

Toward biologically functional ACL repair: from mechanical reconstruction to regenerative strategies

Abstract

Anterior cruciate ligament (ACL) injury is a common orthopedic problem that affects knee stability, athletic function, and long-term joint health. Current ACL reconstruction techniques can restore mechanical stability, but they do not fully reproduce the biological structure and function of the native ligament. This paper reviews healthy ACL anatomy, the failed healing environment after rupture, current reconstruction options, clinical demand, and emerging regenerative strategies. Existing approaches, including autografts, allografts, and synthetic grafts, each address part of the problem but remain limited by incomplete remodeling, graft-to-bone integration challenges, reinjury risk, and long-term joint degeneration. Tissue-engineering strategies offer a promising path forward by combining biomaterial scaffolds, cellular activity, biologic signaling, mechanical conditioning, and interface engineering.

Keywords: anterior cruciate ligament, ACL reconstruction, regenerative medicine, tissue engineering, ligament repair, scaffold

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Abbreviations: ACL, anterior cruciate ligament; BPTB, bone-patellar tendon-bone; BEAR, bridge-enhanced ACL repair; PRP, platelet-rich plasma; PCL, polycaprolactone; PLGA, poly(lactic-co-glycolic acid)

Introduction

ACL injury is one of the most common and clinically significant ligamentous injuries of the knee, particularly among young and physically active populations.^{1,2} Because the ACL is a primary stabilizer of the knee, rupture can lead to functional instability, reduced activity participation, and long-term changes in joint health.^{3,4} Although ACL reconstruction has become the standard surgical approach for restoring stability, clinical outcomes remain imperfect, with many patients failing to return to their pre-injury level of sport and younger athletes remaining at elevated risk for secondary injury.^{5,6}

These limitations reflect a central challenge in ACL treatment: restoring mechanical stability is not the same as restoring native ligament biology.^{2,7,8} Current reconstruction typically replaces the torn ACL with an autograft, allograft, or synthetic substitute, each of which can reestablish gross joint stability but cannot fully reproduce the structure, composition, vascularity, innervation, insertion-site organization, or adaptive behavior of the native ligament.^{2,7,8} As a result, ACL reconstruction remains a powerful but biologically incomplete solution.

This gap has become increasingly important as ACL reconstruction continues to represent a high-volume and economically significant orthopedic procedure.^{9,10} Persistent challenges related to graft remodeling, reinjury risk, return-to-sport outcomes, and long-term joint preservation have motivated interest in therapies that support more complete tissue healing and integration.^{3,5,6,8} Regenerative medicine and tissue engineering offer one pathway toward this goal by combining mechanical support with biological cues designed to guide remodeling, incorporation, and functional restoration.^{7,11,12}

This paper reviews the progression from conventional ACL reconstruction toward emerging regenerative strategies. Healthy ACL

structure and failed healing after injury are first examined to define the biological problem, followed by discussion of current reconstruction products, market demand, translational regenerative approaches, and tissue-engineering directions. Together, these topics highlight the ongoing shift from mechanical replacement toward biologically functional ligament repair.

Healthy ACL structure and function

The ACL is a dense connective tissue structure that extends from the femur to the tibia and contributes substantially to knee joint stability.¹³ The ligament primarily resists anterior tibial translation and also contributes to control of rotational motion during dynamic knee loading.^{13,14} The ACL is commonly described as having two functional bundles: the anteromedial bundle and the posterolateral bundle.¹³⁻¹⁵ The anteromedial and posterolateral bundles become differentially tensioned throughout knee flexion and extension. This bundle organization allows the ACL to contribute to knee stability across multiple joint positions and loading conditions.^{13,14}

At the extracellular matrix level, the ACL is composed primarily of dense, hierarchically organized collagen fibers.¹³ Type I collagen is the dominant structural protein in the ACL and provides much of the ligament's tensile strength.^{12,13} Smaller amounts of type III collagen, proteoglycans, glycoproteins, elastin, and water contribute to the ligament's viscoelastic and biochemical properties.^{12,16} ACL collagen is organized into progressively larger structural units, creating a hierarchical architecture that supports tensile load transmission during knee motion.^{12,13} The extracellular matrix therefore provides both the mechanical strength and the tissue organization required for normal ligament function.^{12,16}

