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Vascularized bioprinting for neuroischemic diabetic foot ulcers and selected ischemic lower-limb wounds: A proposed vascular-surgery design framework

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Abstract

Diabetic foot ulcers (DFUs) are the evidence-dominant neuroischemic target for this review. Non-diabetic chronic limb-threatening ischemia (CLTI) tissue loss and selected post-revascularization or post-debridement arterial defects are included only as ischemic adjacent cohorts, because neuropathy cannot be assumed outside diabetes. Across these groups, perfusion failure, infection risk, persistent inflammation and extracellular-matrix failure compromise the wound bed; neuropathy and neuroimmune dysfunction are defining modifiers primarily in DFU. Three-dimensional bioprinting may help spatially position cells, bioinks and soluble cues for vascular, epithelial, immune and neural support, but current evidence is mainly preclinical and DFU-focused. This narrative review differs from platform- or material-centered reviews by organizing the evidence around vascular assessment, revascularization, infection source control, wound-bed preparation, offloading and limb-salvage endpoints. We define a four-level vascular evidence hierarchy, match candidate materials and payloads to specific wound scenarios, map diabetic molecular injury pathways to measurable design variables and classify predictable failure modes by evidence type. The resulting decision and translational pathways are proposed research heuristics, not clinically validated algorithms. Current evidence supports feasibility, mechanism selection and disease-matched study design; it does not establish clinical limb-salvage efficacy for printed constructs.

Keywords: 3D bioprinting; Diabetic foot ulcer; Chronic limb-threatening ischemia; Vascularization; Neurovascular regeneration; Bioink; Wound repair; Limb salvage

1. Introduction

Chronic lower-limb wounds sit at the intersection of vascular disease, diabetes, infection, neuropathy and tissue loss. In vascular surgery, this problem is most visible in DFU and CLTI, but these categories are not interchangeable: DFU commonly combines ischemia with neuropathy and repetitive loading, whereas non-diabetic CLTI may involve severe tissue ischemia without a neuroischemic phenotype. In both settings, revascularization, debridement, infection control and mechanical protection must be coordinated to preserve limb function. Yet restoring inflow does not automatically rebuild a durable wound bed, because the niche may remain hypoxic, inflamed, mechanically unstable or biologically unable to progress from inflammation to proliferation and remodeling¹⁻³.

Conventional wound dressings and skin substitutes can protect the wound surface and provide a temporary matrix, but they usually offer limited control over the spatial distribution of cells, vasculogenic cues, antimicrobial functions and neural-supportive signals. This limitation is most demanding in neuroischemic DFU, where the reconstructed interface must address vascular, immune, epithelial and neural constraints while withstanding load, bacterial exposure and repeated clinical manipulation. In ischemic adjacent cohorts without documented neuropathy, the vascular, structural and infection-control requirements remain relevant, but a neural payload is not automatically justified⁴⁻⁶.

Three-dimensional bioprinting is attractive in this setting because it can convert biological design into spatial architecture. In principle, printed constructs can place endothelial cells, pericytes, fibroblasts, keratinocytes, stromal cells, extracellular-matrix components, growth factors and vesicle-based therapeutics in reproducible patterns. This does not make bioprinting an established treatment for diabetic foot disease. The field remains dominated by preclinical models, platform demonstrations and general tissue-engineering studies. The useful question is narrower: which parts of bioprinting are most relevant to the neuroischemic wound problem, and how should they be developed for vascular-surgery workflows?⁷⁻¹³.

Recent reviews have summarized 3D bioprinting for DFUs, bioinks for chronic wound healing, diabetic wound models and biomaterials for vascularized or innervated regeneration^{5-7,10-18}. Most are organized around printing platforms, material classes, wound dressings, disease models or broad regenerative targets. The novelty of the present review is its organizing sequence: vascular assessment, revascularization when needed, infection source control, wound-bed preparation,

construct selection, offloading and recurrence-aware limb-salvage endpoints. This sequence turns platform capabilities into stage-specific design requirements and prevents endothelial staining, generic wound closure or a visually skin-like construct from being treated as evidence of functional perfusion or limb salvage.

The review makes four contributions. First, it separates the evidence-dominant neuroischemic DFU phenotype from ischemic adjacent cohorts and converts each into a bounded design brief. Second, it maps direct and indirect evidence so that platform feasibility is not confused with limb-salvage efficacy. Third, it provides a scenario-matching matrix that links perfusion, infection, defect depth and loading to material properties, cellular or molecular payloads, contraindications, minimum evidence and principal risks. Fourth, it integrates predictable failure modes and endpoint hierarchies into a proposed, explicitly unvalidated translational workflow.

This organizing logic also helps interpret newer primary studies without overclaiming. Recent DFU-directed printed scaffold work and xeno-free vascularized skin-graft models strengthen the feasibility case at the wound interface, while clinical reports on DFU plus peripheral arterial disease, post-revascularization soft-tissue reconstruction and long-term recurrence sharpen the translational questions around timing, coverage strategy and durable endpoints rather than proving printed-construct efficacy¹⁹⁻²³.

This review argues that vascularized bioprinting should be framed less as a replacement for existing dressings and more as a programmable repair platform for a coupled vascular, neural, immune and structural defect. Throughout the review, we distinguish evidence that directly concerns diabetic or ischemic wounds from evidence that only informs platform design. We first define the vascular-surgery wound niche, then synthesize printing platforms, vascularization strategies, neurovascular mechanisms and bioink design. We close by proposing a translation pathway that embeds printed constructs within revascularization, debridement, infection control and postoperative surveillance.

The clinical scope has one core group and two adjacent groups. The core group is neuroischemic DFU, which dominates the wound-specific evidence. The adjacent groups are non-diabetic CLTI tissue-loss wounds caused by peripheral arterial disease and selected lower-limb soft-tissue defects after revascularization or debridement where perfusion and durable coverage jointly determine salvage. Pure venous ulcers and isolated pressure injuries are outside scope unless a mixed arterial or neuropathic phenotype makes the design logic relevant. Transfer beyond DFU is a research extrapolation, not evidence of equivalent biology or efficacy.

These groups should not be collapsed. In DFU, neuropathy, repetitive plantar loading, microvascular dysfunction, infection and the diabetic metabolic milieu interact with ischemia; disease-matched models should therefore combine the relevant metabolic, neural, perfusion and mechanical stresses. In non-diabetic CLTI, the dominant lesion is macrovascular and tissue-level perfusion failure, and neural design is conditional on documented neuropathy or nerve injury. Post-revascularization arterial defects share requirements for viable wound-bed coverage, host-vessel connection and retention, but they do not reproduce the diabetic microenvironment. Accordingly, evidence can transfer across groups for perfusion, infection control, coverage and mechanics, whereas neural or metabolic claims require phenotype-specific validation.

1.1. Literature search and scope

This article is a narrative review organized as a vascular-surgery design framework. It is not a systematic review, meta-analysis or formal scoping review. We nevertheless used a transparent scoping-style search to reduce selection opacity and to distinguish direct wound evidence from wound-adjacent and platform evidence. The organizing question was: how should vascularized and neurovascular bioprinting be designed and tested for neuroischemic DFU, and which vascular or structural elements can reasonably be evaluated in selected ischemic lower-limb cohorts after vascular assessment, revascularization, debridement, infection source control and offloading? DFUs remain the core disease target. Non-diabetic CLTI tissue-loss wounds and selected arterial post-revascularization or post-debridement defects are treated as ischemic adjacent cohorts, not as neuroischemic wounds unless neuropathy or nerve injury is independently documented.

Searches were performed on 9 June 2026 in PubMed and OpenAlex. Semantic Scholar was queried during library construction but was not used as a primary database because rate limiting prevented reproducible retrieval. Records were restricted to publications from 2015 onward, with older foundational bioprinting papers retained when they defined the platform. The core PubMed search logic combined disease, printing and repair terms: (diabetic foot ulcer OR diabetic wound OR chronic wound OR ischemic wound OR chronic limb-threatening ischemia OR critical limb ischemia OR peripheral artery disease) AND (3D bioprinting OR bioprinting OR biofabrication OR 3D printed scaffold OR printed bioink) AND (vascularization OR angiogenesis OR perfusion OR endothelial OR neurovascular OR nerve OR innervation OR bioink OR hydrogel OR skin substitute). OpenAlex searches used the same concept blocks plus targeted clusters for vascularized skin, perfusable skin,

angiogenic bioinks, coaxial or microfluidic bioprinting, in situ bioprinting, extracellular vesicle wound repair, tissue-engineered vascular grafts, innervated skin and peripheral nerve scaffolds.

The searches retrieved 608 records (OpenAlex, n = 577; PubMed, n = 31), which yielded 466 unique records after DOI-, PMID- and normalized-title-based deduplication. Titles and available abstracts or metadata were then assigned an additive priority score: bioprinting or biofabrication (+4); vascular-surgery, diabetic-foot, chronic limb-threatening ischemia, ischemic-wound or revascularization relevance (+4); wound, ulcer, repair or regeneration (+3); vascularization, angiogenesis, endothelial or perfusion relevance (+3); neural, nerve or neurovascular relevance (+3); review article (+1); publication in 2021 or later (+2; 2018-2020, +1); and citation count at the time of search of at least 200 (+2; 50-199, +1). Of the 466 unique records, 371 scored at least 7 and 95 scored below 7. Because the eligible set exceeded the prespecified working-map cap, records were ranked by priority score, citation count and publication year, and the first 180 (score range, 10-19) formed the working evidence map; 191 threshold-eligible records fell below this rank cut-off. Final references were selected through expert-led narrative synthesis for their direct relevance to the review questions, specifically to support the review's biofabrication mechanisms, disease and wound context, vascular or neural integration, infection and safety constraints, or translational and clinical-scope arguments. The 180-record evidence map therefore served as a literature-prioritization and organization tool rather than a PRISMA-style study-inclusion set or methodological-quality assessment; redundant or peripheral records were not cited. The final bibliography contains 78 references: 44 from the 180-record map, 3 from the deduplicated pool outside the top-180 cut-off and 31 added during subsequent targeted citation checking and scope updates. Full texts were consulted for all 78 cited references. Supplementary Table S2 reports the complete flow, scoring rules and citation reconciliation.

Records were excluded from the core narrative when they addressed generic tissue engineering without a plausible link to wound repair, vascularization, neural support, diabetic or ischemic biology, clinical wound pathways or manufacturing translation. We also excluded non-biological 3D-printing studies, anatomic phantoms, vascular procedural models and device-training papers unless they directly informed bioprinting translation. We did not perform quantitative synthesis or formal risk-of-bias scoring. Instead, each retained source was assigned an evidence tier: direct clinical context, near-direct wound bioprinting, wound-adjacent vascularized skin or repair evidence, ischemic vascular-repair bridge evidence, neurovascular bridge evidence, or platform and translation evidence. This tiering is the basis for the claim boundaries used throughout the manuscript.

Because direct clinical evidence for bioprinted constructs in neuroischemic diabetic foot ulcers remains sparse, we explicitly separate evidence into interpretive tiers (Table 1) and summarize the closest primary studies in Table 2. Direct clinical context evidence defines the DFU/CLTI wound problem but rarely tests printed constructs. Near-direct bioprinting evidence addresses DFU, chronic wounds, vascularized skin or wound-adjacent models but is still mainly preclinical, scoping or conceptual. Ischemic and neurovascular bridge evidence informs angiogenesis, perfusion, nerve support and tissue quality but usually does not test diabetic foot reconstruction. Platform and translation evidence informs printability, bioinks, manufacturing, sterility, regulation and endpoints but cannot substitute for disease-matched wound evidence. This review therefore evaluates bioprinting as a design and translation framework, not as an established treatment for diabetic foot disease. Study-level printing modality, principal matrix, cellular or molecular payload, model, comparator and vascular-evidence category are provided in Supplementary Table S1.

Table 1. Direct and indirect evidence used in this review.

