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Intelligent bioprinting: Smart bioinks, closed-loop biofabrication, and precision therapeutics

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Intelligent bioprinting: Smart bioinks, closed-loop biofabrication, and precision therapeutics

Running title: Intelligent bioprinting and closed-loop biofabrication

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Abstract

Three-dimensional bioprinting is moving beyond anatomical fabrication toward systems that can respond to biological cues, use process data to guide manufacturing, and support patient-specific applications. Rather than treating every responsive material, artificial-intelligence model, or sensor-equipped platform as intelligent, this review uses four descriptive functions—responsiveness, observability, decision capability, and actuation—to compare the field across three operational categories: responsive components, intelligence-assisted systems, and validated closed-loop systems. These functions are not cumulative prerequisites: responsiveness can exist without sensing, and closed-loop control can operate without a responsive bioink. We synthesize smart bioinks and printing quality, intelligent strategy selection, data-driven monitoring and feedback, post-printing maturation, and regenerative or precision-therapeutic applications. Representative evidence indicates that the most credible closed loops currently address fast manufacturing variables such as extrusion and geometry, whereas biological feedback over hours to weeks, continuously updated digital twins, and high-level autonomy remain early. We also distinguish the evidence needs of implantable regenerative constructs from those of patient-derived drug-testing models. The contribution of this review is therefore a cross-domain functional classification and translational evidence hierarchy, rather than a claim that smart materials, AI-assisted design, or closed-loop bioprinting are themselves new.

Keywords: Intelligent bioprinting; Smart bioinks; Closed-loop biofabrication; Biosensing; Regenerative medicine; Disease models; Precision therapeutics

1. Introduction

Three-dimensional (3D) bioprinting has evolved from a prototyping-oriented technology into an increasingly sophisticated biofabrication platform for tissue engineering, disease modeling, and translational regenerative medicine.^{1,2}

Its central advantage is the ability to couple digital design with biological composition, allowing investigators to reproduce aspects of native tissue architecture that are difficult to achieve with conventional casting, seeding, or self-assembly alone.³⁻⁶

Yet anatomical resemblance is not equivalent to biological function. Most bioprinted tissues remain preclinical, and increasing geometric complexity does not by itself solve vascularization, maturation, immunological integration, reproducibility, or manufacturing constraints.⁷⁻¹⁰

This gap is particularly evident when conventional bioprinting is viewed as an open-loop process. A predefined computer-aided design is converted into toolpaths, material is deposited under preset parameters, and the construct is subsequently evaluated. During printing, however, rheology can drift, extrusion can deviate from the target, and cell-laden materials can respond differently across batches. After printing, the local microenvironment continues to change through hypoxia, inflammation, matrix remodeling, mechanical loading, and cell-mediated degradation. A manufacturing strategy that fixes geometry and material properties at the start of the process therefore captures only one moment in a dynamic biological system.

The term intelligent bioprinting is increasingly used to describe attempts to address this mismatch, but its meaning is not yet uniform. In this review, intelligence is not equated with artificial intelligence (AI) alone. We use responsiveness, observability, decision capability, and actuation as descriptive axes rather than as four cumulative prerequisites. This permits responsive materials, offline computational tools, monitoring platforms, and feedback-controlled systems to be compared without assigning them the same maturity.¹¹⁻¹⁴

The operational categories and minimum connection rules are defined in Section 2; in particular, a validated closed loop requires a measured state to drive a defined decision and actuation around a prespecified target, whereas a responsive material or predictive model alone does not.^{11,15}

The component technologies considered here are not presented as newly invented categories. Prior reviews have separately synthesized 4D/stimuli-responsive materials, machine-learning-enabled biofabrication, AI-driven Quality-by-Design, and autonomous laboratory concepts.^{11,16-18} The

incremental purpose of the present review is different: it uses a common functional vocabulary to distinguish responsive components from intelligence-assisted and validated closed-loop systems, separates fast manufacturing feedback from slower biological feedback, and aligns evidence requirements with the intended use of regenerative implants or patient-derived decision tools. Table A1 (see Appendix) compares representative prior reviews with this cross-domain contribution.

