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REVIEW ARTICLE

Skin bioprinting for burn reconstruction: From stem cell integration to smart in situ regenerative systems

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Abstract

Bioprinting of smart skin structures is emerging as a versatile platform not only for wound coverage but also for potential sensory regeneration, real-time monitoring of structures, and tissue repair. This review presents a comprehensive roadmap to bridge the gap between biofabrication science and clinical translation. We explore investigations related to piezoelectric scaffolds, conductive polymers, and stimuli-responsive inks in preclinical environments to produce functional features such as thermal and tactile sensing. Early clinical case reports have demonstrated the feasibility of *in vitro* skin bioprinting strategies, such as skin patches printed for patient-specific applications using minimally manipulated autologous extracellular matrix and umbilical cord mesenchymal stem cell-laden hydrogels for the management of chronic wounds. In parallel, several preclinical *in situ* bioprinting studies using handheld or microfluidic-assisted devices have shown promising results in full-thickness diabetic and burn wound models in terms of enhanced re-epithelization and neovascularization. We also present inherent differences between *in vitro* bioprinting of autologous dermo-epithelial substitutions and *in situ* strategies based on artificial intelligence-guided print path generation and wound topography mapping. Although sensor-equipped bioprinted grafts have shown promising results, they are still in the early stages of development and require validation in large-scale clinical trials. Nevertheless, integration of stem cell technologies, smart biomaterials, and bio-intelligent control systems may eventually be used to support bioprinted skin constructs not only as replacement tissue, but also as potential living, sensing interfaces. This broad multidisciplinary convergence may be beneficial in redefining skin repair by enabling dynamic interactions between engineered skin grafts and host tissue physiology.

Keywords: Bioinks; Burn wound reconstruction; *In situ* bioprinting; Skin bioprinting; Skin substitutes; Smart skin; Stem cells; Vascularization

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1. Introduction

Burn injuries are more than just skin injuries—they present a global health burden across various populations.[1,2] Each year, millions of people experience burn injuries caused by heat, chemicals, electricity, or radiation. Although high-income countries have specialized burn centers, the burden of burn injuries is overwhelming in low- and middle-income countries where resources are scarce.[2,3] In severe cases, the injury is not simply a patch of damaged tissue, but a precipitant of systemic dysregulation, characterized by uncontrolled inflammation, immune suppression, metabolic imbalance, and increased susceptibility to infection.[2,4] Advances in acute care have significantly improved survival rates, even for burns covering more than 90% of the total body surface area.[5,6] However, survival is accompanied by additional problems, such as slow healing, hypertrophic scarring in up to 70% of patients, contractures, chronic pain, and severe psychosocial impact.[1,6]

Clinically, it is not often easy to repair the skin after a significant burn. The loss of the epidermis and dermis eliminates the natural barrier of the body, causing fluid loss, invasion of organisms, and temperature imbalances.[4,7] In the absence of swift coverage, patients can be exposed to a great danger of dehydration, electrolyte disturbance, and systemic sepsis.[7] Skin grafts or skin substitutes are therefore essential not only to restore a physical barrier but also to provide a provisional matrix for cellular migration and tissue remodeling until native skin regenerates.[1,8] Early closure is critical to prevent organ failure; however, in extensive burns, healthy donor sites are scarce, limiting the feasibility of autologous grafts.[5,7,8] Although coverage is successful, the lack of vascularization in most engineered grafts undermines the integration of these grafts, causing slough and dysfunction.[5] Preventing infections is an ongoing challenge, and effective healing requires not only wound closure but also scar reduction, preservation of mobility, and restoration of appearance to facilitate social reintegration.[1,6]

Although split-thickness skin grafting (STSG) is still considered the gold standard in covering deep burns, its limitations are becoming more apparent.[9–12] Autologous graft success depends on the availability of donor skin, which is often insufficient in extensive injuries.[9,10] The secondary wounds that form as a result of harvesting the donor tissue expose the area to the risks of infections, hyperpigmentation, chronic pain, and esthetics.[10] Clinicians have responded by employing various skin substitutes: from allogenic and xenogeneic grafts to synthetic and tissue-engineered tissue substitutes. Allograft skin is a short-term substitute but is sensitive to immune rejection and disease spread. Xenografts are readily available but immunogenic with a short lifespan, while synthetic scaffolds are completely biologically risk-free for humans but unable to mimic the biomechanical and physiological behavior of native skin.[13]

Over the last 20 years, the therapeutic repertoire has expanded with the development of bioengineered skin substitutes. Human acellular amniotic membrane, a type of acellular scaffold, serves as a biocompatible scaffold with anti-inflammatory and anti-scarring potential; however, it presents challenges related to mechanical strength, vascular integration, and scalable production.[13] Commercial bilayered constructs and cultured autologous cell sheets have demonstrated clinical benefits, including reduced hospital stays and improved scar quality; however, prolonged culture times, Good Manufacturing Practice (GMP) facility requirements, and high costs often delay intervention during critical acute phases.[9,10,14–16] Even modern treatment protocols cannot achieve a compromise between speed, functional recovery, and esthetics, e.g., in wounds with uneven topography, high microbial load, and/or low vascularization.

It is within this context that *in situ* bioprinting has become a paradigm shift in the reconstruction of burns. In contrast to conventional skin substitute fabrication, which takes a few days or weeks to process in sterile facilities, *in situ* bioprinting localizes the processing in the wound bed and accomplishes it with patient-specific, real-time printing of cells, bioinks, and biomaterial deposition.[17,18] This is very beneficial for burn injuries, as the wounds must be covered immediately to save life and avoid infections. By combining imaging, robotics, and custom bioinks, clinicians are able to create scaffolds that are not only capable of closing wounds but also provide regenerative signals, including growth factors, antimicrobials, or vascularization-inducing factors.[19–21] Preclinical studies have shown accelerated re-epithelialization, improved dermal architecture, reduced hypertrophic scarring, and better integration.[22,23]

The key to fully utilizing material potential *in situ* bioprinting is the inclusion of stem cells or stem cell-differentiated skin cells.[17] As opposed to terminally differentiated keratinocytes or fibroblasts, stem cells—mesenchymal, induced pluripotent stem cells (iPSCs)-based, or epidermal progenitors—provide self-renewal, multi-lineage differentiation, and a rich paracrine profile capable of modulating inflammation, promoting angiogenesis, and remodeling the extracellular environment.[24] In preclinical wound models, stem cell-derived constructs have enhanced epithelial coverage, dermal thickness, and vascular infiltration.[25,26] Scalable GMP-compliant systems now enable production of clinically relevant cell numbers within days, and iPSC-derived cells offer a theoretically

limitless source from a minimal patient biopsy—amenable to banking, cryopreservation, and integration into portable bioprinting workflows.[27,28]

Looking into the future, the idea of "smart" bioengineered skin has come into focus, conceptualized as a dynamic structure that could sense, respond, and adapt itself during the healing process. Exploration in preclinical models currently exists, including the use of novel biomaterials with embedded biosensors and microfluidic channels, and proof-of-concept studies are exploring flexible electronics as a means of wireless monitoring.[29–33] Though these approaches have primarily been pursued at the experimental or early case-report stage in the clinic, sensor-integrated grafts have yet to be validated through large-scale trials. Nevertheless, the combination of regenerative medicine, digital health, and tissue engineering describes a forward-looking vision, where bioprinted skin may one day evolve from a replacement tissue to a living interface that senses its environment.[30,34]

2. Clinical translation challenges in skin bioprinting

2.1. Animal skin bioprinting models

Animal models are now inevitable in the fast-emerging field of skin bioprinting, not only as a proof-of-concept model, but as evidence of clinical potential. To capture relevant literature related to studies on bioprinting of skin along with *in vivo* applications, a structured search was conducted in the primary database PubMed (last updated August 2025). We used the basic search terms "bioprinting" and "skin" to obtain a broad pool of references. In this initial stage, no language filters were applied. Titles and abstracts were then manually searched for studies involving *in vivo* testing, particularly those using models of burn wounds or chronic ulcers. Studies in which only *in vitro* experiments, reviews, conference abstracts, or unrelated dermatologic applications were excluded. Screening and data extraction were performed independently by two reviewers, and a consensus was reached if there was disagreement. Details of the search and selection process are presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram (Figure 1).

Initially, we identified 634 papers. After excluding 231 review articles, a total of 403 original research papers remained. We further narrowed down this pool to studies that are specifically associated with skin bioprinting and *in vivo* applications, resulting in a total of 29 relevant articles. Notably, all these chosen studies employed *in vitro* bioprinting with *in vivo t*esting; for example, the skin constructs were initially printed in a controlled laboratory environment and then applied to animal models or human wounds. Among these, two studies reported human clinical trials, detailed in Table 5. The majority of the remaining literature involved animal experiments (27 papers), with 15 studies focusing on mouse wound models (Table 1), and eight studies using rat or porcine models (Table 2). In addition, four studies explored functional restoration, such as glandular or sensory recovery, and are summarized in Table 3. Our analysis of recent preclinical studies, summarized in Tables 1–3, highlights not only the diversity of animal models but also a clear evolution in both bioprinting strategies and regenerative outcomes. Starting with diabetic wounds in mice and progressing to functional sweat gland (SG) regeneration in complex models, the field is advancing beyond simple wound healing toward actual functional tissue replacement. To facilitate standardized comparison between studies, we extracted common healing outcome metrics, including the percentage of wound closure at Days 7 and 14, $CD31^+$ vascular density, re-epithelialization scores, and sample sizes, as shown in Tables S1–S3, Supporting Information. To facilitate readability, we also included trend indicators for wound healing, angiogenesis, and re-epithelialization in each table. Given that the percentage of wound closure was the most consistently reported and comprehensive outcome across studies, we created summary tables showing the median, interquartile range, and a full range of wound closure percentages for studies in Tables 1 and 2 (Table 4). However, for the four studies in Table 3, which emphasized skin appendage functional differentiation and rarely reported wound closure percentages, such summary statistics were not compiled.

The most widely used models are mouse models (Table 1), as they are accessible, cheap, and genetically manipulable. A key trend evident in recent studies is the emergence of these models as a testing ground for bioink innovation. For instance, a photocrosslinkable methacrylated hyaluronic acid-based bioink, when crosslinked with ultraviolet (UV) light, has been used to fabricate three-dimensional (3D)-printed patches that can sustainably release small extracellular vesicles and facilitate wound integration.[35] Although only single-mode photo-crosslinking was used, the system exhibited a strong print fidelity and supported epithelial, vascular, and neural regeneration in diabetic ulcer models. In one notable paper, a thermosensitive double cross-linked gelatin-alginate bioink was developed, allowing *in situ* printing with high structural fidelity and excellent biocompatibility.[36] In addition to significantly enhancing the deposition accuracy and mechanical stability, the coaxial photo-ionic crosslinking formulation also contributed to tissue repair. The printed constructs, when tested *in vivo*, showed very rapid wound healing, lower inflammatory response, and

collagen deposition, indicating that the bioink itself, and not just the scaffold, can serve as a bioactive agent.

Notably, more recently, studies have also started to consider more functionally stratified reconstruction. Integrated tissue-organ printing systems have made it possible to print tri-layered skin grafts that contain not only epidermal and dermal layers, but also hypodermis-like structures and follicle-inductive cells, such as dermal papillae, extending the limits to true skin analogs.[37] These constructs demonstrated basket-weave collagen remodeling and a tiered cellular structure, with the potential for future full-thickness functional reconstruction.

Furthermore, efforts to mimic native mechanical heterogeneity have led to the development of bioinks with gradient stiffness, as demonstrated in the study by Ma *et al*.,[38] which utilized urine models to test the zonal mechanical tuning of dermal equivalents. To reinforce the structure and better adapt to local cell behavior, multiple linear or non-linear gradients were used. Although resolution and complexity tend to be given priority, speed and scale are also important, particularly in trauma care. An early study from Cubo *et al*.[39] featured a bioprinting platform for skin printing that could produce large (100 cm^2) constructs within <35 min and, as such, demonstrated a proof-of-concept for rapid production of clinically relevant skin substitutes on a small animal scale.

Additionally, these constructs also involved the integration of stem cells, human adipose-derived stem cells, and human umbilical cord mesenchymal stem cells (MSCs), widely used for their regenerative capacity and paracrine effects: immune regulation, angiogenesis, and re-epithelialization.[36,40,41] Other studies have gone a step further to add extracellular vesicles or decellularized extracellular matrix (ECM) to form a more natural-like microenvironment.[35,40,41] One group used a xeno-free bioink formulation with four human cell types (fibroblasts, endothelial cells, pericytes, and keratinocytes) to successfully engineer vascularized bilayer skin with rete ridge-like structures—a level of anatomical fidelity that is rarely achieved in small animal models.[42]

Although extrusion-based bioprinting still prevails in murine research, in recent years, the significance of alternative approaches, including laser-assisted and droplet-based bioprinting, is on the rise. As an example, laser-assisted bioprinting (LAB) facilitated the formation of entire cellularized, multi-layered skin constructs with accurate 3D architecture that implanted murine full-thickness wounds.[43] On the same note, bioprinting using droplets, i.e., using bioinks with low viscosity to deposit them with high efficiency, is an effective way to create skin equivalents capable of inducing collagen remodeling and angiogenesis after implantation.[44] These observations imply that bioprinting methods other than extrusion can offer superior control, resolution, and biocompatibility for *in vivo* skin regeneration. Among the most interesting methods is the modified inkjet bioprinting on vascular layer engineering.[45] A modified inkjet bioprinting system was used to fabricate bilayered skin grafts with spatially defined endothelial compartments. The inkjet unit enabled accurate deposition of human microvascular endothelial cells in the dermal layer to promote the formation of prevascular networks. After implantation into full-thickness murine wounds, these grafts led to significant increases in perfusion and revascularization and decreased wound contraction, demonstrating the importance of vascular integration for graft survival. In contrast to the traditional extrusion-based processes, inkjet processes provide increased resolution and droplet control, and therefore, are particularly suited to the patterning of delicate vascular forms. Taken together, the studies described in Table 1 highlight that murine models are not only useful for screening new bioinks but also for modeling complex healing processes (such as angiogenesis, innervation, and full-thickness regeneration), as evidenced by over 60% of high functional outcomes.

Large animal models (Table 2) are not as numerous, but are of vital importance to bridging the translational gap. This is where innovation becomes cellular novelty to scaffold architecture, vascular integration, and immune compatibility. Multiple studies reported the use of fish- or porcine-derived gelatin methacrylate (GelMA) hydrogels enriched with human platelet lysate or recombinant human collagen to enhance bioactivity.[46–49] One group produced a core/shell nanocomposite scaffold system containing antibacterial copper carbon dots and rosmarinic acid, which would provide both antimicrobial and regenerative effects, important for infectious burn wounds.[50] The use of hybrid methods for fabrication, such as a combination of extrusion with electrospinning or digital light processing (DLP) printing, is particularly promising.[48,51] These allow for the building of multi-layered skin analogues, with separated epidermal and dermal compartments and embedded microchannels for nutrient diffusion. A DLP-printed construct tested on pigs demonstrated neovascularization, skin appendage differentiation, and long-term dermal stability, indicating real-world durability.[48] As presented in Table 2, large animal models are instrumental in determining biomechanical durability, vascular maturation, and immune acceptance, and thus serve as a last-stage preclinical validation step before human application.

While much of the attention in the past has been on wound closure metrics such as re-epithelialization rates

and collagen deposition, there is a well-defined evolution toward functional regeneration (Table 3). Several original studies have extended the boundaries by reconstructing appendages such as SG and hair follicles.[52–55] One group bioprinted a construct consisting of stem cell-derived SG cells and dermal microvascular endothelial cells in a matrix with high content of plantar ECM that could restore sweat function in a mouse paw model, a notoriously complex niche.[52] Another study has utilized 3D-printed molds to engineer hair follicle microenvironments, demonstrating functional hair growth after transplantation, including vascularity.[55] These studies, as summarized in Table 3, indicate that functional constructs are not merely theoretical—they are feasible and are already demonstrating restoration of specific skin functions in preclinical studies.

This trend in functional complexity is also driving the need for more precise control of cell position and architecture. Whether by replicating the geometry of the follicle as a 3D-printed microwell or recreating the tri-layered anatomy of native skin, these efforts constitute a paradigm shift from scar minimization to function restoration. Across these models, three broad trends emerge:

(i) Smart bioink design: Bioinks are no longer passive matrices. Whether it is through dual crosslinking, integration with the ECM, or even cell-derived exosomes, they are being designed to interact with the wound microenvironment in a biologically meaningful way.

(ii) Multicellular, vascularized constructs: Grafts composed of a mix of fibroblasts, keratinocytes, endothelial cells, and now pericytes have resulted in constructs that not only survive post-transplantation but also inosculate with host vasculature.

(iii) Functional, not just structural, regeneration: The field is moving definitively away from wound coverage to restoring specialized cutaneous functions: sweat secretion, hair growth, pigmentation, and even sensory reinnervation.

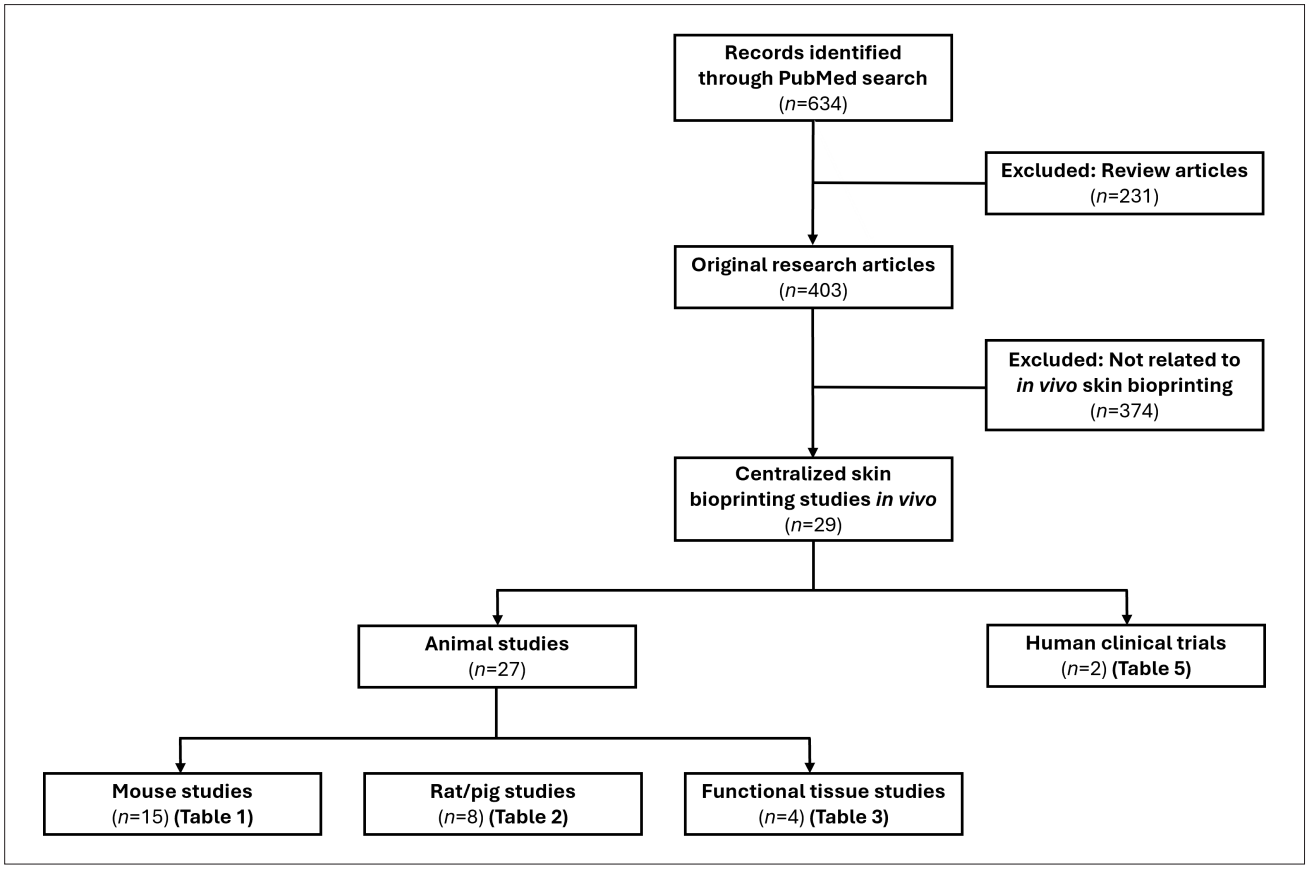

Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study selection for centralized skin bioprinting studies conducted *in vivo*. Flowchart illustrating the identification, screening, and inclusion of original research articles on *in vivo* applications of skin bioprinting in wound healing, encompassing studies on both animals and humans.

Tables 1–3 reflect an emerging consensus opinion: successful skin regeneration is not about copying form, but restoring function. This ambition is mirrored in the selection of animal models. Mice provide a platform for rapid iteration and mechanism. Larger models, such as pigs, provide skin anatomy and immune profiles closer to humans. Functional regeneration models are increasingly designed to answer the question: can we bring skin back to life, not just back to the surface? As the advent of skin bioprinting moves forward toward clinical application, these studies in animals inspire future work. By understanding how these constructs function in living organisms—with real vascular challenges, immune responses, and function demands—we are one step closer to skin substitutes that do not just heal, but also regenerate.

2.2. Clinical skin bioprinting trials

Skin bioprinting is still in its infancy as a clinical tool, yet initial trials are encouraging and already hint at the possibilities of translating engineered constructs from bench to bedside. As highlighted in Table 5, three main clinical strategies have been implemented to date; each of these addresses real-life problems in chronic or complex wounds through highly personalized bioprinting strategies.

An interesting trend is the move toward therapies that are patient-specific and minimally manipulated. Kesavan *et al*.[62] used extrusion-based printing to produce customized patches using minimally manipulated autologous ECM, which was obtained from the patient herself (from adipose tissue). In contrast to isolating stem cells, this protocol maintained native cellular constituents within the ECM, simplifying the workflow while bypassing regulatory considerations of cell expansion. The approach enabled re-epithelialization to be completed in under a month, along with vascular improvement, making it a compelling strategy for personalized, off-the-shelf tissue.

Another evolution is from Zhang *et al*.,[63] who used a hydrogel of gelatin-alginate and human umbilical cord-derived MSCs to treat a chronic wound associated with non-healing after chemical injection treatment. The bioprinted construct could be completely closed in 20 days, and the treated area showed immediate relief from pain and did not recur even a year after treatment. The novelty lay not only in the choice of cell type but also in the spatial programming of cell deposition, which adapts the shape and structure of the cell patch to the precise topography of the wound. This is an example of the potential of imaging, biomaterials, and regenerative biology as a truly integrated clinical workflow.

However, these promising case studies also highlight key limitations. First, sample size and standardization remain significant gaps; more often, published trials are single-patient studies or are not validated in a long-term multicenter study. It is also essential to highlight the limitations of comparability between current trials from the clinical point of view. First, follow-up periods are widely varied, from 4 weeks to >12 months, making it difficult to consistently compare recurrence and long-term outcomes. Second, many studies are not powered or designed for examinations of comparative effectiveness or safety. We have consequently included a concise summary of the risk of bias in Table 5 according to the case report evaluation criteria, providing insight into the current evidence strength. Third, GMP compliance and scalability of cell manufacturing are challenges that must not be ignored. One ongoing trial (NCT04925323) is addressing this by focusing not on the wound itself, but on validating a GMP-compatible pipeline for producing autologous dermo-epidermal grafts. While this trial is still ongoing, its emphasis on regulatory readiness is a vital step toward clinical integration.

Collectively, the studies summarized in Table 5 comprise a transition from experimentally covering wounds to clinically integrated, image-guided, and cell-informed wound repair. These clinical applications place a particular focus on precision medicine and how bioprinting can be used to generate bespoke constructs to treat skin in a patient-specific way consistent with their pathology and anatomy. The clinical space is evolving with a cautious but calculated pace. Instead of mass-producing generic grafts, the focus has shifted to precision bioprinting, customizing bioinks, cell sources, and architectures to cater to each patient's biology and wound profile. Achieving scale, quality, consistency, and cost-effectiveness in deploying these systems remains a significant challenge. For now, bioprinting is transitioning from concept to clinic, one custom patch at a time.

2.3. Regulatory and manufacturing challenge

If skin bioprinting is to translate from concept to clinic, it must first navigate one of the most complex terrains in biomedical translation—regulatory approval and scalable manufacturing.[64–66] The challenge is heightened by the fact that bioprinted skin does not fit neatly within existing regulatory categories. It often sits at the intersection of biologics, medical devices, and gene or cell therapies, depending on its composition and intended use.[67,68] This hybrid nature creates uncertainty at almost every step, including classification, approval, and post-market surveillance.