Evidence tier	Representative sources in the current manuscript	How close it is to DFU/CLTI limb salvage	What it supports	Claim boundary
Direct clinical context	DFU pathophysiology, chronic diabetic wound care, DFU dressings, stem-cell and growth-factor reviews, DFU-oriented cell-therapy translation, post-revascularization soft-tissue reconstruction context, recurrence-focused follow-up literature and CLTI revascularization trials ^{1-4,21-27,53,73-76}	Closest to the clinical problem, but still dominated by non-printed therapeutic or clinical-context evidence	Defines the neuroischemic wound niche, including perfusion failure, neuropathy, inflammation, infection risk, reconstruction timing and recurrence burden	Supports the clinical rationale and endpoint selection; does not show that bioprinted constructs improve closure, recurrence or amputation outcomes
Near-direct bioprinting scope	DFU bioprinting, chronic-wound bioink and diabetic wound-model reviews ^{5-6,14-18}	Directly addresses DFU or chronic wounds, but mainly as scoping or conceptual literature	Shows that 3D bioprinting has been proposed for DFU and chronic wound management and identifies common bioink, model and platform directions	Supports field relevance and design hypotheses; does not establish mature clinical efficacy or superiority over standard care
Wound-adjacent vascularized tissue evidence	Vascularized skin bioprinting, perfusable skin models, growth-factor patterning, vascularization bioinks and wound-facing printed constructs ^{19-20,34-45}	Biologically close to skin or soft-tissue reconstruction, but usually not tested in neuroischemic diabetic feet	Supports feasibility of spatially organized cells, vascular components, instructive cues, oxygen-supportive designs and immunomodulatory payloads	Supports feasibility and mechanism selection; should not be generalized to limb-salvage outcomes without disease-matched testing
Ischemic vascular-repair bridge	Therapeutic angiogenesis and critical-limb-ischemia related exosome/oxygen delivery ^{47,49}	Close to ischemic vascular biology, but not necessarily printed wound reconstruction	Supports the need for perfusion-aware construct design and angiogenic or oxygen-supportive payloads	Supports vascular-surgery relevance; does not show that bioprinting itself adds benefit unless compared with non-printed controls
Neurovascular and nerve-repair bridge	Nerve-graft revascularization, neuroregulation in wound healing, peripheral nerve scaffold design and dual vascular-neural scaffolds ^{31-32,50-52}	Mechanistically relevant to functional reconstruction, but mostly outside DFU clinical trials	Supports the argument that neural repair, matrix guidance and vascular support should be designed together	Supports neurovascular framing; does not justify claims of sensory recovery in diabetic foot ulcers unless directly tested
Platform, biomaterial and translation evidence	General bioprinting, vascular graft engineering, hydrogels, engineered-tissue standards, skin tissue-engineering translation, immunomodulatory and antibiofilm diabetic-wound hydrogels ^{7-9,46,54-58,61-63,71-72}	Indirect for DFU/CLTI but important for engineering and regulatory constraints	Informs printability, matrix selection, vascular engineering risks, manufacturing, sterility, potency, infection compatibility and endpoints	Supports design and translation constraints; cannot substitute for wound-specific preclinical or clinical evidence

Table 2. Primary studies closest to DFU, ischemic wounds or vascularized skin bioprinting.

Study focus	Model or setting	Material/bioink	Cells/payload and printing	Diabetes/ischemia /infection	Vascular and neural endpoints	Controls and main limitation for DFU/CLTI inference
Vascularized perfusable skin graft ³⁴	Human skin-equivalent construct and implantation-oriented testing	Collagen/fibrin-based skin matrix	Keratinocytes, fibroblasts, pericytes and endothelial cells; layered bioprinting	Not DFU, ischemic or infected	Perfusable/vascular skin architecture; no neural endpoint	Non-vascularized/component controls; strong vascularized-skin feasibility but not a diabetic neuroischemic or load-bearing foot model
Spatiotemporal growth-factor patterning ³⁸	Regenerative tissue-patterning model	Printable hydrogel carrier	Patterned growth factors; 3D bioprinting of cue fields	Not DFU-specific	Spatial control of tissue regeneration and angiogenic cue delivery; no neural endpoint	Patterned versus non-patterned cues; demonstrates programmable cues but not wound-bed integration in ischemic diabetic tissue
In situ autologous skin-cell printing ³⁷	Extensive full-thickness excisional wounds	Fibrin/collagen-type wound matrix	Autologous skin cells; in situ bioprinting	Acute non-DFU wound; not ischemic or infected	Wound closure and tissue repair; vascular detail limited; no neural endpoint	Standard wound or non-printed comparisons; geometry matching is clinically intuitive but model lacks diabetic ischemia, infection and recurrence stress
Placental-derived printed bioink ⁴⁰	Skin tissue regeneration and wound healing models	Placental-derived dECM-like bioink	Skin-relevant cells and matrix cues; extrusion-style printing	Not neuroischemic DFU	Angiogenesis and wound-healing behavior; no neural endpoint	Bioink/material controls; useful matrix cue study but donor variability and disease mismatch remain unresolved

Study focus	Model or setting	Material/bioink	Cells/payload and printing	Diabetes/ischemia /infection	Vascular and neural endpoints	Controls and main limitation for DFU/CLTI inference
Microfluidic/coaxial diabetic wound dressing ⁴²	Diabetic wound-dressing concept	Core-shell/microfluidic hydrogel fibers	Therapeutic payloads rather than full skin cell system; microfluidic plus coaxial printing	Diabetic wound relevance; infection/perfusion context limited	Architecture and delivery relevant to angiogenic repair; no neural endpoint	Fiber/formulation controls; closest to DFU-oriented architecture but still dressing-scale and not limb-salvage or perfusion-integrated evidence
Photosynthetic in situ scaffold ⁴³	Wound-healing model with oxygen-supportive living scaffold	Photosynthetic living scaffold	Oxygen-generating biological component; in situ printing	Not established DFU/CLTI setting	Oxygen support and wound repair; no neural endpoint	Non-photosynthetic/scaffold controls; provocative oxygen concept but safety, infection compatibility and clinical acceptability are uncertain
Immunomodulatory exosome bioprinted biomaterial ⁴⁴	In vivo wound-healing and angiogenesis model	Immunomodulatory biomaterial	Engineered exosomes from M2-polarized macrophages; 3D bioprinting	Wound model; diabetic ischemic status not definitive for DFU	Angiogenesis and wound-healing markers; no neural endpoint	Biomaterial/exosome controls; supports paracrine immunovascular design but potency, release and DFU-specific validation are open
Endothelial-patterned skin patches ⁴⁸	Wound-healing skin-patch model	Light-activated bioink	Endothelial cell patterns; in-bath/light-activated printing	Not DFU/CLTI	Angiogenic potential and endothelial patterning; no neural endpoint	Patterned versus less-patterned patch controls; strong test of spatial endothelial organization but not neuroischemic foot reconstruction
Lipoaspirate-derived cell-laden skin constructs ⁶⁰	Full-thickness skin-defect repair	Cell-laden skin construct hydrogel	Human lipoaspirate-derived cells; 3D bioprinting	Not diabetic ischemic wound	Wound closure/tissue repair; vascular readouts secondary; no neural endpoint	Scaffold/cell controls; clinically accessible cell source potential but generic model and endpoints
Gel/dECM/Qcs DFU scaffold ¹⁹	DFU-oriented scaffold repair study	Gelatin, decellularized ECM and quaternized chitosan	Antibacterial scaffold with exosome-loading rationale; extrusion printing	Directly DFU-oriented; infection addressed mainly through material function	Fibroblast compatibility and wound-repair rationale; perfusion validation limited; no neural endpoint	Material/formulation controls; lacks limb perfusion, recurrence, weight-bearing and rigorous non-printed composition controls
Xeno-free vascularized human skin graft ²⁰	Implantable vascularized human skin graft	Xeno-free skin bioink system	Human skin and vascular cells; 3D bioprinting	Not DFU/CLTI	Perfused human microvessels after implantation; no neural endpoint	Non-vascularized/comparator graft logic; advances manufacturability but does not test diabetic ischemic, infected or mechanically loaded wounds

2. The vascular-surgery wound niche: beyond skin closure

2.1 A limb-salvage problem, not only a wound problem

Diabetic foot ulcers and ischemic chronic wounds are often described as non-healing skin defects, but this phrase understates their biology. The wound bed is shaped by macrovascular stenosis or occlusion, microvascular disease, endothelial dysfunction, neuropathy, abnormal macrophage polarization, impaired fibroblast and keratinocyte activity, infection and biofilm. These mechanisms do not act independently. Hypoperfusion lowers oxygen and nutrient delivery, neuropathy delays protective behavior and alters neuroimmune signaling, and persistent inflammation degrades extracellular matrix and growth-factor signaling ^{1,3,24}.

This coupled pathology explains why a vascular-surgery approach cannot end with flow restoration alone. Revascularization is essential when perfusion is inadequate, but it is not equivalent to tissue

reconstruction. A clean, perfused wound still needs granulation tissue, epithelial migration, angiogenic sprouting, immune resolution and mechanical protection. Conversely, a biologically active scaffold may fail if placed into an ischemic or infected wound bed. Any regenerative strategy for limb salvage therefore has to respect both sides of the problem: the vascular status of the limb and the local cellular microenvironment²⁵⁻³⁰.

The neuroischemic phenotype is especially important for a bioprinting review. Neuropathy contributes to pressure injury and delayed presentation, but it also changes local wound biology. Sensory and autonomic nerves regulate vascular tone, inflammation, sweat gland activity and epithelial behavior. In diabetic skin, this regulatory network is disrupted, so printed tissues that only support epithelial coverage may not restore function. This is why vascularized and innervated tissue reconstruction is a stronger long-term target than rapid surface closure alone³¹⁻³².

From this perspective, the clinically useful construct would perform several jobs at once. It would protect the wound, fill an irregular defect, support host-cell infiltration, promote angiogenesis, modulate inflammation, discourage infection and preserve a path toward sensory or autonomic recovery. No current printed construct has achieved this complete profile in routine clinical care for neuroischemic diabetic foot disease. Figure 1 therefore defines the disease-facing design target for this review: a coupled vascular, neural, immune and matrix failure state that must be approached as more than surface closure.

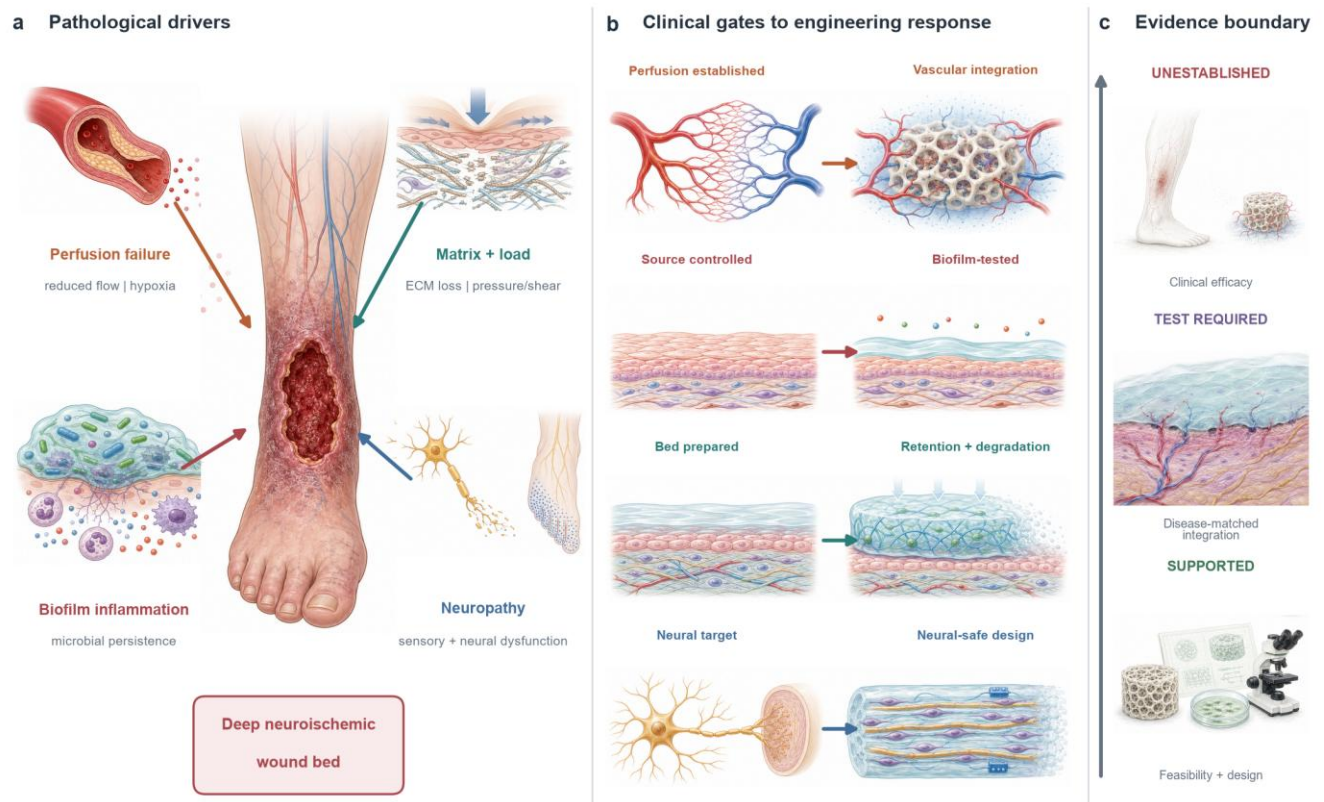


Figure 1. Pathology-to-design logic for the core neuroischemic DFU phenotype and selected ischemic lower-limb wounds. (a) Perfusion failure, biofilm/inflammation, matrix and loading stress, and, in DFU or documented neuropathy, neural dysfunction converge in a wound bed that is not a surface-only defect. **(b)** Each documented pathology becomes a clinical gate and then a construct requirement: perfusion and oxygen tolerance, infection compatibility and host defence, wet-bed adhesion and mechanical durability, and neural support only when the phenotype warrants it. **(c)** The evidence boundary separates supported feasibility and design logic from disease-matched testing requirements and from the presently unestablished claim of clinical limb-salvage efficacy.

