et al 2012[16]	Rats, 6.0 mm segmental defect	20 (10 per group)	Femur	Custom-designed internal fixation: compliant and stiff plates	Each group received 5.0 μg of rhBMP-2. Rats were randomized into groups where limbs were stabilized by either stiff fixation plates or stiff plates that could be dynamized to allowed transfer of compressive ambulatory loads	4 weeks	Loading significantly increased regenerate bone volume and average polar moment of inertia. Functional transfer of axial loads altered rhBMP- induced large bone defect repair by increasing the amount and distribution of bone formed within the defect.
Reverse Dynamization Glatt et al 2016[22]	Rats, large 5.0 mm segmental defect	72 (main study: 12 per group)	Femur	Custom-made external fixator	Each group received 5.5 μg of rhBMP-2. Rats were randomized into 2 different starting stiffnesses: low (114 N/mm) and very low (25.4 N/mm)	High stiffness (254 N/mm) was imposed after 2 weeks	Reverse dynamization starting with very low stiffness was detrimental to healing. The low stiffness group significantly improved healing and exhibited increased mechanical strength, and smaller callus formation.
Glatt et al 2012[25]	Rats, large 5.0 mm segmental defect	36 (12 per group)	Femur	Custom-made external fixator	Each group received 11 μg of BMP-2. Rats were randomized into groups that were allowed to heal with low, medium, or high-stiffness fixators, as well as under conditions of reverse dynamization, in which the stiffness was changed from low to high.	2 weeks	Under constant stiffness, the low-stiffness fixator produced the best healing after 8 weeks. Reverse dynamization provided considerable improvement and resulted in acceleration of the healing process.
Müller et al 2015[26]	Rabbits, 1.0 mm vdefects	14 (7 per group)	Tibia	NiTi-SMA (shape memory alloy) internal implant	Rabbits were randomised into control or noninvasive electromagnetic induction heating groups	3 weeks postop	Electromagnetic induction heating caused successful SMA activation with visible radiographic and macroscopic changes of the implant. All osteotomies healed. Bending stiffness increased over time in the treatment group, although differences were not significant.

eling.[2] Robust secondary fracture healing requires controlled IFM at the fracture site[3] and independent groups have demonstrated how rigid locking plates do not foster this milieu.[3,4] The inherent axial flexibility of long and narrow plates permits bending, but this only results in IFM at the far cortex of the fracture gap while IFM directly beneath the plate is arrested.[3] The undesirable heterogenous healing across the fracture site is clearly demonstrated by the development of asymmetric and inadequate callus formation, fixation failure, and late nonunion.[5,6]

3. Dynamized reconstructions

Dynamic or dynamized locking plates provide homogenous load distributions across the fracture site but do not change mechanical behavior as a function of time. Originally,

dynamization of the construct was achieved by over drilling the near cortex. This arrangement permits the screw and plate to toggle in response to external loading. It has been shown that this technique provides a mechanical environment that improves callus formation and reduces nonunion rates in distal femur fractures.[7] Near cortex over-drilling has been refined, and patented technologies such as Far Cortical Locking (FCL) and MotionLoc screws are examples of commercially available options that provide axial dynamization of locked plating constructs and allow for controlled IFM via elastic flexion of the screw shafts.[8,9]

Several groups have demonstrated that dynamic locking plates effectively reduce overall construct stiffness in cadaveric models[4,10] and improve callus formation in animal models compared with rigid locked plate constructs.[11,12] FCL reconStructions rely heavily on screw purchase on a single

cortex and this represents a potentially fatal flaw in the approach. However, a prospective observational study of distal femur FCL constructs determined that FCL provides safe and effective fixation in humans, as none of the screws used for far cortex fixation failed.[13] The remaining drawback of nontemporal dynamization consists of the potential for early loss of stability before a bridging callus is formed. In these scenarios, complications such as delayed union, refracture, or the development of a secondary deformity are likely to occur.[14]

4. Temporal dynamization

Implant designs and surgical techniques have continued to evolve to better correspond with our current understanding of bone biology. Approaches have been developed to alter the construct stiffness from a rigid to flexible state over time. Several studies have clearly demonstrated how early rigidity of a reconstruction allows for primary bone healing to take place, while the late introduction of motion activates the pathways for secondary healing.[15,16] A variety of other experiments have confirmed that delayed introduction of motion leads to a faster overall rate of healing.[2,17] The combination of primary and secondary healing processes facilitates faster bone remodeling and results in healed bone possessing mechanical strength most similar to intact bone.[11]

Implants can be dynamized with a secondary surgery. The first clinical investigations utilizing this approach were conducted using external dynamic axial fixators on tibial diaphyseal fractures and reported improved rates of healing.[18] In 1985, Kempf et al[19] demonstrated how a diaphyseal femoral shaft fracture can be treated with an intramedullary nail and subsequently dynamized by removing a distal locking screw. In this study, the temporally dynamized implant increased IFM, stimulated more robust callus formation and secondary healing, while successfully guarding against excessive mobility.