Scope and review design. This article was designed as a narrative critical review rather than a systematic review or meta-analysis. Its purpose was to compare concepts, functional connections, evidence maturity, and translational requirements across three prespecified domains: smart bioinks and adaptive microenvironments; data-driven sensing, optimization, and closed-loop biofabrication; and regenerative or precision-therapeutic applications.

Search strategy. Relevant literature was identified through searches of PubMed/MEDLINE, Web of Science Core Collection, and Google Scholar from database inception to July 2026. Database-appropriate Boolean combinations were constructed from terms related to bioprinting ("3D bioprinting," "three-dimensional bioprinting," bioprint*, and biofabrication); smart materials and bioinks ("smart bioink*," "responsive bioink*," "stimuli-responsive hydrogel*," "dynamic bioink*," "cell-instructive bioink*," "therapeutic bioink*," and "4D bioprint*"); computational and closed-loop manufacturing ("artificial intelligence," "machine learning," "computer vision," "digital twin*," biosensor*, "in-line monitoring," "real-time monitoring," "quality control," "feedback control," and "closed-loop"); and regenerative or precision applications ("tissue engineering," "regenerative medicine," "disease model*," "tumor-on-a-chip," "patient-derived model*," "drug screening," "precision medicine," and "precision therapeutic*"). Reference lists of highly relevant primary studies and reviews were examined, and forward citation tracking was used to identify additional publications and recent online articles.

Literature selection and synthesis. Peer-reviewed primary studies, methodological reports, and recent high-level reviews were prioritized, particularly those published from 2018 to July 2026. Earlier landmark studies were retained when they established foundational concepts in bioprinting, vascularization, in situ printing, sensing, or feedback control. Duplicate records, non-peer-reviewed reports, studies without a direct connection to bioprinting, and publications that did not materially inform the predefined conceptual or translational questions were generally excluded. The literature was initially identified and organized by the lead author, and the relevance,

interpretation, and thematic placement of key publications were subsequently reviewed and discussed by the author team. Because this review was designed as an iterative narrative critical synthesis rather than a prospectively logged systematic review, record-level database counts were not captured in a PRISMA-compatible manner; retrospective numerical reconstruction would therefore risk false precision. The revised synthesis cites 109 publications. Figure A1 (see Appendix) transparently summarizes the identification and selection workflow without presenting fabricated screening counts. No formal dual-independent screening, risk-of-bias assessment, quantitative evidence grading, or meta-analysis was performed.

2. From conventional to intelligent bioprinting

Conventional bioprinting has been optimized primarily around deposition accuracy and structural fidelity. Using ASTM-aligned process terminology, extrusion-based bioprinting is governed by bioink rheology, filament continuity, shear exposure, and layer stability; jetting-based bioprinting depends on droplet-generation physics, dispensing reproducibility, and positional accuracy; and vat photopolymerization-based bioprinting is constrained by photochemistry, optical penetration, curing kinetics, and spatial resolution.¹⁹⁻²¹

Across modalities, the underlying logic is similar: a digital geometry is specified first and process success is assessed by how closely the printed object reproduces that geometry.^{6,22,23}

Four-dimensional (4D) bioprinting introduced a temporal dimension by using materials that change shape or properties after fabrication in response to temperature, hydration, pH, light, electrical input, or other cues.^{16,24-26} The conceptual boundary is important: 4D bioprinting describes a preprogrammed time-dependent transformation, whereas intelligent bioprinting additionally incorporates information acquisition and interpretation and, at the closed-loop level, measurement-driven decision and actuation. A construct may therefore be 4D without being closed loop. Conversely, a sensor-controller-actuator system may be closed loop without using a 4D bioink.