The first and most significant challenge is product classification. In the United States, the way a product is classified into one of several categories can be a key determinant of the path to market: 361HCT/P (minimally

Table 1. Summary of three-dimensional *in vitro* bioprinting approaches for skin and wound repair in mouse models

Wound category	Specific wound/ Animal species	Bioprinting modality	Bioink material	Cell type used	Healing outcome	Key technical innovation	Reference
Diabetic wound/ extrusion	Diabetic pressure ulcer; diabetic db/ db mice	Extrusion-based 3D bioprinting (Rokit Invivo 4D2)	MeHA (4% w/v) with Irgacure 2959 (0.1% w/v), used as a photocrosslinkable hydrogel	Human adipose-derived mesenchymal stem cells-derived small extracellular vesicles (1.2 mg/mL)	Improved wound epithelialization, angiogenesis, and innervation	Extrusion-based 3D bioprinting combined with *in situ* UV photocrosslinking for mechanically stable, porous patches	[35]
Excisional wound/ extrusion	Full-thickness skin wound; Institute of Cancer Research mice	Extrusion-based 3D bioprinting (temperature-controlled, coaxial photo/ionic double-crosslinking)	GH/AT hydrogel gel-HPA (10% w/v) + alginate-tyramine (1.5% w/v) with ruthenium/ sodium persulfate initiators (0.5 mM ruthenium and 10 mM sodium persulfate); photo/ionic crosslinking (0.18 M $CaCl_2$/450 nm blue light irradiation)	NIH 3T3 mouse FBs (3×10^6 cells/mL) and human umbilical cord mesenchymal stem cells (3×10^6 cells/mL)	Accelerated wound closure, improved re-epithelialization, enhanced collagen deposition, and reduced inflammation	Development of a thermosensitive, double-crosslinked GH/AT bioink enabling *in situ* printing with high structural fidelity and biocompatibility	[36]
	Full-thickness skin wound; C57BL/6 mice	Extrusion-based 3D bioprinting (single-syringe, monolayer FB-laden patch printing)	GelSilMA (G-S) hydrogel: GelMA (3–5% w/v) + SilMA (4–12% w/v) dissolved in LAP (0.25% w/v) photo-crosslinking	Primary mouse dermal FBs (20×10^6 cells/mL)	Faster wound closure, enhanced collagen deposition, and improved angiogenesis	Customized single-syringe printing of cell-laden GelMA/SilMA composite hydrogel patches with tunable mechanical and degradation properties for skin repair	[56]
	Full-thickness skin wound; BALB/c mice	Extrusion-based 3D bioprinting (layer-by-layer with dual thermosensitive + photocrosslinking)	Composite hydrogel of decellularized adipose tissue ECM (dECM, 1.125% w/v) + GelMA (7.5% w/v) + HAMA (1% w/v), with LAP (0.25% v/v) photo-crosslinking	hADSCs (1×10^7 cells/ mL)	Enhanced wound closure, improved collagen deposition, increased angiogenesis, and blood perfusion	Integration of patient-derived adipose dECM with GelMA/HAMA in a UV-crosslinked, hADSC-laden 3D-printed skin substitute for improved vascularized wound healing	[40]
	Full-thickness skin wound; BALB/c nude mice	Extrusion-based 3D bioprinting (layer-by-layer with dual thermosensitive + photocrosslinking)	Composite hydrogel of dECM (1.125% w/v) + GelMA (7.5% w/v) + HAMA (1% w/v), with LAP (0.25% v/v) photo-crosslinking	hADSCs (1×10^7 cells/ mL)	Accelerated wound closure, enhanced neovascularization, increased collagen secretion, and remodeling	Integration of patient-derived adipose dECM and ADSCs into a dual-crosslinkable GelMA–HAMA scaffold for high bioactivity, better cytocompatibility, and improved *in vivo* regenerative performance	[41]

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Table 1. *Continue...*

Wound category	Specific wound/ Animal species	Bioprinting modality	Bioink material	Cell type used	Healing outcome	Key technical innovation	Reference
	Full-thickness skin wound; C.B-17 SCID/bg immunodeficient mice	Extrusion-based 3D bioprinting (layer-by-layer dermis + epidermis)	Xeno-free dermal bioink: human collagen type I (0.6% w/v), human fibronectin (0.1% w/v), VitroGel; Xeno-free epidermal bioink: KC medium with KGF (5 ng/mL), $CaCl_2$ (1.64 mM), ascorbic acid (50 μg/mL)	Xeno-free dermal bioink formulated with 4.5×10^6/mL human FBs, 4.5×10^6/mL human ECs, and 5.5×10^5/mL human placental PCs; xeno-free epidermal bioink formulated with 2×10^6/mL human KCs	Formation of mature stratified epidermis with rete ridge-like structures; perfused human EC-lined vessels within 2 weeks; prevention of graft necrosis; host angiogenic vessel integration	First demonstration of fully xeno-free bioprinted vascularized bilayer human skin graft using four primary human cell types and xeno-free matrix components, showing *in vivo* vascularization and integration	[42]
	Full-thickness skin graft over integrated cartilage construct; BALB/c nude mice	Extrusion-based 3D bioprinting (INKREDIBLE)	Nanofibrillated cellulose/alginate (NFC/Alg); crosslinked with $CaCl_2$ (100 mM)	Human nasal chondrocytes (20%), human bone marrow-derived mesenchymal stem cells (80%)	Skin grafts integrated well with 3D-bioprinted constructs; a tight connection between the fibrous vascularized capsule and the skin graft; no necrosis observed; the skin survived environmental exposure	Demonstrated that *in vivo*-integrated 3D-bioprinted cartilage can serve as a sufficient base for full-thickness skin grafts, enabling potential auricular reconstruction applications	[57]
	Full-thickness skin wound; mouse	Extrusion-based 3D bioprinting	Gelatin–alginate hydrogel with gradient stiffness; cross-linked via calcium substrate	Adipose-derived stem cells	Enhanced angiogenesis and wound healing via improved paracrine secretion and scaffold stability	Gradient stiffness hydrogel mimicking dermal stiffness microenvironment via calcium-mediated secondary cross-linking during printing	[38]
	Full-thickness skin wound; athymic nude mice	Integrated tissue and organ printing, extrusion bioprinting with CAD	Fibrinogen (3% w/v)-based bioink with gelatin (3.5% w/v), glycerol (100 μL/mL), hyaluronic acid (0.3% w/v), aprotinin (40 μg/mL); crosslinked with thrombin (20 IU/mL)	Epidermis: human KCs + melanocytes (9:1); dermis: human FBs, follicle dermal papilla cells, dermal microvascular ECs (6:1:1); hypodermis: human preadipocytes	By Day 21, all bioprinted skin wounds closed via epithelialization (not contraction); restored basket-weave collagen organization; stratified epidermis; dermal maturation; vascularization; human cell integration	First quantification of collagen remodeling in bioprinted skin-treated wounds; demonstrated phenotypically normal skin regeneration with layered tri-cellular architecture, including hypodermis, dermis, and epidermis	[37]

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Wound category	Specific wound/ Animal species	Bioprinting modality	Bioink material	Cell type used	Healing outcome	Key technical innovation	Reference
	Full-thickness skin wound on face-shaped dorsal skin structure; athymic nude mice	Extrusion-based 3D bioprinting using the in-house integrated tissue-organ printing system	Composite hydrogel: hyaluronic acid (0.3% w/v), glycerol (10% v/v), gelatin (3% w/v), fibrinogen (2% w/v); porous polyurethane (PU) support layer; crosslinked with thrombin (20 U/mL)	Epidermis: human epidermal KCs (1×10^7 cells/mL); dermis: human dermal FBs (5×10^6 cells/mL)	Accelerated wound closure, regeneration of epidermis and dermis, improved integration with surrounding tissue	Patient-specific, computer tomography image-based BioMask design; triple-layer construct (PU dressing, KC hydrogel, FB hydrogel) fitting complex facial contours	[58]
	Full-thickness skin wound; immunodeficient mice	Extrusion-based 3D bioprinting	Human plasma-based bioink with fibrin	Primary human FBs and KCs from skin biopsies	Generated skin structurally and functionally similar to human skin, indistinguishable from handmade bilayered equivalents	Rapid fabrication of 100 cm^2 bilayered human skin in <35 min, automated process, reduced production time from weeks to minutes	[39]
	Full-thickness skin wound; C.B-17 SCID/bg immunodeficient mice	Extrusion-based bioprinting (Bio X, CELLINK)	Dermal bioink: rat tail type I collagen (0.35% w/v) + FBS + HAM-F12 + foreskin dermal FBs, ECs, ±placental PCs; Epidermal bioink: KC growth medium + differentiation supplements + KCs; crosslinked with nebulized $NaHCO_3$ (2.2% w/v)	Dermal bioink formulated with 7.0×10^5/mL human FBs and 7.0×10^5/mL human ECs, with/without 3.5×10^5/mL human PCs; epidermal bioink formulated with 2×10^6/mL human KCs	Formation of multilayered epidermis; EC-lined vascular structures inosculated with mouse microvessels and became perfused within four weeks; PCs enhanced host vessel invasion and epidermal rete formation	Inclusion of PCs in dermal bioink to improve both dermal vascularization and epidermal maturation; optimization of KC: FB and PC: FB: EC ratios to mimic native skin structure; pre-vascularized construct enabling inosculation with host vasculature	[59]
Excisional wound/ inkjet	Full-thickness skin wound; Athymic nude mice (homozygous nude *Foxn1*^{nu}/*Foxn1*^{nu}; strain name: J:NU)	Modified inkjet bioprinting (for vascular layer)	Collagen type I gel (0.32% w/v) with neonatal human dermal FBs, fibrin gel with human microvascular ECs, and collagen gel with neonatal human epidermal KCs	Human dermal FBs (2×10^6 cell/mL); human microvascular ECs (2×10^6 cell/mL.); human epidermal KCs (2×10^6 cell/mL)	Improved wound contraction (~10% better than controls), regenerated neoskin with dermis and epidermis resembling normal skin, and survival of implanted cells	Bilayer skin graft with printed endothelial microvasculature integrated with FBs and KCs for enhanced graft survival and vascularization	[45]
	Full-thickness skin wound; mouse	Inkjet droplet-based 3D bioprinting/ nebulization	Collagen-based bioink	Human dermal FBs, human epidermal KCs	Promoted skin regeneration with improved collagen deposition and vascularization	Use of low-viscosity droplet-based bioprinting/ nebulization for high-viability deposition and systematic construction of human skin equivalents with morphologically native-like dermis and epidermis	[44]

Continue...

Table 1. ***Continue...***

Wound category	Specific wound/ Animal species	Bioprinting modality	Bioink material	Cell type used	Healing outcome	Key technical innovation	Reference
Excisional wound/ laser	Full-thickness wound in the dorsal skin fold chamber; BALB/c nude mice	Laser-assisted bioprinting	Collagen type I (rat tail) on Matriderm® scaffold	NIH3T3 FBs (1.5×10^6 cells/mL), HaCaT KCs (1.5×10^6 cells/mL)	Multi-layered epidermis with beginning differentiation, stratum corneum formation, FB collagen production, vascular ingrowth from the wound bed	Precise spatial placement of different cell types in a 3D pattern onto a stabilizing matrix, enabling complex skin tissue formation	[43]

Abbreviations: 3D, three-dimensional; CAD, computer-aided designing; ECs, endothelial cells; ECM, extracellular matrix; FB, fibroblast; GelMA, gelatin methacryloyl; GH/AT, gelatin-alginate; HAMA, hyaluronic acid methacryloyl; hADSCs, human adipose-derived stem cells; KCs, keratinocytes; LAP, photo-initiator lithium phenyl-2,4,6-trimethylbenzoylphosphinate; MeHA, methacrylated hyaluronic acid; PCs, pericytes; SilMA, silk fibroin methacrylate.

manipulated, homologous use) or under the more stringent 351 pathway, which requires an investigational new drug application and a complete Biological License Application.[69] Constructs that contain allogeneic cells, genetic manipulation, or more than minimal manipulation (combining stem cells with synthetic scaffolds) will almost always fall into 351, requiring extensive pre-clinical and clinical requirements. The "Same Surgical Procedure Exception" in 21 CFR 1271.15(b) can be applied to certain autologous, intraoperative uses, but bioprinting workflows are often outside these very narrow confines in terms of multiple procedural manipulations, storage steps, or incorporated bioactive components.[70]

In Europe, the European Medicines Agency (EMA) considers bioprinted products under the umbrella of advanced therapy medicinal products (ATMPs).[71–73] While the "hospital exemption" clause allows for limited flexibility in terms of custom, non-commercial uses, products still require high bars for GMP compliance, traceability, and defined mechanisms of action.[74,75] The absence of global consistency between the Food and Drug Administration (FDA) and EMA requirements is an additional component in the burden of regulatory requirements, particularly for developers who aim to conduct multinational trials or eventually commercialize their therapies.[76] Due to the regulatory uncertainty, we listed the existing types of dossiers as well as the current classification pathways for bioprinted skin in the FDA and EMA systems (Tables 6 and 7). Table 6 summarizes the types of regulatory dossiers and product characteristics that trigger each, and Table 7 groups classification into four regulatory pathways to help present the regulatory route and dossier requirements for each scenario in the FDA and EMA guidance. These summaries are used to help delineate the different regulatory expectations for products based on their cellular content and structural characteristics, as well as when drugs or electronics are incorporated into the product. For example, entirely acellular scaffolds could follow a medical device pathway. In contrast, scaffolds that contain live cells, growth factors, or a great deal of manipulation would follow the more rigorous biologics or combination product route. The tables not only detail the applicable areas and approval pathways, but also the documentation that is needed, from GMP compliance to device technical files, biodiversity and biocompatibility reports, and clinical trial applications. These differences can be significant for developers to recognize their regulatory responsibilities up-front to prevent misclassification and optimize clinical translation between jurisdictions.

Meanwhile, GMP manufacturing remains a significant bottleneck.[74,75,77,78] Bioprinting is not merely about stacking cells; one must stack cells in a controllable,

Table 2. Summary of three-dimensional *in vitro* bioprinting approaches for skin and wound repair in large animal models

Wound category	Specific wound/ Animal species	Bioprinting modality	Bioink material	Cell type used	Healing outcome	Key technical innovation	Reference
Diabetic wound	Full-thickness skin wound in a diabetic model (50 mg/kg streptozotocin-induced); Wistar rat	Extrusion-based 3D printing (low-temperature manufacturing system)	Chitosan (6% w/v) in acetic acid (2% v/v) with D-(+)-raffinose pentahydrate	Normal dermal human fibroblasts (1×10^5 cells/mL) and human keratinocytes (HaCaT, 1×10^5 cells/mL)	Improved wound closure and better tissue quality vs. commercial patch or no treatment	Low-temperature extrusion-based printing of chitosan scaffolds; optional chitosan film base to retain cells inside the scaffold	[60]
Excisional wound	Critical-sized full-thickness skin wound; Wistar rat	Extrusion-based 3D bioprinting (CELLINK)	Fish skin-derived GelMA (10% w/v) hydrogel supplemented with HPL (5% v/v); crosslinked with 365 nm UV light	Human ASCs, 5×10^6 cells/mL)	Delayed wound contraction, enhanced collagen deposition, and increased neovascularization compared to the untreated and GelMA-only groups	Development of fish skin-based GelMA bio-ink with tunable methacrylation degree and extrusion-printability, enabling ASC + HPL delivery for improved wound healing	[46]
	Full-thickness skin wound; Sprague Dawley rat	Extrusion-based 3D bioprinting (Biomaker 2, SunP Biotech)	GelMA (7.5% w/v, porcine skin) + rhCol3 (0.8–3.2% w/v); cross-linked with 405 nm UV light	HDFs (1×10^6/mL), human epidermal keratinocytes (HaCaTs, 3.3×10^5 cells/mL)	rhCol3 promoted faster epidermal confluence (~100% by Day 3), enhanced dermal and epidermal growth, improved wound closure, and tissue regeneration vs. rhCol3-free	Use of recombinant human type III collagen as a bioactive component in GelMA bioink to accelerate skin cell proliferation, epidermal confluence, and wound healing	[47]
	Full-thickness skin wound; Sprague Dawley rat	3D printing (Tongli micro-nano technology), combining electrospinning and extrusion printing	Outer layer: PLGA nanofiber membrane (15% w/v in HFIP, electrospun) inner layer: alginate hydrogel (crosslinked in 5% $CaCl_2$)	None (acellular scaffold)	Bleomycin scaffold showed the fastest and best skin regeneration, enhanced neovascularization (CD31), increased collagen I/III deposition, and reduced interleukin-1 beta and tumor necrosis factor alpha expression compared to PLGA, alginate, and untreated control	Bilayer design (outer PLGA for antibacterial and moisture retention, inner porous alginate for cell adhesion, and proliferation); integration of electrospinning and 3D printing for skin-mimicking structure; acellular scaffold reduces immune rejection	[51]
	Full-thickness skin wounds; rat	3D-embedded bioprinting	Thermosensitive thiolated Pluronic F127 (PF127-SH) + HAMA hydrogel	Not specified	Enhanced wound healing, promoted re-epithelialization, accelerated collagen deposition, angiogenesis, and modulated inflammation	Stepwise multi-cross-linking bioink strategy: Michael addition at low temperature, hydrophobic self-assembly at body temp, thiolene click photo-cross-linking	[61]

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Table 2. ***Continue...***

Wound category	Specific wound/ Animal species	Bioprinting modality	Bioink material	Cell type used	Healing outcome	Key technical innovation	Reference
	Full-thickness skin wound; rat	Extrusion-based 3D printing (core/shell scaffold fabrication)	PLA shell; core: hyaluronic acid (HA), chitosan hydrogel, copper carbon dots (Cu-CDs, 0.25–2% w/v), rosmarinic acid	L929 fibroblast stem cells	Significantly improved wound healing after 15 days compared to PLA scaffold alone; enhanced histological regeneration; upregulated PDGF, TGF-β, and MMP-1 expression	Core/shell nanocomposite scaffold integrating antibacterial Cu-CDs with HA/chitosan/rosmarinic acid for combined antimicrobial and regenerative effects	[50]
	Full-thickness skin wound; Sprague Dawley rat; Bama little pig	DLP-based 3D bioprinting	GelMA (5% w/v) + HA-NB (1.25% w/v) + LAP (0.1% v/v) + phenol red (0.04% w/v); cross-linked with 365 nm UV light	HSFs (4×10^5 cells/mL); HUVECs (4×10^5 cells/mL)	Promoted skin regeneration, enhanced neovascularization, formation of skin appendages, and superior dermal regeneration	Bioink with HA-NB for photocrosslinking and tissue adhesion; DLP printing enabling high-resolution microchannels for nutrient transport; rapid fabrication of functional living skin for large-area wounds	[48]
	Not specified; Animal	3D bioprinting (modality not explicitly stated)	GelMA + collagen (Col) doped with tyrosinase (Ty)	Human melanocytes, human keratinocytes (HaCat), HDF	Formation of epidermis and dermis *in vivo*; high (>90%) cell viability; Ty enhanced melanocyte proliferation, inhibited fibroblast overgrowth, and supported balanced skin regeneration	Tyrosinase-doped GelMA/Col bioink; dual crosslinking via enzymatic and photocrosslinking for enhanced mechanical strength; bioactive role of Ty in pigmentation and wound healing	[49]

Abbreviations: 3D, three-dimensional; ASCs, adipose tissue-derived mesenchymal stromal cells; DLP, digital light processing; GelMA, gelatin methacryloyl; HA-NB, N-(2-aminoethyl)-4-(4-(hydroxymethyl)-2-methoxy-5-nitrosophenoxy) butanamide linked hyaluronic acid; HAMA, hyaluronic acid methacrylate; HDFs, human dermal fibroblasts; HFIP, hexafluoroisopropanol; HPL, human platelet lysate; HSFs, human skin fibroblasts; HUVECs, human umbilical vein endothelial cells; LAP, photo-initiator lithium phenyl-2,4,6-trimethylbenzoylphosphinate; MMP-1, matrix metalloproteinase 1; PDGF, platelet-derived growth factor; PLA, poly(lactic acid); PLGA, poly(lactic-co-glycolic) acid; rhCol3, recombinant human type III collagen; TGF-β, transforming growth factor beta; UV, ultraviolet.

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Table 3. Summary of three-dimensional *in vitro* bioprinting approaches for skin functional tissue regeneration

Wound category	Specific wound/ Animal species	Bioprinting modality	Bioink material	Cell type used	Healing outcome	Key technical innovation	Reference
Functional tissue regeneration	Sweat gland injury/ regeneration model (including thermal injury in mouse paw pad); C57BL/6 mice, CAG-tdTomato mice, Sprague Dawley rats	Extrusion-based 3D bioprinting (Regenovo)	Sodium alginate (1% w/v) + gelatin (3% w/v) + plantar dermis ECM (58 μg/mL); crosslinked with $CaCl_2$ (2.5% w/v)	ADSCs (1×10^7 cells/mL) differentiated into SGCs (4.8×10^2 spheroids/mL), co-cultured with DMECs (4.8×10^5cells/mL)	Promoted physiologically relevant vascularized sweat gland morphogenesis, restored sweat secretion, enhanced vascularization *in vitro* and *in vivo*	Creation of a vascularized sweat gland regeneration model combining 3D-bioprinted SGC spheroids and prevascularized ECM scaffolds to mimic SG-vascular niche reciprocal interactions	[52]
	Burn injury on paw pad; C57BL/6 mice	Extrusion-based 3D bioprinting (Bio-Architect PRO, Regenovo)	Gelatin (10% w/v) + alginate (2% w/v) hydrogel with paw pad dermal homogenates (PD, 58 μg/mL); crosslinked with $CaCl_2$ (100 mM)	MSCs (1×10^6 cells/mL)	Regeneration of functional sweat glands confirmed by acetylcholine-induced sweat test; restoration of glandular morphology; enhanced sweat gland gene expression	Identification of *CTHRC1* (biochemical cue) and *Hmox1* (structural cue-responsive factor) as synergistic regulators directing MSC differentiation into SGCs; integration of biochemical (ECM proteins) and structural (3D microarchitecture) cues in printed constructs	[53]
	Burn injury on paw pad; C57BL/6 mice	Extrusion-based 3D bioprinting (Bio-Architect PRO, Regenovo)	Composite hydrogel of gelatin (20% w/v) and sodium alginate (4% w/v) with paw pad dermal homogenates and EGF (15 ng/mL); crosslinked with $CaCl_2$ (10% w/v)	Epidermal progenitor cells (from mouse dorsal skin)	Functional restoration of sweat glands *in vivo*	Creation of a 3D ECM mimic providing spatial inductive cues to direct epidermal progenitors into sweat gland lineage, enabling regeneration in injured tissue	[54]

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Table 3. ***Continue...***

	Full-thickness dorsal midline excision with silicone chamber implantation; Immunodeficient nude mice (*athymic nude, Crl:NU(NCr)-Foxn1nu*)	3D-printed molds (Objet24, UV-curable material VeroWhite) to create hair follicle microwells	Type I collagen gel for the dermal layer embedded with 3D-printed mold structures	Human dermal fibroblasts (1.25×10^5 cells/mL), dermal papilla cells (*LEF1*-transfected to enhance hair follicle induction), neonatal keratinocytes, GFP-tagged human umbilical vein endothelial cells (HUVECs for vascularization, 2×10^6 cells/mL)	Formation of human hair follicles within engineered skin constructs; vascularized grafts grew hair effectively after transplantation into mice	Biomimetic developmental approach: 3D-printed mold to recapitulate human fibroblast microenvironment geometry; *LEF1* overexpression restores dermal papilla cell inductive capacity; pre-vascularization improves survival and function	[55]

Abbreviations: 3D, three-dimensional; ADSC, adipose-derived mesenchymal stem cell; DMECs, dermal microvascular endothelial cells; ECM, extracellular matrix; GFP, green fluorescent protein; MSCs, mesenchymal stem cells; SGCs, sweat gland cells; UV, ultraviolet.

sterile, and reproducible manner. Unlike traditional biologic manufacturing, which is conducted in centralized manufacturing facilities, the focus of many bioprinting applications (especially *in situ* systems) is real-time deposition at the bedside. This raises challenging questions about process validation, bioprinter calibration, sterility assurance, and documentation. Even centralized workflows (whereby derivatives are printed and matured before implantation) have challenges with batch-to-batch consistency, long lead times, and GMP-compliant facilities. Quality systems for traditional drugs rarely translate into dynamically growing, patient-specific constructs produced on demand.

Despite the scientific maturation of 3D-bioprinted skin, the regulatory landscape remains fragmented and unprepared to address the complexity of this technology.[65] In essence, bioprinted constructs are hybrid products (a complex of cellular, structural, and sometimes genetic components), leading to overlapping regulatory spaces between the laws and regulations related to biologics, devices, and tissue controls.[72,79,80] Such products have been categorized in various ways, on a case-by-case basis, depending on the level of manipulation, cell source, and clinical purpose. As the regulatory agencies, such as the FDA and EMA, have yet to unambiguously define the bioprinted constructs, there is a level of ambiguity in the regulatory pathway and risk categorization for the bioprinted constructs.[81]

To deal with the operational complexity of hybrid constructs—characterized by cellular, structural, and device elements—regulatory authorities have begun to provide pathway-specific guidance. The FDA's Office of Combination Products offers the Request for Designation mechanism to resolve the primary mode of action and whether a hybrid construct should be regulated as a biologic, device, or combination product. In the European Union, developers will need to engage early on with both EMA and notified bodies to determine whether the construct is covered by either ATMP or device directives. In Japan, the Pharmaceuticals and Medical Devices Agency permits conditional approvals for regenerative products with minimal efficacy requirements, a structured path for iterative development of regenerative products. However, these tools are underutilized in bioprinting, making formalized hybrid construct classifications frameworks necessary. Without such tools, developers are left dependent on ad hoc consultation, which can slow translational clinical development, as well as complicate global coordination processes.