The cellular population of the ACL consists primarily of fibroblast-like ligament cells embedded within the extracellular matrix.^{12,16} These cells maintain matrix homeostasis by regulating collagen turnover, extracellular matrix remodeling, and tissue repair responses.^{12,16} Ligament cells are mechanosensitive, meaning their behavior can be influenced by mechanical strain and other physical cues within the tissue environment.^{17,18} Mechanical loading can affect

cell differentiation, collagen organization, and matrix production in ligament and tendon tissues. This relationship between loading and cellular activity is an important feature of normal ligament biology.^{17,18}

The ACL has a limited vascular supply compared with many extra-articular connective tissues.^{2,19} Its vascularity is derived primarily from branches of the middle genicular artery, with vessels entering the ligament through the surrounding synovial sheath.¹³ This vascular organization supports the metabolic needs of the native ligament but is relatively limited compared with tissues that heal more effectively after injury. The ACL's intra-articular location and vascular pattern are therefore important biological features of the native ligament environment.^{2,19}

The ACL also contains neural elements that contribute to proprioceptive function. Mechanoreceptors within the ligament provide sensory feedback related to joint position and movement. This sensory role means that ACL function involves both mechanical restraint and neuromuscular control of the knee. Proprioceptive input from the ACL contributes to functional joint stability during dynamic movement.²⁰

The ACL inserts into bone through a specialized ligament-to-bone interface known as the enthesis. The native enthesis transitions from ligament to fibrocartilage to mineralized fibrocartilage to bone.^{21–23} This graded structure helps distribute mechanical loads between soft ligament tissue and hard bone.²³ Together, the ACL's bundle anatomy, collagen hierarchy, cellular composition, vascular supply, proprioceptive function, and enthesis structure define the biological complexity of healthy ligament tissue.^{13,20,23} These features establish the biological baseline that is disrupted after ACL rupture.

ACL injury and the failed healing environment

ACL rupture disrupts the organized structure of healthy ligament tissue.^{2,19} The injury interrupts collagen fiber continuity and prevents the ligament from transmitting normal tensile loads across the knee joint.^{2,19} Loss of ACL function increases anterior tibial translation and rotational instability. These biomechanical changes can affect knee motion during cutting, pivoting, landing, and deceleration activities.^{4,13} ACL rupture therefore changes both the local ligament structure and the broader mechanical environment of the knee joint.^{3,4}

The ACL has limited capacity for spontaneous healing compared with extra-articular ligaments such as the medial collateral ligament.^{2,19} Successful ligament healing typically requires formation of a provisional fibrin clot that bridges the torn tissue ends and supports cellular migration into the injury site.² The ACL is located within the intra-articular synovial environment, which interferes with the formation and persistence of a stable bridging clot after rupture. Synovial fluid can dilute or disrupt the provisional clot, preventing the torn ACL ends from forming a durable scaffold for repair. Without a stable bridging matrix, reparative cells cannot effectively span the injury gap, and intrinsic ACL healing is limited.^{2,19}

The biological environment after ACL rupture is also influenced by inflammation, hemarthrosis, matrix degradation, and altered cell signaling within the joint.^{2,19} These post-injury changes can involve cartilage, meniscus, synovium, and subchondral bone. Meniscal injury and cartilage damage are commonly associated with ACL rupture and contribute to long-term joint degeneration. Post-traumatic osteoarthritis remains a major long-term consequence of ACL injury, even in patients who undergo reconstruction. This suggests that ACL rupture should be understood as a whole-joint injury rather than only an isolated ligament tear.^{3,4}

Injured ACL tissue differs from healthy ACL tissue in several key biological and structural ways. Healthy ACL tissue contains continuous collagen fiber organization, resident ligament cells, vascular support, proprioceptive innervation, and specialized ligament-to-bone interfaces.^{13,20,23} Injured ACL tissue loses collagen continuity, mechanical load transmission, and the local structural environment required for effective bridging repair. The intra-articular environment further limits healing by disrupting clot formation and exposing the injured ligament to synovial fluid. These biological differences explain why ACL rupture rarely heals reliably without intervention.^{2,19} The contrast between healthy and injured ACL tissue is illustrated in Figure 1.