2.2 Why a regenerative construct must be matched to perfusion status

For a vascular surgeon, the first translational question is not whether a biomaterial can close a wound in an animal model. It is whether the wound bed can support repair. Perfusion status determines oxygen delivery, inflammatory resolution, antimicrobial defense, matrix synthesis and cell survival. A construct applied before adequate inflow is restored may become an expensive biological dressing in a hostile bed. Conversely, a construct applied after revascularization may help convert restored flow into organized granulation and tissue reconstruction²⁸⁻³⁰.

This timing issue gives bioprinting a practical niche. Printed constructs could be designed for different stages of limb salvage. Early post-debridement constructs might emphasize exudate control, antimicrobial activity and angiogenic stimulation. Post-revascularization constructs might emphasize endothelial ingrowth, matrix deposition and epithelial support. Later reconstructive constructs might prioritize mechanical durability, contour restoration and neural-supportive cues. A single product is unlikely to solve all stages.

2.3 Defining a neuroischemic design brief

The design brief for a neuroischemic wound construct should include five requirements. First, it should tolerate low but improving oxygen tension. Second, it should support vascular ingrowth or microvascular stabilization. Third, it should modulate chronic inflammation without suppressing antimicrobial defense. Fourth, it should allow epithelial migration and matrix remodeling. Fifth, when functional reconstruction is claimed, it should include a plausible route to neural recovery or neuroimmune normalization. These requirements are demanding, but they make the translational target clearer than generic wound closure.

3. Why bioprinting is relevant: spatial control rather than another dressing

3.1 From material choice to spatial biological programming

Bioprinting differs from conventional scaffold fabrication because it links material composition to spatial patterning. Extrusion printing can deposit cell-laden hydrogels in layered or filamentous architectures. Light-based printing can improve resolution for photo-crosslinkable bioinks. Coaxial and microfluidic printing can form hollow or core-shell structures. In situ bioprinting can adapt constructs to irregular wounds. These approaches are not interchangeable. Extrusion systems are robust and accessible, but they may compromise cell viability through shear stress. Light-based methods can improve precision, but they require careful control of photochemistry and material formulation^{7-8,10-12,33}.

The reason to use bioprinting is therefore not that every wound needs a printed dressing. Ordinary hydrogels, electrospun scaffolds, advanced dressings and commercial skin substitutes are more appropriate when the therapeutic goal is moisture balance, barrier coverage, antimicrobial delivery, offloading support or a relatively uniform matrix. Bioprinting becomes difficult to replace only when the intended function depends on spatial organization: placing endothelial and perivascular cells in a defined zone; separating barrier, stromal, vascular and host-interface layers; positioning growth factors or vesicles as gradients rather than bulk additives; conforming a construct to an irregular post-

debridement defect; or creating channels and aligned matrix paths that can be tested as vascular or neural guidance features. In other words, printing is justified when architecture is part of the mechanism, not when the same material could be cast, injected or applied as a simpler dressing.

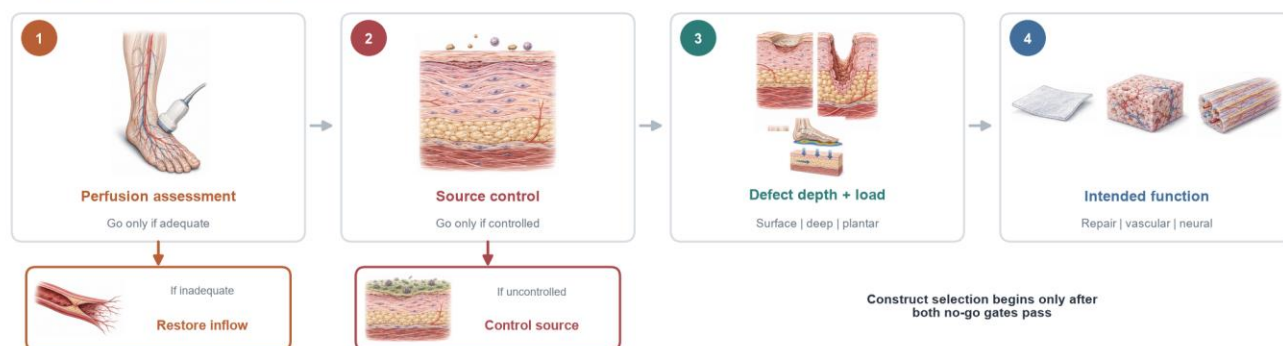
For wound reconstruction, the most relevant feature is not visual complexity. It is the ability to assign biological functions to regions of a construct. A surface-facing layer may prioritize keratinocyte support and barrier formation. A deeper layer may promote fibroblast remodeling and vascular ingrowth. A channel-rich region may support perfusion or fluid transport. A perivascular niche may include endothelial cells and pericytes. A neural-supportive region may contain aligned architecture, Schwann-cell cues or neurotrophic signals. This spatial logic is difficult to achieve with standard dressings, but it still has to prove value against composition-matched non-printed controls.

Several skin and wound bioprinting studies support the plausibility of this approach. Vascularized and perfusable skin graft models have combined keratinocytes, fibroblasts, pericytes and endothelial cells to mimic layered skin with vascular features³⁴. Other perfusable or stretchable skin-equivalent systems and multicompartiment human skin equivalents show how epidermal, dermal, hypodermal and vascular components can be organized in vitro, even when they are not designed for diabetic foot reconstruction³⁵⁻³⁶. A later xeno-free vascularized human skin graft study extended this logic by showing formation of perfused human microvessels after implantation, while also moving the platform closer to clinically acceptable cell sourcing and manufacturing conditions²⁰. In situ bioprinting of autologous skin cells accelerated repair in extensive full-thickness excisional wounds, illustrating how direct deposition can be adapted to irregular wound geometry, although this was not a diabetic neuroischemic model³⁷. Growth-factor patterning has also been used to control tissue regeneration in space and time³⁸. Gelatin-based vascularization bioinks, placental-derived bioinks and large dermo-epidermal substitutes further illustrate how hydrogel chemistry, printability, endothelial organization, angiogenic wound-healing behavior and scale-up can be tuned together³⁹⁻⁴¹. More directly, a DFU-oriented extrusion-printed Gel/dECM/Qcs scaffold study reported antibacterial activity, fibroblast compatibility and a rationale for exosome loading, but it remained a preclinical materials demonstration rather than a limb-salvage study¹⁹. These examples do not prove clinical efficacy in diabetic foot ulcers, but they justify the strategy map in Figure 2: spatial control should be evaluated by whether it creates biologically useful modules for host integration, not by visual tissue mimicry alone.

The main limitation is that many demonstrations are performed in simplified models. Acute wounds, healthy animals, small defects or non-load-bearing sites do not reproduce the ischemic, neuropathic,

infected and mechanically stressed environment of a diabetic foot. A vascular-surgery-oriented review should therefore avoid treating all wound-healing models as equivalent. Evidence from generic skin repair is useful for mechanism and platform selection, but diabetic and ischemic models should carry more weight when the claim concerns limb salvage.

a Gate-controlled construct selection



b Scenario-matched construct and evidence target

	Shallow	Post-revascularization	Deep structural	Functional
Clinical state	Clean surface defect	Perfused residual defect	Exposed deep structure	Neural target
Candidate construct	Acellular matrix	Angiogenic filler	Layered construct	Neurovascular construct
Evidence target	Tolerance	Host connection	Retention	Neural safety

Proposed research heuristic | not clinically validated

Figure 2. Proposed scenario-to-construct research decision map. (a) Perfusion adequacy and infection source control are no-go gates before defect depth, loading and intended function are used to select a design. **(b)** Clean shallow wounds, post-revascularization defects, deep exposed structures and late functional targets are matched to proportionate candidate constructs, material priorities, cell or payload logic and minimum evidence. The map is a research heuristic, not a validated clinical treatment algorithm, and candidate constructs require composition-matched non-printed controls.

3.2 Printing modalities and their vascular-surgery implications

Extrusion bioprinting is the most intuitive platform for wound constructs because it can deposit viscous, cell-laden hydrogels into centimeter-scale shapes. It is suitable for layered skin-like constructs, wound fillers and in situ repair concepts. Its limitations are resolution, shear stress and the difficulty of printing very soft matrices that still retain shape. For diabetic foot applications, extrusion may be most useful when defect conformity and clinical robustness matter more than microscale precision.

Light-based approaches, including digital light processing and stereolithography-like methods, offer higher resolution and faster curing. They are well suited for patterned hydrogel networks and microarchitectures, but their clinical use depends on photoinitiator safety, light penetration, sterility and material choices. Coaxial and microfluidic printing can generate channels or core-shell fibers that resemble vascular or ductal features. A diabetic wound-dressing study combining microfluidics with coaxial 3D bioprinting illustrates this direction by linking fiber architecture and payload delivery to diabetic wound repair needs ⁴². These methods are attractive for perfusion design, although the central translational challenge remains host integration.

In situ bioprinting has special relevance for vascular surgery because wounds are irregular and change after debridement. A handheld or robotic system could map the wound and deposit material directly into the defect. This idea fits clinical workflow, but it also raises hard requirements: speed, sterility, operator training, intraoperative imaging, printable formulations that work under wet wound conditions and quality assurance at the bedside ^{12,37}. Table 3 summarizes how the major printing modalities should be matched to neuroischemic wound requirements rather than treated as interchangeable platforms.

Table 3. Printing modalities for neuroischemic wound applications.

Modality	Technical advantage	Best-fit wound use	Bioink constraints	Vascular/neural opportunity	Main limitation in DFU/CLTI
Extrusion	Handles viscous and cell-laden hydrogels; scalable to centimeter defects	Layered skin-like grafts, wound fillers, post-debridement constructs	Must balance viscosity, shear, cell survival and shape fidelity	Can place endothelial, stromal and barrier modules in defined layers	Lower resolution, shear injury and weak mechanics in very soft matrices
DLP/light-based	Higher resolution and rapid photopatterning	Microarchitecture, gradients, thin patches and patterned endothelial zones	Requires photocrosslinkable bioinks, safe initiators and controlled light dose	Precise cue fields and microchannels may guide vascular ingrowth	Limited material palette, light penetration issues and phototoxicity concerns
Coaxial	Generates core-shell fibers or hollow-like filaments	Channel-like dressings, sustained release, vascular-mimetic strands	Needs matched inner/outer viscosities and stable crosslinking	Can combine payload delivery with perfusion-inspired geometry	Printed channels may not connect to host circulation; validation often stops at

					morphology
Microfluidic	Allows continuous mixing, gradients and fiber architecture	Multi-component dressings and spatially varied drug/cell delivery	Formulations must remain stable during flow and gelation	Can tune gradients, release kinetics and endothelial-supportive niches	Device complexity, scale-up and sterility are difficult at the bedside
In situ printing	Matches irregular surgical geometry directly	Post-debridement wounds, complex contours and exposed structures	Must print under wet, contaminated and time-limited clinical conditions	Enables defect-specific placement after perfusion and infection assessment	Quality assurance, operator training, sterility and regulatory control are unresolved

3.3 What current evidence can and cannot support

The current literature supports feasibility and mechanism selection more strongly than clinical effectiveness. It shows that bioprinting can create layered skin constructs, vascular-like channels, patterned growth factors, prevascularized tissues, cell-laden wound scaffolds and oxygen- or paracrine-supportive matrices^{34-38,40-45}. Recent DFU-focused reviews and scaffold summaries reach a similar boundary: printed constructs are technically plausible and increasingly disease-facing, but most evidence still comes from preclinical, model or platform studies rather than comparative limb-salvage trials¹⁴⁻¹⁶.