Additionally, the materials implemented in bioinks make it more complex.[82,83] Most are still in an experimental

Table 4. Summary statistics of percentage wound closure in animal models of skin bioprinting

Model type	Timepoint	Median (%)	Interquartile range (%)	Range (%)
Mouse	Day 7	79.67	59.5–84.8	50.0–91.0
	Day 14	99.2	90.0–100.0	72.0–100.0
Rat	Day 7	78.0	72.2–85.0	50.0–90.0
	Day 14	100.0	100.0–100.0	94.0–100.0

Note: Among the mouse data from the 15 studies listed in **Table 1**, three lacked full-text access and were therefore excluded. This resulted in 12 studies being included in **Table S1, Supporting Information**. Among these, five did not report quantitative wound closure data and were excluded from the final analysis. Summary statistics were calculated from the remaining seven studies and are presented as medians, interquartile ranges, and full ranges. Among the rat data from the eight studies listed in **Table 2**, two lacked full-text access and were, therefore, excluded. This resulted in six studies being included in **Table S2, Supporting Information**. Among these, one did not report quantitative wound closure data and was excluded from the final analysis. Summary statistics were calculated from the remaining five studies and presented as medians and full ranges.

stage, with pure and stability profiles still not clearly defined and often containing animal-derived or xenogenic materials. This raises concerns about safety and sterility, especially since conventional sterilization methods (e.g., radiation or ethylene oxide) may compromise the functionality of bioink or harm embedded cells.[84–87] Additionally, no bioinks currently on the market are approved for human use, and well-developed criteria for biocompatibility testing for living, patient-specific constructs are presently not available.

Risk profiles are also challenging to assess. Most hazard analyses for conventional devices fall short when applied to dynamic, on-demand constructs involving live cells. Other features of these grafts, such as immune response, tumorigenicity, or variability of vascular integration, have not been sufficiently characterized. This is further compounded by the decentralization of manufacturing. Many bioprinting systems perform *in situ* bioprinting by the bedside, a marked difference from centralized GMP-certified facilities. This trend of re-distributed manufacturing challenges traditional notions of quality control, traceability, and liability.[88]

Additionally, product shelf-life remains a regulatory blind spot.[89] Viable cell-laden components are time-sensitive, yet protocols for expiration dating, packaging, and transport remain underdeveloped. In parallel, standardization of testing, particularly regarding print fidelity, structural integrity, and functional outcome, is still evolving. Only a few American Society for Testing and Materials (ASTM) standards have been proposed, and most are restricted to extrusion-based bioprinting.

Post-market surveillance is another critical gap.[90] Authorities lack data on the real-world performance and adverse events, with limited clinical data and long-term follow-up. Few trials have progressed beyond feasibility or safety endpoints, such that long-term integration, remodeling, and regeneration outcomes are unknown. This is further complicated by living autologous cells, whose heterogeneity across patients makes outcome prediction difficult.

Complicating things is the fragility of the bioprinting supply chain. Clinical-grade bioinks, or especially those with recombinant collagen, growth factors, or decellularized ECM, are difficult to obtain in a GMP-certified fashion.[74] Batch-to-batch variation, cold-chain logistics, and a short shelf life put a product at risk of delay or failure. Moreover, devices such as cryopreserved, stem cell-laden cartridges—designed to support portable or point-of-care printing—are still in early development and have yet to be commercially scalable.

There is an international push toward regulatory harmonization; however, considerable confusion exists regarding the classification of bioprinted skin constructs. Although the key principles in the International Council for Harmonisation (ICH) Q8–Q11 guidance documents on drug development, quality risk management, and quality systems are increasingly being discussed for emerging therapies such as tissue-engineered products, bioprinted or tissue-engineered constructions remain outside their scope, underscoring the need for dedicated regulatory guidance in this area.[91–94] Similarly, the World Health Organization has published international standards through the Expert Committee on Biological Standardization, but actual conformity is not well enforced.[95] For instance, the FDA regulates complex autologous grafts under the HCT/P framework (361 or 351 pathways), whereas the EMA classifies them as ATMP under Regulation (EC) No 1394/2007, requiring centralized marketing authorization.[96,97] In contrast, Japan's Pharmaceuticals and Medical Devices Agency has placed a conditional time-limited approval system in place for regenerative therapies, speeding up access but requiring post-marketing surveillance.[98,99] The International Medical Device Regulators Forum has developed harmonized definitions and regulatory pathways for personalized medical devices (custom-made, patient-matched, and modular devices)

Table 5. Clinical summary of three-dimensional *in vitro* bioprinting approaches for skin and wound repair

Wound type	Design/Sample size	Bioprinting modality	Bioink material	Cell type used	Follow-up/ Bias risk	Healing outcome	Key technical innovation	Reference
Diabetic foot ulcer (chronic, neuropathic, located below the malleoli)	Randomized controlled trial/17 (test group); 16 (control group)	Extrusion-based 3D bioprinting (ROKIT Dr INVIVO)	Minimally manipulated autologous extracellular matrix (MA-ECM) from adipose tissue	Native adipose-derived cellular components within MA-ECM (no ADSC isolation)	24 weeks/ low-moderate (no blinding)	Complete re-epithelialization in ~4 weeks; accelerated wound closure; improved vascularization	Custom patient-specific wound patch bioprinted from autologous MA-ECM; integration of imaging-to-G-code workflow	[62]
Chronic non-healing wound caused by bleomycin A5 intralesional injection for plantar warts (with infection, superficial phlebitis)	Case report/1	Extrusion-based 3D bioprinting (Regenovo Biotechnology)	Alginate (1% w/v) + gelatin (3% w/v); crosslinked with $CaCl_2$	Human umbilical cord-derived mesenchymal stem cells (hUCMSCs, 1×10^6 cells/mL)	One year/ Moderate (no comparator)	Complete wound closure in 20 days after first application; improved vascularity; pain reduction within 3 days; no recurrence at 1-year follow-up	Patient-specific wound-shaped skin substitute with hUCMSCs; precise spatial arrangement of cells; customization of bioink and print pattern for individual wounds	[63]
Surgical wound tissue (from plastic/ reconstructive surgery)— used for generating dermo-epidermal autologous skin substitute	GMP validation/25	Not specified	Not specified	Keratinocytes, fibroblasts (isolated and expanded from healthy patient surgical waste tissue)	Not applicable	Trial focuses on GMP validation and *in vitro* product generation, not clinical wound healing	GMP-compliant automated bioprinting process for dermo-epidermal skin substitute; integration of keratinocyte and fibroblast expansion with bioprinting workflow	ClinicalTrials.gov Identifier: NCT04925323; status: recruiting (as of last update June 14, 2021)

Abbreviations: 3D, three-dimensional; ADSC, adipose-derived mesenchymal stem cell; GMP, good manufacturing practice.

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Table 6. Overview of regulatory dossier types and their applicability in bioprinting

Dossier type	Investigational new drug	Biologics license application	Device technical file	Good manufacturing practice
Applicable region	U.S. FDA	U.S. FDA	U.S./EU	Global
Application type	Clinical trial approval	Marketing authorization (biologics)	Medical device	Manufacturing
Purpose	Required for products containing drugs or biological components (e.g., stem cells or tissues). Must submit to the FDA before the clinical trial begins	If the product passes clinical trials and seeks marketing, a biologics license application must be submitted to the FDA	For acellular or scaffold-based products, such as ECM or electronic sensor components, a technical file must be submitted to a notified body (EU) or the FDA (U.S.)	Required for biological products and some medical devices to ensure consistency, safety, and traceability
Evaluation documents	• Animal toxicology and preclinical safety • CMC (chemistry, manufacturing, control) • Clinical trial protocol	• Clinical trial data (efficacy and safety) • GMP compliance • Risk management system	• Design documentation and engineering validation reports • Safety and performance data • Biocompatibility data • User instructions	• Aseptic processing • Batch record • Equipment calibration and maintenance • Raw material control • Quality control
When required	For products containing allogeneic cells, drug components, growth factors, or extensively manipulated autologous cells	For products containing live cells or therapeutic components (e.g., autologous or allogeneic stem cell skin substitutes, or gene-modified constructs)	For device-classified products such as acellular ECM, three-dimensional-printed scaffolds, and devices with electronic components (but no live cells)	Almost all products intended for human application involving biologics require GMP, e.g., harvested tissues, expanded stem cells, or cell-laden printed constructs

Abbreviations: ECM, extracellular matrix; EU, European Union; FDA, Food and Drug Administration; GMP, good manufacturing practice; U.S.: United States.

that are especially relevant to *in situ* bioprinting platforms where the bioprinter and printed tissue or structure are an inseparable combination product.[100] Australia's Therapeutic Goods Administration has, in line with the International Medical Device Regulators Forum guidance, amended its regulatory framework to specifically cover 3D-printed devices intended for personalized medicine, including devices produced using new technologies such as bioprinting, in acknowledgement of their increasing presence in the clinic and the inherent risks in combining biological material with devices.[101] Despite these advances, there is a constant regulatory delay due to the absence of standardized technical guidelines specific to bioprinting processes. However, in comparison to the more mature standards used to guide traditional biologics and medical devices, bioprinting-specific standards are sparse and narrow in scope. For instance, to date, only extrusion-based bioprinting has seen proposed technical standards, such as ASTM WK65680 (New Test Methods for Printability of Bioinks and Biomaterial Inks) and ASTM WK72274 (Printability of Bioinks for Extrusion-based Bioprinting).[64] Additionally, ASTM F2900-11, a guideline for characterization of hydrogels for their use in regenerative medicine, is often used, but does not cover the full range of new applications of bioprinting. Existing standards are not able to cope with new modalities such as embedded bioprinting (e.g., freeform reversible embedding of suspended hydrogels) or light-based bioprinting, such as stereolithography and volumetric photopatterning, that are becoming increasingly popular due to their high resolution and structural complexity.[102] In addition, existing frameworks are primarily focused on centralized manufacturing and are therefore inadequate for point-of-care bioprinting, where ensuring quality control, sterility assurance, and traceability is crucial in dynamic clinical settings. Thus, parallel to international regulatory harmonization, technical specifications must be revised and expanded for future safety, consistency, and cross-border interoperability of bioprinted therapies.

Good Manufacturing Practice compliance of bioprinted products is a unique task due to the dynamic, personalized, and often decentralized nature of production. In Europe, ATMPs are subjected to EudraLex Volume 4, Annexes 1 (Manufacture of Sterile Medicinal Products) and 2 (Manufacture of Biologically Active Substances and Medicinal Products for Human Use), which emphasize aseptic processing, validated cleaning procedures, and risk-based environmental monitoring. The additional requirements of Grade A/B clean areas during bioink deposition increase implementation challenges, especially on *in situ* platforms. In the United States, traceability, donor screening, and adverse event reporting are required for

Table 7. Regulatory pathways and dossier requirements for bioprinted skin products under the Food and Drug Administration and the European Medicines Agency frameworks

Pathway	Condition	Regulatory route	Dossier required
Path A (Simplest and least stringent regulatory route)	Autologous, minimal manipulation, *in situ*, no drug/electronics e.g., point-of-care use with autologous ECM directly printed onto the wound	FDA: 361 HCT/P (21 CFR Part 1271)	• GMP-lite • Traceability
		EMA: Hospital Exemption (Regulation (EC) No 1394/2007)	• National authority approval • Hospital-grade GMP • IRB/Ethics oversight
Path B (Full regulatory pathway for biologics)	Allogeneic or more-than-minimal manipulation (culture or gene modification) e.g., centralized bioprinting using expanded cells or allogeneic stem cells	FDA: IND → BLA (351 Biologic, regulated under Section 351 of the Public Health Service Act)	• IND • BLA • GMP-full
		EMA: ATMP Central Route	• CTA • ATMP • EU-GMP
Path C (Combination product with drug or electronic components)	Any path + Drug delivery or Electronics e.g., smart skin bioprinting with sensors, growth factors, or antibiotic gels	FDA: Combination product (Biologic + Medical device)	• IND • BLA • Device technical file • GMP (21 CFR 210/211 + 21 CFR Part 4) • QSR (21 CFR 820)
		EMA: ATMP + Medical Device Regulation (EU 2017/745)	• CTA • ATMP • Device technical file • EU-GMP (EudraLex Vol 4, Annex 13) • MDR QMS (ISO 13485)
Path D (acellular, device-based product)	Acellular products or decellularized matrix only e.g., scaffold-based skin substitutes without live cells	FDA: 510(k) or De Novo	• Device dossier (510(k) or De Novo) • Biocompatibility report (ISO 10993) • QSR (21 CFR 820)
		EMA: CE-marked device under MDR (EU 2017/745)	• Technical file (Annex II of MDR) • CER • CE mark under MDR • QMS/ISO 13485

Abbreviations: ATMP, advanced therapy medicinal product; BLA, biologics license application; CE, Conformité Européenne; CER, clinical evaluation report; CFR, Code of Federal Regulations; CTA, clinical trial application; EC, Ethics Committee; ECM, extracellular matrix; EMA, European Medicines Agency; EU, European Union; FDA, Food and Drug Administration; GMP, good manufacturing practice; HCT/P, human cells, tissues, and cellular and tissue-based products; IND, investigational new drug; IRB, Institutional review board; ISO, International Organization for Standardization; MDR, Medical Device Regulation; QMS, quality management system; QSR, quality system regulation.

both 21 CFR Part 210/211 (biologics) and Part 1271 (HCT/Ps), and innovative solutions such as closed-cartridge systems, single-use sterile nozzles, and real-time particle counters are helping to ensure asepsis in the operating room.[69,103] Some institutions are considering GMP-in-a-box models—cleanroom-grade modules rolling in next to surgical theatres. Furthermore, quality by design and process analytical technology are currently being explored to track print fidelity, nozzle temperature, and shear stress, all of which affect cell viability.[104,105] As regulators start acknowledging decentralized constructions for point-of-care applications, it is necessary to develop clearer GMP pathways for mobile bioprinters.

Ethical oversight in bioprinting will need to consider the dual complexity of the cellular content and dynamic manufacturing. Products that are autologous and minimally manipulated might qualify for expedited Institutional Review Board review, particularly if processed within the same surgical session (per FDA's 21 CFR 1271.15).[69,70] Most bioprinted skin constructs are beyond the threshold structure, where expanded cell culture, allogeneic components, or artificial intelligence (AI)-guided wound modeling are used, thereby requiring full Institutional Review Board or Ethics Committee scrutiny. There are also new issues of digital accountability, as patient imaging data for wound modeling must be General Data Protection Regulation or Health Insurance

Portability and Accountability Act compliant, especially as it may be stored in cloud-based planning systems.[106,107] Additionally, algorithmic bias in wound shape mapping or bioink distribution creates new dynamics of ethical accountability, where transparent validation and oversight of the operator(s) is needed. Informed consent becomes complicated when constructs include donor-derived or gene-edited elements or when devices are applied in an emergency, where it is challenging to give preoperative counseling. These types of scenarios require strong ethical protocols, as well as interdisciplinary oversight to ensure patients' safety, data security, and equitable access.

Ultimately, what is needed is not only better technology but also stronger infrastructure. This hybrid nature of bioprinted skin creates a need for regulatory frameworks to adapt to the unique circumstances.[108] Manufacturing platforms need to be designed with compliance and scalability in mind.[109,110] Cooperation across disciplines between engineers, cell biologists, regulators, and clinicians must be implemented. Until these challenges are resolved, even the most scientifically promising constructs may remain stuck in the pre-clinical pipeline. Bioprinting has demonstrated to us what is possible; the task now is to make it viable and legally accessible to the patients who need it the most.

2.4. Patient stratification and wound complexity

Not all wounds are the same, and neither should be treatment. In skin bioprinting, patient stratification is more than clinical categorization; it is a roadmap for tailoring biofabrication strategies to real-world complexity. Whether it is an extensive, third-degree burn wound or a diabetic ulcer that is healing slowly, each type of wound presents its own biological, mechanical, and logistical challenges.

Consider, for example, extensive burn injuries. These are not only large in surface area but often involve volatile wound environments—acidic pH, high protease activity, dehydration, and thermal stress.[111,112] That is why ink stability becomes the main technical bottleneck. Unlike standard inks, which are stored in a laboratory environment, bioinks used in this process must withstand printing times, high ambient temperatures, and biochemical chaos, while still maintaining cell viability and structure.[113] If the ink breaks apart in the middle, then the entire treatment is compromised.

Chronic ulcers, such as diabetic foot wounds, present a different type of challenge. These wounds are typically irregular in shape, poorly perfused, often infected, and surrounded by fibrotic tissue.[114,115] Precision is of paramount importance, but the execution of *in situ* printing becomes difficult in such non-ideal microenvironments. Any minor deviation of the nozzle traveling or deposition speed will lead to uneven or cell loss. The inflammatory milieu that is constantly present may negate any regenerative advantages, making these wounds not only challenging to treat but also difficult to heal.

In battlefield or field-trauma settings, portability is paramount. But most current bioprinters are not built for dusty, humid, and temperature-variable environments. Their dependence on stable electricity, controlled sterile conditions, and vibration-free operation means that they are not suitable for real-life trauma zones.[116] The technical bottleneck here lies in ruggedizing the system—creating compact, pre-calibrated devices that can be plugged in and print even on a moving vehicle or field hospital. It is not only about miniaturizing the technology, but also about making it more resilient.

Esthetic dermal repair, such as scar revisions and cosmetic skin restoration, presents a different challenge.[117,118] Here, the urgency is not the driving factor; rather, it is the demand for perfection. If there are minor discrepancies in print resolution, texture, or pigmentation, then the results are less than ideal. Adding to that, the regulatory bar is higher for non-life-threatening indications, especially when long-term cosmetic effects are involved. The cost–benefit ratio becomes a critical issue, confronting companies with difficult questions about insurance coverage, patient out-of-pocket costs, and whether the investment can ultimately be justified.

2.5. Clinical and emergency integration

Regardless of its technological novelty, a solution that cannot be integrated into established clinical workflows is unlikely to find adoption in the operating room. One of the biggest hurdles for skin bioprinting is not the bioinks or the cells—it is the system-wide integration of how this technology fits into surgical routines, trauma protocols, and emergency timeframes.

In elective or scheduled surgeries, there is at least time to plan, prepare the printer, run sterility checks, and align the construct design with imaging. However, such cases remain the exception rather than the rule. Burn care is a race against time—early wound coverage within 48–72 hours can make a difference between survival and sepsis.[4,119,120] In battlefield trauma scenarios, clinicians must contend with chaotic environments, limited sterility, unreliable power sources, and the necessity of operating within minutes. In these situations, even the slightest delay in operating a bioprinter or calibrating a nozzle is clinically unacceptable.

Additionally, surgical teams also possess limitations. Bioprinting cannot require numerous additional steps or reliance on specialized personnel beyond those already

available within the hospital. Seamless integration requires that the device be intuitive, fast, and readily deployable in a plug-and-play manner.[121,122] If the printer cannot be used by a trained operating room staff with minimal training (and without halting/slowing the flow of the surgery), then it is not ready to be integrated in the operating room. Most current systems are too fragile, bulky, or slow for such applications.

Moreover, logistics is also a key challenge. Sterile packaging, cell storage, power management, and digital design transmission must be standardized before bioprinting can be routinely used in trauma bays or burn units. Workability alone is insufficient as the printer must be able to survive transport, sterilization cycles, and sudden deployment on a 24/7 clinical clock.

Additionally, if complications arise during printing—such as a printer jam, construct delamination, or bioink batch failure—the question of accountability becomes critical.[123] Hospitals will not purchase systems without clear standard operating procedures, contingency plans, and regulatory coverage. In many jurisdictions, this remains a regulatory grey area. Ultimately, successful clinical integration depends less on continuous innovation and more on effective simplification. Skin bioprinting does not need to revolutionize the operating room; it needs to integrate into it seamlessly. Until then, even the most advanced bioprinted skin may never leave the benchtop.

2.6. Technological readiness and operative integration

In the case of skin bioprinting, being technology-ready entails not only that the device functions properly, but also that the entire system can be implemented seamlessly within existing clinical workflows. Most existing bioprinting systems work well in controlled lab settings, but as they move into real-world surgery, challenges rapidly accrue.

First, there is the issue of real-time scanning and printing.[124] In actual surgical scenarios, everything happens on the clock. Patients are anesthetized, and there is minimal time to scan the wound, model the defect, plan the print path, and begin printing. This entire process needs to be seamless and fast. However, most currently available imaging devices are not geared toward high resolution, low latency, scanning in dynamic wound sets that might be actively bleeding or changing. Any delay or data error can throw the whole workflow off balance.

Subsequently, there is the printing itself. Technical accuracy alone is not enough, as the printer must be compact, modular, and foolproof.[125,126] Operative teams cannot afford to take time out to manually calibrate the print head, resolve temperature drift, or change materials mid-surgery. The system needs to be smart enough to auto-adjust parameters and simple enough to be operated by trained surgical staff—not engineers—in a high-pressure setting. If it cannot be handled like any other surgical tool, it will not be adopted.

Another huge challenge is integration with the current operating room infrastructure. This is more than installing a printer in the sterile field. Printers must be synced with hospital information technology systems, extracting imaging data from picture archiving and communication systems, complying with sterile packaging protocols, and powering up on standard operating room outlets without risk of voltage sags or overheating.[124]

Another often-overlooked challenge is post-operative data capture and traceability. Bioprinted grafts are not a one-and-done treatment—they require follow-up, performance monitoring, and digital documentation.[124,127] The opportunity of iterative improvement and regulation compliance is lost if there are no integrated data logging, cloud synchronization, and feedback integration systems in place. In short, every print should have a digital footprint.

From scanning and modeling to printing and intraoperative execution, every part of the bioprinting workflow must reach a level of operational simplicity before it can truly enter the operating room. Skin bioprinting does not need to reinvent the surgical process—it needs to fit into it, quietly and efficiently. The point at which it is no longer treated as a centerpiece but instead functions as a routine tool on the operating room tray will signify its readiness for clinical integration.

2.7. Cost-benefit considerations and reimbursement barriers

Regardless of how advanced skin bioprinting becomes, it will not achieve mainstream adoption unless it is economically viable—for hospitals, payers, and patients. Right now, one of the biggest challenges is cost. Bioprinters are not cheap, whereas bioinks are specialty products, and cell expansion under GMP is resource-intensive.[128] Additionally, the requirement for trained personnel, validated cleanroom protocols, and potentially downtime for calibration or quality control measurements increases the overall cost.

Compared to the gold standard—autologous STSG—STSG has a low material cost and decades of clinical familiarity.[129–131] It does not need sophisticated hardware or involve much regulatory navigation. However, it possesses several limitations, such as donor site morbidity, limited availability of grafts in extensive burns, recurrent surgery, increased length of hospital stay, and often less than optimal esthetic or functional outcomes. With additional rehabilitation time, wound care supplies, and

complications, such as infection or hypertrophic scarring, the cost of STSG increases.

Skin bioprinting, by contrast, offers the promise of one-and-done treatments.[121,122,132] Personalized constructs could decrease the number of surgeries, accelerate epithelialization, decrease the risk of infection, and potentially shorten Intensive Care Unit time. For complex or pediatric cases, this could equate to significant long-term savings. However, currently, these advantages are just theoretical in the absence of extensive clinical data.

Reimbursement presents another challenge. Currently, no standardized coding or payment structure exists for bioprinted grafts, leaving payers uncertain whether to classify them as tissue grafts, medical devices, or cellular therapies. Unclear costs associated with implementing bioprinting, even if hospitals are willing to take on the investment, they cannot be assured of recouping expenses. In the absence of reimbursement, patients are left to pay the cost (not viable for the majority of people, particularly in low-resource environments).

Cosmetic and elective uses—such as scar revision or pigment correction—face an even steeper hill,[117,118] which are often not covered by insurance. In spite of the ability of the technology to provide outstanding esthetic outcomes, the market for such applications is limited unless the cost decreases or value can be demonstrated.

To move forward, bioprinting needs a better value proposition: not just faster healing, but measurable cost offsets.[133] Reduced length of stay or fewer complications, or an earlier return to work, may help to justify reimbursement. A key part of building this case will be through collaboration with payers, health economists, and real-world data studies. In the end, bioprinting will succeed not merely by producing superior skin, but by demonstrating that the value of the skin justifies its cost. Until this threshold is met, even the most elegant constructs will falter in their justification for employment in a cost-sensitive health care system.