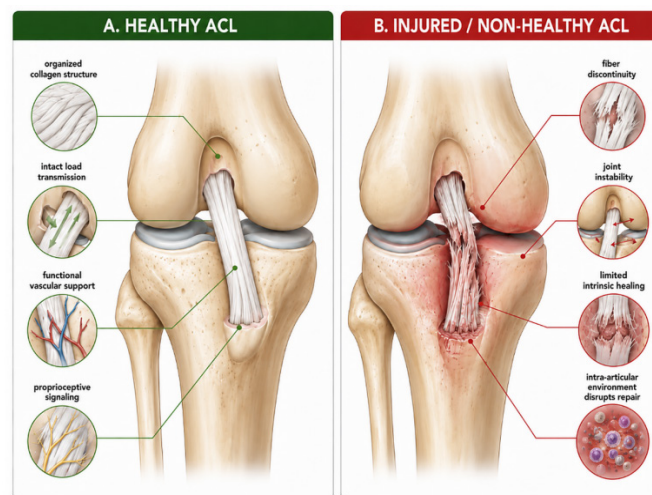


Figure 1 Healthy versus injured ACL tissue.

The image compares healthy ACL tissue with injured/non-healthy ACL tissue, highlighting organized collagen structure, intact load transmission, vascular support, proprioceptive signaling, fiber discontinuity, joint instability, limited intrinsic healing, and disruption of repair in the intra-articular environment.

Current clinical solutions for ACL reconstruction

Because the ruptured ACL does not reliably re-establish this structure on its own, current clinical care relies primarily on surgical reconstruction to restore functional knee stability.^{2,7} ACL reconstruction replaces the torn native ligament with a graft that is positioned to approximate the course of the original ACL between the femur and tibia.^{4,15} In a standard reconstruction, tunnels are created in the femur and tibia, and the graft is passed through these tunnels to recreate a functional restraint across the knee joint. The graft is then fixed within or near the bone tunnels using fixation devices such as interference screws, suspensory buttons, posts, or staples.^{4,15} Although surgical techniques vary, the overall goal is to restore knee stability by replacing the torn ACL with a structure capable of resisting anterior tibial translation and rotational loading.^{4,13}

Autografts are among the most commonly used graft options for ACL reconstruction, particularly in young and active patients. Autograft reconstruction uses the patient's own tissue, most commonly bone–patellar tendon–bone or hamstring tendon grafts. Bone–patellar tendon–bone grafts include a central strip of patellar tendon with bone plugs harvested from the patella and tibial tubercle. The bone plugs can support bone-to-bone healing within the femoral and tibial tunnels, which is one reason this graft type has been widely used in athletic populations. Hamstring autografts are typically harvested from the semitendinosus tendon, with or without the gracilis tendon, and are folded or bundled to create a multi-strand soft tissue graft.^{15,24}

Hamstring grafts avoid harvesting the central patellar tendon, but they depend on soft tissue-to-bone healing within the tunnels rather than direct bone-to-bone healing.^{21,24}

Autografts are clinically attractive because they use living patient-derived tissue and avoid the disease transmission and processing concerns associated with donor tissue. However, autograft harvest creates a second surgical injury at the donor site. Bone–patellar tendon–bone graft harvest is associated with anterior knee pain, kneeling discomfort, and potential morbidity at the patellar tendon harvest site. Hamstring tendon harvest can contribute to flexion strength deficits and changes in hamstring function after surgery. These tradeoffs make autograft selection dependent on patient age, activity level, sport demands, surgeon preference, and risk tolerance.^{4,24}

Allografts provide an alternative graft source by using donor tissue rather than tissue harvested from the patient. Common allograft sources include tibialis anterior tendon, Achilles tendon, patellar tendon, and other cadaveric soft tissues.^{15,24} Allografts avoid donor-site morbidity and can reduce operative time because no autologous graft harvest is required. Allografts are also useful in revision reconstruction or multiligament knee injuries, where additional graft tissue may be needed.^{4,24} However, allografts are processed before implantation, and sterilization or preservation methods can influence graft mechanical properties and biological incorporation. Allografts generally incorporate more slowly than autografts, and higher failure rates have been reported in young and highly active patients.²⁴

Synthetic grafts were developed to provide immediate mechanical stabilization while avoiding limitations related to tissue harvesting and donor tissue availability.^{25,26} Synthetic ACL devices have included materials such as expanded polytetrafluoroethylene, polyester, polyethylene terephthalate, and other polymer-based structures. Commercial and historical examples include Gore-Tex ligaments, Dacron grafts, Leeds-Keio ligaments, and the Ligament Advanced Reinforcement System. These devices are designed to act as artificial load-bearing substitutes or reinforcements for the torn ACL. Their technical appeal comes from their predictable manufacturing, high initial tensile strength, immediate availability, and avoidance of donor-site morbidity.^{25,26}