Recent studies illustrate these different functional levels. Near-infrared-triggered shape morphing provides a clear example of material-level responsiveness.²⁷

Machine-learning models for formulation or printability optimization provide intelligence-assisted design without automatic feedback.²⁸⁻³¹

Integrated microscopy and thermal imaging create observability during manufacturing, while iterative optical coherence tomography (OCT) feedback and convolutional-neural-network (CNN)-based extrusion correction connect measurement to process adjustment.³²⁻³⁵ These examples are used throughout the review to separate responsive, observational, intelligence-assisted, and closed-loop implementations rather than grouping them under a single “smart” label. This distinction also clarifies the role of AI. A model that predicts printability before fabrication is an intelligent design aid, but the printing process remains open-loop unless measured outputs are returned to the system. Conversely, a closed-loop controller can be intelligent without a deep neural network if robust sensing and model-based control are sufficient. The most mature conceptual framework is therefore not 'AI plus bioprinting,' but a materials-process-structure-function loop in which computation is used where it improves prediction, adaptation, or quality assurance.

An operational definition is useful because the field spans systems with very different levels of autonomy. Four functions can be distinguished: responsiveness, observability, decision capability, and actuation. Responsiveness describes a material or construct that changes when exposed to a cue; observability means that relevant process or biological states can be measured; decision capability converts information into a prescribed action; and actuation implements that action through printing, crosslinking, culture, stimulation, or therapeutic release. These functions are descriptive axes, not a cumulative checklist. For the purposes of this review, a responsive component exhibits a defined material or biological response but no measurement-mediated decision loop; an intelligence-assisted system uses sensing and/or computation to inform design, monitoring, or a human decision without automatic feedback actuation; and a validated closed-loop system connects observability → decision → actuation around a prespecified target and demonstrates a measurable advantage over an appropriate open-loop, baseline, or control condition. Responsiveness is optional for a closed-loop controller. The term autonomous adaptive system is reserved for repeated, self-directed closed-loop adaptation across multiple variables or time scales with qualified change control, uncertainty handling, fault detection, and a safe human-override pathway. Current evidence does not justify treating this last category as a generally achieved state.

This taxonomy has practical consequences for reporting. To improve consistency, we use a simple R–O–D–A coding rubric for representative studies: 0 = not demonstrated; 1 = demonstrated in the

reported system; and 2 = quantitatively validated against a reference, comparator, or relevant range. No composite score is calculated because the four functions are not interchangeable and this rubric has not been externally validated as a maturity scale. A responsive component requires $R \geq 1$; an intelligence-assisted system may demonstrate O and/or D but lacks automatic measurement-driven actuation; a validated closed loop requires $O \geq 1$, $D \geq 1$, and $A \geq 1$ around a prespecified target together with evidence that the loop improves a quality or biological endpoint relative to an appropriate baseline or control. Autonomous adaptive systems additionally require repeated operation across variables or time scales, uncertainty and fault handling, change control, and a safe human-override pathway. The same material or algorithm can therefore occupy different categories depending on implementation and validation.

Table 1. Operational taxonomy and minimum criteria for intelligent bioprinting.

Category	Operational definition	Minimum connection rule	Minimum R-O-D-A coding criterion	Representative example	Evidence interpretation
Preprogrammed 4D / responsive component	A material or construct that changes state in response to a predefined cue without measurement-mediated decision-making or automatic feedback.	A cue produces a defined material or construct response; no measurement-mediated decision loop is present.	$R \geq 1$; $O = 0$; $D = 0$; A is not measurement-driven	NIR-responsive shape-morphing bioink	Material-level responsiveness; not a closed loop.
Intelligence-assisted design or monitoring	A system in which sensing and/or computation informs design, monitoring, prediction, or human decision-making without automatic actuation.	Sensing and/or computation informs design, monitoring, prediction, or a human decision; automatic feedback is absent.	O and/or $D \geq 1$; $A = 0$	ML-based printability prediction; machine-vision monitoring	Open-loop or observational intelligence assistance.