The critical weaknesses are consistent across the field. Many studies use healthy acute wounds, small dorsal defects or in vitro skin models, then discuss chronic diabetic wounds as the destination. Perfusion is often inferred from endothelial staining or vessel-like morphology rather than demonstrated with anastomosis, oxygenation or flow-sensitive imaging. Infection is commonly absent or simplified, even though bacterial burden and biofilm can determine whether a biologically rich construct succeeds or fails. Weight-bearing, shear, footwear/offloading, recurrence and repeat debridement are rarely modeled. Finally, many studies compare a printed construct with blank or poorly matched controls rather than with a cast hydrogel or scaffold containing the same material, cells and payload. Without those controls, the added value of printing remains uncertain.

4. Vascularization strategies for printed wound constructs

4.1 Vascularization as the central viability bottleneck

Vascularization is the central bottleneck for any thick or metabolically active printed tissue. Cells placed far from host capillaries experience diffusion limits, hypoxia and nutrient deprivation. In an ischemic limb, this problem is amplified by impaired inflow, microvascular dysfunction and endothelial injury. Vascularized bioprinting therefore has two distinct goals: to keep the construct viable before host integration and to stimulate durable anastomosis with the wound bed^{9,46-47}.

One strategy is to print or pattern endothelial cells, pericytes and stromal cells in architectures that favor capillary-like organization. Endothelial cells provide the lining of new vessels, while pericytes and mesenchymal stromal cells can stabilize nascent networks and secrete angiogenic factors. Printed skin models containing endothelial and perivascular components show how these cell combinations can be organized within tissue-like constructs^{34,39}. Placental-derived bioinks and endothelial-patterned skin-patch designs further support the idea that vascular cell organization and angiogenic matrix cues can be engineered together, although these studies remain wound-adjacent rather than definitive DFU/CLTI evidence^{40,48}.

A second strategy is to use soluble cues. Vascular endothelial growth factor, fibroblast growth factor and other angiogenic mediators can be incorporated into hydrogels, microspheres, extracellular vesicles or patterned matrices. The key challenge is dosing and timing. Too little stimulation may fail to overcome ischemia; uncontrolled stimulation may generate immature or leaky vessels. Spatiotemporal growth-factor printing is important because it suggests that angiogenesis can be guided rather than merely induced^{24,38,49}. Oxygen-supportive and photosynthetic printed scaffolds add a related design principle: in hostile wound beds, supporting local oxygen availability may be as important as delivering angiogenic signals, but this remains a preclinical strategy requiring careful safety and infection-context evaluation⁴³.

A third strategy is to create perfusable channels through coaxial printing, sacrificial inks or microfluidic designs. These approaches are attractive for large constructs, but their clinical relevance depends on how they connect to host circulation. For a diabetic foot wound, a printed channel that remains isolated from tissue perfusion may be less useful than a construct that rapidly recruits host vessels after revascularization. The design target should therefore be integration with the post-debridement wound bed, not perfusion in a device alone. Coaxial and microfluidic diabetic wound-dressing work is useful here because it brings the architecture question closer to diabetic wound biology, even though it still does not establish limb-salvage outcomes⁴².

The vascular-graft literature is useful but should be used carefully. Tissue-engineered vascular grafts address conduit replacement and bypass, whereas vascularized wound constructs address microvascular integration and tissue repair. Still, graft engineering highlights issues that also matter for printed wound tissues: thrombosis, compliance, endothelialization, remodeling, scale-up and long-term patency^{9,46}. These concepts can inform, but not substitute for, wound-specific evidence.

4.2 Angiogenic cues, vascular cells and perfusable geometry

Angiogenic design can be organized into three layers. The molecular layer includes VEGF, FGF, nitric oxide, oxygen-releasing systems, extracellular vesicles and other pro-angiogenic signals. The cellular layer includes endothelial cells, pericytes, mesenchymal stromal cells and macrophage-modulating payloads. The architectural layer includes channels, gradients, pores and aligned matrix features that guide vessel invasion. A strong construct will likely combine all three rather than rely on one.

For neuroischemic wounds, the risk is not only insufficient angiogenesis but disorganized angiogenesis. Chronic inflammation, diabetes and ischemia can produce vessels that are immature, leaky or poorly connected. Vascular evidence should therefore be reported in four non-equivalent levels: (1) endothelial organization or marker-positive structures; (2) a lumenized network shown to be perfusable within the construct; (3) anastomosis or direct connection with host vessels; and (4) functional tissue perfusion demonstrated by flow-sensitive imaging, tracer delivery, oxygenation or an equivalent physiological measure. Higher levels support stronger translational claims, but none alone establishes durable limb salvage. Relevant safety and quality endpoints include vessel maturity, edema, bleeding, inflammation, granulation quality and durability under load.

4.3 Lessons from vascular graft engineering

Small-diameter vascular graft engineering offers useful lessons for bioprinted wound constructs. It shows how difficult it is to reproduce vascular function, especially when blood contact, thrombosis, compliance and remodeling are involved. Wound constructs do not need to behave like bypass conduits, but they do need to support microvascular integration. The graft field also emphasizes that endothelialization alone is not enough; long-term function depends on matrix mechanics, host remodeling and inflammatory compatibility.

4.4 Revascularization and construct timing

A vascularized construct should be considered in relation to revascularization timing. Before revascularization, the construct may need to act as a protective, antimicrobial and oxygen-supporting matrix. After revascularization, it may need to amplify angiogenesis and organize granulation. In no-option ischemia, it may be tested as an adjunct to therapeutic angiogenesis or cell-derived paracrine therapy, but claims should remain cautious. A phase I pilot study in patients with DFU and peripheral arterial disease who were not amenable to surgical revascularization illustrates this boundary well: topical and intravenous hUC-MSC administration showed favorable safety, rapid wound

improvement and 3-year amputation-free survival, yet did not provide direct evidence of reversal of major-vessel obstruction ²¹. The same printed product may not suit all perfusion states.

5. The neurovascular interface: nerve repair, innervation and wound physiology

5.1 Why nerves belong in a wound-reconstruction review

The nervous system is not a decorative endpoint in tissue reconstruction. Peripheral nerves regulate sensation, vascular tone, inflammation and epithelial behavior. In diabetic foot disease, loss of protective sensation increases mechanical injury, while autonomic dysfunction and altered neuroimmune signaling may impair repair. A printed construct intended for functional limb reconstruction should therefore consider neural support as part of the wound niche, not as a separate late-stage feature ³².

The evidentiary status of this argument is uneven. Direct evidence that a bioprinted DFU construct restores protective sensation, autonomic regulation or functional innervation is essentially absent in the current literature summarized in Table 2. The stronger evidence is indirect: diabetic wound biology supports the importance of neuropathy and neuroimmune dysfunction; nerve-graft literature shows that ischemia limits Schwann-cell survival and axonal regeneration; and scaffold studies outside DFU show that aligned matrices, vascular support and neurotrophic cues can influence nerve repair ^{31-32,50-52}. These sources justify a design requirement, not a claim of demonstrated diabetic-foot reinnervation.

For wound bioprinting, neurovascular design could take several forms. A construct might include aligned microarchitecture to guide host nerve ingrowth, neurotrophic factors to support axonal extension, Schwann-cell-compatible matrices, conductive or mechanoresponsive materials, and vascular cues that protect metabolically active neural cells. Dual-functional scaffolds that aim to support neovascularization and nerve regeneration illustrate this direction, although most remain far from diabetic foot translation ⁵⁰⁻⁵².

The field should also distinguish reinnervation from neural signaling. Full sensory recovery may be a long-term and difficult endpoint, especially in diabetic neuropathy. Earlier translational targets may include improved neuroimmune balance, reduced neuropathic inflammation, support of Schwann-cell survival or preservation of host nerve ingrowth. These endpoints are more modest, but they are biologically meaningful and experimentally tractable.

5.2 Neurovascular coupling as a design principle

Neurovascular coupling is a reciprocal cellular and molecular constraint rather than the simple co-presence of nerves and vessels. On the vascular side, VEGF-A/VEGFR2 signalling promotes endothelial sprouting, while PDGF-BB/PDGFRbeta and ANG1/TIE2 signalling are relevant to pericyte recruitment and vessel stabilization; endothelial markers alone therefore cannot establish mature perfusion. On the neural side, NGF/TrkA and BDNF/TrkB signalling support axonal and Schwann-cell programmes, while sensory neuropeptides and autonomic signals can modify vascular tone, keratinocyte behaviour and inflammation^{24,31-32,47,49-50,52}. These pathways define testable design targets, but they do not show that a printed DFU construct restores protective sensation or autonomic control.

Diabetes disrupts both arms of this relationship. Hyperglycaemia-associated AGE-RAGE and protein-kinase-C signalling, mitochondrial reactive oxygen species and persistent inflammatory cytokines reduce endothelial nitric-oxide bioavailability, impair vascular responsiveness and destabilize the matrix. In parallel, oxidative and metabolic stress impairs Schwann-cell support, axonal maintenance and neuropeptide-mediated feedback; prolonged TNF-alpha and IL-1beta activity can further oppose reparative macrophage and stromal programmes^{1,3,24,27,32,53}. The resulting chain is therefore not simply "diabetes causes poor healing": metabolic stress produces endothelial dysfunction and neural-support failure, which reinforce hypoxia, inflammation and matrix breakdown.

5.3 Candidate neural-supportive strategies

Printed design can map each link in this chain to a variable and an endpoint. An endothelial-pericyte zone with spatially controlled VEGF or FGF and stabilization cues should be judged by lumen formation, pericyte coverage, host anastomosis, leakage and functional perfusion. An oxygen-buffering or antioxidant compartment should be tested by oxygen tension, reactive oxygen species and eNOS/nitric-oxide readouts rather than closure alone. An aligned, Schwann-compatible compartment with staged NGF or BDNF delivery should be tested by Schwann-cell viability, neurite orientation, axon trajectory and later sensory function or pain. Immunomodulatory payloads require paired TNF-alpha, IL-1beta and reparative-marker measurements together with bacterial clearance. These modules must be evaluated under combined hyperglycaemic, ischemic and inflammatory stress. Functional reinnervation claims require disease-matched functional testing and cannot be inferred from marker expression^{31-32,50-52}.

6. Bioinks and cellular payloads for instructive wound microenvironments

6.1 Bioink requirements for diabetic and ischemic wounds

A bioink for DFU or selected ischemic wound repair has to do more than print cleanly. It must provide a permissive matrix, protect cells during fabrication, degrade at a useful rate, match the mechanical demands of the wound site and deliver biological cues without aggravating inflammation or infection. Natural polymers such as collagen, gelatin methacrylate (GelMA), fibrin, alginate, chitosan, hyaluronic-acid (HA) derivatives and decellularized extracellular matrix (dECM) are attractive because they resemble extracellular-matrix environments, but they differ sharply in printability, mechanics, degradation and biological signaling^{11,54}. Recent diabetic-wound hydrogel studies also show why material design must be tied to disease biology: biomineralized, immunomodulatory, bioadhesive or macrophage-polarizing hydrogels can accelerate repair in diabetic wound models, but their benefit depends on inflammation, oxidative stress, infection and mechanical context rather than printability alone⁵⁵⁻⁵⁸. Table 4 matches materials, cells and minimum evidence to clinical scenarios, while Table 5 catalogues component options that should be used conditionally rather than as a universal recipe.

GelMA is attractive because it is photocrosslinkable, tunable and widely used in DLP or extrusion-light hybrid workflows, but it may require careful control of photoinitiator dose, stiffness and degradation to avoid impairing fragile wound cells. Alginate prints well and gels rapidly with ions, which helps shape fidelity, but it is biologically inert unless modified or blended and may persist without mammalian enzymatic remodeling. Collagen and fibrin provide strong cell-adhesive and wound-relevant cues, but they are mechanically weak, contractile or fast-degrading unless reinforced. Chitosan brings hemostatic and antimicrobial potential, especially through quaternized derivatives, but solubility, pH sensitivity and batch variability can complicate cell-laden printing. HA supports hydration, migration and CD44-related repair signaling but usually needs chemical modification or blending for print fidelity. dECM offers tissue-specific biochemical cues and can improve cell response, yet source variability, decellularization residue, sterilization and regulatory characterization are major hurdles. These trade-offs matter more in hypoxic or infected wounds than in ideal culture conditions: a material that is excellent for print fidelity may be too stiff for cell migration, whereas a material that is excellent for cells may collapse, dissolve or fail under exudate and load.

Cell choice should follow the failure mode of the wound. Keratinocytes and fibroblasts support re-epithelialization and matrix remodeling. Endothelial cells and pericytes support vascular

organization. Mesenchymal stromal cells can provide immunomodulatory and pro-angiogenic signaling. Macrophage-modulating strategies may help shift the chronic inflammatory state toward repair. Schwann cells or Schwann-supportive cues may be relevant when neural recovery is part of the intended function ^{25,53,59}. For example, 3D-bioprinted human lipoaspirate-derived cell-laden skin constructs have been tested for full-thickness skin-defect repair, providing a wound-facing example of adipose-derived cellular payloads, but not yet a neuroischemic DFU model ⁶⁰.