Despite these advantages, synthetic grafts have had variable clinical performance. Earlier synthetic ligaments were associated with complications such as graft rupture, tunnel widening, synovitis, wear debris, and foreign-body responses. More recent synthetic systems have attempted to improve biocompatibility, fatigue resistance, and tissue ingrowth through changes in material structure and surface architecture. However, synthetic grafts remain fundamentally different from native ligament tissue because they are manufactured devices rather than living, remodeling tissues.²⁶ As a result, synthetic grafts may provide mechanical reinforcement without fully recreating the biological organization, cellular remodeling, proprioceptive function, or enthesis structure of the native ACL.^{13,20,23,26}

Overall, current clinical solutions can restore functional knee stability by replacing the torn ACL with autograft, allograft, or synthetic material.^{2,7,24} Autografts provide reliable clinical performance but require donor tissue harvest. Allografts reduce donor-site morbidity but have slower incorporation and higher failure risk in certain high-demand populations.²⁴ Synthetic grafts offer immediate mechanical support but have historically struggled with biological integration and long-term performance.^{25,26} These differences show that current reconstruction strategies solve the immediate problem of mechanical instability, but they differ substantially in how they interact with

the biological environment of the knee.^{2,7,24} Representative graft categories and examples are summarized in Figure 2.

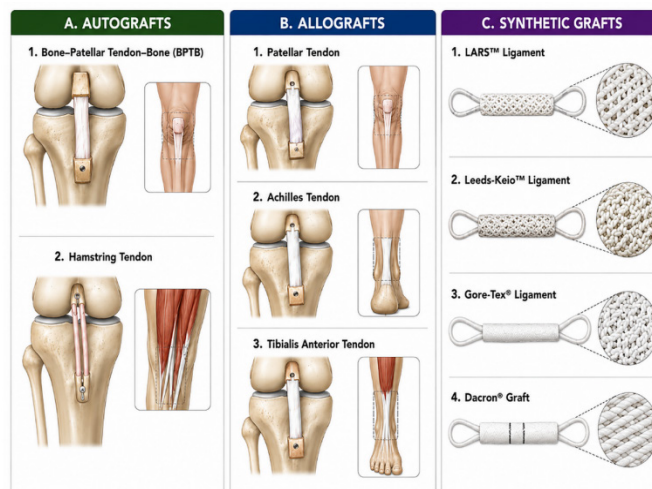


Figure 2 Current ACL reconstruction options.

The image summarizes current ACL reconstruction options, including autografts, allografts, and synthetic grafts, with representative graft types and artificial ligament examples.

Persistent biological and functional limitations after reconstruction

Although ACL reconstruction can restore functional knee stability, the implanted graft does not immediately function as a fully biological replacement for the native ACL.^{2,7} After implantation, the graft undergoes a prolonged remodeling process known as ligamentization, which includes cellular repopulation, revascularization, extracellular matrix remodeling, and gradual mechanical adaptation. However, this process is variable and does not consistently recreate the native ligament structure as previously described.^{8,22,27}

One major limitation is that reconstruction depends on graft remodeling rather than true regeneration of the original ACL. While the native ACL contains specialized matrix organization, vascular features, neural elements, and graded insertion sites, reconstructed grafts typically regain these properties incompletely and unpredictably.^{2,8,20,23} As a result, surgical reconstruction can restore gross mechanical stability without fully restoring the biological complexity of the original tissue.^{2,8}

Graft-to-bone healing remains a particularly important challenge after reconstruction. Rather than re-forming the original native enthesis, the implanted graft must incorporate within surgically created femoral and tibial bone tunnels.^{21,22} Soft tissue grafts depend on tendon-to-bone integration rather than bone-to-bone healing, making tunnel incorporation especially important for hamstring and other soft-tissue grafts.^{21,24} Incomplete or delayed tunnel integration can affect graft maturation, fixation strength, and long-term remodeling.^{21,22}

Clinical outcomes also demonstrate that reconstruction does not fully eliminate functional risk after ACL injury.^{5,6} Many patients do not return to their pre-injury level of sport after ACL reconstruction. Younger and highly active athletes remain at elevated risk for secondary ACL injury after surgery. These outcomes reflect not only graft choice and surgical technique, but also biological graft remodeling, neuromuscular recovery, rehabilitation, sport demands, and patient-specific risk factors.^{5,6,16}

Long-term joint degeneration remains a major concern even after technically successful reconstruction. ACL injury is associated with increased risk of post-traumatic osteoarthritis, particularly when meniscal or cartilage damage is also present. Reconstruction can improve stability, but it does not necessarily normalize the biological and biomechanical environment of the joint. This suggests that mechanical stabilization alone is insufficient to fully reverse the long-term consequences of ACL rupture.^{3,4}