3. *In situ* bioprinting in wound medicine: Opportunities for burn care translation

Bioprinting technologies have evolved rapidly in recent years, and their clinical relevance is no longer confined to laboratory benchtops. The field has traditionally been dominated by *in vitro* bioprinting (constructing skin equivalents under controlled conditions before implantation).[134] These approaches provide unprecedented control over structural fidelity, cell positioning, and maturation conditions. Layered bilayered grafts, vascularized skin equivalents, and pigmented or hair follicle-containing constructs have all been achieved through *ex vivo* fabrication, using extrusion-based, inkjet, or laser-assisted techniques. In this context, recent advancements in 3D bioprinting have led to a vast expansion of the field of engineered skin constructs by embedding complex cell lineages, vascularization techniques, and functional appendages. Baltazar *et al.*[59] demonstrated a multilayered, vascularized skin graft composed of keratinocytes, fibroblasts, endothelial cells, and pericytes, which achieved perfusion and host integration *in vivo*, marking a significant step toward clinically relevant skin substitutes. de Bengy *et al.*[135] developed a 3D *ex vivo* sebaceous gland model that preserved sebocyte lipid metabolism and function for over 6 weeks, opening new directions for studying glandular skin physiology and drug screening. In a biomimetic approach to recreating dermal papilla cells and spatial follicular organization, Abaci *et al.*[55] were able to recover the *de novo* hair follicle formation in human skin constructs. Min *et al.*[136] demonstrated the *in vitro* bioprinting of a biomimetic skin model containing melanocytes that successfully recapitulated UV-independent pigmentation patterning—a crucial step forward in modeling skin color and its associated diseases. In the same line, Yamauchi *et al.*[137] used muse cells to construct pigmented 3D human skin, in which endogenous adult stem cells were able to regenerate melanocytes, keratinocytes, and fibroblasts in an integrated scaffold. Kolesky *et al.*[138] recently presented a paradigm change in thick tissue engineering by co-printing multiple cell types together with perfusable vasculature and keeping tissues thicker than 1 cm viable and functional beyond 6 weeks. Huang *et al.*[54] designed a 3D-printed ECM that mimicked the glandular niche and enabled epithelial progenitor cells to differentiate into SG lineages both *in vitro* and *in vivo*—demonstrating how spatially defined biochemical cues can dictate lineage-specific outcomes. These advances are visually summarized in Figure 2, in which the central panel highlights the multilayered vascularized graft by Baltazar *et al.*[59]. The insets around it illustrate specialized constructs, such as biomimetic pigmentation models,[136,137] sebaceous gland analogs,[135] *de novo* hair follicle formation,[55] perfusable thick tissue,[138] and spatially guided sweat gland differentiation.[54] Clinically, this figure highlights the increasing potential of *in vitro* 3D bioprinting for the recreation of functional skin constituents with a growing level of fidelity and complexity. However, as visually compelling as these developments are, they are limited by factors such as scalability, sterility requirements, and the way that static constructs can be adapted to dynamic environments such as a patient's wound.

In vitro constructs are frequently subject to complex culture requirements, bioreactors, prolonged

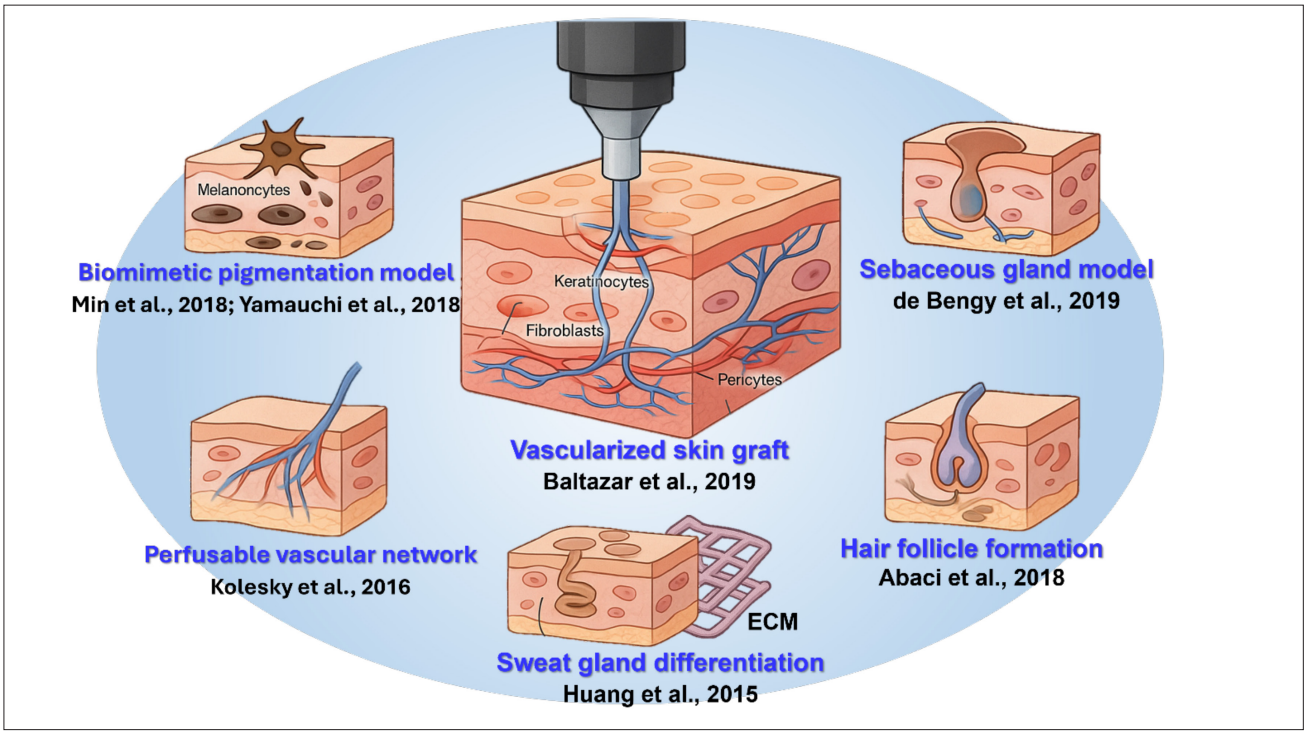

Figure 2. Recent advances in three-dimensional (3D) bioprinting for engineered skin constructs. This illustration highlights key breakthroughs in 3D bioprinting of human skin tissue. The middle panel shows the multilayered, vascularized skin graft grown by Baltazar *et al.*,[59] incorporating keratinocytes, fibroblasts, endothelial cells, and pericytes, and showing successful *in vivo* perfusion and host integration, a key milestone toward clinical skin substitutes. Surrounding insets depict complementary advances: biomimetic pigmentation models using melanocytes,[136,137] an *ex vivo* sebaceous gland model maintaining sebocyte function,[135] hair follicle formation via dermal papilla restoration,[55] perfusable vascular networks in thick tissues,[138] and spatially guided sweat gland differentiation via engineered extracellular matrices (ECM).[54] Figure created using illustrations generated via ChatGPT (OpenAI image tools), with final layout and annotations edited in Microsoft PowerPoint.

preconditioning, and cryopreservation, which are factors slowing down the delivery to the clinical setting.[139] In addition, scaling up to large surface areas (e.g., for extensive burns) is logistically, sterility, and storage challenging. More importantly, the static geometry of *in vitro* grafts cannot accommodate the dynamic irregularities of wound beds in the real world.

A number of bioprinting modalities have recently been revolutionized *in vitro*, including extrusion-based, inkjet, and laser-based bioprinting, all of which feature different advantages in terms of printing accuracy, resolution, and bioink compatibility.[140–142] Extrusion-based bioprinting, for example, enables printing of high-viscosity bioinks and multicellular structures, which makes it suitable for dermal-epidermal layering. Inkjet printing is fast, and viable cells can be deposited, but only over a limited viscosity range and vertically. LAB provides high precision with low shear stress induced by a nozzle, which is appropriate for spatially delicate structures such as melanocyte patterning or microvascular network bioconstruction.

However, *in vitro* bioprinting is still limited by being static and pre-manufactured.[143–145] Models are created in perfect laboratory conditions that are optimized for sterility, nutrient supply, scaffold support—but rarely mimic the complex, heterogeneous nature of real wound environments. Additionally, the time of bioreactor conditioning, vascularization, and post-print maturation, as well as the infrastructure the processes demand, creates delays that are incompatible with acute clinical situations such as burn trauma, where time is of the essence. These limitations show the increasing demand for bioprinting platforms that can function beyond the walls of the controlled laboratory.

This is the paradigm that *in situ* bioprinting redefined, not by replacing the *in vitro* strategy, but by translating bioprinting to an on-demand, in-theater therapeutic device. It allows printing of bioactive materials, cells, or matrix-mimicking hydrogels directly on the wound bed without the need for pre-cultured grafts. This shift from construct fabrication to real-time tissue reconstruction offers distinct advantages for burn care.

3.1. The potential of *in situ* bioprinting in burn medicine

Speed matters when treating burn injuries. Severe burns need early coverage of wounds (preferably within 48–72 h) to avoid fluid loss, infection, and systemic complications.[2,120,146] Traditional grafting procedures often have several delays, such as donor site harvest, graft preparation, and transfer.[120] In contrast, *in situ* bioprinting enables on-site, direct deposition of cells and biomaterial without lengthy preparation and enables real-time tissue fabrication directly onto the wound bed.[124,147]

The other key strength is customization. Burn wounds are rarely uniform—they are large, irregularly shaped, and biologically hostile. *In situ* systems can digitally scan wound topography and print constructs that match the wound's exact shape, depth, and geometry, layer-by-layer.[140] Not only does this customized fit aid in graft integration, but it also minimizes material wastage and handling errors.

This method is also minimally invasive and repeatable. Unlike autografting, which involves sacrificing healthy skin, *in situ* printing avoids donor site morbidity, a significant advantage for patients with large total body surface area burns.[140] Moreover, the process is inherently modular, allowing for repeated applications as the wound evolves.

To better contextualize the clinical advantages of *in situ* bioprinting in burn care, it is essential to contrast it with the more traditional *in vitro* bioprinting approach. While both are focused on fabricating functional tissue constructs, their operational workflows, clinical readiness, and applications are very different. *In vitro* bioprinting is often performed by building up tissue constructs *in vitro* before implantation, while *in situ* bioprinting could directly fabricate tissue constructs in real time on wound beds. As described in Table 8, significant differences are (i) printing location: sterile lab versus operating room, (ii) personalization level: scaffold is predefined versus real-time 3D scan-based structure, (iii) cell viability: decreased *in vitro* due

Table 8. Comparative overview of *in vitro* and *in situ* bioprinting approaches

Aspect	*In vitro* bioprinting	*In situ* bioprinting
Definition	Fabrication of tissue constructs in a controlled lab environment before implantation	Direct printing of biomaterials and cells onto or within the defect site in the body
Environment	Sterile, static, and tightly controlled laboratory or cleanroom settings	Dynamic, often irregular, and biologically active surgical or wound site
Application timing	Construct is printed first, then implanted later	Printing occurs intraoperatively or immediately at the point of care
Surface stability	Stable, flat substrates (e.g., glass slides, petri dishes)	Soft, curved, moving tissues (e.g., breathing lung, beating heart, bleeding wounds)
Workflow	Computer-aided design modeling → Print → Mature in incubator → Implant	Scan → Model → Print → Crosslink (real-time, on-site)
Time to treatment	Requires time for pre-fabrication and post-printing maturation	Enables rapid or immediate wound coverage
Precision and resolution	High precision is possible due to a stable environment	Moderate to high; depends on scanner accuracy and motion compensation
Device complexity	Often complex and large-scale bioprinters	Ranges from simple handheld tools to advanced robotic platforms
Surgeon control	Surgeon performs implantation, but not fabrication	A surgeon may guide printing directly (handheld) or through a robotic interface
Customization	Generic constructs may not match patient-specific anatomy	Fully personalized constructs based on real-time wound geometry
Use case examples	Organ-on-chip, tissue graft production, lab-grown cartilage or skin	Burn wound repair, bone defect filling, corneal repair, and muscle regeneration
Crosslinking method	Performed post-printing using light (ultraviolet/visible), thermal, ionic, or enzymatic methods in a controlled environment such as an incubator or ultraviolet chamber	Requires integrated, real-time crosslinking using on-site UV/blue light, thermal control, ionic co-axial extrusion, or enzymatic triggers
Portability	Low; equipment is lab-bound	High (handheld) to moderate (robotic); designed for intraoperative use
Scalability	Suitable for mass production of constructs	Tailored for individualized therapy
Challenges	Vascularization, maturation before implantation	Bioink retention on wet/moving surfaces, sterilization, and accuracy under surgical conditions
Clinical readiness	More mature in terms of regulatory pathways and manufacturing	Rapidly evolving, promising for point-of-care regenerative therapies

to time/storage versus increased *in situ* by immediate use, and (iv) integration pathway: separate implantation versus seamless deposition. These differences are shown in **Table 8**, demonstrating the differences between these two modalities that play important but separate yet complementary roles in translational skin medicine. *In vitro* printing is still suitable for engineered grafts with complex stratification and maturation, and long-term maturation; *in situ* bioprinting, in contrast, provides a handy, portable, on-demand system in the closed wound environment.

A clear example of the translational potential of *in situ* skin bioprinting was shown by Cheng *et al.*,[25] who used a porcine full-thickness burn model to demonstrate a handheld bioprinting instrument for depositing wound-conformal skin precursor sheets directly onto sites of injury. This hand-held platform combined 3D scanning with precise deposition of dermal and epidermal cell-laden biomaterials, fitting snugly to the complex geometries of deep burns. Re-epithelialization, vascularization, and wound contraction returned at a quicker pace in treated wounds versus control groups. Notably, the device was suitable for point-of-care use, obviated traditional graft fabrication workflows, and was feasible in clinically relevant, large animal models.

3.2. Technical architecture of *in situ* bioprinting

In situ bioprinting systems can be classified by deployment modality (robotic-assisted vs. handheld) and printing mechanism (extrusion-based, inkjet, or laser-assisted).[18,19,147] Most current *in situ* systems, whether robotic or handheld, rely on extrusion-based techniques due to their robustness and compatibility with cell-laden bioinks. Inkjet and laser-assisted deposition techniques are still in their clinical translation, but they offer promise for smaller diameter applications such as fine pattern deposition or vascular microstructure.

3.2.1. Deployment modality

In situ bioprinting is emerging as a paradigm-shifting approach in regenerative medicine, where biomaterials and cell-laden constructs can be fabricated and functionalized in real time and customized for specific wounds or tissue defects. Within this broad field, two key classes of systems have been established based on the interface, level of automation, and clinical applicability, namely hand-held bioprinting devices and robotic-assisted systems.[18,19,147] These categories embody two philosophies of surgical integration: one predicated upon precision through automation, the other simple portability.

3.2.1.1. Robotic-assisted in situ bioprinting

Robotic-assisted systems represent the high-tech frontier of *in situ* bioprinting.[148–150] Typically, these configurations have a robotic arm of multiple degrees of freedom (DOF) attached to modular print heads capable of extrusion, inkjet, or even LAB. The high precision positioning and controlled movement of the robotic arm in 3D space are relevant to complex and irregular wound geometry.

In the robotic-assisted modality, the standard workflow starts with 3D scanning of the defect site by structured light, stereo vision, or light detection and ranging (LiDAR).[151] The resulting digital mesh is then read into a computer-aided design (CAD) software and translated into G-code, which generates a layer-by-layer printing path.[152] This automation allows high reproducibility and spatial accuracy, which is especially useful for microsurgical applications such as corneal, cartilage, and even neurosurgeonic bioprinting.[148,153]

An example of such robotic-assisted *in situ* bioprinting was recently demonstrated by Zhao *et al.*,[23] who have designed a custom extrusion-based robotic arm platform with dual-nozzle bioprinting and real-time 3D scanning. This system enabled platelet-rich plasma augmented bioinks to be deposited one layer at a time directly onto the full-thickness wounds of rats. The automated path planning and nozzle switching enabled fast multilayer building, leading to enhanced wound closure, vascularization, and less inflammation.

However, robotic systems have major caveats.[148] These devices are expensive, time-consuming to learn, and must be sterilized, while requiring operating room space, which are barriers to clinical implementation. These systems often need a team of engineers and clinicians to tune them and make them work properly. Furthermore, deformation of tissue, wet surfaces, and varying intraoperative conditions can impact fidelity unless adaptive compensation schemes are available.

To effectively tackle these issues, adaptive printing frameworks have been suggested in which the feedback from the scanning system can be used to adapt the deposition trajectory in real-time. This dynamic correction allows the robotic printer to track along the contours of living tissue, even when there is a small motion artifact. Additionally, incorporation of magnetic or electric field-assisted crosslinking to improve scaffold alignment and mechanical robustness during deposition is being investigated.[154]

Taken together, robotic-assisted bioprinting has excellent potential for complex tissues with multiple layers, especially in deep tissue or high-resolution reconstruction applications. Its long-term potential is the integration into minimally invasive robotic surgery platforms, in which the

internal bioprinting is carried out through the laparoscopy or endoscopy.[155,156]

3.2.1.2. Handheld in situ bioprinting

Handheld bioprinting is an easier-to-use and more accessible technology that foregoes automation for portability and intuitive control. These devices are typically pen-like or pistol-grip tools containing motorized or pneumatic extrusion systems, small cartridge reservoirs, and sometimes integrated light-based crosslinking.[157–159]

Typically, the device is positioned by the operator, usually a surgeon, and its deposition is directed across the target site to provide direct-write fabrication in real time. This makes the use of handheld printers especially appropriate for non-uniform wounds, anatomically challenging areas, or a field setting where it would be impractical to use complete robotic setups.[160–162]

A well-known example of handheld *in situ* bioprinting was shown by Cheng *et al.*,[25] who designed a modified handheld extrusion-like delivery system that can be used with a microfluidic printhead and a compliant silicone wheel. This system allowed the precise deposition of a fibrinogen/thrombin/hyaluronic acid bioink containing MSCs derived from cord tissue (1×10^6 cells/mL) directly on top of full-thickness burn wounds in a porcine model. The device was capable of deposition control, even on inclined surfaces up to 45°, and proved to greatly improve re-epithelialization, neovascularization, and dermal cell repopulation. This study confirmed the potential of wound conformal delivery systems to improve outcomes of healing for complex burn wounds. Importantly, the ease of operation and the small footprint and sterilization capability of the tool also made the tool suitable for point-of-care and on-site use, even in low-resource settings.

The benefits of handheld systems are numerous, including low cost, ease of sterilization, minimal training requirements, and flexibility for a wide variety of clinical settings.[160] They are beneficial in the field of military or disaster response applications, where portability and speed are more critical than micrometer-quality accuracy. Further, these instruments allow on-the-spot manipulation by clinicians in response to dynamic changes in wound contour due to bleeding, swelling, or debridement.

However, handheld printing is not without challenges.[163] Without automated control, variable cut of uniformity across constructs is possible, particularly with larger wounds. Operator fatigue, variable speeds, and no feedback loops can reduce reproducibility. To compensate for this, some teams have incorporated planar guide rails or rotating wheels that help to keep the nozzle stable and the filament thickness consistent over large surfaces.

Furthermore, the resolution of handheld systems is mostly determined by nozzle diameter and extrusion rate, which might not be comparable with the ultra-fine control available from the robotic platforms.[158] However, ongoing advancements—such as multi-material planar nozzles and modular handheld print heads—are progressively narrowing this gap.

3.2.1.3. Toward a hybrid future

Despite the distinctions between robotic-assisted and handheld modalities, each holds an important and complementary place in the growing ecosystem of *in situ* bioprinting. While robotic platforms are great for complex multi-tissue reconstructions, handheld tools are ideal for single-tissue reconstructions and in situations that need a rapid response time.

It is conceivable that, in the future, these systems will converge, bringing together technological advances into more unified and clinically deployable platforms. For instance, semi-automated robotic-assisted handheld devices could integrate surgeon-controlled motion with real-time stabilization algorithms.[164,165] Meanwhile, both AI-based path correction and smart bioinks and tactile feedback may further endow handheld printing with machine-like accuracy.[166–168]

Ultimately, robotic versus handheld *in situ* bioprinting should be dictated clinically through wound complexity, anatomical location, surgical logistics, and desired resolution. As these technologies mature, they are poised to expand the surgeon's repertoire—from mobile, pen-like printers to fully autonomous bioprinting stations—each designed with the specific challenges of regenerative care in mind.

3.2.2. Printing mechanism

In addition to deployment modality, *in situ* bioprinting systems are also defined by the underlying printing mechanism. Each method, extrusion-based, inkjet, and laser-assisted, has its own advantages and limitations with respect to resolution, bioink compatibility, mechanical stability, and clinical adaptability.[19] While extrusion-based bioprinting is still the most mature and widespread technique with regard to *in situ* applications, other mechanisms like inkjet and laser-assisted printing are in constant development, especially for niche or high-precision applications. As summarized in Figure 3, the broad bioink compatibility and simplicity of operation in extrusion-based bioprinting make it ideal for deep wound reconstruction, with associated trade-offs in resolution and cell shear stress. Inkjet printing, in contrast, has a high resolution and minimal cell damage and will therefore be well-suited for patterning of epidermis

or printing of appendages, yet is hindered by the low viscosity requirement and risk of clogging. In contrast, LAB provides unsurpassed precision at the microscale, which is suitable for a vascular or neural construct but is restricted due to bulky optics and potential damage to cells from elevated temperatures. The combination of modality-specific features (resolution, viscosity compatibility, cell viability, and clinical adaptability) reported in Figure 3 is graphically summarized as a functional scheme of their involvement in different conditions of wound healing. This comparative framework not only facilitates technology choice for specific wound types but also suggests practical

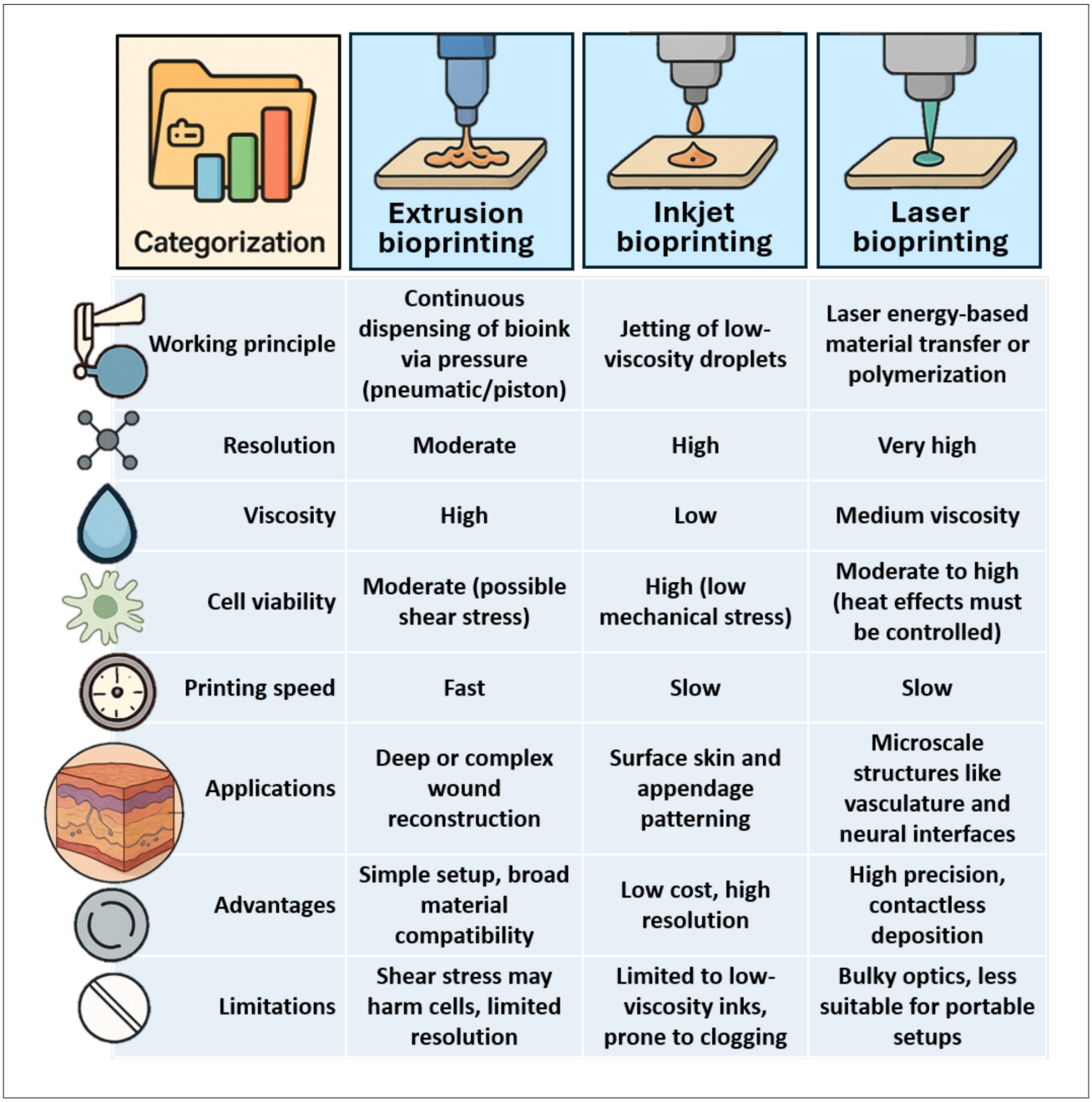

Figure 3. Comparison of bioprinting techniques: extrusion, inkjet, and laser-assisted methods. This figure summarizes the main differences in operating principles, material handling, print resolution, scalability, and limitations of the three main bioprinting approaches currently used in tissue engineering and *in situ* applications. Figure created using illustrations generated via ChatGPT (OpenAI image tools), with final layout and annotations edited in Microsoft PowerPoint.

limitations that require attention for clinical translation of *in situ* bioprinting systems.