The timing of dynamization is important. In the case of comminuted or highly unstable fractures, early introduction of IFM may hinder fracture stabilization and remodeling.[20] If timed appropriately, however, application of controlled loads to these severe injuries still improves secondary bone healing and avoids stress shielding.[11] The timing of a secondary dynamization surgery is typically left to the discretion of the attending surgeon. To date, there is limited consensus on this subject, which may be due to the diversity of dynamization strategies, variations in experimental design and variables related to patient comorbidities, fracture type, and fragment geometry. Small animal models have been used to explore how temporal dynamization improves histologic and biomechanical properties compared with statically rigid or flexible implants. Using a rat femur model, Claes et al[17] demonstrated superior results when dynamization was initiated at 3 and 4 weeks postsurgery compared with 1 week. Similar results were reported by Boerckel et al[16] who demonstrated that the functional transfer of axial loads by modulation of fixation plate stiffness from stiff to compliant at 4 weeks in a rat femur defect model significantly enhanced BMP-mediated repair.

Expansion of this treatment paradigm to applications in human implants appears promising. In a very recent study, Schultz et al[21] delayed dynamization by developing a locking screw with a threaded degradable polymer locking mechanism. Upon initial implantation, the construct provided biomechanical fixation similar to a locking plate, but IFM was gradually introduced into the reconstruction as the polymer resorbed over time. This study was conducted in a synthetic bone model, but devices following this architype hold promise for future large animal and clinical trials. There is currently a dearth of FDA-approved fracture fixation devices specifically developed to employ temporal dynamization and this is an area that requires significant research.

5. Reverse dynamization

Recently, a theory of "reverse dynamization" has emerged, which directly contrasts the techniques discussed in the previous section. Specifically, loads are applied during the initial healing process and arrested after callus formation. Several critical defect animal model studies have shown that this approach shortens healing time in comparison with a control group utilizing standard rigid fixation approaches.[22,23] It is posited that this phenomenon occurs because flexible fixation promotes greater callus formation during the proliferative phase of healing, while the greater callus size allows fragments to be stabilized and mineralization to occur faster.[24,25]

Novel implant designs are being developed to eliminate the need for external fixators to deliver reverse dynamization to a fracture site. For example, Müller et al[26] utilized nitinol, a shape-memory alloy to build fixation plates that provide in situ temporal variation of bending stiffness. The efficacy of this design was tested in a rabbit tibial osteotomy model and the nitinol implants led to a trend of higher bending stiffness of the healed tibiae. This study stands as an important first step toward optimizing a noninvasive reverse dynamization model. This provides an intriguing option for repairing large segmental defects in long bones, as these injuries do not heal spontaneously and FDA-approved treatment options are scarce. Clinical translation for reverse dynamization is on the horizon. Because experiments performed thus far have investigated only large segmental defect models, it is unclear whether reverse dynamization will prove effective in subcritical size defects and comminuted fractures. Additionally, further research is required to understand the cascading biological mechanisms involved in reverse dynamization.

6. Applications for additive manufacturing (AM)

Dynamization of fracture implants represents a significant design challenge, but fortunately, AM may provide a much-needed tool to help solve this problem. To the best of our knowledge, there are no research endeavors that are currently exploring the use of AM to design and produce implants specifically for dynamized or reverse dynamized applications. However, it is easy to envision the development of sophisticated dynamized implant concepts that are developed with functionally graded or bio-absorbable 3D-printed materials.

A wide variety of processes and biocompatible materials are available for various orthopaedic contexts, which offers significant potential for patient-specific medical implant design. Additively manufactured biocompatible materials include metallic materials, polymers, and ceramics. Metallic alloys are typically used for load-bearing applications, and commonly used implant materials include stainless steel, cobalt-chrome alloys, titanium alloys, and tantalum.[27] Magnesium, iron, and zinc have also shown great promise, as these materials biodegrade over time,[28–30] and therefore may provide desirable degradation of mechanical properties for temporal dynamization. Bioceramic materials such as hydroxyapatite (HA) and calcium phosphate are osteogenic;

however, they are too brittle for load-bearing applications.[31] Commonly used 3D printed polymers include polycaprolactone (PCL), polylactic acid (PLA), polylactic-c- glycolic acid, and polyethylene glycol. Polyether ether ketone is another 3D-printed polymer used in biomedical applications that demonstrates desired mechanical properties for orthopaedic implants; however, it does not promote bone in-growth.[27]