Together, these limitations reveal the central gap between ACL reconstruction and ACL regeneration. Current approaches can replace the torn ligament with a mechanically stabilizing graft, but they do not reliably restore the full biological function of native ACL tissue. This gap has motivated continued interest in regenerative and tissue-engineered strategies that aim to support not only knee stability, but also more complete biological restoration of ligament structure and function.^{7,11,12}

Market size, clinical demand, and unmet need

The limitations of current ACL reconstruction are especially important because ACL injury represents a high-volume clinical problem.^{1,10} An estimated 200,000 to 300,000 ACL reconstructions are performed annually in the United States. The economic burden of ACL injury is substantial, with direct surgical costs, rehabilitation expenses, lost productivity, and long-term osteoarthritis-related costs contributing to the overall societal impact. Procedure-level costs are commonly estimated in the range of several thousand to tens of thousands of dollars per reconstruction, depending on surgical setting, graft type, insurance coverage, rehabilitation, and associated injuries.¹⁰

The commercial market for cruciate ligament repair reflects this sustained procedural demand. The United States cruciate ligament repair market is projected to expand at a compound annual growth rate of approximately 6% through 2030. The global cruciate ligament repair market is projected to grow at a compound annual growth rate approaching 7% over a similar period. This growth is driven largely by ACL reconstruction procedures, which represent the dominant share of cruciate ligament repair interventions. North America currently represents a major share of the ligament repair market, while the Asia-Pacific region is projected to show rapid growth due to expanding healthcare infrastructure and increasing surgical adoption.⁹

ACL reconstruction dominates the cruciate ligament repair market because ACL injuries are more common and more frequently treated surgically than posterior cruciate ligament injuries. This market distribution highlights the disproportionate clinical burden of ACL rupture compared with other cruciate ligament injuries.^{1,9} The high procedural volume also means that even modest improvements in graft healing, reinjury rates, return-to-sport outcomes, or long-term joint preservation could have meaningful effects at the population level.^{5,6,10}

The market opportunity is therefore not simply the result of increasing procedure numbers. Rather, it reflects an unmet need for therapies that improve the biological and functional quality of ACL repair. Current reconstruction products address mechanical instability, but persistent limitations in graft remodeling, joint degeneration, and functional recovery indicate that there remains room for more biologically restorative approaches.^{2,3,8} The scale of ACL reconstruction creates a strong clinical and commercial rationale for regenerative strategies that can improve long-term outcomes while remaining surgically practical and translatable.^{7,11,12} These market trends are summarized in Figure 3.

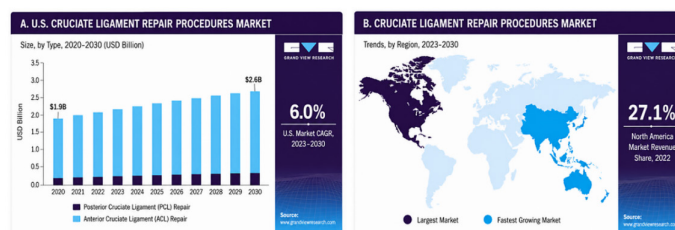


Figure 3 Cruciate ligament repair market trends 9.

The image shows market trends for cruciate ligament repair procedures, including projected U.S. market growth and regional market distribution.

Clinical translation: current regenerative trials and products

The unmet need in ACL reconstruction has led to increasing clinical interest in regenerative strategies that aim to improve the biological quality of ACL repair.^{2,7} Current translational approaches include collagen-based repair scaffolds, biologic augmentation with platelet- or marrow-derived therapies, biodegradable scaffold systems, combined intra-articular repair strategies, and rehabilitation protocols designed to optimize graft remodeling.^{28–30,33,35,36} While these approaches differ in design, they share a common goal of improving healing, integration, and long-term function beyond mechanical stabilization alone.^{2,8}

Bridge-Enhanced ACL Repair (BEAR) is one of the most advanced regenerative approaches currently being evaluated for ACL treatment. The BEAR technique uses a collagen-based scaffold placed between the torn ACL ends to support intrinsic ligament healing. The scaffold is combined with the patient's blood to create a provisional matrix that bridges the rupture site. This strategy directly addresses one of the key biological barriers discussed earlier: the failure of a stable clot to persist between torn ACL ends in the synovial joint environment.^{2,19} Early clinical studies have reported patient-reported outcomes and knee stability measures comparable to autograft reconstruction in selected patients.^{30,31} However, long-term durability, patient selection, healing consistency, and broader clinical indications remain important questions for continued study.^{2,31}