Category	Operational definition	Minimum connection rule	Minimum R-O-D-A coding criterion	Representative example	Evidence interpretation
Validated closed-loop system	A system in which an observed state drives a defined decision and actuation around a prespecified target, with benefit demonstrated against an appropriate baseline or control.	A measured state drives a defined decision and actuation around a prespecified target; benefit is demonstrated versus baseline/control.	O $\geq$ 1; D $\geq$ 1; A $\geq$ 1; R optional	CNN-controlled extrusion correction; OCT-guided iterative feedback	Closed-loop process intelligence.
Autonomous adaptive system	A validated closed-loop system capable of repeated adaptation across multiple variables or time scales, with uncertainty/fault handling, change control, and safe override.	Repeated closed-loop adaptation across multiple variables or time scales, plus uncertainty/fault handling, change control, and safe override.	O/D/A repeatedly validated; R optional	Self-driving bioprinting laboratory as an emerging target	Developmental/aspirational unless end-to-end validation is shown.

Figure 1 summarizes this evolution and the three core pillars that structure the remainder of this review. © The Authors.

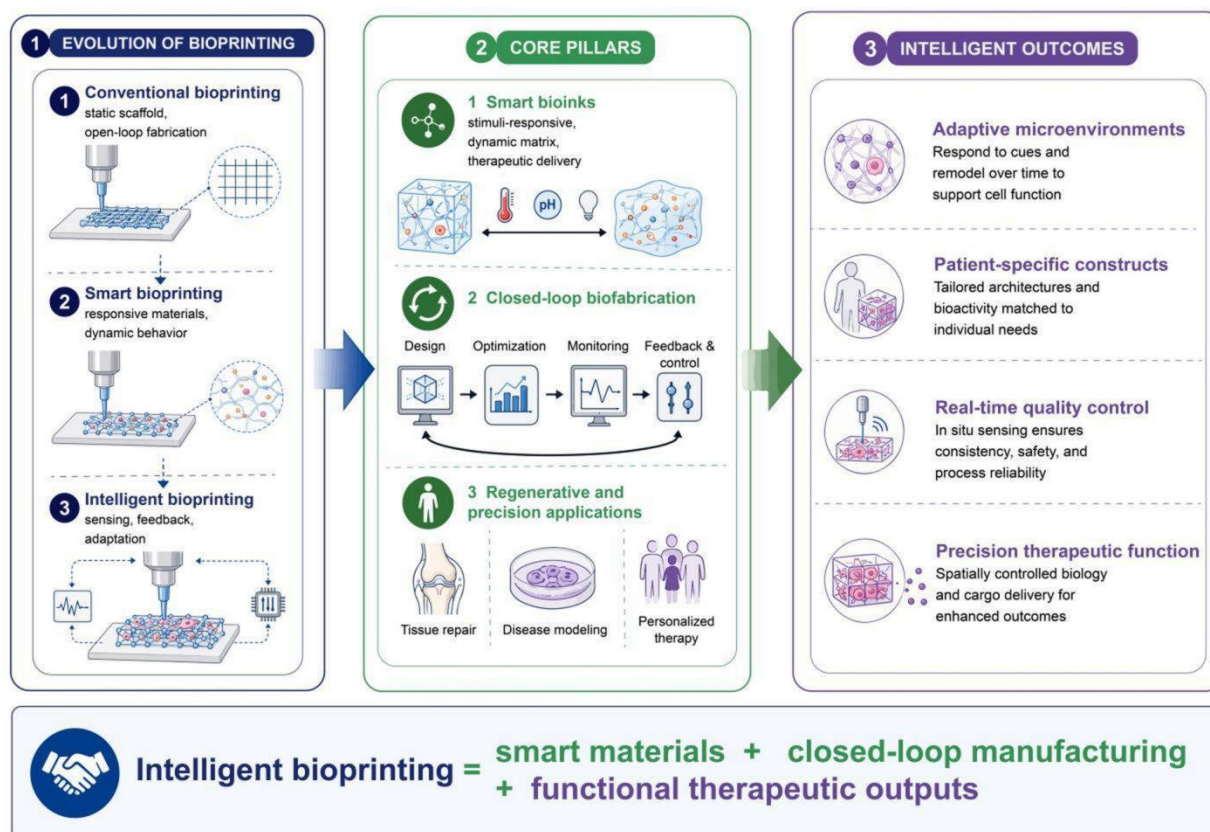


Figure 1. Conceptual framework of intelligent bioprinting. (1) Evolution from conventional structure-centric bioprinting to smart bioprinting and then to systems in which sensing, interpretation, and adaptation become explicit functions. (2) Three core pillars considered in this review: smart bioinks, closed-loop biofabrication, and regenerative/precision applications. (3) Representative functional outcomes, including adaptive microenvironments, patient-specific constructs, real-time quality control, and precision therapeutic function. The four functions defined in the text are descriptive axes rather than cumulative prerequisites, and this figure is a conceptual architecture rather than a validated maturity scale. Smart bioinks or AI-assisted design should not be interpreted as closed-loop intelligence unless a measurement–decision–actuation pathway is demonstrated. Abbreviation: AI, artificial intelligence. © The Authors.

3. Smart bioinks as material-level intelligence

3.1. From printability to printing quality and biological function