3.2.2.1. Extrusion-based bioprinting

Extrusion-based bioprinting is the prevailing technology for *in situ* applications due to its robustness, versatility, and ability to process high-viscosity biomaterials, such as bioinks.[169] This method consists of the continuous dispensing of cell-loaded materials from nozzles moved by pneumatic, mechanical (piston or screw), or solenoid-based extrusion systems.[170] In particular, it has proven to be optimal for printing hydrogels like GelMA, alginate, or decellularized ECM that can encapsulate cells and maintain their viability during printing.[113,171]

One of the significant benefits of extrusion-based bioprinting is its ability to supply multiple bioinks at a time through multi-nozzle geometries, allowing for heterogeneous tissue constructs with spatially controlled cell distribution. Its mechanical simplicity and ability to print directly onto deforming and irregular wound beds make it ideal for use with both robotic and handheld *in situ* platforms. Furthermore, its past clinical use in arthroscopic cartilage repair procedures provides clinical analogy and regulatory familiarity that is favorable for translational development.[172,173]

However, the extrusion rate of extrusion-based bioprinting is usually restricted by nozzle diameter, while high extrusion pressure may cause shear stress on encapsulated cells. Despite this, considerable progress in nozzle design, pressure control, and bioink rheology has contributed to improved cell viability and construct fidelity in recent studies.[174–176]

3.2.2.2. Inkjet bioprinting

Inkjet bioprinting entails driving bioink droplets onto a substrate in a controlled delivery, either in a continuous stream or on a drop-on-demand (thermal, piezoelectric, and electrostatic actuation).[177] This method is based on conventional inkjet technology and, as such, benefits from a high number of commercially available components and is thus cost-effective and relatively easy to implement.[178]

High-resolution inkjet-based systems are better suited for patterning low viscosity bioinks in thin coatings. They are beneficial for deposition of growth factors, small molecules, or single-cell suspensions, and have proven potential for the fabrication of epidermal layers and skin appendages. Their low force for deposition reduces shear stress, thereby increasing cell viability.[179]

However, inkjet bioprinting is restricted by strict viscosity requirements of the bioinks, nozzle clogging, and relatively low volumetric throughput.[180] The limitations of this application tend to constrain its use in deeper wounds or high-volume constructs. As a result, inkjet bioprinting is currently more suited to surface-level tissue repairs or adjunctive patterning in combination with other techniques.

3.2.2.3. Laser-assisted bioprinting

Laser-assisted bioprinting utilizes laser energy to print bioink with ultra-high spatial resolution.[181] Typically, laser-induced forward transfer or stereolithography techniques are used to propel or polymerize bioink onto a target substrate.[182] These techniques provide the possibility of microscale patterning where cell placement and tissue architecture can be fine-controlled.[183]

Applications in which laser bioprinting has been particularly successful are those that require high-precision microfabrication, such as vascular microchannels or neural tissue interfaces.[182,184,185] It is suitable for various materials, including photocrosslinkable hydrogels, and has the potential for contactless, non-invasive deposition, an attractive feature in sterile surgical settings.

However, laser bioprinting still has a few challenges to overcome for *in situ* deployment. Laser power or exposure to high-intensity UV light produces heat that can be deleterious to the viability of the cell.[182] In addition, many of the optical systems necessary for laser bioprinting are bulky and not particularly suitable for handheld or portable systems. In future systems, the miniaturization of stereolithographic heads or fiber-optic-based light delivery may be integrated to mitigate these limitations.

3.3. Operational components and workflow integration in *in situ* bioprinting

Beyond hardware classification and printing mechanisms, the performance of *in situ* bioprinting systems depends heavily on the seamless integration of scanning, modeling, printing, and stabilization.[17,143,147,186] This whole pipeline includes scanner modules, printheads, trajectory planning, crosslinking strategies, and ultimately, each of these must operate in real time, and often under unpredictable surgical circumstances. This section describes the fundamental working design framework of how the *in situ* bioprinters move from digital design to biological reality to provide precision tissue reconstruction at the point of care.

3.3.1. From scan to stabilization: A four-step operational pipeline

Nearly every *in situ* bioprinting workflow follows a familiar path: scan, model, print, and crosslink, as depicted in Figure 4. The algorithm begins with the acquisition of the actual topography of the wound in real time. Surface contours, depth, and curvature are obtained by structured light, stereo cameras, or even LiDAR sensors in irregular

and fluid-exposed environments.[187,188] This step is crucial to creating a site-specific framework that informs the remaining steps in the process. The scanned geometry is converted to a printable geometry in 3D printing technology. Using CAD software, the platform creates a path that takes into account material type, layer height, and target tissue areas (spatial map) for multi-material deposition.[189–191] During the printing stage, the printing head (handheld, robotic) moves along the intended pathway layer-by-layer while depositing bioinks laden with cells or acellular scaffolds with millimeter-scale accuracy. Finally, crosslinking or curing the printed structure by light, heat, or ion interaction stabilizes the printed structure and ensures functionality.[192–194] This simplified pipeline allows *in situ* bioprinting to provide precision in high-stakes surgical conditions under real-world limitations. Each of these steps is graphically summarized in Figure 4 and highlights the clinical importance of the presented pipeline: real-time, patient-specific tissue reconstruction is possible at the point-of-care and despite evolving surgical conditions. This modularity and adaptability are further promoted by the visual loop between imaging, biofabrication, and functional stabilization.

3.3.2. Scanner modules: Visualizing before printing

Accurate printing begins with precise visualization. Therefore, the use of scanner modules is necessary for mapping the defect geometry in real time.[195] Most systems today use structured light or infrared depth sensors to generate point clouds of the wound surface.[196,197] For example, a robot-guided 3D scanning platform was presented to enable computer-controlled sub-millimeter wound reconstruction, utilizing a structured-light scanner attached to a 7-DOF arm, which is capable of accurately modeling complex wound geometries such as those caused by chronic ulcers and burn injuries.[198,199] These scanners enable the system to adapt to asymmetric or evolving geometries and develop a wound-conformal deposition plan.

Some higher-end platforms include thermal imaging or multispectral imaging sensors to scan tissue viability before printing.[200,201] More recent systems are using AI-based depth reconstruction to compensate for movement or challenging lighting conditions, producing more accurate surface models for irregular and dynamic wounds.[202,203]

3.3.3. Printhead configurations: Tailoring the tool for the task

The printhead is the interface between the design and the biological delivery of a bioprinting system.[143] Most *in situ* printheads use extrusion-based mechanisms, driven by pneumatic or mechanical pistons to dispense viscous, cell-laden hydrogels.[204–206] While early systems were based on just simple single-nozzle print heads, modern systems include coaxial, multi-nozzle, or modular printheads.[207,208]

Coaxial structures can be used for simultaneous deposition of a bioink core and a shell containing crosslinkers (essential for structure maintenance during extrusion).[209–211] Modular heads take it one step further,

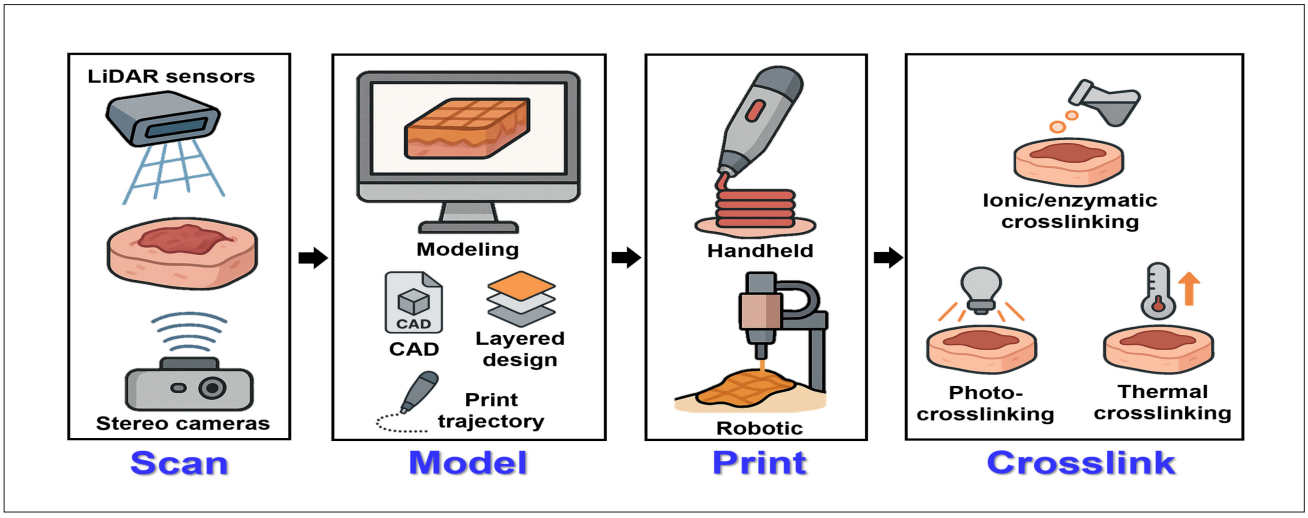

Figure 4. Four-step operational pipeline of *in situ* bioprinting. Schematic representation of the combined workflow of *in situ* bioprinting. The process starts with a scan, during which the geometry of the wound is recorded by light detection and ranging (LiDAR) sensors or stereo cameras. Next, the print trajectory for each wound, modeled according to its topology, is created in the model phase using layered design and computer-aided design (CAD) tools. The print step involves the deposition of bioink using handheld extrusion or robotic extrusion systems. Finally, in the crosslink stage, the printed materials are stabilized using ionic, enzymatic, photo, or thermal crosslinking methods. This four-stage loop allows individual, patient-specific, point-of-care tissue reconstruction in evolving surgical settings. Figure created using illustrations generated via ChatGPT (OpenAI image tools), with final layout and annotations edited in Microsoft PowerPoint.

providing a plug-and-play functionality for various types of materials or cell types, depending on different crosslinking modes. Multi-material ink developments now enable the modulation of the mechanical properties and biological cues of the bioink in real time during printing, providing improved control over tissue architecture, particularly for reconstructing multilayered or mechanically heterogeneous defects.[212]

3.3.4. Trajectory planning: Printing on a living, moving canvas

In vitro bioprinting is typically performed on a static surface, whereas *in situ* bioprinting occurs directly within the dynamic environment of the wound or tissue site. Human tissue is soft, irregular, and frequently in motion due to breathing, a heartbeat, or involuntary muscle contractions. That makes trajectory planning one of the most challenging and distinctive aspects of *in situ* platforms.[213]

Advanced systems now feature adaptive slicing algorithms, which dynamically adjust the print path based on the amount of material available to the printer, providing real-time feedback from the scanner.[214–216] A system that can adapt to variations in tissue topology in real-time and optimize the position, velocity, and angle of the nozzle for consistent print quality, even when used on curved or moving surfaces, has been developed. It relies on sensor readings and feedback control based on machine learning.[217] This *in situ* adaptation is of utmost importance for both the safety and preservation of the structural integrity of the material being worked on, especially when working in proximity to any sensitive structures such as nerves or blood vessels.

Some systems also include predictive compensation by incorporating deformation models to predict motion and pre-adjust trajectories (similar to a global positioning system that reroutes before you encounter traffic).[218] In robotic systems, this is typically associated with closed-loop control that utilizes visual or force feedback for micrometer-scale corrections.

3.3.5. Crosslinking and stabilization: Securing the print

Once bioink is laid down, it must be stabilized immediately—especially in the moist, dynamic environment of living tissue. Crosslinking of the biomaterial ensures that the construct maintains its mechanical structural integrity until cellular integration occurs.

Currently employed methods include photocrosslinking, in which photo-sensitive hydrogels, such as GelMA, undergo polymerization upon UV or blue light exposure.[219–221] Some platforms incorporate light sources into the nozzle tip, allowing for pointwise curing.[185] Another approach, based on the phenomenon of thermal gelation, involved using heated nozzles or cooled wound surfaces to induce gelation in temperature-sensitive bioinks.[206,222]

A common approach in the development of coaxial extrusion architectural designs is to incorporate crosslinkers, such as calcium ions or transglutaminase, into the sheath to facilitate ionic or enzymatic gelation through contact.[211,223,224] A more recent method is stimulus-assisted crosslinking. Recent *in situ* applications have shown that using electric and magnetic fields during deposition can also accelerate crosslink formation, trigger cell orientation alignment, or modulate cell fate decisions without compromising print fidelity.[20] These multimodal strategies go beyond making the material stick; they provide a new level of control over tissue programming at the point of care.

There is no one-size-fits-all implementation for *in situ* bioprinting. Some wounds require robotic precision, while others require quick, handheld agility. What makes next-generation systems powerful is their integration, which combines high-resolution scanning with intelligent path planning, modular printheads, and multimodal crosslinking onto a single, cohesive platform. As these technologies are honed, we are closer to the vision of *in situ* bioprinters that are not simply machines but instead deployed as intelligent surgical instruments to enable real-time tissue engineering at the bedside with patient-specific tissue engineering properties.

3.4. Bioink engineering for on-site applications

While the spotlight in *in situ* bioprinting often falls on the robotics or handheld hardware, the reality is that even the most advanced system is only as good as the material it prints.[17,225,226] Not all bioinks are the same, especially in the clinical or operatorial setting where time is limited, conditions are not well controlled, and the safety of patients is a significant concern. More than just a good bioink, what was needed was a clinically ready, fast-acting, biologically compatible, and truly bedside-operable material. Figure 5 describes six fundamental design principles that are key to the success of *in situ* bioprinting, especially under clinical limitations. These metrics—from *in vitro* performance to biological function—serve as a basis for translating bioinks developed in the lab to a functional therapeutic device.

3.4.1. Ready-to-use and operational stability

In a surgical setting, clinicians do not have time to conduct powder weighing or make last-minute decisions about polymer concentrations. Bioinks, which can be used for *in situ* printing, must be ready-to-use straight out of the package or require minimal preparation, such as gentle warming

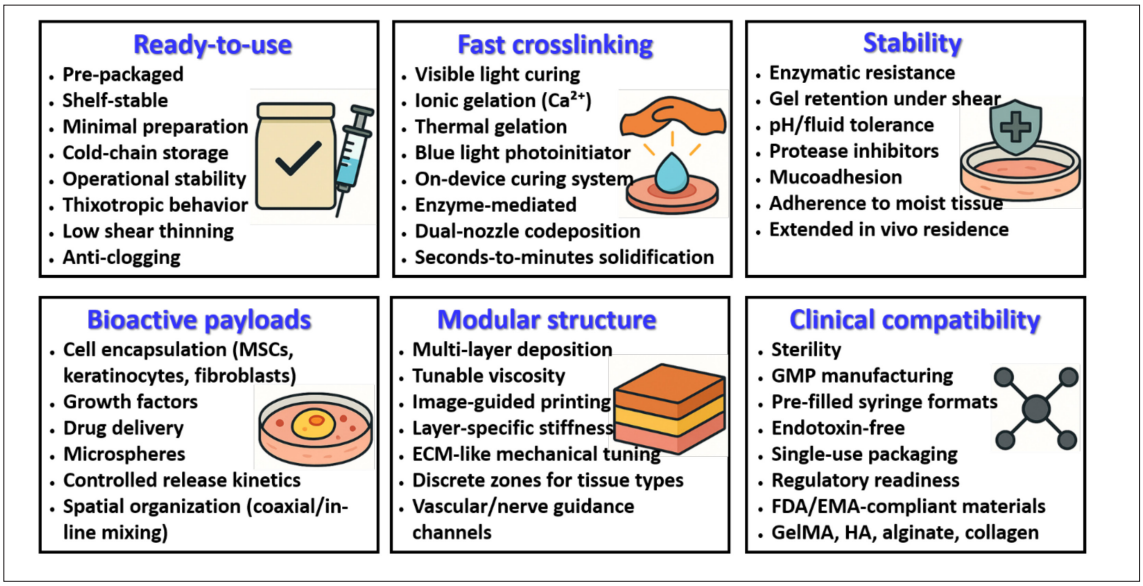

Figure 5. Core design criteria for bioinks in on-site *in situ* bioprinting. The figure maps out the six critical features needed for bioinks as scaffolds *in situ* bioprinting: (i) off-the-shelf ready for immediate clinical use, (ii) rapid crosslinking for dynamic surgical settings, (iii) physical and biochemical stability on inflamed or exuding beds, (iv) adaptability with bioactive payloads such as cells or therapeutics, (v) compatibility with modular and layered tissues, and (vi) clinical-grade safety, sterility, and regulatory compliance. Figure created using illustrations generated via ChatGPT (OpenAI image tools), with final layout and annotations edited in Microsoft PowerPoint. Abbreviations: ECM, extracellular matrix; EMA, European Medicines Agency; FDA, Food and Drug Administration; GelMA, gelatin methacryloyl; GMP, good manufacturing practice; HA, hyaluronic acid.

or a quick vortex following refrigeration. Embodiments that can be stored for an extended time on a shelf without losing functionality, and that can be stored in a cold chain without losing functionality, are desirable, particularly for use in mobile or resource-limited environments.

Of equal importance is the rheological stability of the ink in the printing process. The viscosity should stay consistent, with minimal risk of nozzle clogging or material backflow.[227] Slight variances in temperature or humidity—common in operating rooms—would not affect flow rates. For this reason, pre-tested low-shear-thinning bioinks with high thixotropy are favorites under these circumstances. Such ease of use has a direct impact on emergency burn care situations, where it is crucial to be able to deploy biomaterials quickly.

3.4.2. Fast and field-compatible crosslinking

In situ bioprinting does not take place in the controlled sterility of a laboratory—it unfolds in the complexity and messiness of real wounds. That means bioinks need to solidify fast, ideally within seconds to a few minutes.[228,229] Any longer, and the material risks deforming, sliding, or mixing with exudates on the wound bed. Crosslinking techniques such as visible-light curing, ionic gelation (e.g., Ca^{2+}), thermal gelation, or enzyme-mediated systems are widely used due to their speed, safety, and simplicity.[230-232]

Importantly, these crosslinking mechanisms must be non-toxic and compatible with living tissues.[233] For example, although glutaraldehyde exhibits good bonding strength, it is not suitable for use on live wounds due to its toxicity.[234] Alternatively, new systems use photoinitiators that are activated by low-intensity blue light, allowing rapid crosslinking without heating or damaging surrounding cells.[235]

Handheld platforms usually incorporate on-device light sources or two-nozzle systems that co-deposit crosslinking agents on the fly.[236,237] Regardless of the delivery format, the ink must react quickly and consistently to the trigger without complex timing, guarding, or external gearing.

3.4.3. Stability in challenging wound environments

Burn wounds and other complex defects are biologically hostile environments characterized by inflammation, changes in pH, enzymatic breakdown, and rapid fluid turnover.[2] This means that a bioink must gel and stay gelled even when exposed to proteases, wound exudate, or mechanical shear from dressing changes. Selected examples, showing their strengths in clinical settings and existing limitations that have to be optimized, are summarized in Table 9.

Natural hydrogels, such as alginate, off-the-shelf gelatin derivatives (e.g., GelMA), and hyaluronic acid-based combinations, have proven to be good candidates

due to their ability to preserve their structure under harsh environments.[238,239] Crosslinked hydrogels that remain in a hydrated, semi-solid form despite enzymatic attack are particularly useful. In more advanced formulations, protease inhibitors or enzyme-resistant backbones have been incorporated to increase the residence time of the compound in the body.[240]

Another factor to consider is surface adherence. Bioinks must remain in intimate contact with tissue, even if the substrate is moist or bleeding. Mucoadhesive properties or secondary bonding mechanisms (e.g., fibrin integration) can help keep printed constructs exactly where they are needed.[222,241,242] Several bioinks have been developed with *in situ* usability in mind, designing for fast gelation, printability, and bioactivity. Bioinks that can persist and function in hostile environments within the wound extend the treatment window and reduce the frequency of repeat treatments. Interestingly, a common theme is the trade-off between bioactivity and resilience: bioinks not only have to carry therapeutic agents or cells, but also must stay attached and intact in the dynamic proteolytic environment of chronic wounds.

3.4.4. Bioactive payload compatibility

Beyond serving as a scaffold, bioinks are often expected to carry living cells or therapeutic agents.[128,243,244] More complex than this is the fact that the material must not only be suitable in terms of printing mechanics but also maintain and protect the biological activity.[245,246] Common types of cells include keratinocytes, fibroblasts, MSCs, and even endothelial progenitors for vascularization. The ink must be physiologically isosmotic, facilitate nutrient transport, and protect against the shear injury caused by extrusion.

Additionally, controlled release kinetics, rather than an initial burst release, are essential for bioinks carrying drugs, growth factors, or antimicrobial peptides.[247] Delivery systems or particle encapsulation (e.g., with microspheres) can allow phased bioactivity, particularly for wounds that heal in a stepwise manner.[248–250] Recent work has also investigated the concept of coaxial printing or inline mixing to provide spatial control of bioactive cues, enabling the deposition of epidermal, dermal, and vascular components in specific layers or zones within the same construct.[209]

3.4.5. Modular and multi-layer printing capability

In wound repair, especially in burn wounds, multi-layered tissue structures are often required.[251,252] A single uniform gel is not enough. Instead, bioinks must be formulated to be suitable for modular deposition, i.e., with tunable viscosity, gelation kinetics, and mechanical stiffness to accommodate different tissue strata.[253–255]

For example, a softer hydrogel with nutrients that support epidermal regeneration can be used, whereas a stiffer hydrogel that mimics the ECM supports dermal fibroblasts and vessel ingrowth.[256,257] In more complex reconstructions, separate channels can be printed to guide vascularization or support nerve regrowth.[258,259] For this to work, the ink must remain printable across a range of viscosities, without interfering with the downstream stability of the other layers. In addition, inks for use with image-guided printing systems, where the geometry of a scanned plane determines the nozzle path, must be able to maintain a constant width and fidelity of the filament over increasingly complex paths.[168,260]

3.4.6. Clinical compatibility and regulatory readiness

Ultimately, no bioink—regardless of its level of advancement—can enter clinical usage without meeting the basic standards for sterility, traceability, and safety.[64,82,83] Materials have to be either FDA/EMA compliant for clinical use or at least be made from components of a known regulatory track record.[76,81] That often limits the usage of *in situ*-compatible bioinks to well-studied materials like collagen, gelatin (including GelMA), hyaluronic acid, alginate, or their combinations. Sterilization procedures used (gamma irradiation or filtration) should not affect the functionality of the ink.[82,83] Packaging should be hermetic, single-use, and easy to use, e.g., in pre-filled syringes or cartridges that connect to standard printers. The ability to perform GMP-compliant manufacturing and quality control testing—including endotoxin levels and batch consistency—remains a significant determinant of translational success.[74,75]

In situ bioprinting is as much a materials problem as it is a robotics one. Bioinks for bedside fabrication must strike the right balance between biological performance, physical reliability, and clinical feasibility. As research opens the doors to what can be printed, the challenge is no longer about finding new materials—it is about ensuring they function under pressure, in real time, and in real patients. At their best, the ideal bioinks are not only printable-they are surgical-grade tools, designed to be equally at home on an operating table as they are on the lab bench. Figure 5 is therefore not only a visual checklist to guide ink developers, but also a translational roadmap of steps to ensure that printed materials are effective, safe, and functionally competent at the point of care.

3.5. Preclinical validation: *In vivo* applications of *in situ* skin bioprinting

To translate *in situ* bioprinting from laboratory benches to living tissues, rigorous preclinical validation is necessary. Animal models, particularly full-thickness skin wounds in rodents and pigs, have become crucial platforms for testing the technical feasibility, healing outcomes, and limitations

Table 9. Representative bioinks for *in situ* skin bioprinting: advantages and limitations

Bioink	Advantage	Limitation	Reference
Gelatin methacryloyl + LAP (visible light cured)	Rapid photopolymerization; high cell compatibility	Requires a light source; limited penetration in deep or irregular wounds	[236,261–263]
Alginate + Ca^{2+} (ionic crosslink)	Instant gelation; good stability; low toxicity	Poor cell adhesion; mechanical strength is often insufficient alone	[160,261,264,265]
Gelatin-alginate dual-crosslink bioink	Dual crosslinking (ionic + photonic); tunable mechanical properties	Requires precise crosslinking control; more complex formulation	[36]
Methacrylated hyaluronic acid + stem cells	Suitable for slow-release; good for chronic wound healing	Mechanical integrity is often weak and sensitive to enzymatic degradation	[35]
Fibrinogen + thrombin	Blood-derived; naturally biocompatible; rapid clot-like gelation	Short *in vivo* stability; rapid degradation limits structural support	[22,25,160,266–268]

Abbreviation: LAP, photo-initiator lithium phenyl-2,4,6-trimethylbenzoylphosphinate.

of such systems under relevant biological constraints. To identify relevant studies, we performed a dedicated search in the PubMed database using the keywords "in situ bioprinting" and "skin," which provided a curated set of studies for screening. The search was conducted without date and language restrictions and was updated in August 2025. Titles and abstracts were manually screened by two independent reviewers, and disagreements were resolved through discussion. In particular, we included original research articles reporting on *in vivo* applications of *in situ* bioprinting to the skin, including burns, diabetic wounds, and full-thickness excisions. Studies were excluded if they only included *in vitro* experiments, were performed on non-cutaneous tissues, or did not use a bioprinting method. The selection process is detailed in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram (Figure 6). A total of 49 search results were identified, 18 of which were excluded as review articles, leaving us with 31 original research papers. After further screening for relevance to *in situ* skin bioprinting, 29 studies were retained. Of these, eight papers were limited to *in vitro*-only experiments and were therefore excluded from further analysis. The remaining 21 *in vivo* studies form the basis of the summary presented in Table 10. In Table 10, we present a curated summary of *in vivo* studies by different wound types and bioprinting modalities.