Platelet-rich plasma and bone marrow-derived biologics have also been investigated as methods to enhance ACL healing and graft incorporation. Platelet-rich plasma contains concentrated platelets and associated growth factors that may influence inflammation, cell recruitment, angiogenesis, and extracellular matrix remodeling.^{28,29} Bone marrow-derived therapies contain heterogeneous cell and signaling populations that may contribute to tissue repair through paracrine effects and regenerative signaling.^{29,32} These approaches are often intended to improve the biological environment around the graft or repair site rather than provide mechanical stability on their own.^{28,29} Clinical outcomes remain variable, partly because biologic preparations differ in cellular composition, platelet concentration, leukocyte content, activation method, delivery timing, and patient population.^{29,32}

Biodegradable scaffold-based approaches represent another translational strategy for ACL repair and reconstruction.^{33,34} These scaffolds are designed to provide temporary structural support while permitting cellular infiltration, extracellular matrix deposition, and gradual tissue remodeling.^{7,34} Early biodegradable scaffold systems demonstrated the feasibility of scaffold-guided ligament regeneration but were limited by challenges related to mechanical strength, degradation timing, integration, and long-term durability.^{7,33,34} More

recent scaffold designs have focused on improving fiber organization, biomaterial architecture, and biologic incorporation to better match the structural and mechanical demands of ligament healing.^{11,12,34}

Clinical translation has also emphasized that ACL healing depends on the broader joint and rehabilitation environment.^{35,36} Combined ACL-meniscus repair strategies reflect the fact that ACL rupture often occurs alongside meniscal injury and broader intra-articular pathology.³⁵ Rehabilitation optimization studies also recognize that controlled mechanical loading can influence graft maturation, functional recovery, and long-term outcome.^{17,18,36} These efforts reinforce the idea that ACL repair is not only a question of graft material, but also of biological context, mechanical environment, and post-operative remodeling.^{2,17,18}

Overall, current regenerative trials and products represent important progress toward biologically informed ACL repair.^{2,30,31} BEAR attempts to restore intrinsic ligament healing by replacing the missing provisional scaffold at the rupture site.^{30,31} PRP and bone marrow-derived therapies attempt to improve the signaling environment for healing and remodeling.^{28,29,32} Biodegradable scaffolds attempt to provide temporary templates for new tissue formation.^{33,34} However, these approaches also illustrate the difficulty of reliably combining mechanical strength, biological activity, integration, and long-term functional restoration.^{7,11,12} This translational gap provides the rationale for examining tissue-engineering strategies in greater detail (Table 1).

Table 1 Overview of current regenerative ACL repair strategies and translational considerations

Approach	Goal	Key takeaway	References
BEAR implant	Promote intrinsic ACL healing using a collagen scaffold combined with autologous blood or biologic matrix.	Patient-reported outcomes and knee stability can be comparable to autograft reconstruction in selected populations, but long-term durability, patient selection, and consistency across broader cohorts remain important questions.	30,31
PRP augmentation	Enhance graft incorporation and modulate the intra-articular healing environment.	Strong biologic rationale exists, but clinical studies and systematic reviews show variable results that may depend on preparation method, delivery timing, and patient population.	28,29,32
Bone marrow-derived biologics	Provide heterogeneous cell and signaling populations that may support tissue repair through paracrine signaling.	These therapies may improve the healing environment, but their cellular composition and biologic activity are difficult to standardize across patients and preparation methods.	29,32
Biodegradable scaffold systems	Enable scaffold-guided ACL repair or reconstruction using temporary resorbable structures.	Early systems demonstrated feasibility but were limited by mechanical strength, degradation timing, integration, and long-term durability.	7,33,34
Combined ACL-meniscus repair	Address concomitant intra-articular injury to support more complete joint restoration.	This approach recognizes that ACL rupture is often a whole-joint injury involving meniscus, cartilage, synovium, and subchondral bone.	3,4,35
Rehabilitation/loading optimization	Determine whether controlled mechanical loading improves graft maturation and clinical recovery.	Mechanical loading may influence graft remodeling and tissue properties, but optimal rehabilitation timing and long-term benefits remain to be defined.	17,18,36