Extracellular vesicles and exosomes are particularly interesting because they can deliver paracrine signals without requiring long-term survival of transplanted cells. In diabetic wounds and ischemic models, vesicle-based approaches have been investigated for angiogenesis, inflammation control and tissue repair ^{49,59}. Exosome-loaded microneedle and extracellular-matrix hydrogel studies strengthen this direction by showing that vesicle delivery can be coupled to diabetic wound repair and skin regeneration, although these remain non-printed or only indirectly printed paradigms ⁶¹⁻⁶². For bioprinting, vesicles could be incorporated into hydrogels or patterned within constructs. Recent work using engineered exosomes from M2-polarized macrophages in an immunomodulatory bioprinted biomaterial provides a concrete example of this strategy, linking exosome delivery to in vivo wound healing and angiogenesis ⁴⁴. The key unresolved questions are potency, stability during printing, release kinetics, manufacturing consistency and regulatory classification.

Antimicrobial, oxygenating and immunomodulatory functions may be as important as cell compatibility. Diabetic foot wounds often contain bacterial burden or biofilm, and ischemia limits oxygen-dependent repair. Biofilm-focused DFU literature and recent antibiofilm-antioxidant hydrogel work make infection compatibility a central design issue rather than a secondary dressing feature ^{58,63}. Materials that release nitric oxide, oxygen, nanoparticles or antibacterial agents could be useful, but they introduce trade-offs. A bioactive additive that improves bacterial control may harm fragile cells or endothelial organization. A construct that improves oxygenation may degrade too quickly or fail under load. These trade-offs should be evaluated in disease-relevant models rather than idealized acute wounds.

Table 4. Scenario-matched material, cell and evidence requirements for DFU and selected ischemic lower-limb wounds.

Clinical scenario	Entry criteria or no-go condition	Material or architecture requirement	Candidate cells or payloads	Minimum evidence before translation	Principal failure risk
Clean shallow DFU	Adequate perfusion; debrided viable bed; infection controlled	Conformal, wet-bed adhesive and exudate-tolerant matrix; HA/GelMA, fibrin or chitosan-containing blend	Acellular matrix or extracellular vesicles first; keratinocytes/fibroblasts only if barrier reconstruction is required	Cytocompatibility; bacterial regrowth after debridement; retention under shear; epithelialization versus a composition-matched non-printed control	Detachment, infection amplification or payload cytotoxicity
Post-revascularization ischemic soft-tissue defect	Restored inflow documented; viable bed; source control secure	Low-oxygen-tolerant angiogenic filler with controlled degradation; fibrin/GelMA/dECM options	Endothelial cells plus pericytes, or stromal cells/vesicles with controlled VEGF/FGF signalling	Host-vessel connection; functional perfusion; necrosis; leakage; retention; wound-specific comparator	Residual ischemic necrosis or immature/leaky vessels
Deep defect with exposed tendon, bone or hardware	Adequate perfusion; stable debridement margin; mechanical/offloading plan	Layered construct with reinforced interface and differential degradation; hybrid structural phases are architecture analogies only ⁶⁷⁻⁶⁸	Keratinocytes/fibroblasts plus stromal cells; endothelial/perivascular cells only when thickness requires vascular support	Interface integration; delamination under load; fibrosis; deep infection; durability versus matched non-printed material	Delamination, fibrosis, deep infection or mechanical failure
Biofilm-prone or actively infected wound	Active or uncontrolled infection is a no-go condition for a living construct	Initially non-living, antimicrobial-compatible matrix with controlled release and repeat-debridement compatibility	No live cells initially; antimicrobial, oxygenating or nitric-oxide payload only after cytotoxicity testing	Mono- and polymicrobial biofilm challenge; regrowth; resistance selection; host-cell toxicity; repeat-debridement test	Construct-mediated infection amplification or resistance
Later neurovascular functional target	Durable perfusion and source control; documented neural deficit; functional endpoint justified	Aligned compliant neural compartment coupled to a vascular or oxygen-supportive zone	Schwann-compatible cells or staged NGF/BDNF cues with endothelial/perivascular support	Schwann-cell survival; axon orientation and trajectory; perfusion; pain/neuroma surveillance; later sensory function	Neural ischemia, disordered axon growth or neuropathic pain
Non-diabetic CLTI or arterial adjacent cohort	Ischemic tissue loss documented; neuropathy not assumed; cohort stratified by neural phenotype	Vascular and structural design matched to perfusion, defect depth and loading	Acellular or angiogenic payload; neural component only with documented nerve injury or neuropathy	Reperfusion status; tissue viability; host connection; retention; separate analysis from DFU	Scope misclassification, cohort heterogeneity or recurrent ischemia

Table 5. Cells and functional payloads for DFU and selected ischemic lower-limb wound research.

Component class	Examples	Intended role	Vascular relevance	Neural relevance	Main translational risks
Endothelial/perivascular cells	Endothelial cells, microvascular endothelial cells, pericytes	Prevascular structures and host vascular integration	Direct capillary-like network formation and vessel stabilization	Indirect support through oxygen and nutrient supply	Poor survival in ischemic or infected beds, source standardization and abnormal vessel maturation
Skin-lineage cells	Keratinocytes, dermal fibroblasts	Barrier formation and matrix remodeling	Fibroblasts secrete angiogenic and matrix-remodeling factors	Indirect support through improved tissue architecture	Limited function without perfusion, variable donor quality and culture time
Stromal/progenitor cells	MSCs, adipose-derived stromal cells, stromal vascular fraction	Paracrine immunomodulatory, angiogenic and matrix-remodeling support	Strong endothelial-supportive signaling potential	Possible neurotrophic and anti-inflammatory effects	Potency variation, cell-source differences, storage and release testing
Neural-supportive cells/cues	Schwann cells, Schwann-like cells, neurotrophic factors, aligned matrices, conductive hydrogels	Nerve ingrowth, Schwann-cell survival or neuroimmune normalization	Neural cells require vascular support	Mechanistic relevance to sensory or autonomic repair	Difficult endpoints, slow recovery, limited DFU-specific validation and complex manufacturing
Extracellular vesicles	MSC-derived, adipose-derived or engineered exosomes	Paracrine pro-angiogenic, immunomodulatory or regenerative signaling	Can promote angiogenic signaling and ischemic repair pathways	May modulate neuroinflammation	Potency assays, loading stability, release kinetics, scale-up and regulatory classification
Growth-factor systems	VEGF, FGF, PDGF, neurotrophic factors, patterned release systems	Angiogenesis, matrix remodeling and cell migration	Central to angiogenic induction and vascular maturation	Neurotrophic factors may support axonal growth	Burst release, ectopic or leaky vessels, dose control and short half-life
Antimicrobial/oxygenating systems	Silver, chitosan derivatives, antimicrobial peptides, oxygen carriers, nitric oxide donors	Infection control, hypoxia buffering and oxidative-stress modulation	Infection control protects endothelial ingrowth	Indirect support by reducing inflammatory and metabolic stress	Cytotoxicity, resistance, uncontrolled release and mismatch with biofilm biology

6.2 Cell combinations and paracrine payloads

A rational cell combination should match the intended construct function. Keratinocytes and fibroblasts are logical for layered skin-like constructs. Endothelial cells and pericytes are logical for vascularized constructs. Mesenchymal stromal cells or adipose-derived stromal cells are logical when immunomodulation and angiogenic paracrine signaling are central. Schwann cells or neural-supportive cells may be considered for constructs that aim to influence innervation.

However, adding more cell types is not automatically better. Each cell type increases manufacturing complexity, release testing, storage constraints and regulatory burden. The translational path may favor simpler constructs first: acellular printed matrices with controlled release, vesicle-loaded hydrogels, standardized stromal-cell constructs or endothelial-supportive matrices. Highly complex,

multi-cellular and neurovascular constructs may be better suited for later-stage development after disease-specific proof of concept is established.

6.3 Immune and infection constraints

The diabetic foot wound is not a sterile tissue-engineering chamber. Biofilm, recurrent contamination and chronic inflammation are common, and biofilms can reduce antimicrobial susceptibility, prolong inflammation and make apparent closure a fragile endpoint⁶³⁻⁶⁴. Uncontrolled infection is a no-go gate for a living construct: debridement, drainage when required and guideline-concordant antimicrobial treatment must precede definitive placement. A nutrient-rich hydrogel or cellular matrix may itself retain organisms or become a substrate for biofilm if source control is incomplete. A recent burn-patient pilot study examining perioperative antibiotics and the skin-grafting microbiome is adjacent rather than DFU evidence, but it reinforces the need to measure microbial ecology around reconstructive materials rather than recording infection only as a binary event⁶⁵.

Infection compatibility should be tested as a design property, not added as a label. Preclinical comparisons should include clinically plausible mono- and polymicrobial biofilm challenge after debridement; bacterial biomass and regrowth; repeat-debridement compatibility; and testing that antimicrobial additives do not injure keratinocytes, stromal cells, endothelial networks or Schwann-supportive cells. Release kinetics, local cytotoxicity and resistance selection must be evaluated alongside angiogenesis and closure^{58,63-65}. Immunomodulation should also be calibrated because broad suppression of inflammation may impair host defence. Material chemistry and mechanics can influence macrophage phenotype, so immune readouts must be interpreted as material-dependent responses rather than a generic M1-to-M2 target⁶⁶.

6.4 Proposed scenario-based construct selection

Figure 2 provides the gate sequence and Table 4 makes the resulting choices explicit. Perfusion adequacy and infection source control are entry gates; defect depth, load and intended function then determine the minimum construct complexity. Table 4 links each scenario to material or architectural requirements, candidate cells or payloads, no-go conditions, minimum evidence and the principal failure risk. These are research-development rules, not prescriptive clinical recommendations.

A clean shallow DFU with adequate perfusion favors a conformal acellular or vesicle-loaded matrix. A viable post-revascularization defect can justify an angiogenic filler only when host-vessel connection and functional perfusion are measured. Deep defects require layered retention and interface testing rather than a skin-like appearance alone. Active infection is a no-go condition for a

living construct. A neurovascular module is reserved for a documented neural deficit after durable perfusion and source control. Hybrid bone and osteochondral printing are retained only as architecture analogies for a reinforced phase and are not treated as wound evidence⁶⁷⁻⁶⁸.

Each scenario also has a matched comparator and failure test: bacterial regrowth and cytotoxicity for antimicrobial matrices; necrosis, host connection and leakage for angiogenic designs; delamination, fibrosis and load durability for deep constructs; and nerve trajectory, pain and sensory function for neural-supportive designs. Composition-matched non-printed controls remain necessary to show that spatial printing, rather than material composition alone, adds value.

7. Translating vascularized bioprinting into limb-salvage workflows

7.1 A staged clinical pathway

Clinical translation will depend less on whether a construct looks like skin and more on whether it fits the vascular-surgery pathway. The proposed workflow begins with objective perfusion assessment, wound classification, infection evaluation and defect imaging. Revascularization should be performed when perfusion is inadequate, and definitive living-construct placement should stop when infection source control or wound-bed viability is uncertain. After debridement, a construct may be selected according to defect depth, exposed structures, perfusion status and mechanical demands. Adjacent flap practice, including ICG-guided assessment before pedicled-flap division, illustrates the clinical importance of testing perfusion before advancing reconstruction, although it is not evidence for bioprinted constructs⁶⁹. Offloading, surveillance and repeat intervention remain part of treatment rather than background care^{22,28-30,64,69-70}.

Figure 3 converts this design logic into a proposed, gate-controlled translational workflow and explicitly labels it as not clinically validated. The central rule is that a construct is considered only after limb perfusion, infection status and the wound bed have been defined. A failed gate stops progression and triggers vascular, infectious or wound-bed management rather than escalation of construct complexity.

Timing is a major unresolved issue. A construct placed before adequate revascularization may fail from ischemia. A construct placed too late may miss a window when the wound bed is most responsive to regenerative cues. One translational strategy is staged use: first restore flow and control infection, then apply an angiogenic or immunomodulatory construct to accelerate granulation, and finally use a barrier or skin-like construct to support closure. Another strategy is intraoperative or

bedside in situ printing after debridement, but this would require rapid sterilizable workflows and robust quality control.