The earliest practical definition of a bioink was dominated by printability, but intelligent manufacturing requires a broader concept of printing quality. Relevant outputs include filament-width consistency, dimensional accuracy, pore fidelity, strand continuity, layer alignment, interlayer stability, surface quality, cell viability, and batch-to-batch reproducibility. Bioink rheology and crosslinking define the feasible process window; computational models can predict

parameter combinations within that window; in-line sensing can detect deviation from target geometry; and feedback can correct the process. Bioink design is therefore relevant to intelligent bioprinting when material properties are linked to measurable manufacturing or biological objectives rather than treated as an isolated formulation problem.

Decellularized extracellular matrix (dECM) bioinks exemplify this shift because they retain tissue-derived proteins, glycosaminoglycans, and matrix-associated signals that are difficult to reproduce with a single synthetic polymer.³⁶ Their biological richness can improve tissue-specific cell behavior, but it also introduces source variability, compositional complexity, and sterilization challenges. Conductive formulations containing PEDOT:PSS or carbon-based components can provide electrical cues for neural, muscle, or cardiac tissues, while magnetic formulations containing iron oxide particles can support remote actuation or alignment.^{37,38} These examples illustrate a key design principle: functionalization should be justified by a biological task, not by the number of added components.

3.2. Material-level responsiveness and dynamic matrices

Stimuli-responsive bioinks translate physical, chemical, or pathological cues into a material response. Common triggers include temperature, light, pH, reactive oxygen species (ROS), enzymes, electrical fields, and magnetic fields. The response may involve gelation, cleavage, swelling, changes in stiffness, deformation, or payload release. For critical comparison, reporting should include trigger range, response time, mechanical change, reversibility or fatigue, degradation or mass-loss kinetics, cumulative release fraction and retained bioactivity when applicable, and the resulting biological endpoint. These parameters are inconsistently reported across the literature, which limits direct comparison and is one reason why material-level responsiveness should not automatically be equated with validated system intelligence.