Emerging tissue-engineering directions for ACL regeneration

Because current regenerative trials have not yet fully resolved the challenge of restoring both mechanical function and biological organization, preclinical tissue-engineering strategies have increasingly focused on recreating key features of native ligament tissue.^{7,11,12} These approaches generally aim to combine biomaterial scaffolds, cellular activity, biochemical signaling, and mechanical conditioning to support organized ligament-like tissue formation. Rather than treating the ACL graft as only a passive structural replacement, tissue-engineering strategies seek to guide the formation, remodeling, and integration of new tissue within the joint environment.^{7,11,12}

Scaffold design is one of the central components of ACL tissue engineering.^{7,11,12} A scaffold can provide temporary structural support while creating a three-dimensional environment for cell attachment, migration, proliferation, and extracellular matrix deposition.^{7,11} Natural biomaterials such as collagen and silk have been investigated because they can support cell attachment and provide biochemical cues similar to native extracellular matrix.^{11,12,37} Synthetic polymers such as polycaprolactone and poly(lactic-co-glycolic acid) have

also been explored because their mechanical properties, degradation rates, and architecture can be engineered more precisely.^{7,11,38} Hybrid scaffolds attempt to combine the biological advantages of natural materials with the mechanical tunability of synthetic polymers.^{11,38}

A major design priority is recreating the aligned and anisotropic structure of ligament extracellular matrix.^{11,12} Native ACL collagen fibers are organized along functional loading directions, and this alignment contributes to tensile load transmission.^{12,13} Electrospinning, braiding, and textile-based fabrication methods can generate fiber-aligned scaffolds that help orient cells and guide matrix deposition.^{11,34,38} Braided biodegradable scaffolds have been studied for ACL regeneration because they can provide tensile reinforcement while allowing tissue ingrowth between fibers.³⁴ Electrospun polycaprolactone grafts have also been evaluated as ligament scaffolds because their fibrous architecture can mimic aspects of extracellular matrix organization.³⁹ However, engineered scaffolds must balance porosity, fiber alignment, degradation, and mechanical strength to support both early stabilization and long-term remodeling.^{7,11,39}

Cell-based strategies have also been explored to improve ligament regeneration.^{7,12,40} Potential cell sources include ligament fibroblasts, tendon-derived cells, bone marrow-derived mesenchymal stem cells,

adipose-derived stem cells, and other progenitor cell populations.^{7,40} These cells may support matrix production, remodeling, and ligament-like differentiation within engineered constructs.^{12,40} Mesenchymal stem cells are of particular interest because they can respond to biochemical and mechanical cues and may contribute to tissue repair through both differentiation and paracrine signaling. However, cell-based approaches face challenges related to cell survival, phenotype stability, delivery method, manufacturing consistency, cost, and regulatory complexity.^{32,40}

Biologic signaling strategies are often used to enhance cellular recruitment, matrix deposition, vascularization, and graft integration.^{29,32} Growth factors such as platelet-derived growth factor, transforming growth factor beta, vascular endothelial growth factor, and bone morphogenetic protein-related signals have been studied for their roles in connective tissue repair, angiogenesis, matrix remodeling, and bone integration.^{32,38} Platelet-rich plasma and bone marrow-derived products represent clinically accessible biologic sources, but their effects remain difficult to standardize because their composition varies across preparation methods and patients.^{29,32} Controlled release systems may improve biologic delivery by localizing signaling molecules within the scaffold and regulating their release over time.^{11,38}

Mechanical stimulation is another important direction in ACL tissue engineering because ligament cells respond to physical loading. Cyclic strain can influence cell alignment, collagen synthesis, matrix organization, and differentiation in ligament and tendon tissues. Bioreactor systems have therefore been used to mechanically condition engineered ligament constructs before implantation. These systems attempt to expose developing constructs to controlled loading environments that encourage organized extracellular matrix deposition and improved mechanical properties.^{12,17,18} Mechanical conditioning is especially relevant for ACL regeneration because the native ligament functions in a dynamic joint environment rather than a static load-free setting.^{17,18}

Ligament-to-bone interface engineering is also critical for improving ACL repair.^{21–23} As discussed earlier, the native ACL attaches to bone through a graded enthesis rather than a simple soft tissue-to-bone junction. Tissue-engineered strategies have therefore explored multiphasic scaffolds, mineralized scaffold regions, and gradient biomaterials designed to support more organized integration between ligament-like tissue and bone.^{23,34} Improved interface engineering could enhance fixation strength, reduce stress concentration, and support more durable graft maturation over time.^{21,22,23}