Endpoints should also be chosen for vascular surgery, not only for tissue engineering. Wound area reduction is useful but insufficient. Relevant outcomes include time to complete epithelialization, durability after weight bearing, recurrence, infection, need for further debridement, major and minor amputation, pain, sensation, perfusion measures, quality of life and cost. Imaging-based endpoints, such as perfusion mapping or vascular-network assessment, could help connect construct biology to clinical outcome⁷¹⁻⁷³. Translational work on ABCB5-positive dermal mesenchymal stem cells for non-healing diabetic foot ulcers illustrates the kind of angiogenesis-oriented, wound-specific development logic that printed constructs will also need: product identity, potency, safety, application context and clinically meaningful wound endpoints must be defined before efficacy claims become persuasive⁷⁴. Contemporary CLTI revascularization trials such as BASIL-2 and BASIL-3 also show why limb-salvage endpoints should be interpreted within treatment pathway, anatomy, perfusion restoration and follow-up context rather than as a simple wound-product endpoint⁷⁵⁻⁷⁶. A recent comparative analysis estimated a pooled 3-year DFU recurrence rate of 58% and a CLTI reintervention rate of 50%, emphasizing that healed wounds and technically successful limb salvage should be treated as surveillance states rather than as final endpoints²³.

Regulatory and manufacturing issues will be substantial. Patient-specific constructs, live cells, bioactive factors and combination products complicate quality control. Sterility, batch consistency, release criteria, cell sourcing, storage, transport and point-of-care fabrication must be addressed before clinical trials. For this reason, the first vascular-surgery applications may not be fully living, innervated skin replacements. More realistic early products may be acellular or cell-derived bioactive printed matrices, angiogenic wound fillers, or standardized cellular constructs for well-defined post-debridement defects.

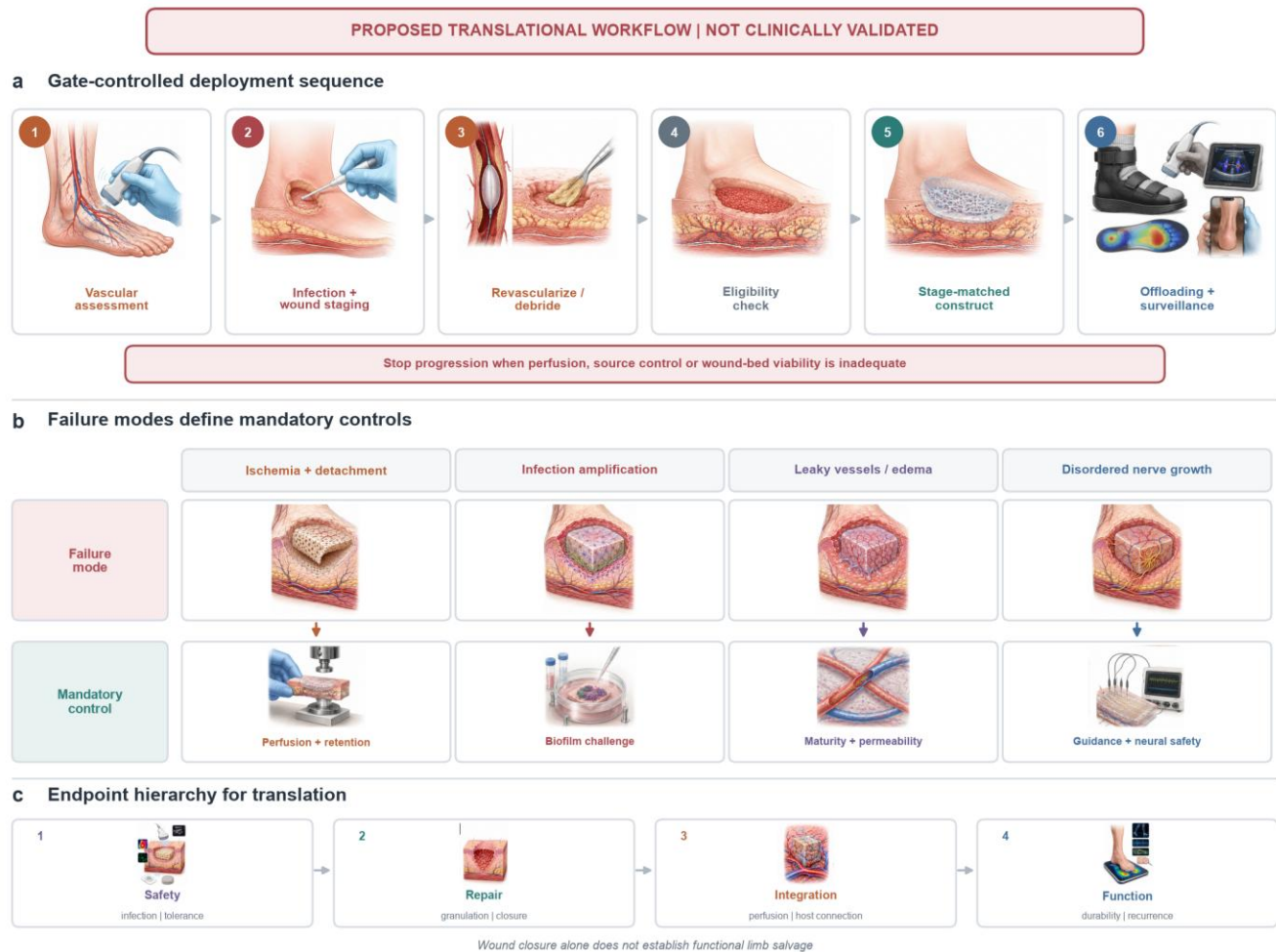


Figure 3. Proposed translational workflow, mandatory failure controls and endpoint hierarchy. The workflow is explicitly not clinically validated. (a) Vascular assessment and infection/wound staging precede revascularization, debridement, eligibility checking, stage-matched construct selection, offloading and surveillance; progression stops when a gate fails. **(b)** Predictable failures include ischemic necrosis or detachment, infection amplification, immature/leaky vessels or bleeding, and painful or disordered nerve growth, each paired with a mandatory control. **(c)** Endpoints progress from safety to repair, biological integration and function. Wound closure alone does not establish functional limb salvage.

7.2 Failure modes and mandatory controls

Failure should be specified before benefit is claimed. In an underperfused bed, a construct may undergo ischemic necrosis; under exudate, shear or plantar load, it may detach or delaminate. A biologically rich matrix can amplify infection when source control is incomplete. Excess or poorly matured angiogenic stimulation can produce leaky vessels, edema or bleeding rather than useful

perfusion. Foreign-matrix responses, fibrosis or maladaptive inflammation can block integration. Neural-supportive designs add a distinct risk of disordered axon growth, neuropathic pain or painful neuroma rather than useful reinnervation^{58,63,66,77-78}.

The evidence status differs by risk. DFU cell-therapy sources directly inform product safety, application feasibility and wound or amputation follow-up, but they do not validate printed-construct retention, vessel maturity or neural safety^{21,74}. Post-revascularization reconstruction and recurrence literature directly establish durability and reintervention as clinically relevant endpoints²²⁻²³. Skin-tissue engineering and graft literature identifies integration, infection and coverage limitations, but does not quantify failure of bioprinted DFU constructs⁷². Leaky or immature vessels, fibrosis and disordered nerve growth remain mechanistic or adjacent-field risks supported by vascular, biomaterial and nerve-repair literature^{9,24,31-32,46,49-50,52,54,66,71,77-78}. They are therefore prospective failure hypotheses, not complications already demonstrated in clinical trials of bioprinted DFU or CLTI constructs.

Studies should prospectively pair efficacy endpoints with perfusion and necrosis, retention under load, bacterial regrowth, vessel maturity and bleeding, fibrosis and immune compatibility, and nerve trajectory, pain and sensory function. Figure 3 makes these controls mandatory and keeps clinically observed contextual endpoints separate from inferred construct-specific risks.

7.3 Trial design and endpoints

Early clinical studies should probably begin with narrowly defined wounds rather than all diabetic foot ulcers. Candidate settings include post-debridement wounds after successful revascularization, exposed tendon or soft-tissue defects with adequate perfusion, or chronic ulcers that have failed standard advanced dressings but do not have uncontrolled infection. No-option ischemia is biologically important but may be too heterogeneous for first-in-human studies. The first printed products may therefore be evaluated less like replacement skin and more like adjunctive advanced wound products with clearly defined perfusion, infection and offloading prerequisites^{28-30,64,70}.

Endpoints should be layered. Short-term endpoints can include safety, infection, local tolerance, pain and feasibility of application. Intermediate endpoints can include granulation rate, epithelialization, wound-area reduction and need for repeat debridement. Mechanistic endpoints can include perfusion, vascular ingrowth, oxygenation, histology and imaging. Long-term endpoints should include durable closure, recurrence, amputation, walking function and quality of life. The recurrence burden documented in recent DFU/CLTI follow-up literature argues that these long-term measures are not

optional add-ons, but part of the core definition of success^{23,28}. These endpoints would make the work legible to both tissue engineers and vascular surgeons.

7.4 Manufacturing and regulatory realism

A living, patient-specific, multi-cellular, vascularized and neurotrophic construct is scientifically attractive but operationally difficult. Manufacturing must control sterility, cell identity, potency, matrix composition, mechanical properties, degradation, storage, transport and release criteria. Point-of-care fabrication adds additional complexity because the hospital becomes part of the manufacturing environment. These constraints do not make translation impossible, but they should shape product design early.

For this reason, the first clinically viable products may be less ambitious than the final biological vision. A standardized angiogenic printed matrix, an acellular bioactive wound filler, a vesicle-loaded hydrogel or an endothelial-supportive scaffold may have a clearer regulatory route than a fully living neurovascular skin substitute. The field should view these simpler products as stepping stones rather than failures of imagination. Table 6 summarizes a proposed research pathway and is not a clinically validated treatment sequence.

Table 6. Proposed clinical-development pathway for vascular surgery-oriented bioprinted wound constructs.

Development stage	Target product type	Best initial clinical scenario	Key preclinical evidence needed	Candidate endpoints
Stage 1	Acellular or vesicle-loaded printed matrix	Clean post-debridement diabetic foot wound with adequate perfusion	Diabetic wound model, cytotoxicity, release kinetics and infection compatibility	Safety, tolerance, granulation and wound-area reduction
Stage 2	Angiogenic printed filler or scaffold	Post-revascularization soft-tissue defect	Perfused-vessel density, oxygenation and host integration	Granulation quality, time to closure and perfusion imaging
Stage 3	Cellular vascularized skin-like construct	Deep wound with exposed tendon or complex soft-tissue loss	Endothelial survival, epithelialization and mechanical durability	Closure durability, recurrence, infection and need for grafting
Stage 4	Neurovascular construct	Selected neuropathic or neuroischemic wounds after perfusion optimization	Nerve ingrowth, Schwann-cell support and neuroimmune markers	Sensory metrics, pain, recurrence and tissue quality
Stage 5	Patient-specific in situ or image-guided bioprinting	Irregular surgical defects after debridement	Sterile workflow, geometry matching and bedside quality control	Feasibility, operative time, construct retention and cost-effectiveness

8. Future directions

8.1 Disease-matched models

The field needs disease-matched models. Constructs intended for diabetic foot ulcers should be tested in diabetic, ischemic, infected or mechanically stressed settings whenever possible. Healthy acute wound models remain useful for early screening, but they cannot support strong claims about neuroischemic wound repair. Recent reviews of diabetic wound models and preclinical DFU translation reinforce that model choice should be matched to the intended clinical claim, especially when ischemia, neuropathy, infection or recurrence are central to the argument¹⁷⁻¹⁸. Comparative studies should ask whether spatially patterned constructs outperform non-patterned hydrogels with the same composition.

The field also needs integrated vascular and neural endpoints. A construct that accelerates closure but does not improve perfusion, innervation or tissue quality may still be clinically useful, but it should not be described as functional reconstruction. Conversely, a construct that improves vascular ingrowth but delays epithelial closure may require a different clinical niche. Clear endpoint hierarchies will help avoid overclaiming.

Finally, vascular surgeons, wound-care specialists, biomaterials scientists and biofabrication engineers should design studies together. The clinical problem defines constraints that are easy to miss in the laboratory: ischemia, infection, pressure, exudate, variable wound geometry, comorbid patients and repeated interventions. Bioprinting can address some of these constraints only if they are treated as design requirements from the start.

8.2 Comparative design studies

The next generation of studies should compare spatial patterning against composition-matched controls. If a printed construct contains the same bioink and cells as a cast hydrogel, the study should ask whether printing improves vascular organization, epithelial migration, mechanical stability or functional repair. Without this comparison, it is difficult to know whether the benefit comes from bioprinting or simply from the biomaterial.