3.5.1. Burn wound applications: Conformal delivery and topographic adaptation

The work of Cheng *et al*., which dealt with the technical complexity of treating full-thickness burns in pigs using a handheld extrusion-based device, is an excellent example.[25] The system was a combination of a microfluidic printhead and a silicone wheel, which can conformally deposit bioink sheets on inclined or irregular surfaces—a huge difference from rigid, flat-layer printing. The bioink mixture (fibrinogen, thrombin, and hyaluronic acid) was enzymatically crosslinked at the site of delivery, allowing the rapid gelling of the ink on live wound beds.

Notably, the microfluidic architecture was capable of consistent sheet extrusion, and the roller provided gentle and consistent contact with the skin, even at a 45° angle. The system was capable of controlling deposition in real time and improving re-epithelialization and vascularization outcomes. However, it is a bespoke non-commercial product, and its deposition requires surface contact, which poses challenges when applied to moving or highly contoured anatomical areas. Additionally, multi-layer or heterogeneous tissue constructs might not necessarily fit into a sheet-based delivery device.

3.5.2. Chronic wounds: Addressing hypoxia and complex microenvironments

In the models of chronic diabetic wounds, Wang *et al*.[261] used a coaxial microfluidic-assisted extrusion system for the direct delivery of living photosynthetic scaffolds into ischemic wound sites. Their solution inspired a new concept of incorporating *Chlorella* microalgae in a bilayer hydrogel, which could enable *in situ* autotrophic oxygen generation. The two layers were crosslinked with dual triggers (ionic and UV) to create a hollow oxygenating structure after deposition of the layer containing GelMA and alginate on the outside and gelatin and $CaCl_2$ on the inside. This setting improved hypoxia at the local level, as well as collagen deposition and angiogenesis. The tubular printing at the wound site was realized using a custom coaxial chip, which substituted the conventional printer nozzle for a bi-layer tubular printing method. However, due to the complexity of the fabrication process and the use of non-standard biological elements (e.g., microalgae), this system poses challenges for translation into a clinical setting, primarily due to regulatory approval and sterility issues.

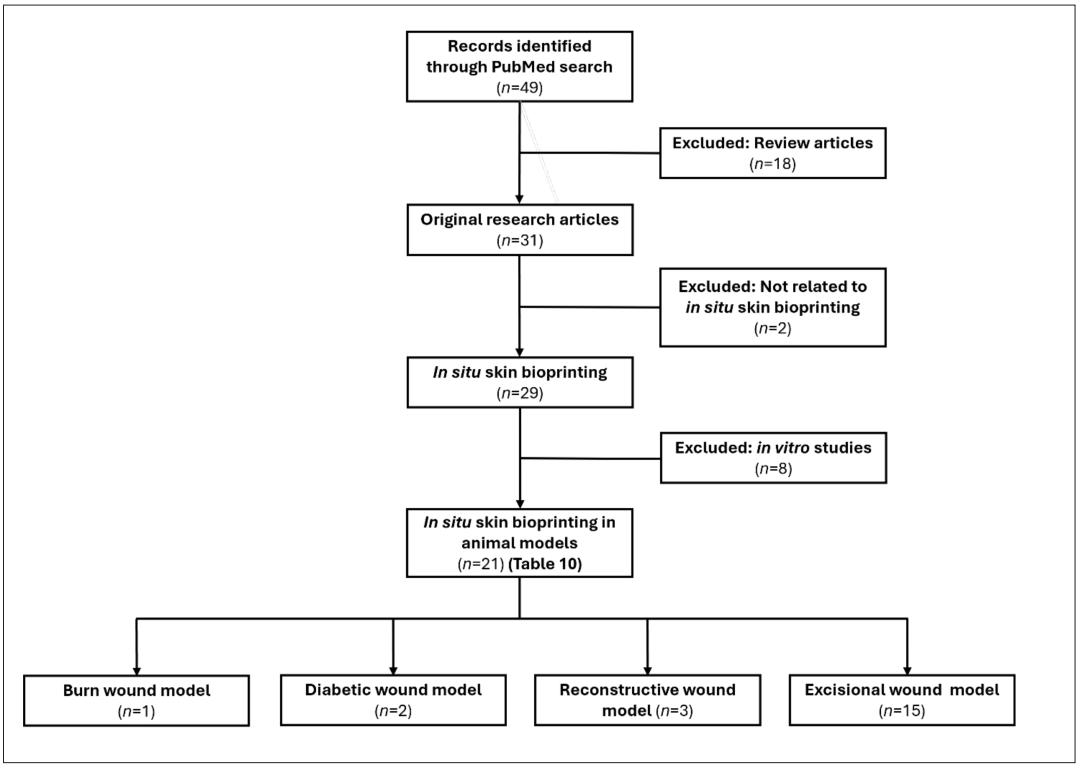

Figure 6. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection for *in vivo* applications of *in situ* skin bioprinting in preclinical animal models. The diagram illustrates the systematic selection of original research articles sourced from the literature, reporting on *in vivo* applications of *in situ* skin bioprinting in animal models. After screening 49 PubMed entries, 21 papers were found to use *in situ* bioprinting in preclinical wound models (burn, diabetic, reconstructive wound, excisional wound).

In a separate study, Zhou *et al.*[262] developed the "SkinPen," a handheld bioprinter integrating ultrasound and UV systems for real-time crosslinking. It produced a bioadhesion and antibacterial activity-enhanced GelMA/copper-doped bioactive glass nanoparticle bioink. The composite energy-based method (ultrasound cavitation and UV curing) provided fast solidification and increased adherence to moist, irregular wound beds.

3.5.3. Reconstructive applications: Extending beyond skin to craniofacial and osseous repair

In situ bioprinting has been extended beyond skin to craniomaxillofacial regeneration, where reconstruction of soft and hard tissues is required. Keriquel *et al.*[156,163] used LAB systems to deliver nano-hydroxyapatite and collagen inks, with or without stromal cells, onto calvarial defects in mice.They demonstrated laser-directed *in situ* delivery of a five-ink carousel system with high resolution using LAB. These studies showed restoration of bone volume and histologic evidence of osteogenesis; however, the results were variable. Laboratory experiments still involve technically challenging tasks, where the laser beam must be aimed accurately, optical components must be capable of withstanding demanding conditions, and laser safety procedures are stringent.

Moncal *et al.*[266] took this a step further by demonstrating hybrid *in situ* bioprinting using extrusion-based hard tissue ink and inkjet-based soft tissue bioinks in a rat craniofacial defect model. Their multi-arm robotic platform enabled the spatially precise co-deposition of dermal and osseous components, mimicking the native architecture. The bioprinted constructs showed bone regeneration of ~50% and skin closure of ~80% after 6 weeks and 10 days, respectively. A key emphasis of this study is on modular deposition through multi-ink integration. However, the operation complexity and absence of commercially available counterparts prevent its widespread adoption at the present level.

3.5.4. Excisional wounds: Dominant model for feasibility and versatility testing

Full-thickness excisional wounds in rodent and swine have been used as gold standard test beds for *in situ* systems. Among the most technically advanced is the work of Zhao *et al.*,[23,269] who developed a 6-DOF motion-controlled robotic arm-assisted dual-nozzle bioprinting system coupled with real-time 3D scanning. Their platform could

Table 10. Summary of preclinical *in situ* skin bioprinting studies on wound models, printing modalities, and healing outcomes

Wound category	Specific wound/ Animal species	Bioprinting modality	Bioink material	Cell type used	Healing outcome	Key technical innovation	Reference
Burn wound/ extrusion	Full-thickness skin burn (thermal injury with a 200°C aluminum plate for 20 s); Pig	Handheld extrusion-like device with microfluidic printhead and silicon wheel (not a commercial printer; customized system)	Fibrinogen (2% w/v) + thrombin (500 IU/mL) + hyaluronic acid (0.5–2% w/v); crosslinked via thrombin	Umbilical cord-derived MSCs at 1×10^6 cells/mL	Improved re-epithelialization, neovascularization, and dermal cell repopulation	Handheld wound-conformal printer with compliant wheel and microfluidic sheet delivery; deposition on inclined surfaces (up to 45°); real-time deposition control	[25]
Diabetic wound/ extrusion	Full-thickness skin diabetic wound induced by STZ (50 mg/kg); C57BL/6 mice	Microfluidic-assisted extrusion bioprinting (custom-made coaxial capillary microfluidic chip with 3D printer platform)	Microalgae-laden hollow fibers: outer phase (GelMA 5% w/v, sodium alginate 2.5% w/v), and LAP 0.1% v/v); inner phase (gelatin 5% w/v and $CaCl_2$ 0~2% w/v); crosslinked by $CaCl_2$ (0–2% w/v) and UV (365 nm)	Microalgae (*Chlorella pyrenoidosa*, 1×10^6 cells/mL)	Faster wound closure, enhanced angiogenesis (CD31), reduced hypoxia (hypoxia-inducible factor 1 alpha), and higher collagen deposition (51.6%)	*In situ* microfluidic-assisted bioprinting with photosynthetic microalgae for autotrophic oxygenation; custom coaxial capillary chip replacing printer nozzle	[261]
	Diabetic wound (full-thickness, chronic infected wound); Rat	Extrusion-based handheld bioprinter ("SkinPen") with integrated US and UV system	GelMA and copper-containing bioactive glass nanoparticles (Cu-BGn); UV crosslinking + US-induced cavitation	Not mentioned	Promoted blood clotting, normalized vascularization, accelerated wound closure, improved bioadhesion (≥3× shear strength)	Portable handheld "SkinPen" uses combined US and UV for instant *in situ* gelation and enhanced bioadhesion; designed for field or clinical use	[262]
Reconstructive wound	Calvarial critical-size bone defect; OF-1 mice	Laser-assisted bioprinting; automated workstation	Nano-HA	Not mentioned	Preliminary bone regeneration observed; heterogeneous results	Laser-based bioprinting platform designed for high-throughput and computer-assisted surgery	[156]
	Calvarial critical-size bone defect; BALB/c mice	LAB, automated laser workstation (Nd:YAG laser, 1,064 nm)	Type I collagen (0.2% w/v) + nano-HA (1.2% w/v); collagen crosslinks thermally	Mouse bone marrow stromal precursor cells (D1 line); 120×10^6 cells/mL; 693 or 796 cells/mm^2	Enhanced bone regeneration; bone volume and mineral density assessed by micro-computed tomography and histology	High-resolution LAB platform with 5-ink carousel; *in situ* laser printing onto exposed dura mater	[183]

Continue...

Wound category	Specific wound/ Animal species	Bioprinting modality	Bioink material	Cell type used	Healing outcome	Key technical innovation	Reference
	Craniomaxillofacial defect model; F344 rat	Hard bone bioprinting: extrusion-based multi-arm bioprinter for hard-tissue ink (HT-ink); skin composite bioprinting: custom-designed inkjet droplet-based bioprinter (jetlab® 4, MicroFab Technologies Inc.) for soft-tissue ink (ST-ink)	ST-ink: collagen (0.2% w/v) + fibrinogen (2% w/v) + thrombin crosslinker; HT-ink: chitosan (2% w/v) + collagen (0.9% w/v) + nano-HA	Extrusion-based bone bioprinting: rat bone marrow MSCs (rBMSCs)-laden HT-ink (5 × 10^6 cells/mL); droplet-based skin bioprinting: rat primary dermal fibroblasts (rDFs)-laden ST-ink (1.33 × 10^5 cells/mL)	~80% bone regeneration in six weeks; ~60% skin closure in six days; ~80% skin + 50% bone closure in 10 days (composite)	Hybrid IOB using extrusion and droplet-based modes for layered hard/soft tissue reconstruction; stratified deposition of multiple inks for composite tissue reconstruction; real-time, spatially controlled bioprinting	[266]
Excisional wound/robotic extrusion	Full-thickness skin wound; BALB/c nude mice	Extrusion-based and robot-assisted *in situ* 3D bioprinting (NORM series)	GelMA (2.5%, 5%, & 10% w/v), with LAP (0.1% v/v); photocrosslinked by 405 nm UV	Epidermal stem cells: 5×10^7/mL skin-derived precursors: 1×10^8/mL	Full skin regeneration, including epidermis, dermis, hair follicles, blood vessels, and sebaceous glands	Robot-assisted bioprinting system with *in situ* precision delivery and crosslinking; use of dual stem cells for regeneration	[263]
	Full-thickness skin wound; BALB/c nude mice	Extrusion-based robotic bioprinting with 6-DOF manipulator and closed-loop visual tracking system	Matrigel (no added crosslinker); shear-thinning; gelation at 22–37°C	Epidermal stem cells: 5×10^7 cells/mL; skin-derived precursors: 1×10^8 cells/mL	Complete wound healing in four weeks; regeneration of epidermis, dermis, blood vessels, sebaceous glands, and hair follicles; hair retention up to 10 months	Adaptive multi-degree-of-freedom (6-DOF) *in situ* bioprinting robot; closed-loop 3D scanning and visual tracking; eye-in-hand camera setup; automatic conformal path planning	[269]
	Full-thickness skin wound; Sprague-Dawley rat	Extrusion-based robotic arm bioprinting (6-DOF; with dual-jet system and *in situ* scanning; custom-built)	PRP-integrated alginate-gelatin composite hydrogel bioink: Alginate + gelatin + PRP (0%, 2%, 5%, 10% v/v) crosslinked with transglutaminase (1 % w/v); gelatin: dissolved in PBS; alginate: magnetically stirred at 37°C overnight	Human primary dermal fibroblasts (1×10^6/mL) and rat epidermal stem cells (1×10^7/mL); dual-layer bioprinting	Accelerated high-quality wound closure; promoted vascularization (CD31, α-SMA), re-epithelialization (hematoxylin & eosin staining), reduced inflammation (CD68, CD3, myeloperoxidase)	Custom robotic *in situ* printer with real-time 3D scanning (binocular), dual-nozzle, bilayer printing; point cloud-based path planning (ΔL = 0.2 mm; planning time ~3 s); automated layer switch	[23]
	Circular full-thickness skin wound; Wistar rat and Wiesenau minipig	Extrusion-based articulated robotic arm (KUKA); automatic with real-time skin movement tracking	Viscoll sterile porcine collagen (8% w/v), + platelet lysate (10%); crosslinking by temperature-sensitive polymerization	Fibroblasts: 1×10^6 cells/mL (rat & pig primary)	Enhanced adhesion, angiogenesis, reduced inflammation; improved histological regeneration in both models	First commercial articulated bioprinter; KUKA robot + end-effector with cooling (Peltier) + breathing sensor; real-time adaptive extrusion software	[264]

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Table 10. *Continue...*

Wound category	Specific wound/ Animal species	Bioprinting modality	Bioink material	Cell type used	Healing outcome	Key technical innovation	Reference
	Full-thickness skin wound; nude mice	Extrusion-based; Automatic; Livprint 3D bioprinter (NORM series)	Matrigel with embedded cells; no explicit crosslinking (physical gelation)	Epidermal stem cells: 5×10^7 cells/mL; skin-derived precursors: 1×10^8 cells/mL	Hair follicle regeneration (4 weeks); other appendages also regenerated; histology confirmed regeneration	Customized *in situ* printing workflow based on wound dimensions; computer-aided design modeling + automatic dispensing via Livprint NORM bioprinter; nozzle control at 2 mm height	[270]
	Full-thickness skin wound; Athymic nude mice	Pressure-driven extrusion-based system; automated three-axis in-house bioprinting platform	Heparin-conjugated HA (1% w/v) + Gelin-S (thiolated gelatin, 1% w/v), with PEGDA crosslinker (2% w/v); UV (365 nm) photopolymerization	Human amniotic fluid-derived stem cells (5×10^6 cells in 500 µL hydrogel)	Improved wound closure, re-epithelialization, increased vascularization, and ECM production; histological evidence up to 14 days	Custom-developed three-axis bioprinter with dual-nozzle printhead for cell/hydrogel + crosslinker; *in situ* photocuring via integrated UV	[26]
	Full-thickness skin wound; Athymic nude mice	Pressure-driven extrusion-based system; automated three-axis in-house bioprinting platform	Fibrinogen (5% w/v) + type I collagen (0.22% w/v); crosslinked via thrombin (20 IU/mL)	Human amniotic fluid-derived stem cells, human bone marrow-derived MSCs, both 16.6×10^6 cells/mL	Enhanced wound closure, increased re-epithelialization, elevated microvessel density and capillary diameter (Days 0, 7, 14); temporary cell integration	Custom-built automated extrusion bioprinter; multilayer gel/cell printing; green fluorescent protein-based cell tracking; proteomic analysis of secretome	[267]
Excisional wound/handheld extrusion	Full-thickness skin wound; mouse and pig	Handheld, extrusion-based, pressure-driven; manually operated	Alginate-collagen sheet: Alginate (2% w/v), collagen type I (0.25% w/v); dermal bioink: 1.25% (w/v) fibrinogen, HA (0.25% w/v) and collagen (0.25% w/v); epidermal bioink: Fibrinogen (2.5% w/v) and HA (0.25% w/v); crosslinking: ionic ($CaCl_2$), enzymatic (thrombin), thermal (collagen)	Dermal: 4×10^5 human fibroblasts/mL; epidermal: 1.25×10^6 human keratinocytes/mL	Demonstrated *in situ* sheet deposition; compatibility with inclined/moving surfaces	Lightweight handheld skin printer with microfluidic cartridge, active roller-based motion control, and onboard syringe pumps	[160]
	Full-thickness skin wound; Yorkshire pig	Extrusion-based handheld bioprinter (custom-built syringe-pump with motorized plunger, UV LED for crosslinking, gauge 22 conical nozzle)	GelMA (9% w/v), crosslinked with LAP (0.067% v/v) using 395 nm blue light LED; VEGF added at 400 ng/mL	No cells printed	Reduced contraction (18±4%), increased epithelial thickness (165±28 µm), higher rete ridges (9.32/mm), lower scar elevation index (1.09±0.01), increased vascularization (vWF staining), and lower inflammation	Handheld partially automated printer with integrated UV light; adjustable flow rate (4–18 µL/s); designed for *in situ* curved surface printing	[236]

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Wound category	Specific wound/ Animal species	Bioprinting modality	Bioink material	Cell type used	Healing outcome	Key technical innovation	Reference
	Full-thickness skin wound; Sprague-Dawley rat	Extrusion-based, handheld, programmable, smartphone-controlled	Granular hydrogel: Component A + Component B; Crosslinking via 405 nm blue light; component A: PEGDA (5% w/v), HA (0.5 % w/v), and LAP (0.5 % v/v), UV light pre-crosslinking; component B: PEGDA (10% w/v) and LAP (0.5 % v/v), UV light pre-crosslinking	HUVECs (2.5×10^6 cells/mL) + rat PRP mixture	Wound closure, PRP hydrogel integration, histological hematoxylin and eosin staining for healing observation	Handheld programmable printer; pneumatic and mechanical extrusion modes; smartphone web app control; multi-ink switching; microchannel nozzles	[237]
	Full-thickness skin wound; C57BL/6J mice	Extrusion-based (Regenovo Bio-architect SR), desktop bioprinter, not handheld or robotic	Hemostatic alginate-based bioink (AL@FM): AlgMA (4% w/v) + LAP + PVP + CMC + glycerol + ε-PL; crosslinking via 405 nm light LED	No cells printed	Wound closure rate, angiogenesis (CD31), fibroblast activation (vimentin, fibronectin 1), immune regulation (F4/80, LY6G/C, CD86, arginase 1) at day 7 and 14	Photocrosslinkable alginate-based bioink with rapid hemostasis, antibacterial, and injectable properties	[265]
Excisional wound/inkjet	Full-thickness skin wound; Athymic nude mice	Inkjet-based *in situ* bioprinting; likely handheld/manual device (device not explicitly specified)	N/A (bioink unspecified)	Human keratinocytes and fibroblasts; concentration N/A	Wound closure by three weeks; organized dermal collagen and fully formed epidermis; human cells incorporated into skin appendages	Novel *in situ* bioprinting device for direct wound delivery of cells in full-thickness skin injuries	[271]
	Full-thickness skin wound; Athymic nude mice and Yorkshire pigs	Drop-on-demand inkjet bioprinting (custom mobile *in situ* skin bioprinter with integrated imaging)	Fibrinogen (2.5% w/v) + collagen I (0.11% w/v); crosslinked with thrombin (20 IU/mL)	Human dermal fibroblasts (1.875×10^6/0.5 mL) and human keratinocytes (3.75×10^6/0.5 mL); ratio 1:2 (dermal:epidermal)	Accelerated wound closure, reduced contraction, enhanced re-epithelialization, organized collagen fibers, mature vascularization, proliferating keratinocytes (CD31, α-SMA, Ki67)	Mobile handheld bioprinter with integrated imaging for layered *in situ* autologous/allogeneic cell delivery	[22]
	Full-thickness skin wound, craniomaxillofacial zone; Rowett Nude Rat immunodeficient nude rat	Inkjet droplet-based bioprinting using Jetlab® 4 (MicroFab Technologies), micro-valve dispensing device (INKX0517500A)	Fibrin-based bioink: fibrinogen (0.5% w/v) + human adipose-derived ECM (1–2% w/v); crosslinked via thrombin + Factor XIII 2 U/mL thrombin + coagulation Factor XIII (0.1% w/v) in $CaCl_2$ (10 mM)	Human adipose-derived MSCs (1×10^6 cells/mL)	~91–93% wound closure by Day 14; faster re-epithelialization (~70% by Day 7); enhanced adipogenesis; hair follicle-like downgrowths; increased vascularization (CD31 expression); collagen deposition	IOB directly on the surgical wound; micro-solenoid valve system for precise droplet control; stratified dermis/hypodermis structure; Jetlab® 4 bioprinter; smart use of patient-derived materials	[268]

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Table 10. ***Continue...***

Wound category	Specific wound/ Animal species	Bioprinting modality	Bioink material	Cell type used	Healing outcome	Key technical innovation	Reference
Excisional wound/laser	Not mentioned (but applied to dermis, muscle, brain tissue); Mouse	Laser-assisted (Two-photon, intravital; automated via multiphoton microscope)	Photosensitive polymer hydrogel; crosslinked via two-photon bio-orthogonal cycloaddition (>850 nm)	Donor muscle-derived stem cells	*De novo* formation of myofibres in skeletal muscle	*In vivo* 3D bioprinting using multiphoton microscopy for accurate positioning inside live tissue	[272]

Abbreviations: 3D, Three-dimensional; AlgMA, methacrylate alginate; α-SMA, alpha smooth muscle actin; CMC, carboxymethyl cellulose; DOF, degrees of freedom; ECM, extracellular matrix; ε-PL, epsilon-polylysine; GelMA, methacrylate gelatin; HA, sodium hyaluronate; HUVECs, human umbilical vein endothelial cells; IOB, intraoperative bioprinting; LAB, laser-assisted bioprinting; LAP, photo-initiator lithium phenyl-2,4,6-trimethylbenzoylphosphinate; LED, light emitting diode; MSCs, mesenchymal stem cells; PEGDA, polyethylene glycol diacrylate; PRP, platelet-rich plasma; PVP, polyvinylpyrrolidone; rDFs, rat primary dermal fibroblasts; STZ, streptozotocin; UV, ultraviolet; VEGF, vascular endothelial growth factor; vWF, von Willebrand factor.

automatically generate a point-cloud map of the wound and plan bi-layered deposition paths in seconds. The group found that the use of platelet-rich plasma-enriched bioink resulted in increased vascularization and reduced inflammation and dermal repair in rats.

Alternatively, Chen *et al.*[263,270] produced more efficient automated platforms (NORM series) for Matrigel-based hydrogels embedded with epidermal stem cells and dermal precursors. It consistently regenerated full skin structures, including hair follicles and glands, as confirmed with histological analyses. Simultaneous dual cell population and robotic precision directed nearly native skin regeneration.

Other investigations, e.g., Albanna *et al.*[22] and Hakimi *et al.*,[160] applied a manual held extrusion printer or drop-on-demand inkjet printer to deliver stratified layers of keratinocytes and fibroblasts directly to wound beds. These platforms highlighted the benefit of simplicity and flexibility, but typically lacked closed-loop control or robotic precision. These findings represent an increasing maturity in preclinical validation pipelines, and Table 10 can be considered as both a reference map and a benchmark summary for the state-of-the-art in *in vivo* testing of *in situ* bioprinting systems.

4. Stem cells in skin bioprinting: Applications and potentials

Stem cells are not only now seen as sources of cell agents for replacement, but also as performing bio-units with the ability to form dynamic regenerative environments, characterized by plasticity and the secretome, as well as interactive behavior within printed constructs. When applied to skin bioprinting in the context of burn healing, stem cells, including MSCs and iPSCs, provide cellular plasticity and paracrine signaling that stimulate tissue repair, immunomodulation, and vascularization.[251,273] This section reviews the current applications and future potential of various types of stem cells for skin bioprinting, comparing their functional potential, differentiation status, and translational possibilities.

4.1. Stem cells as functional units in biofabricated skin

Stem cells in skin bioprinting are no longer a passive building block; instead, they are becoming an active mechanism in the regeneration process. Compared to conventional somatic cells, iPSCs and MSCs exhibit distinct combinations of expandability, plasticity, and biological responsiveness, making them ideally suited for biofabrication.[274,275] These cells are not simply printed to fill out space; they play an active role within the post-printing tissue microenvironment, secreting trophic factors, altering

immune responses, and stimulating neovascularization via paracrine signaling.[276–280] That qualifies them to be especially helpful in complex wound healing in burned or damaged skin.