Despite their promise, tissue-engineered ACL strategies remain difficult to translate clinically.^{7,8,11} Constructs must provide enough early mechanical strength to stabilize the knee while also remaining porous, degradable, and biologically active enough to support tissue ingrowth and remodeling.^{7,11} Materials that are mechanically strong may not degrade or remodel appropriately, while highly bioactive materials may lack sufficient early tensile strength.^{7,11} Cell-seeded and growth factor-loaded products introduce additional challenges related to manufacturing, sterilization, storage, reproducibility, cost, and regulatory approval.^{32,40} These barriers explain why many regenerative ACL concepts remain preclinical despite strong biological rationale.^{7,8,11}

Overall, emerging tissue-engineering strategies represent a shift from replacing the ACL toward guiding its biological restoration. Scaffold architecture, fiber alignment, cellular activity, biologic signaling, mechanical stimulation, and interface engineering each address different aspects of the native ligament environment.^{7,11,12} However, no single strategy has fully solved the combined requirements of strength, remodeling, integration, proprioceptive recovery, and long-term joint protection.^{7,8,11} The next stage of ACL product development will likely require hybrid designs that integrate multiple tissue-engineering principles into a surgically practical and clinically scalable system (Table 2).^{7,11,38}

Table 2 Overview of tissue-engineering directions for ACL regeneration

Strategy	Role in ACL regeneration	Key translational challenge	References
Scaffold design	Provides temporary structural support and a three-dimensional environment for cell attachment, migration, proliferation, and matrix deposition.	Must balance early mechanical strength with porosity, degradation, tissue ingrowth, and manufacturability.	7,11,12,38
Aligned fiber architecture	Uses electrospinning, braiding, or textile-based fabrication to guide cell orientation and ligament-like matrix deposition along loading directions.	Highly aligned structures must still permit cellular infiltration, vascular access, remodeling, and durable load transfer.	11,12,13,34,38,39
Cell-based strategies	Uses ligament fibroblasts, tendon-derived cells, mesenchymal stem cells, adipose-derived stem cells, or other progenitor cells to support matrix production and remodeling.	Cell survival, phenotype stability, manufacturing consistency, storage, cost, and regulatory complexity remain major barriers.	7,12,32,40
Biologic signaling and controlled release	Uses growth factors, PRP, bone marrow-derived products, or controlled delivery systems to enhance recruitment, matrix deposition, vascularization, and integration.	Biologic effects are difficult to standardize because composition, dose, timing, and patient-specific responses vary.	11,29,32,38
Mechanical conditioning	Uses cyclic strain or bioreactors to promote cell alignment, collagen synthesis, extracellular matrix organization, and improved mechanical properties.	Preclinical loading environments may not fully reproduce the dynamic mechanical and biological conditions of the knee joint.	12,17,18
Ligament-to-bone interface engineering	Uses multiphasic scaffolds, mineralized regions, or gradients to better recreate the native enthesis between soft ligament tissue and bone.	The regenerated interface must integrate with bone tunnels while limiting stress concentration and supporting long-term fixation strength.	21,22,23,34

Conclusion

ACL reconstruction remains an important clinical solution for restoring mechanical knee stability, but current graft-based approaches do not fully recreate native ACL biology.^{2,7,8} Persistent challenges in graft remodeling, ligament-to-bone integration, reinjury risk, incomplete functional recovery, and long-term joint degeneration continue to motivate more biologically restorative strategies.^{3,4,21,22,27}

The progression from conventional reconstruction toward regenerative repair reflects a broader shift in ACL treatment goals. Rather than focusing only on replacing the ruptured ligament with a mechanically stabilizing graft, emerging strategies aim to support tissue remodeling, cellular activity, biologic signaling, mechanical adaptation, and more organized integration with bone. Current translational approaches such as BEAR, biologic augmentation, biodegradable scaffolds, combined intra-articular repair, and rehabilitation optimization demonstrate meaningful progress, but they also show how difficult it is to reliably combine biological activity with sufficient mechanical performance and long-term durability.^{28–36}

Future ACL repair will likely depend on clinically practical strategies that integrate several tissue-engineering principles into one coordinated system. Scaffold architecture, fiber alignment, cell recruitment, controlled biologic signaling, mechanical conditioning, and ligament-to-bone interface engineering each address different limitations of current reconstruction, but none is sufficient alone. The most promising direction is therefore not a purely mechanical graft or a biologic-only therapy, but a surgically practical approach that can restore stability while guiding durable biological remodeling and integration.^{7,11,12,38}

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Conflict of interest

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