8.3 Toward functional reconstruction

Functional reconstruction should be defined before it is claimed. For vascular-surgery wounds, function may include durable closure under load, perfusion recovery, reduced recurrence, pain reduction, partial sensory recovery, resistance to infection or restoration of contour over exposed

structures. Post-revascularization reconstruction studies and recurrence-focused DFU/CLTI follow-up make this especially clear: soft-tissue coverage and initial closure are only partial successes if breakdown, reintervention or loss of function remain common²²⁻²³. A construct does not need to meet every endpoint to be useful, but the intended function should be explicit. This will help align material design, animal models and clinical trial endpoints.

9. Limitations

This review has several limitations. First, it is a narrative and problem-oriented synthesis rather than a systematic review or meta-analysis. The search strategy, evidence map and reference verification were designed to support a translational argument, but they do not provide pooled effect estimates or formal risk-of-bias grading. Second, direct clinical evidence for bioprinted constructs in neuroischemic diabetic foot ulcers is still sparse. Many cited studies are therefore wound-adjacent, platform-oriented or derived from broader vascular, neural, hydrogel or skin-engineering fields. Third, several translational claims depend on biological plausibility and engineering logic rather than disease-matched comparative testing. These boundaries are central to the review's interpretation: the framework is intended to guide construct design, model choice and endpoint selection, not to establish current clinical efficacy.

10. Conclusion

Vascularized bioprinting offers a useful research framework for neuroischemic DFU because it can organize cells, biomaterials and instructive cues in space. Selected non-diabetic CLTI tissue-loss wounds and post-revascularization arterial defects provide ischemic adjacent test settings for vascular, structural and coverage questions, but they should not be labelled neuroischemic or assigned neural payloads without documented neural injury. Any clinical role, if established, would be adjunctive to vascular assessment, revascularization, infection source control, debridement, offloading and surveillance. The novelty of this review is to organize the evidence around that limb-salvage sequence, link stage-specific construct choices to explicit evidence levels and failure controls, and map diabetic molecular injury pathways to measurable design variables. Current evidence supports feasibility, mechanism selection and disease-matched study design, not a clinically validated treatment algorithm or proven limb-salvage efficacy. Progress now requires composition-matched controls, functional perfusion and host-connection measures, biofilm challenge, mechanical retention, neural safety and recurrence-aware outcomes before increasingly complex constructs are justified.

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Conflict of interest

The authors declare no conflicts of interest.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

No new datasets were generated or analyzed for this narrative review. The literature search records, evidence-mapping files and reference-verification outputs are available in the project archive.

Further disclosure

AI-assisted tools were used to support language editing, literature organization, citation-format checking and figure layout refinement. The authors reviewed, edited and approved all AI-assisted output and take full responsibility for the content, scientific accuracy, originality and integrity of the manuscript. No AI-assisted tool is listed as an author.

References

1. Deng H, Li B, Shen Q, Zhang C, Kuang L, Chen R, et al. 2023. Mechanisms of diabetic foot ulceration: A review. *J Diabetes*. 15(4):299-312. doi:10.1111/1753-0407.13372.
2. Oyebo OA, Jere SW, Houreld NN. 2023. Current Therapeutic Modalities for the Management of Chronic Diabetic Wounds of the Foot. *J Diabetes Res*. 2023:1359537. doi:10.1155/2023/1359537.
3. Aitcheson SM, Frentiu FD, Hurn SE, Edwards K, Murray RZ. 2021. Skin Wound Healing: Normal Macrophage Function and Macrophage Dysfunction in Diabetic Wounds. *Molecules*. 26(16):4917. doi:10.3390/molecules26164917.
4. Jiang P, Li Q, Luo Y, Luo F, Che Q, Lu Z, et al. 2023. Current status and progress in research on dressing management for diabetic foot ulcer. *Front Endocrinol (Lausanne)*. 14:1221705. doi:10.3389/fendo.2023.1221705.
5. Tan CT, Liang K, Ngo ZH, Dube CT, Lim CY. 2020. Application of 3D Bioprinting Technologies to the Management and Treatment of Diabetic Foot Ulcers. *Biomedicines*. 8(10):441. doi:10.3390/biomedicines8100441.
6. Abuhamad AY, Masri S, Fadilah NIM, Alamassi MN, Maarof M, Fauzi MB. 2024. Application of 3D-Printed Bioinks in Chronic Wound Healing: A Scoping Review. *Polymers (Basel)*. 16(17):2456. doi:10.3390/polym16172456.
7. Zhang H, Wu C. 2023. 3D printing of biomaterials for vascularized and innervated tissue regeneration. *Int J Bioprint*. 9(3):706. doi:10.18063/ijb.706.
8. Liu N, Zhang X, Guo Q, Wu T, Wang Y. 2022. 3D Bioprinted Scaffolds for Tissue Repair and Regeneration. *Front Mater*. 9:925321. doi:10.3389/fmats.2022.925321.
9. Carrabba M, Madeddu P. 2018. Current Strategies for the Manufacture of Small Size Tissue Engineering Vascular Grafts. *Front Bioeng Biotechnol*. 6:41. doi:10.3389/fbioe.2018.00041.
10. Murphy SV, Atala A. 2014. 3D bioprinting of tissues and organs. *Nat Biotechnol*. 32(8):773-785. doi:10.1038/nbt.2958.
11. Groll J, Burdick JA, Cho DW, Derby B, Gelinsky M, Heilshorn SC, et al. 2019. A definition of bioinks and their distinction from biomaterial inks. *Biofabrication*. 11(1):013001. doi:10.1088/1758-5090/aaec52.
12. Sun W, Starly B, Daly AC, Burdick JA, Groll J, Skeldon G, et al. 2020. The bioprinting roadmap. *Biofabrication*. 12(2):022002. doi:10.1088/1758-5090/ab5158.

13. Moroni L, Burdick JA, Highley C, Lee SJ, Morimoto Y, Takeuchi S, et al. 2018. Biofabrication strategies for 3D in vitro models and regenerative medicine. *Nat Rev Mater.* 3(5):21-37. doi:10.1038/s41578-018-0006-y.
14. Biondo M, Tomasello L, Giordano C, Arnaldi G, Pizzolanti G. 2024. The promising approach of 3D bioprinting for diabetic foot ulcer treatment: A concise review of recent developments. *Heliyon.* 10(17):e36707. doi:10.1016/j.heliyon.2024.e36707.
15. Li X, Ai X, Wang B, Luo M, Miyamoto A, Kuchay MS, et al. 2024. Application of 3D printing in the treatment of diabetic foot ulcers: current status and new insights. *Front Bioeng Biotechnol.* 12:1475885. doi:10.3389/fbioe.2024.1475885.
16. Glover K, Mathew E, Pitzanti G, Magee E, Lamprou DA. 2023. 3D bioprinted scaffolds for diabetic wound-healing applications. *Drug Deliv Transl Res.* 13(8):2096-2109. doi:10.1007/s13346-022-01115-8.
17. Phang SJ, Arumugam B, Kuppasamy UR, Fauzi MB, Looi ML. 2021. A review of diabetic wound models-Novel insights into diabetic foot ulcer. *J Tissue Eng Regen Med.* 15(12):1051-1068. doi:10.1002/term.3246.
18. Wang H, Wan J, Zhang Z, Hou R. 2024. Recent advances on 3D-bioprinted gelatin methacrylate hydrogels for tissue engineering in wound healing: A review of current applications and future prospects. *Int Wound J.* 21(3):e14533. doi:10.1111/iwj.14533.
19. Zhong Y, Ma H, Lu Y, Cao L, Cheng YY, Tang X, et al. 2023. Investigation on repairing diabetic foot ulcer based on 3D bio-printing Gel/dECM/Qcs composite scaffolds. *Tissue Cell.* 85:102213. doi:10.1016/j.tice.2023.102213.
20. Baltazar T, Jiang B, Moncayo A, Merola J, Albanna MZ, Saltzman WM, et al. 2023. 3D bioprinting of an implantable xeno-free vascularized human skin graft. *Bioeng Transl Med.* 8(1):e10324. doi:10.1002/btm2.10324.
21. Zhang C, Huang L, Wang X, Zhou X, Zhang X, Li L, et al. 2022. Topical and intravenous administration of human umbilical cord mesenchymal stem cells in patients with diabetic foot ulcer and peripheral arterial disease: a phase I pilot study with a 3-year follow-up. *Stem Cell Res Ther.* 13(1):451. doi:10.1186/s13287-022-03143-0.
22. Kedar DJ, Suh HS, Park CJ, Hong JP. 2024. Soft Tissue Reconstruction After Revascularization. *Int J Low Extrem Wounds.* 23(1):27-32. doi:10.1177/15347346231210144.
23. Armstrong NS, Armstrong AA, Mills JL, Conte MS, Tan TW, Swanson RS, et al. 2025. Three-Year Recurrence in People With Diabetic Foot Ulcers and Chronic Limb Threatening Ischemia Is Comparable to Cancer. *Int Wound J.* 22(8):e70724. doi:10.1111/iwj.70724.

24. Liu Y, Liu Y, Deng J, Li W, Nie X. 2021. Fibroblast Growth Factor in Diabetic Foot Ulcer: Progress and Therapeutic Prospects. *Front Endocrinol (Lausanne)*. 12:744868. doi:10.3389/fendo.2021.744868.
25. Yu Q, Qiao GH, Wang M, Yu L, Sun Y, Shi H, et al. 2022. Stem Cell-Based Therapy for Diabetic Foot Ulcers. *Front Cell Dev Biol*. 10:812262. doi:10.3389/fcell.2022.812262.
26. Jiang X, Zeng YE, Li C, Wang K, Yu DG. 2024. Enhancing diabetic wound healing: advances in electrospun scaffolds from pathogenesis to therapeutic applications. *Front Bioeng Biotechnol*. 12:1354286. doi:10.3389/fbioe.2024.1354286.
27. Rai V, Moellmer R, Agrawal DK. 2022. Stem Cells and Angiogenesis: Implications and Limitations in Enhancing Chronic Diabetic Foot Ulcer Healing. *Cells*. 11(15):2287. doi:10.3390/cells11152287.
28. Armstrong DG, Boulton AJM, Bus SA. 2017. Diabetic Foot Ulcers and Their Recurrence. *N Engl J Med*. 376(24):2367-2375. doi:10.1056/NEJMra1615439.
29. Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, et al. 2019. Global vascular guidelines on the management of chronic limb-threatening ischemia. *J Vasc Surg*. 69(6S):3S-125S.e40. doi:10.1016/j.jvs.2019.02.016.
30. Fitridge R, Chuter V, Mills J, Hinchliffe R, Azuma N, Behrendt CA, et al. 2024. The intersocietal IWGDF, ESVS, SVS guidelines on peripheral artery disease in people with diabetes and a foot ulcer. *Diabetes Metab Res Rev*. 40(3):e3686. doi:10.1002/dmrr.3686.
31. Pereira C, Lazar SV, Wang A. 2023. Bioengineering approaches for nerve graft revascularization: Current concepts and future directions. *WIREs Mech Dis*. 15(4):e1609. doi:10.1002/wsbm.1609.
32. Al Mamun A, Shao C, Geng P, Wang S, Xiao J. 2025. Recent advances in the role of neuroregulation in skin wound healing. *Burns Trauma*. 13:tkae072. doi:10.1093/burnst/tkae072.
33. Kolesky DB, Truby RL, Gladman AS, Busbee TA, Homan KA, Lewis JA. 2014. 3D bioprinting of vascularized, heterogeneous cell-laden tissue constructs. *Adv Mater*. 26(19):3124-3130. doi:10.1002/adma.201305506.
34. Baltazar T, Merola J, Catarino C, Xie CB, Kirkiles-Smith NC, Lee V, et al. 2020. Three Dimensional Bioprinting of a Vascularized and Perfusable Skin Graft Using Human Keratinocytes, Fibroblasts, Pericytes, and Endothelial Cells. *Tissue Eng Part A*. 26(5-6):227-238. doi:10.1089/ten.tea.2019.0201.
35. Maggiorotto F, Dalla Valle E, Fietta A, Visentin LM, Giomo M, Cimetta E. 2025. 3D bioprinting of a perfusable skin-on-chip model suitable for drug testing and wound healing studies. *Mater Today Bio*. 33:101974. doi:10.1016/j.mtbio.2025.101974.