Several studies have demonstrated the utility of AM by making changes to lattice structure and porosity of the implant. It is generally understood that osseointegration, cell growth, and vascularization is improved with pores ranging between 300 and 600 μm in size.[32] The shape of the lattice makes an impact on healing. For example, AM titanium-mesh scaffolds have been mechanobiologically optimized using a honeycomb-like structure. This process resulted in enhanced bone formation in large segmental bone defects in sheep.[33] Recently, a group created a graft substitute made of 3D-printed PLA with a variable lattice structure, which emulated the gradient porosity of real bone.[34]

The use of blended PLA-based copolymers in AM implant and scaffold designs has garnered considerable interest from the research community. The use of multiple printed materials creates a dynamized effect in which the implant is resorbed by the body in multiple stages. For example, implant fixation devices such as screws, pins, and bone plates have been 3D printed in PLA that has been loaded with selected drugs for localized, temporal delivery.[35] PLA can also be altered by adding HA to the polymer. Porous 3D-printed scaffolds composed of PLA and HA have been used to characterize the shape recovery potential of PLA scaffolds when exposed to direct heat.[36] Results demonstrated the potential for PLA/HA scaffolds to be used as selffitting small bone defect implants. Through the fused deposition modeling (FDM 3D-printing) process, PLA/HA scaffolds have been shown to bear load while promoting osteointegration.

Other biodegradable materials also have significant potential to be used for AM-based dynamized implant designs. First is a PCL/magnesium hydroxide nanoparticle blend. PCL is a well-established biodegradable polymer that has a slow degradation rate. When combined with bioabsorbable magnesium hydroxide nanoparticles, 3D-printed porous scaffolds made of this blend have demonstrated enhanced osteoblast adhesion and an accelerated scaffold degradation rate.[37] Due to the adjustable degradation properties of this composite material, it represents a viable option for manufacture of internal implants that incorporate temporal dynamization. Another experiment used a rabbit model to explore the effects of 3D printing implants with 2 materials: a polyglycolide (polylactic-c-glycolic acid)/lactide based polymer and a polydioxanone-based polymer, which have different degradation kinetics.[38] It was shown that the osteointegration of the polymer 3D-printed implants was comparable to Ti6A14V implants in the control group, which confirmed the biological efficacy and safety of the novel devices. It has also been shown that 3D-printed beta tri-calcium phosphate scaffolds are biocompatible and resorbable, and lead to bone regrowth with concurrent reduction in scaffold volume.[39] From this, beta tri-calcium phosphate demonstrates the potential to be used for dynamized implant applications. As a last example, a recent pilot study successfully facilitated bone formation in femoral critical sized defects in sheep using 3D-printed biomimetic polybutylene terephthalate scaffolds.[40] Because these implants were created with AM techniques, it was possible to create these scaffolds in an inverse trabecular pattern to promote bone ingrowth that mimicked normal trabecular bone.

Further research should be conducted to examine the utility of gradient lattice structures created with 3D-printed bioresorbable composite materials, which may represent a key design element when creating implants with dynamization and reverse dynamization applications in mind. Topology optimization methods, which optimize the performance of a material layout based on given loads and boundary conditions, can also improve biomechanical performance, promote osseointegration, and reduce weight and material costs of implants. Additionally, AM can reduce the time it takes to design and produce a patientspecific implant for time-sensitive surgeries.

7. Implications for clinical practice

This review has summarized the most current and significant advances related to dynamic implant designs, fracture healing, and bone regeneration. Based upon the studies presented here, there is no one-size-fits-all approach to optimization of fracture healing, just as there is no single set of mechanical conditions that is suitable for all stages of fracture repair. Despite the lack of consensus on a single approach, it has been clearly demonstrated that bone fracture treatment is enhanced by systematically altering the construct stiffness throughout the different phases of healing, which may be achieved with AM implant designs. Ultimately, decreasing the time to full healing will also involve improving decisions with respect to early weight bearing and postoperative rehabilitation protocols. Although this review refrained from intimately discussing the biological components that orchestrate fracture healing, considerations from tissue engineering, and regenerative medicine are also needed to better understand this topic.

Temporal dynamization of constructs has the potential to shift paradigms of orthopaedic and regenerative medicine. Modulation of stiffness via internal or external fixation strategies to achieve union, especially in the presence of challenging fractures, has tremendous potential to improve functional outcomes while simultaneously reducing healthcare costs. Advancements in AM techniques will likely help to revolutionize the development and application of dynamized implants. However, before these designs can be incorporated into clinical practice, robust and comprehensive experiments must be performed in the arenas of engineering and basic science.

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