Stem cells are additionally more easily expanded and standardized in batches than primary patient-derived cells, which often suffer from limited proliferative potential and donor variability. Immortalized cell lines, such as HaCaT, are easy to expand and provide a convenient model for experimental systems; however, they suffer from genetic abnormalities and a lack of clinical translatability.[43,47,49,60] Stem cells, on the other hand, strike a balance between biological functionality and their potential for production. Another significant advantage is their immunological profile: autologous iPSCs can be tailored to the individual patient, and ongoing efforts to develop universal donor lines will help resolve the present limitations associated with immune rejection.[264,281]

However, these come with caveats. One of the remaining technical challenges, especially with iPSCs, is differentiation consistency. While MSCs show high paracrine activity and are relatively easy to handle, their lineage-specific functionality in forming complete skin structures is limited.[282,283] Furthermore, the regulatory and manufacturing requirements for stem cell-derived bioprinted constructs are significantly higher than those for standard cell types, making clinical translation particularly challenging.[69,72,73,76,78]

Nevertheless, stem cells continue to enjoy momentum as the basic building blocks of engineered skin. Their potential to be structure-forming and function-regulating agents distinguishes them in the emerging field of regenerative medicine. As bioprinting technologies mature, stem cells are increasingly positioned not just as a superior alternative to other cell sources, but as indispensable agents of tissue-specific regeneration. Table 11 provides a comparative overview of stem cells, primary cells, and immortalized cell lines in relation to skin bioprinting applications. Some of the differences between these cell types are outlined in terms of expandability, immunocompatibility, technical requirements, and clinical potential. As shown in Table 11, stem cells have superior clinical translatability and maintenance properties in comparison to immortalized lines, but are still inferior with regard to the reproducibility of directed differentiation to primary keratinocytes or fibroblasts. Despite the regulatory complexity that sometimes makes stem cells a more challenging choice, this table provides a clear, side-by-side overview that will help demystify stem cell sourcing and selection in pre-clinical and clinical settings. Stem cells are now increasingly placed not simply as a better alternative to other cell sources, but as critical agents of tissue-specific regeneration. This is visually summarized in Figure 7, which illustrates the multifaceted role of stem cells, specifically, MSCs and iPSCs, in bioprinted skin applications. The figure schematically shows how stem cells contribute not only to wound healing and craniofacial reconstruction, but also to the regeneration of complex skin appendages such as sweat glands. Notably, their double functional character is illustrated in Figure 7: as structural (through differentiation) and as biological mediators (through the secretion of trophic factors and modulation of the immune system). Additionally, the figure illustrates the integration of both robotic and handheld bioprinting strategies (ST-ink for soft tissue and HT-ink for hard tissue), demonstrating their technical versatility in creating stratified tissue architecture. However, Figure 7 also identifies some key challenges, such as lineage selectivity, reproducibility of differentiation, and regulatory challenges, reaffirming that stem cells remain powerful yet imperfect tools in regenerative bioprinting.

4.2. Comparative overview of stem cell sources in skin bioprinting

Not every stem cell is made equal in the growing area of skin bioprinting. While the umbrella term stem cell tends to imply flexibility and regenerative potential, different sources—such as iPSCs, MSCs, amniotic fluid stem cells (AFSs), and endothelial progenitor cells—carry distinct biological traits and limitations that make them more or less suitable for skin fabrication applications.[274,288] When selecting an appropriate cell type, it is essential to trade off several aspects: scalability, differentiation potential, immunogenicity, and, more recently, paracrine signaling potential.

The unmatched plasticity of iPSCs is outstanding. Their ability to differentiate into essentially any cell lineage makes them theoretically ideal for reconstructing complex, layered skin.[289] They can be expanded indefinitely, providing a steady and renewable source of cells. Nevertheless, iPSCs present practical challenges, particularly in terms of consistency of differentiation, genomic instability, and the high cost of production. So far, their use has been primarily confined to *in vitro* systems or preclinical modeling, with clinical translation still on the horizon.[290–297]

Mesenchymal stem cells, by contrast, are far more mature in their therapeutic development. Though their differentiation potential is more limited—especially when it comes to generating fully functional epidermal structures—they are well-regarded for their paracrine activity. MSCs can actively direct the wound environment by secreting cytokines, growth factors, and extracellular vesicles that promote angiogenesis, alter inflammation,

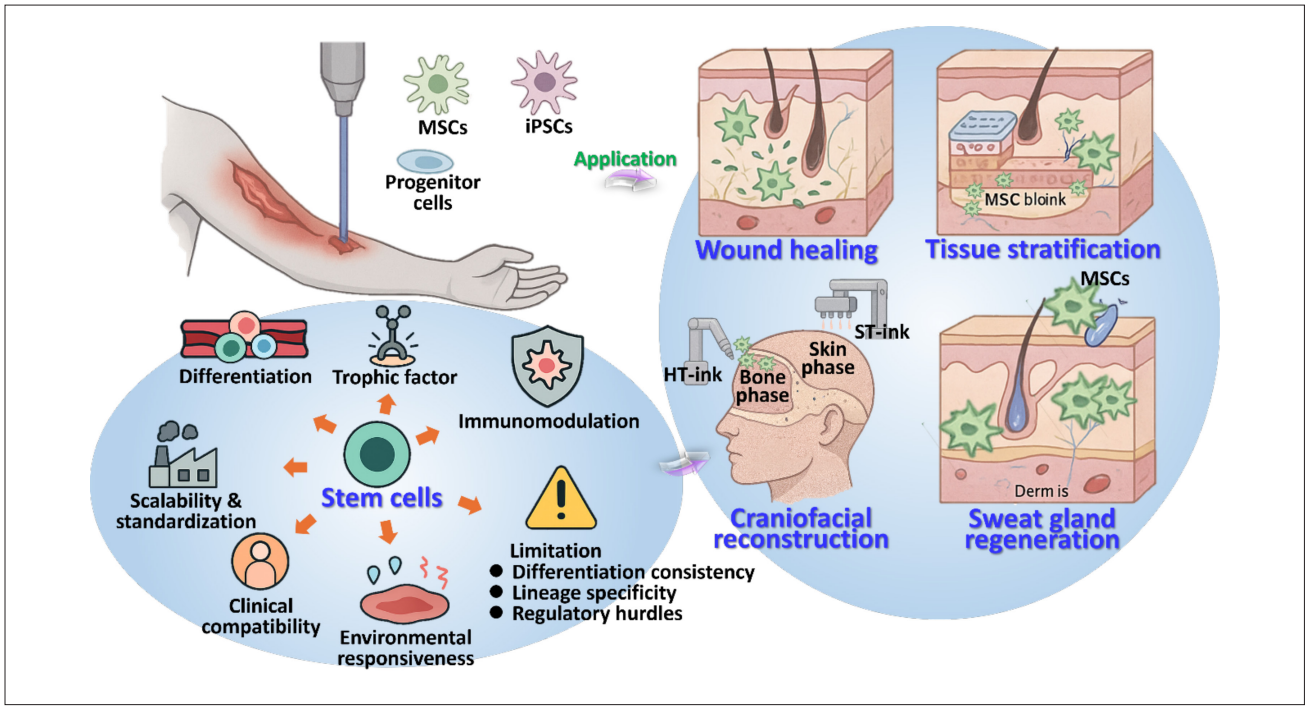

Figure 7. Multifaceted roles and applications of stem cells in skin bioprinting. Schematic representation of stem cells as active biological agents in skin bioprinting. Stem cells, such as mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and progenitor cells, are used through bioprinting platforms for wound healing, stratification, craniofacial reconstruction, and functional regeneration of skin appendages, including sweat glands. They are not only differentiated but also secrete trophic factors, modulate the immune system, and respond to changes in their environment. However, issues remain, such as lineage selectivity, reproducibility of differentiation, and pathway control. As shown, both handheld and robotic printing approaches can spatially control the delivery of different cell-laden bioinks (e.g., ST-ink for soft tissue and HT-ink for hard tissue), underscoring their versatility and translational potential in regenerative applications. Figure created using illustrations generated via ChatGPT (OpenAI image tools), with final layout and annotations edited in Microsoft PowerPoint.

Table 11. Comparison of stem cells, primary cells, and immortalized cell lines for use in skin bioprinting

Cell type	Expandability	Immunocompatibility	Cost and technical demand	Differentiation consistency	Clinical feasibility	Bioprinting performance	Reference
Stem cells (e.g., mesenchymal stem cells)	High	Personalizable (autologous)	High	Challenging	Emerging	Promising (requires further validation)	[25,26,36,52,53,63,266,267]
Primary cells (Patient-derived)	Limited	High (autologous)	Moderate	Stable	Already used	Most commonly used	[23,39,42,56,264,266]
Immortalized cell lines (e.g., HaCaT)	High	Poor	Low	Stable	Research use only	Low (due to genetic abnormalities)	[0,47,49,22,284–287]

and promote epithelial regeneration.[298,299] These secretory effects are increasingly viewed as an independent therapeutic mechanism, valuable even in the absence of complete lineage commitment.

On the other hand, AFSs offer a favorable compromise. They are relatively easy to expand, show a preference for skin-related lineages, and also possess notable paracrine effects.[300] They are considered moderate in their immunogenicity and may be manageable through immunosuppression methods or by matching the donor. Preclinical work suggests they may soon enter broader translational pipelines, particularly for pediatric or congenital skin disorders.[26,267,301]

Endothelial progenitor cells bring a narrower functional profile but fill an essential niche in vascular bioengineering.[302] They are dedicated to endothelial

Table 12. Comparative features of different cell types relevant to skin bioprinting

Cell type	Expandability	Differentiation	Paracrine	Immunogenicity	Status
Induced pluripotent stem cell	High	Versatile	Moderate	Customizable	Preclinical [290]
Mesenchymal stem cell	Moderate	Limited	High	Low	Clinical[63]; preclinical [25,36,52,53,266,267]
Amniotic fluid stem cell	High	Skin lineage	High	Moderate	Preclinical [26,267]
Endothelial progenitor cell	Moderate	Endothelial only	Medium	Variable	Preclinical [302–304]

lineages, making them highly applicable in promoting neovascularization in printed scaffolds. However, their *in vivo* data are sparse, and their immunogenicity behavior is not yet well characterized; thus, they are less predictable in clinical situations.

Comprehensively, the choice of stem cell source should be based on the targeted therapeutic objectives: is the proposed therapy focused on developing full-thickness skin equivalents, promoting vascular integration, or utilizing the secretome to regulate tissue? As summarized in Table 12, each stem cell type offers a distinct constellation of strengths and trade-offs that must be carefully matched to both technical capabilities and clinical strategies. Importantly, paracrine signaling is now recognized as an independent regenerative mechanism—beyond cell differentiation—that plays a central role in immune modulation, angiogenesis, and epithelial repair.

4.3. Applications of mesenchymal stem cells in skin bioprinting

Among all stem cell types explored for skin regeneration, MSCs have arguably garnered the most clinical and experimental attention—particularly in the context of burn and wound healing.[283,305–307] MSCs are considered multipotential (stromal) cells that can develop into different mesodermal lineages, including fibroblasts, osteoblasts, and adipocytes. However, their actual usefulness in regenerative medicine may be a lot more than their ability to differentiate. The strength of MSCs for skin bioprinting lies in their high paracrine activity, which is characterized by the secretion of a vast range of cytokines, growth factors, and extracellular vesicles that influence the wound microenvironment. These secreted factors have the potential to increase angiogenesis, reduce inflammation, and stimulate re-epithelialization, effectively transforming MSCs into potent cellular pharmacies that dynamically regulate the repair process. Numerous preclinical and clinical studies have confirmed these therapeutic benefits. For instance, recent reviews have reported MSC-mediated enhancement of burn wound closure, decreases in scar appearance, and increases in vascular density.[251] A recent *in vivo* study in 2024 further showed that bone marrow MSC transplantation (1×10^6 cells/wound) not only accelerated re-epithelialization in burn injuries but also regulated inflammatory cytokines such as interleukin 6 and transforming growth factor beta, promoting a more regenerative and less fibrotic healing environment.[308] These findings strengthen the hypothesis that MSCs actively and multi-dimensionally coordinate tissue regeneration not only through cellular replacement.

Zhang *et al.*[63] have provided a rare clinical perspective on MSC-based bioprinting by treating a chronic, therapy-refractory wound with a 3D bioprinted skin substitute containing human umbilical cord MSCs (1×10^6 cells/mL). In this case, the patient had a wound due to intralesional injections of bleomycin to treat plantar warts that were not responding to standard treatments such as platelet-rich plasma and autologous skin grafting, and hyperbaric oxygen therapy. The bioprinted construct—composed of alginate-gelatin bioink and loaded with human umbilical cord MSCs—was directly applied to the wound and resulted in rapid re-epithelialization, granulation tissue formation, and no observed adverse effects. The novelty in this case lies in the ability of MSC bioprinting to be translated from the bench to the bedside, addressing an actual wound with structural complexity and a high microbial burden. Nevertheless, the study has a limitation in that it is a one-case, open-label study, and no wider clinical validation has been conducted yet.

In an earlier and widely cited preclinical effort, Cheng *et al.*[25] introduced a handheld *in situ* bioprinting device capable of delivering umbilical cord-derived MSCs (1×10^6 cells/mL) directly into full-thickness burn wounds in a porcine model. These MSCs were not mere fillers, as they actively contributed to improved re-epithelialization, neovascularization, and re-population of dermal cells, resulting in considerably improved wound healing relative to the controls. The development of a microfluidic printhead capable of depositing conformal skin precursor sheets on wound surfaces, both in oblique and irregular shapes, with real-time deposition control, represents a

significant advance in this study and can be ascribed great clinical importance for acute burn care. However, there were still some limitations: long-term functional records on after-healing skin regeneration were still lacking.

Using craniofacial tissue, Moncal *et al.*[266] demonstrated in a large animal model a hybrid intraoperative bioprinting strategy for craniomaxillofacial reconstruction. They developed a bioprinting system that involves extrusion-based bioprinting (hard tissue, HT-ink) and inkjet droplet-based bioprinting (soft tissue, ST-ink), allowing the deposition of bone and skin components in a single surgical operation. More specifically, MSCs isolated from rat bone marrow (5×10^6 cells/mL) were encapsulated within a chitosan–collagen matrix and printed as the bone phase. In contrast, primary rat dermal fibroblasts (1.33×10^5 cells/mL) were encapsulated in a gelatin-collagen ink for the skin layer. These dual-ink approaches raised 60–68% skin closure and 80% bone regeneration within 10 days and 6 weeks, respectively, with layer-specific and spatially controlled healing. Compartmentalized regeneration of hard and soft tissues was possible through this stratified cell-ink combination. However, the use of fibroblasts—rather than MSCs—in the skin compartment meant the soft tissue lacked regenerative signaling typical of MSCs, and no skin appendages were observed. This restricts skin functional recovery and emphasizes the importance of MSC-based soft tissue optimization in subsequent versions.

From a foundational perspective, Skardal *et al.*[267] demonstrated that bioprinted AFS could significantly enhance healing in large skin defects in mice. Their automated, pressure-driven 3D extrusion platform printed a fibrinogen-collagen hydrogel loaded with human AFS and human bone marrow-derived MSCs, each at a density of 16.6×10^6 cells/mL. The printed constructs applied to the full-thickness skin wounds of immunodeficient mice enhanced wound closure, re-epithelialization, and microvascular density. Interestingly, their proteomic study on the cell secretome highlighted that therapeutic efficacy was primarily a result of paracrine signaling, rather than direct tissue regeneration. However, cell integration remained temporary, and long-term stability or skin organoid formation was not achieved.

More recently, Hao *et al.*[36] presented a temperature-sensitive gelatin-alginate hydrogel bioink that was crosslinked using a photo- and ionic approach, and customized for extrusion printing in a 3D format for wound healing applications. The bioink consisted of a co-culture of NIH 3T3 mouse fibroblasts (3×10^6 cells/mL) and human umbilical cord MSCs (3×10^6 cells/mL). When applied to excisional wounds in Institute of Cancer Research mice, the combination significantly promoted wound contraction, re-epithelialization, collagen deposition, and reduced inflammation. Importantly, this work highlighted the capacity of an appropriately engineered matrix to synergistically combine with MSC activity, achieving not just a scaffold but a truly active partner in tissue repair. Despite promising outcomes, the lack of comparative *in vivo* control groups using MSCs alone limits our understanding of how much benefit was material-driven versus cell-mediated.

In a remarkable effort of functional skin appendage regeneration, Yao *et al.*[53] utilized mouse MSCs (1×10^6 cells/mL) wrapped in a 3D-bioprinted hydrogel composed of gelatin and alginate, further supplemented with paw pad homogenates of the dermis. Their bioprinting concept, using an extrusion-based approach, developed a matrix that could direct MSCs into lineages of an SG. Notably, the biochemical cues (collagen triple helix repeat containing 1) and structural cues (heme oxygenase-1) were introduced into the construct to drive differentiation. Exciting results were obtained for SG's structural and functional restoration through re-exposure to acetylcholine-induced sweat-mediated responses and the expression of SG-specific genes. Based on this paradigm, Yuan *et al.*[52] further extended the regeneration of SG by establishing a vascularized SG regeneration model (SVIM). In the study, adipose-derived mesenchymal stem cells (1×10^7 cells/mL) were first differentiated into SG cells (100 pcs/cm^2), then bioprinted together with dermal microvascular endothelial cells (1×10^5 cells/cm^2) into a composite hydrogel composed of sodium alginate, gelatin, and plantar dermal ECM. This co-culture approach allowed the printed constructs not only to resume glandular architecture and secretory function but also to develop physiologically applicable vascularization. The research demonstrated how the reciprocal interactions between the SG niche and its vasculature could be modeled, showing the ability to achieve a new level of bioprinting of integrated tissue systems. But even based on the technical novelty, an unresolved issue was the scalability of the model and the long-term functional follow-up in systems other than the murine model.

Collectively, these studies paint a picture of MSCs as a highly versatile addition to the bioprinting toolkit, not only in the successful closure of wounds, but also in modulating the wound niche itself, tissue compartmentalization, and even initiating specialized tissue regeneration. However, some constraints remain as follows: cell fate after printing is challenging to monitor, and lineage commitment is not yet at high levels, especially in the reconstruction of complex appendages or stratified tissues of the skin. With the advancement of bioinks and the improvement of knowledge on how MSCs interact with the ECM, there is

a strong possibility that MSCs will still hold a prominent place in the second generation of clinically applicable skin substitutes.

5. Smart bioengineered skin

Skincare reconstruction has not only moved beyond the classic notion of a passive barrier in the changing setting of the regenerative medical industry. The development of bio-engineered skin as a smart functional interface with sensory perception, dynamic monitoring, and adaptive response remains primarily at the proof-of-concept stage in preclinical and early clinical settings.[309–311] With deep burns and chronic wounds persisting to defy the norms of skin grafting, the emergence of electronic skin (e-skin) technologies, piezoelectric scaffolds, and biocompatible materials has created alternative directions for regaining the sense of touch and temperature.[312–314] Current prototypes not only restore physiological function but also have the potential for two-way communication between engineered tissues and external devices (such as sensor-integrated grafts, which are currently conceptual or in very early stages of development). In parallel, developments in the field of wearable biosensing wound dressings allow for a more immediate proof of concept; for example, Kalasin *et al.*[315] demonstrated the FLEX-AI bandage system, a combination of a pH-sensitive hydrogel with a radio frequency sensor and neural network that achieved a near 95% accuracy in predicting chronic wound healing trajectories.

In parallel with this shift, a concept of smart bioinks has emerged, which involves formulations incorporating conducting polymers, piezoelectric composites, and stimuli-responsive compounds, thereby enabling a certain level of structural fidelity as well as functional integration with the bioprinting process.[316–318] Furthermore, artificial skin can be equipped with smart sensors and wireless modules to monitor wound healing, pH values, and possible infection continuously to assist decision-making in clinics.[311,319,320]

The overall integration of AI and Internet of Things (IoT) technologies also has potential applications in bioengineered skin.[321,322] The next generation of skin substitutes will fundamentally change treatment paradigms due to their ability to assess wounds with data, provide self-reporting solutions, and utilize cloud-based systems, allowing therapy to become adaptive and autonomous.[168,323,324] This section discusses the interdisciplinary approaches that support this change—materials science to digital health—and describes the new blueprints of creating genuinely intelligent skin systems. This system-level transformation is summarized in Figure 8, which schematically depicts the integration of 3D bioprinting, electronic skin, intelligent inks, and AI/IoT monitoring into next-generation smart skin grafts. As shown in the diagram, the grafting of different types of wounds can be applied to burns, diabetic ulcers, and excision wounds, and may include sensor inks, thermal/pH response units, and cloud-based data loops for real-time monitoring. The figure further highlights the clinical paradigm shift from conventional passive dressings to actively sensing and adaptive wound platforms, which enable personalized and data-driven therapy at the point of care. This graphical design suggests that smart skin constructs are not only about structure anymore, but may also become diagnostic and therapeutic devices that open up new and exciting directions for the field of wound care through smart responsiveness and digital health.

5.1. Strategies for tactile and thermal sensory restoration

Restoring the ability to feel—whether it is the warmth of sunlight or the gentle pressure of contact—is a key milestone in making bioengineered skin feel alive again. Conventional grafts can close a wound, but they fail to communicate with the nervous system. This is where tactile and thermal sensory restoration takes center stage, advancing beyond reconstruction to focus on reconnection—rebuilding skin that not only covers, but feels.[325]

The e-skin, also known as electronic skin, is at the center of this transformation. Designed to emulate the stretchability and sensitivity of native skin, e-skin platforms are now integrating soft, flexible circuits and embedded sensors that respond to temperature changes, mechanical strain, or pressure.[326–328] To provide better adhesion and biocompatibility when transferred into the clinical setting, these systems are increasingly printed on hydrogel-based substrates to closely mimic the hydration and softness of native tissue.[329–331] For example, e-skin sheets can now detect minor temperature differences using flexible thermistors and resistive sensors, allowing for thermal feedback to be achieved.[332–334]

Piezoelectric scaffolds represent one of these promising technologies, complementary to e-skin, that can convert mechanical deformation into electrical signals.[335–337] These bionic platforms are typically constructed from materials such as polyvinylidene fluoride or synthetic proteins like silk fibroin, which creates an interface between motion and perception.[338,339] When incorporated into engineered dermal structures, they can provide localized electromechanical feedback, which may in the future be connected directly to peripheral nerves or read by wearable processing units.

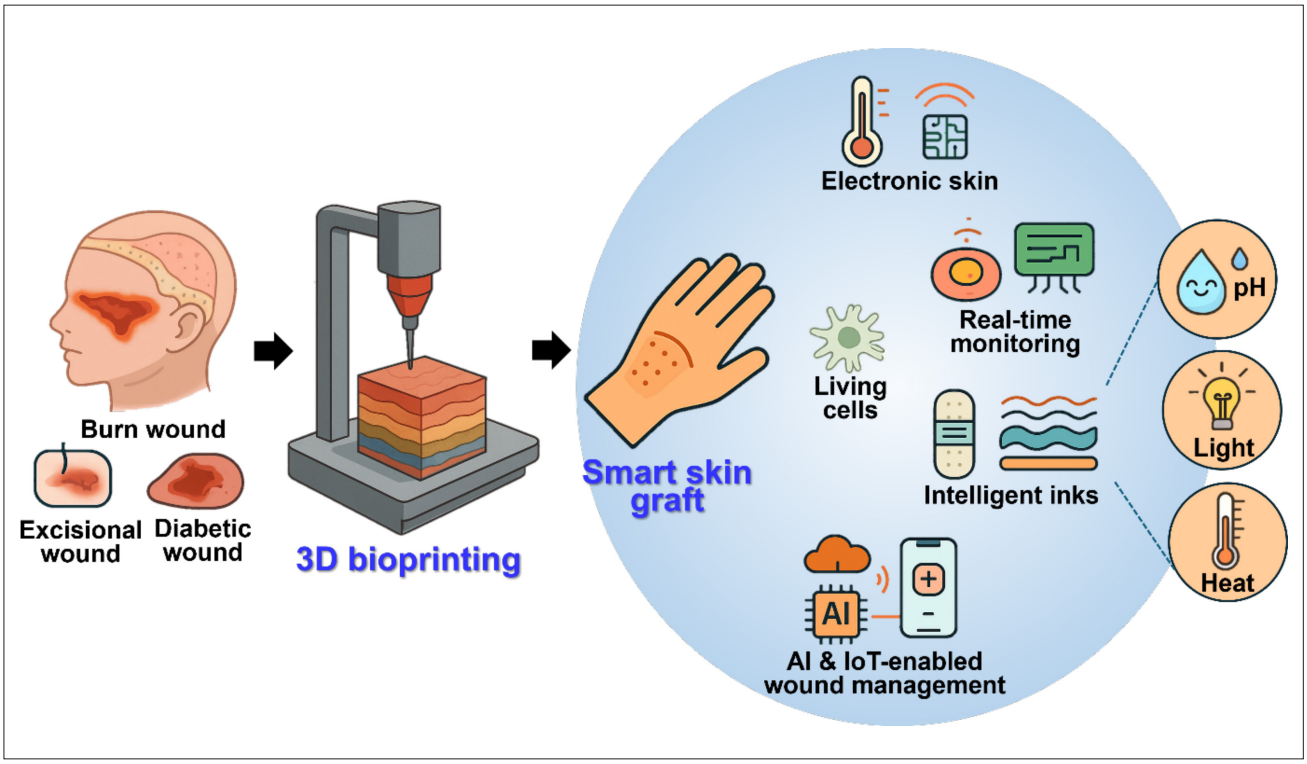

Figure 8. Smart skin grafts integrating three-dimensional (3D) bioprinting with intelligent sensing and digital health technologies. Development of smart skin grafts using 3D bioprinting technologies for different types of wounds (burn, diabetic, and excisional). The next generation of intelligent systems is a hybrid of living cells and smart materials, including electronic skin, intelligent inks, and responsive hydrogels, which facilitate the real-time tracking of physiological signals (e.g., pH, light, and heat). The combination of artificial intelligence (AI) and Internet of Things (IoT) technologies enables continuous wound monitoring, autonomous data analysis, and cloud-based reporting. Collectively, these are a step away from passive wound dressings to active therapeutic surfaces that can sense, adapt, and facilitate individualized care. Figure created using illustrations generated via ChatGPT (OpenAI image tools), with final layout and annotations edited in Microsoft PowerPoint.