36. Gao C, Lu C, Qiao H, Zhang Y, Liu H, Jian Z, et al. 2022. Strategies for vascularized skin models in vitro. *Biomater Sci.* 10(17):4724-4739. doi:10.1039/d2bm00784c.
37. Albanna M, Binder KW, Murphy SV, Kim J, Qasem SA, Zhao W, et al. 2019. In Situ Bioprinting of Autologous Skin Cells Accelerates Wound Healing of Extensive Excisional Full-Thickness Wounds. *Sci Rep.* 9(1):1856. doi:10.1038/s41598-018-38366-w.
38. Freeman FE, Pitacco P, van Dommelen LHA, Nulty J, Browe DC, Shin JY, et al. 2020. 3D bioprinting spatiotemporally defined patterns of growth factors to tightly control tissue regeneration. *Sci Adv.* 6(33):eabb5093. doi:10.1126/sciadv.abb5093.
39. Leucht A, Volz AC, Rogal J, Borchers K, Kluger PJ. 2020. Advanced gelatin-based vascularization bioinks for extrusion-based bioprinting of vascularized bone equivalents. *Sci Rep.* 10(1):5330. doi:10.1038/s41598-020-62166-w.
40. Bashiri Z, Rajabi Fomeshi M, Ghasemi Hamidabadi H, Jafari D, Alizadeh S, Nazm Bojnordi M, et al. 2023. 3D-printed placental-derived bioinks for skin tissue regeneration with improved angiogenesis and wound healing properties. *Mater Today Bio.* 20:100666. doi:10.1016/j.mtbio.2023.100666.
41. Cubo N, Garcia M, Del Cañizo JF, Velasco D, Jorcano JL. 2016. 3D bioprinting of functional human skin: production and in vivo analysis. *Biofabrication.* 9(1):015006. doi:10.1088/1758-5090/9/1/015006.
42. Fratini C, Weaver E, Moroni S, Irwin R, Dallal Bashi YH, Uddin S, et al. 2023. Combining microfluidics and coaxial 3D-bioprinting for the manufacturing of diabetic wound healing dressings. *Biomater Adv.* 153:213557. doi:10.1016/j.bioadv.2023.213557.
43. Wang X, Yang C, Yu Y, Zhao Y. 2022. In Situ 3D Bioprinting Living Photosynthetic Scaffolds for Autotrophic Wound Healing. *Research (Wash D C).* 2022:9794745. doi:10.34133/2022/9794745.
44. Dutta SD, An JM, Hexiu J, Randhawa A, Ganguly K, Patil TV, et al. 2025. 3D bioprinting of engineered exosomes secreted from M2-polarized macrophages through immunomodulatory biomaterial promotes in vivo wound healing and angiogenesis. *Bioact Mater.* 45:345-362. doi:10.1016/j.bioactmat.2024.11.026.
45. Liu L, Spessot E, Lim KS, Wang Z, Mithieux SM, Maniglio D, et al. 2025. Bioprinting vascularized skin analogs: a stepwise approach. *Burns Trauma.* 13:tkaf018. doi:10.1093/burnst/tkaf018.

46. Leal BBJ, Wakabayashi N, Oyama K, Kamiya H, Braghiroli DI, Pranke P. 2020. Vascular Tissue Engineering: Polymers and Methodologies for Small Caliber Vascular Grafts. *Front Cardiovasc Med.* 7:592361. doi:10.3389/fcvm.2020.592361.
47. Chen X, Yu W, Zhang J, Fan X, Liu X, Liu Q, et al. 2023. Therapeutic angiogenesis and tissue revascularization in ischemic vascular disease. *J Biol Eng.* 17(1):13. doi:10.1186/s13036-023-00330-2.
48. Shukla AK, Ahn M, Gao J, Lee D, Yoon S, Oh SO, et al. 2026. Exploring the angiogenic potential of skin patches with endothelial cell patterns fabricated via in-bath 3D bioprinting using light-activated bioink for enhanced wound healing. *Biomaterials.* 325:123575. doi:10.1016/j.biomaterials.2025.123575.
49. Zhong T, Gao N, Guan Y, Liu Z, Guan J. 2023. Co-Delivery of Bioengineered Exosomes and Oxygen for Treating Critical Limb Ischemia in Diabetic Mice. *ACS Nano.* 17(24):25157-25174. doi:10.1021/acsnano.3c08088.
50. Yu L, Bennett CJ, Lin CH, Yan S, Yang J. 2024. Scaffold design considerations for peripheral nerve regeneration. *J Neural Eng.* 21(4):041001. doi:10.1088/1741-2552/ad628d.
51. Zhu M, Li W, Dong X, Yuan X, Midgley AC, Chang H, et al. 2019. In vivo engineered extracellular matrix scaffolds with instructive niches for oriented tissue regeneration. *Nat Commun.* 10(1):4620. doi:10.1038/s41467-019-12545-3.
52. Li G, Han Q, Lu P, Zhang L, Zhang Y, Chen S, et al. Construction of Dual-Biofunctionalized Chitosan/Collagen Scaffolds for Simultaneous Neovascularization and Nerve Regeneration. *Research (Wash D C).* 2020; 2020:2603048. doi:10.34133/2020/2603048
53. Yu X, Liu P, Li Z, Zhang Z. 2023. Function and mechanism of mesenchymal stem cells in the healing of diabetic foot wounds. *Front Endocrinol (Lausanne).* 14:1099310. doi:10.3389/fendo.2023.1099310.
54. Zhao L, Zhou Y, Zhang J, Liang H, Chen X, Tan H. 2023. Natural Polymer-Based Hydrogels: From Polymer to Biomedical Applications. *Pharmaceutics.* 15(10):2514. doi:10.3390/pharmaceutics15102514.
55. Kim N, Lee H, Han G, Kang M, Park S, Kim DE, et al. 2023. 3D-Printed Functional Hydrogel by DNA-Induced Biomineralization for Accelerated Diabetic Wound Healing. *Adv Sci (Weinh).* 10(17):e2300816. doi:10.1002/advs.202300816.
56. Fu YJ, Shi YF, Wang LY, Zhao YF, Wang RK, Li K, et al. 2023. All-Natural Immunomodulatory Bioadhesive Hydrogel Promotes Angiogenesis and Diabetic Wound Healing by Regulating Macrophage Heterogeneity. *Adv Sci (Weinh).* 10(13):e2206771. doi:10.1002/advs.202206771.

57. Zhou Z, Deng T, Tao M, Lin L, Sun L, Song X, et al. 2023. Snail-inspired AFG/GelMA hydrogel accelerates diabetic wound healing via inflammatory cytokines suppression and macrophage polarization. *Biomaterials*. 299:122141. doi:10.1016/j.biomaterials.2023.122141.
58. Pranantyo D, Yeo CK, Wu Y, Fan C, Xu X, Yip YS, et al. 2024. Hydrogel dressings with intrinsic antibiofilm and antioxidative dual functionalities accelerate infected diabetic wound healing. *Nat Commun*. 15(1):954. doi:10.1038/s41467-024-44968-y.
59. Ding JY, Chen MJ, Wu LF, Shu GF, Fang SJ, Li ZY, et al. 2023. Mesenchymal stem cell-derived extracellular vesicles in skin wound healing: roles, opportunities and challenges. *Mil Med Res*. 10(1):36. doi:10.1186/s40779-023-00472-w.
60. Zhang D, Fu Q, Fu H, Zeng J, Jia L, Chen M. 2023. 3D-bioprinted human lipoaspirate-derived cell-laden skin constructs for healing of full-thickness skin defects. *Int J Bioprint*. 9(4):718. doi:10.18063/ijb.718.
61. Yuan M, Liu K, Jiang T, Li S, Chen J, Wu Z, et al. 2022. GelMA/PEGDA microneedles patch loaded with HUVECs-derived exosomes and Tazarotene promote diabetic wound healing. *J Nanobiotechnology*. 20(1):147. doi:10.1186/s12951-022-01354-4.
62. Song Y, You Y, Xu X, Lu J, Huang X, Zhang J, et al. 2023. Adipose-Derived Mesenchymal Stem Cell-Derived Exosomes Biopotentiates Extracellular Matrix Hydrogels Accelerate Diabetic Wound Healing and Skin Regeneration. *Adv Sci (Weinh)*. 10(30):e2304023. doi:10.1002/advs.202304023.
63. Afonso AC, Oliveira D, Saavedra MJ, Borges A, Simões M. 2021. Biofilms in Diabetic Foot Ulcers: Impact, Risk Factors and Control Strategies. *Int J Mol Sci*. 22(15):8278. doi:10.3390/ijms22158278.
64. Senneville É, Albalawi Z, van Asten SA, Abbas ZG, Allison G, Aragón-Sánchez J, et al. 2024. IWGDF/IDSA guidelines on the diagnosis and treatment of diabetes-related foot infections (IWGDF/IDSA 2023). *Diabetes Metab Res Rev*. 40(3):e3687. doi:10.1002/dmrr.3687.
65. Tejiram S, Keyloun JW, Oliver MA, Pinto DN, Chen See JR, et al. 2025. Examining the effect of preoperative antibiotics for skin grafting surgery on the microbiome in burn patients: a pilot study. *Plast Aesthet Res*. doi:10.20517/2347-9264.2024.109.
66. Jackson J, Samarah H, Palmer W, Kaplan Z, Nicodem M, et al. 2025. The impact of biomaterial characteristics on macrophage phenotypes in tissue engineering: a review. *Plast Aesthet Res*. doi:10.20517/2347-9264.2024.166.

67. Wang Y, Hou Y, Vyas C, Huang B, Bartolo P. 2025. An integrated hybrid 3D bioprinting of heterogeneous and zone-specific construct resembling structural and biofunctional properties of osteochondral tissue. *Mater Futures*. 4:025401. doi:10.1088/2752-5724/adb7f6.
68. Zou Z, Yang C, Yang M, Zhu Y, Xin X, Huang M, et al. 2026. Waste-to-healthcare: eggshell-derived 4D-printed biphasic scaffolds for precision bone regeneration. *Mater Futures*. 5:015402. doi:10.1088/2752-5724/ae1e1a.
69. Almadani H, Van YR, Brazio PS. 2024. Office-based indocyanine green fluorescent angiography for surgical planning of pedicled flap division. *Plast Aesthet Res*. doi:10.20517/2347-9264.2024.111.
70. Bus SA, Armstrong DG, Crews RT, Gooday C, Jarl G, Kirketerp-Moller K, et al. 2024. Guidelines on offloading foot ulcers in persons with diabetes (IWGDF 2023 update). *Diabetes Metab Res Rev*. 40(3):e3647. doi:10.1002/dmrr.3647.
71. Sekar MP, Budharaju H, Zennifer A, Sethuraman S, Vermeulen N, Sundaramurthi D, et al. 2021. Current standards and ethical landscape of engineered tissues-3D bioprinting perspective. *J Tissue Eng*. 12:20417314211027677. doi:10.1177/20417314211027677.
72. Yu JR, Navarro J, Coburn JC, Mahadik B, Molnar J, Holmes JH 4th, et al. 2019. Current and Future Perspectives on Skin Tissue Engineering: Key Features of Biomedical Research, Translational Assessment, and Clinical Application. *Adv Healthc Mater*. 8(5):e1801471. doi:10.1002/adhm.201801471.
73. Wang Y, Wu H, Pan Y, Xiao Y, Chen Y, Yang S, et al. 2025. Innovations in hydrogel therapies for diabetic wound healing: bridging the gap between pathophysiology and clinical application. *Burns Trauma*. 13:tkaf025. doi:10.1093/burnst/tkaf025.
74. Kerstan A, Dieter K, Niebergall-Roth E, Klingele S, Jünger M, Hasslacher C, et al. 2022. Translational development of ABCB5+ dermal mesenchymal stem cells for therapeutic induction of angiogenesis in non-healing diabetic foot ulcers. *Stem Cell Res Ther*. 13(1):455. doi:10.1186/s13287-022-03156-9.
75. Bradbury AW, Moakes CA, Popplewell M, Meecham L, Bate GR, Kelly L, et al. 2023. A vein bypass first versus a best endovascular treatment first revascularisation strategy for patients with chronic limb threatening ischaemia who required an infra-popliteal, with or without an additional more proximal infra-inguinal revascularisation procedure to restore limb perfusion (BASIL-2): an open-label, randomised, multicentre, phase 3 trial. *Lancet*. 401(10390):1798-1809. doi:10.1016/S0140-6736(23)00462-2.

76. Bradbury AW, Hall JA, Popplewell MA, Meecham L, Bate GR, Kelly L, et al. 2025. Plain versus drug balloon and stenting in severe ischaemia of the leg (BASIL-3): open label, three arm, randomised, multicentre, phase 3 trial. *BMJ*. 388:e080881. doi:10.1136/bmj-2024-080881.
77. Lee JC, Trott S, Wax MK. 2025. Novel approaches in peripheral nerve repair: a review of current and emerging therapies. *Plast Aesthet Res*. doi:10.20517/2347-9264.2024.122.
78. Sheckley M, Lowney M, Hahn WW, Chen K, Gurtner GC. Role of mechanical forces and skin tension in scar pathophysiology. *Plast Aesthet Res*. 2026; 13:19. doi:10.20517/2347-9264.2026.08.