In the meantime, bio-conductive materials establish the fundamental connection between the structure and the signal. Without electrical conductivity, none of these technologies could communicate.[340,341] Conductive poly(3,4-ethylenedioxythiophene) (PEDOT): polystyrene sulfonate (PSS), graphene derivatives, or carbon nanotube-laced hydrogels have been refined to be highly conductive and cell-compatible.[342–344] Such smart substrates can be used not only to transmit signals but also to facilitate cell adhesion and differentiation, including those of neural and epidermal lineages. Moreover, they can be co-printed with living cells through multi-ink bioprinting, allowing for a match between functionality and regenerative capability.

Together, these technologies present a vision for skin substitutes of the future that could someday lead to closing wounds, while also restoring sensory functions; however, validation to date has been limited to animal tests and early feasibility reports. This is not merely to replace lost tissue, but to renew communication between the skin and brain, injury and response, using engineered, living, and sensing interfaces.

5.2. Design and applications of intelligent inks

When printing skin, the ink applied should not only retain its shape; it must also think, react, and even feel. This is where intelligent inks can play a role. Compared to traditional bioinks, which are designed to ensure cell viability and print fidelity, intelligent inks are triggered by their surroundings and take an active role in functional regeneration.[345,346]

One of the most explored families in this space is conductive polymers. Materials like PEDOT:PSS, polyaniline, and polypyrrole introduce electrical conductivity into the bioprinting world, enabling printed constructs to support cells and transmit signals.[347–349] These polymers are advantageous when an individual wants to construct skin that can detect temperature, touch, or even subtle ionic variations. Their conductivity can be tuned through doping, and their compatibility with the body can be enhanced without sacrificing performance by embedding them in hydrogels.[350–352] For instance, it has recently been demonstrated that a straightforward mixture of PEDOT: PSS and GelMA or silk fibroin can produce

printable and functional inks that bridge the gap between electrical response and biological incorporation.[353]

Piezoelectric composites are materials that physically produce voltage as they are bent or stretched. These are not inert fillers but active ingredients that mimic natural skin behavior in response to movement and deformation.[354,355] Polyvinylidene fluoride-based blends, barium titanate nanoparticles, or silk-based matrices with piezoelectric components are often used.[356] When incorporated into printed dermal layers, these composites enable the conversion of mechanical input, such as pressure or stretch, into usable electrical signals.[357,358] This opens up the possibility of establishing feedback loops in skin interfaces or even training AI models that have been learned on motion-based data.

The last example is the stimulus-sensitive inks—the bioprinting chameleons. Such materials respond to external stimuli, such as light, heat, or pH, by changing color, stiffness, or conductivity.[359,360] For example, hydrogels loaded with photochromic molecules or temperature-sensitive polymers, such as poly(N-isopropylacrylamide), can shift their properties in real time, giving researchers control over how skin constructs behave after printing.[361,362] This responsiveness can be highly beneficial in the wound care field, such as a printed patch that stiffens upon an increase in temperature around the wound due to infection, or one that releases drugs in a clinical environment upon exposure to light.

Smart inks help fine-tune the line between material and functionality. Instead of merely anchoring cells, these inks are also involved in the healing process, including sensing, responding, and even communicating. The implication of this, in the context of bioprinted skin, is that the constructs are not only capable of surviving after implantation but also actively promote recovery. The design space of smart inks will continue to expand as printer heads become more accurate and multi-material systems become available. What was once merely a support material has now become an essential co-therapist—printing not just tissue, but function.

5.3. Integration of real-time monitoring systems

While the fabrication of skin constructs is crucial, monitoring their post-printing performance is equally vital, as wound healing is a dynamic and patient-specific process rather than a fixed event. They swell, fluctuate, become infected, or suddenly close rapidly.[363] Next-generation skin constructs must be capable of more than sitting quietly on a wound to detect these shifts in real time. They need to observe, record, and sometimes respond.[364] This is precisely the functionality now being integrated into bioengineered skin through real-time monitoring systems.[314,365]

An example would be pH-responsive patches. Changes in local pH are often the first signs that something is going wrong. A decrease in pH might represent an inflammation or bacterial growth, while an increase could signal tissue necrosis.[366] The concept of a color-changing smart patch is no longer a far-fetched idea, and it has already demonstrated its potential in preclinical applications. These visualization materials, commonly involving phenol red or bromothymol blue trapped in hydrogel matrices, can be visualized immediately.[367–369] Even more advanced iterations can convert pH fluctuations into electrical signals that are captured and analyzed, providing clinicians or caregivers with more than just a color indication.[370,371]

However, passive sensing is not enough. Embedded biosensors are miniaturized systems implanted directly into the skin.[372,373] Built using materials such as stretchable gold nanowires, conductive ink, or soft silicone microfluidics, embedded sensors can monitor oxygen saturation, hydration levels, or inflammatory cytokines, depending on their specific tuning.[374–376] Importantly, many of these sensors are now thin and flexible enough to conform to the skin, thereby avoiding the stiffness mismatch that once made implantation difficult.[377–379]

The final component in this framework involves wireless data transmission modules. Detecting physiological signals represents only part of the process; effective translation requires that this information be accurately transmitted and analyzed in real time. Whether it is a phone application, a cloud database, or an AI model that examines wound development patterns, the wireless transmission of sensor data is central to making bioengineered skin truly smart.[380,381] Low-energy Bluetooth, near-field communication, and even energy-harvesting radio systems are being adapted for skin-level interfaces.[382–384] This permits continuous, non-invasive monitoring, without requiring any additional wires, external readers, or hospital-only systems. A healing patch can now silently send updates to a connected device, alerting clinicians only when it detects a deviation from expected healing patterns.

When these factors combine, pH-sensitive materials enable the establishment of an early warning, an embedded sensor provides more information, and wireless technology ensures the data flow, all of which make printed skin more than just a scaffold. It becomes an intelligent collaborator in care. No longer just a surface covering, but a networked, communicative, diagnostic platform that watches the wound in real time and evolves with it. Such responsiveness

may mean the difference between regular healing and early intervention that prevents complications.

5.4. Artificial intelligence and Internet of Things-enabled wound management platforms

Information must become action, and in wound care, time is of the essence. The actual magic lies in the fact that skin constructs cease to be mere passive data recorders and become active participants in the healing process. This is where AI and the IoT come into play, turning real-time monitoring into something smarter: predictive, autonomous, and connected.[385–387]

Predictive healing analytics are a good starting point. Consider a printed skin patch that not only monitors pH or hydration levels but also learns from that information over time. By using machine learning models trained on thousands of wound cases, these systems can begin to identify patterns—what healing looks like, what early infection signals resemble, and when a wound is deviating from its expected course.[388,389] Rather than waiting till the symptoms escalate, clinicians can receive early alarms before anything becomes visibly wrong. These models are not just general-purpose; with enough data, predictions can be personalized to the patient's age, comorbidities, and wound type. This is preventative care rather than reactive treatment.

Next, autonomous wound reporting closes the feedback loop.[390] Under the traditional system, the information must be manually examined and interpreted, and undergo a series of steps before a decision is reached. But what if the system could flag an issue itself? Or auto-record daily healing data. It is now not inconceivable that we will see platforms where the printed skin, with its embedded sensors, raises alerts—e.g., through a smartphone notification or a clinician dashboard—when healing does not follow the expected patterns. They can operate around the clock, gathering data even in the absence of human observation, and can be used in home care and outpatient settings.

The backbone of all this is cloud-based data integration. Without seamless, secure data storage and accessibility, these systems may not be able to function.[391] Cloud platforms enable the centralized collection, cleaning, and analysis of biosensor data from printed patches, often in real-time. They also enable the passive construction of cross-patient comparisons and research-grade datasets. That means better models, better diagnostics, and even remote consultations without requiring the patient to travel. This becomes even more key for rural or resource-scarce areas where experts may not always be available, but smart infrastructure can bridge the gap.

Artificial intelligence and IoT, together, not only add layers of technology but also bring a completely different approach to wound management. Healing can be observed, comprehended, and even anticipated before complications occur. To patients, it means fewer trips to the hospital, quicker interventions, and greater assurance of healing. To clinicians, it presents an opportunity to shift their practices of relying on charts to make guesses to data-based decision-making. And for the printed skin itself? Although currently proof-of-concept platforms are far from being clinically validated treatments, in principle, such constructs could function as intelligent interfaces between biological and electronic components.

6. Future perspectives

6.1. Technological bottlenecks and future directions in skin bioprinting

Although skin bioprinting efforts to date are promising, technical bottlenecks still need to be overcome before it can be fully realized clinically. Focusing on new bioinks and smart systems receives a lot of attention, but from a systems perspective, deeper systemic challenges, from materials to machine interfaces to regulatory ecosystems, must be addressed holistically. This section outlines the primary limitations and provides realistic future directions, drawing on the current literature and trends in translational bioprinting.

6.1.1. Bioink stability and functional limitations

Modern-day bioinks still struggle under the conditions of actual wound environments, including extreme pH levels, inflammation, thermal damage, and oxidative stress.[111,112] Despite exhibiting good performance *in vitro*, many formulations fail to maintain their integrity under *in vivo* conditions, either in terms of physical stability or bioactivity. Cell viability during deposition, especially when using shear-sensitive stem cells, remains a significant concern.[392,393] Moreover, most clinically explored bioinks (like alginate or GelMA) offer limited bioresponsiveness and mechanical tunability.[171] Irregularities in viscosity make the printability and resolution difficult, whereas crosslinking kinetics remain either too sluggish or inconsistent to permit steady intraoperative use.[44,180,227,255]

For future strategic directions, bioinks that are xeno-free, GMP-compliant, and that can react dynamically to real-time stimuli such as wound pH, enzymes, or even wireless stimuli are needed. This includes the exploration of ECM-derived smart hydrogels, as well as thermo- and light-curable, and multi-phase co-axial constructs capable of adjusting themselves after deposition. Inks with integrated sensing and feedback loops will, in addition,

have the potential to fill a gap between passive grafts and responsive, living tissues.

6.1.2. Hardware: Portability, precision, and adaptability

Large bioprinters, however, are bulky, consume a significant amount of power, and are too complicated to print quickly in an emergency or surgical environment. Even handheld bioprinters experience nozzle clogging/or uneven print speeds, and poor resolutions when printing on uneven wound surfaces.[124,147]

A new generation of rugged, handheld bioprinters that can automatically scan, model, and print with little human input. To minimize operator error, these systems should incorporate smart material recognition, lidar surface mapping, and dynamic calibration systems, be haptics aware, and allow printing in irregular, moist, and bleeding wounds. Robotic surgical arms with wound-specific motion prediction are also worth exploring.

6.1.3. Clinical workflow integration

Although bioprinting has excellent potential, it can be challenging to integrate it into the real-world operating room. Existing workflows are associated with a significant amount of setup, validation of biocompatibility, and qualified operators—factors that are not always available in high-speed trauma or burn units. [90,186]

Thus, there is a need to critically advance toward the development of true plug-and-play platforms. Consider, for example, prefillable single-use cartridges, on-device image processing, and cloud-connected design pipelines that enable surgeons to upload wound images and receive a ready-to-print file in minutes.[90,186,196,197,380,391,394] Automated nozzle cleaning, wireless feedback from biosensors, and instant printing presets should be built into smart systems, ensuring that just-in-time grafting does not impede operating room schedules.[29,174,207,310,311,313,316,319,332–334,355]

6.1.4. Cell source and differentiation challenges

One of the most significant biological barriers is the unreliability of stem cell-derived constructs. For example, primary cells exhibit unpredictable differentiation and senescence, while iPSCs raise concerns regarding tumorigenicity and epigenetic drift.[27,28,53,60] Scale-up cell expansion remains slow, costly, and difficult to effect.

Induced progenitor cells with lineage biases (i.e., epidermal, glandular, or neural) could be a potential strategy to overcome this challenge.[52–54,135,184,224,258,259,284,291,293,340] Such *in situ* differentiation using spatially guided biochemical gradients combined with feedback loops driven by machine learning can help control cell fate after cell implantation. The integration of biosensors, monitoring gene expression or secretion profiles, provides dynamic control of regeneration.

6.1.5. Vascularization and functional appendage integration

While vascular grafts have significantly evolved to this point, the prospect of making fully perfusable, anastomosis-ready constructs that exhibit appendage integration (sweat glands, sebaceous units, pigmentation, sensation) is still an uphill effort.[52–54,135,137,313,332,334] Constructs frequently have issues with necrosis or fail to reconstitute sensory-motor functions.

Technologies such as microfluidic vascular scaffold, coaxial printing for channels resembling vessels, and growth factor gradients for controlling angiogenesis show promise.[42,45,59,71,145,161,175,185,260,279,290,302,303] Neural regeneration is also gaining popularity, with piezoelectric or conductive scaffolds demonstrating their potential to direct axon growth.[395,396] Efforts should now be directed toward imitating the appendage-specific architecture, as shown in recent skin models, which exhibit rudimentary gland formation.[52–54,135]

6.1.6. Manufacturing, regulation, and standardization

A less widely discussed problem is regulatory uncertainty. Depending on the jurisdiction, bioprinted skin can be classified as a "biologic," "medical device," or "ATMP" product.[64,66,68,71,72] Without standard manufacturing pipelines and testing criteria, even the most innovative of technologies risk being locked up in preclinical limbo.

There have been increasing demands for additional global harmonization of regulatory pathways, particularly between the FDA and the EMA. Establishing consistent quality control standards for sterility, degradation kinetics, and bioactivity is necessary. Companies should also advocate for pre-qualified clinical-grade bioinks, off-the-shelf sterile GMP cartridges, and point-of-care manufacturing units with real-time traceability over the cloud.

6.1.7. Cost, reimbursement, and ethics

Lastly, cost remains a significant barrier. In the absence of established reimbursement codes and scant long-term outcome data, bioprinting currently exists on the periphery of the health insurance system.[123,129,130] Furthermore, the ethical issues that accompany gene-edited cells or AI-directed surgical interventions are not extensively discussed.

As bioprinting moves closer to clinical reality, subsequent trials should incorporate economic outcomes measures, including shorter hospital stays, fewer graft revisions, and improved functional recovery. Collaborations

involving health economists, payer advisory boards, and ethics panels should be started early on. This field is still in its early stages, and, as it develops, new ethical guidelines will be needed to ensure cross-border data sharing and informed consent procedures.

6.2. Emerging directions in smart skin bioprinting: From concept to early translation

While current advances have primarily focused on resolving specific technological barriers, several conceptual and translational trends are beginning to redefine the long-term vision for skin bioprinting. Although many are in preclinical or early explorative stages, they represent important directions for further development. The skin we print today is smarter than it was 5 years ago—but it is nowhere near reaching its full potential. This is only the first chapter of a far larger narrative, in which tissue regeneration, biosensing, and smart feedback loops converge to form living systems that not only correct damage but also evolve to become responsive to it.[7,29,391,397] In the future, the most radical growth in this area may not be in the materials themselves, but in the way systems communicate, acquire knowledge as they process data, and evolve. These conceptual trends, which range from autonomous *in situ* printing to regulatory integration, are summarized in Figure 9, providing a system-level roadmap of how these innovations can converge in future smart skin platforms.

One of the most exciting directions lies in fully autonomous *in situ* bioprinting platforms.[140] Although it is still heavily reliant on manual control today, future systems may behave more like robotic surgeons, scanning wounds in real-time, deciding on the ideal cell and ink mix, adjusting print parameters on the fly, and embedding sensors during a single automated pass. Solutions based on real-time image and route planning using AI would significantly reduce the guesswork and variation in wound reconstruction. The structure that we are heading to is that the printer reacts to the wound as a living, evolving environment—not just a surface to be covered but a dynamic interface to be interpreted.

We shall also see a dramatic growth in multi-functional ink formulations, particularly those integrating regenerative, sensory, and therapeutic purposes. Instead of layering different materials for structure, signal, and drug delivery, future inks may be able to do all three simultaneously. Imagine a single extrusion containing cells, a responsive polymer that stiffens with temperature, and a time-release antibiotic triggered by infection markers.[29,34,398] These inks will be more complex and will require increased effort in formulation science and printer hardware, but the reward will be skin-like constructs that act more like the skin, which is flexible, interactive, and self-assembling.

Predictive models trained on large datasets of healthcare data will come to the forefront of digital innovation. All printed patches, embedded sensors, and uploaded wound logs contribute to an expanding knowledge graph. This data can then be used to predict healing schedules, prescribe interventions, or optimize print plans in real-time using machine learning models.[217,389] Smart skin, combined with smart software, enables personalized wound care that was once an elusive dream.[168,202] Connectivity with hospital networks and wearable health ecosystems will both push these systems into daily clinical operations, quietly gathering data behind the scenes, only intervening when there is something to be addressed.

Of course, regulatory pathways and ethical frameworks must evolve in parallel.[64–66,76] As we proceed with autonomous wound management and AI-powered diagnostics, issues regarding data security, clinical accountability, and long-term monitoring will need to be addressed directly. Who owns the data from a sensing patch? In what situations is it appropriate to assist human judgment with an AI in critical care situations? They are not only technical challenges, but also social ones, as they will determine the way in which these technologies are incorporated and adopted.

Lastly, the horizon is not restricted to wound care. The principles developed here—adaptive bioprinting, intelligent sensing, and cloud-integrated healing—will eventually spill into broader applications, including soft robotics, brain–machine interfaces, and artificial organs.[166,309,324,399] The starting point might be smart skin, but the ultimate goal is to create a generation of biohybrid systems that push the boundary between biology and engineered intelligence.

In brief, it is not merely a better graft that is the future of smart bioengineered skin. It is about designing systems that think, feel, and respond—skin that listens to the body, learns from it, and helps it heal faster, smarter, and more completely.[166,168,327] Figure 9 is a strategic synthesis of this vision, not as a visual synopsis of the vision, but as a framework to interconnect technological innovation and translational readiness. As a whole, it sketches out a systemic convergence: autonomous robotic platforms, real-time wound interpretation and adaptive printing behavior, multi-functional materials for single-step formulations, machine learning systems, cumulative sensors for personalized and predictive wound care plans, and regulatory and ethical realms as co-requisites for clinical translation. Taken together, these pieces serve to highlight a paradigm change—one from printing skin to

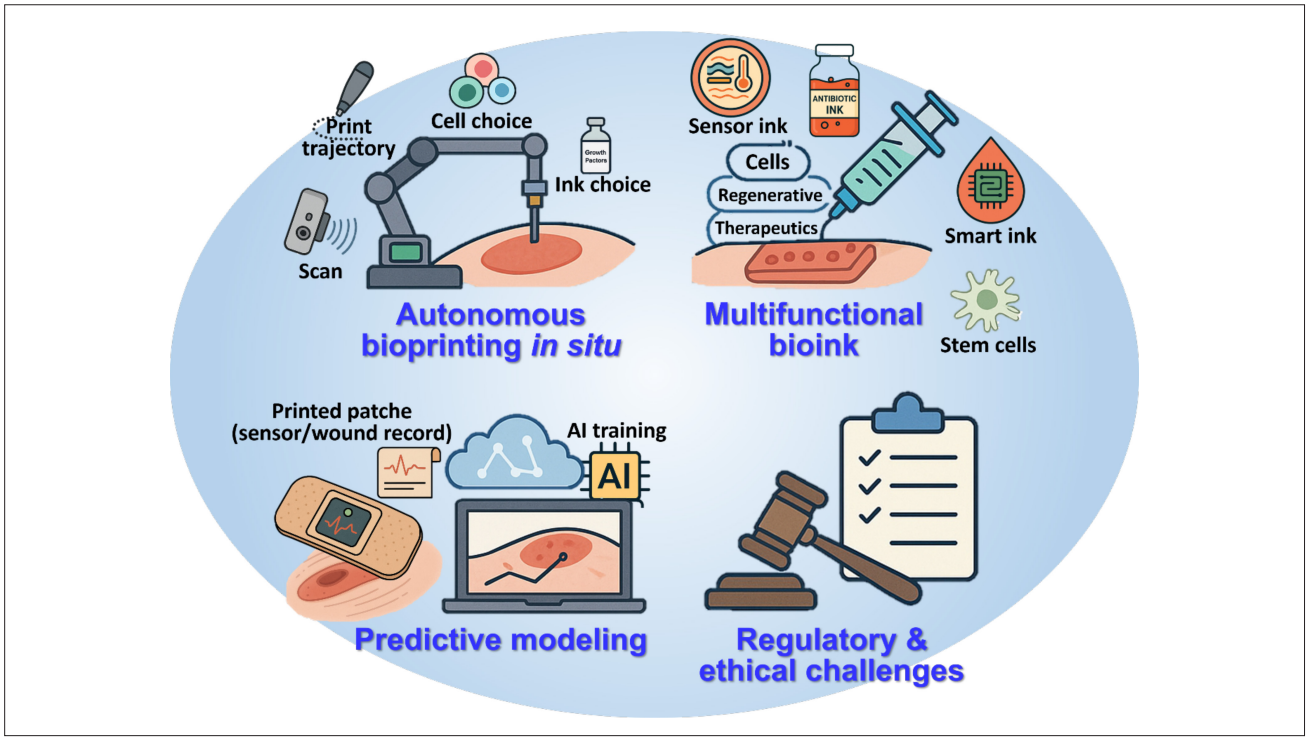

Figure 9. Future roadmap of smart skin bioprinting: Autonomous systems, multifunctional inks, predictive modeling, and ethical integration. Map of the future bioprinting landscape of smart skin. The top-left portion of the figure shows an entirely autonomous *in situ* bioprinting system, enabled by real-time imaging, intelligent print path planning driven by artificial intelligence (AI), and intelligent material selection. The top right shows the advancement of integrated bioinks containing living cells, smart therapeutics, and responsive sensors (e.g., the release of antibiotics, heat-cleaving polymers, and signaling light-emitting ink). The bottom-left corner reflects the rise of AI-enhanced wound care platforms, where printed patches are embedded with sensors, linked to cloud databases, and capable of performing predictive modeling through deep learning. Finally, the bottom-right refers to those regulatory and ethical challenges related to data ownership, clinical accountability, and authorization pathways that must be developed in tandem with the technology. This skin becomes an active system—communicating and intelligent—and this technology represents a novel paradigm in regenerative medicine where skin substitutes become active systems. Figure created using illustrations generated via ChatGPT (OpenAI image tools), with final layout and annotations edited in Microsoft PowerPoint.

creating responsive healing systems. Such a visual roadmap is critical to understanding not only where we are, but where we need to be to make regenerative skin truly smart.

7. Conclusion

Skin is no longer just something we aim to replace—it is something we now seek to upgrade. With the convergence of bioprinting, smart materials, and digital health technologies, bioengineered skin has begun to evolve into not only a structural replacement but also a living, sensing, and responsive system. This transformation represents a paradigm shift in our approach to wound care and tissue repair, transitioning from a passive, data-driven, and functionally disjointed process to an active, data-driven, and functionally unified one.

Here, we discussed the key factors driving this shift, including both tactile and thermal restoration approaches, the development of smart inks that enable sensing and reaction, and real-time biosensing networks, as well as wound management platforms utilizing AI. All these combine to create a blueprint of the new generation of skin constructs: biocompatible systems, as well as communicative, adaptable, and intelligent.

The challenges that await, in optimization of materials, unification of devices, and regulation, are significant, and so is the potential. Smart skin bioprinting is no longer confined to the lab bench. It is stepping into the clinic, into homes, and eventually, into a broader vision of human–machine symbiosis. What we print today will determine how the body heals tomorrow—and perhaps, how it relates to the world in ways it has never dreamed of.

Abbreviations

ASCs	adipose tissue-derived mesenchymal stromal cells
ATMPs	advanced therapy medicinal products

CAD	computer-aided designing
DOF	degrees of freedom
ECs	endothelial cells
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (United States)
GelMA	gelatin methacryloyl
HCT/P	human cells, tissues, and cellular and tissue-based products
ICH	International Council for Harmonisation
IND	investigational new drug
IoT	Internet of Things
iPSCs	induced pluripotent stem cells
ISO	International Organization for Standardization
LAB	laser-assisted bioprinting
LAP	photo-initiator lithium phenyl-2,4,6- trimethylbenzoylphosphinate
MSCs	mesenchymal stem cells
PEGDA	polyethylene glycol diacrylate
PLGA	poly(lactic-co-glycolic) acid
SG	Sweat gland
STSG	split-thickness skin grafting

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Conflict of interest

The authors declare they have no competing interests.

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