Thermoresponsive systems can decouple extrusion from stabilization by flowing under one thermal condition and forming a more stable network near physiological temperature. Photoresponsive chemistries provide spatial control over crosslinking or post-printing remodeling. Near-infrared-triggered alginate/polydopamine systems have demonstrated remote shape morphing of cell-laden constructs, providing a representative bridge between 4D actuation and tissue engineering.^{27,39,40}

Pathology-responsive materials are particularly attractive because the trigger originates from the disease environment rather than the operator. Reactive-oxygen-species-responsive networks can exploit oxidative stress in inflamed tissues, while pH-sensitive formulations can couple acidic microenvironments to viscosity, adhesion, degradation, or cargo release.⁴¹⁻⁴³

Dynamic matrices reproduce selected viscoelastic and remodelable features of native extracellular matrix. Supramolecular interactions and dynamic covalent bonds can provide shear thinning during extrusion, rapid self-healing after deposition, and stress relaxation after printing.⁴⁴ Quantitative examples illustrate why these metrics matter: mixing dynamic cross-linkers has been reported to tune stiffness and stress relaxation across approximately two orders of magnitude, whereas clickable dynamic bioinks achieved about a tenfold increase in shear elastic modulus one hour after secondary crosslinking and allowed post-printing modification over at least seven days.^{45,46} Such results are more informative than the label 'dynamic' alone because they connect material response to magnitude and time scale.

3.3. Dynamic and cell-instructive adaptation

A smart bioink should not be judged only by how it responds to a stimulus; it should also be evaluated by the quality of the cell-material interaction it creates. Adhesive ligands, growth factors, degradable motifs, matrix-bound cues, nanomaterials, and topographic features can be combined to regulate cell attachment, migration, lineage commitment, angiogenesis, and immune phenotype. The challenge is to preserve this instructive function without compromising printing behavior or creating an excessively complex formulation that is difficult to characterize.

This tradeoff is particularly important for stem-cell-based constructs. A stiff, highly crosslinked network may preserve shape fidelity but restrict spreading and matrix deposition; a rapidly relaxing network may support remodeling but lose geometric definition. Similarly, adding conductive or magnetic nanomaterials can introduce useful functionality while also affecting viscosity, sedimentation, optical curing, and biological response.^{47,48} Intelligent bioink design therefore requires simultaneous optimization of processability, mechanical evolution, transport, cell compatibility, and the intended biological output.

3.4. Therapeutic actuation and programmable delivery

The incorporation of therapeutic cargo transforms a printed construct into a spatially organized delivery platform. Growth factors, small molecules, nucleic acids, nanoparticles, and extracellular

vesicles (EVs) can be distributed within different regions of a construct and released through diffusion, network degradation, affinity interactions, or stimulus-triggered mechanisms. In the R–O–D–A framework, passive release is delivery rather than intelligence; preprogrammed stimulus-triggered release represents material-level responsiveness; and only sensor-mediated, decision-controlled release would constitute closed-loop therapeutic actuation. This distinction prevents therapeutic complexity from being mistaken for system intelligence.

Extracellular-vesicle (EV)-containing bioinks have been investigated as a way to combine cell-compatible scaffolding with paracrine signaling. In osteochondral models, extracellular matrix/GelMA systems incorporating mesenchymal-stromal-cell-derived exosomes have supported cartilage- and bone-repair-associated responses.^{49,50}

Hybrid EV-liposome formulations have been used to prolong microRNA delivery, while engineered EVs containing miR-199a-3p have been incorporated into printed cardiac patches to enhance cell survival. Nanoparticles provide parallel strategies for remote magnetic actuation, photothermal control, or sustained drug release.⁵¹⁻⁵³

The therapeutic-bioink concept is attractive but should not be interpreted as an automatic gain in product quality. Each added active component creates new questions regarding identity, loading efficiency, spatial distribution, release kinetics, stability, dose, batch consistency, and interaction with the printing process. For translational products, 'more functional' formulations may therefore be less manufacturable unless a clear critical quality attribute (CQA) framework is established. Immunomodulatory printing is a promising example: local control of inflammatory signaling may be highly valuable for regeneration, but mechanistic and dose-response evidence must accompany increasingly complex material designs.⁵⁴

Figure 2 summarizes the material-level mechanisms through which smart bioinks create adaptive microenvironments. © The Authors.

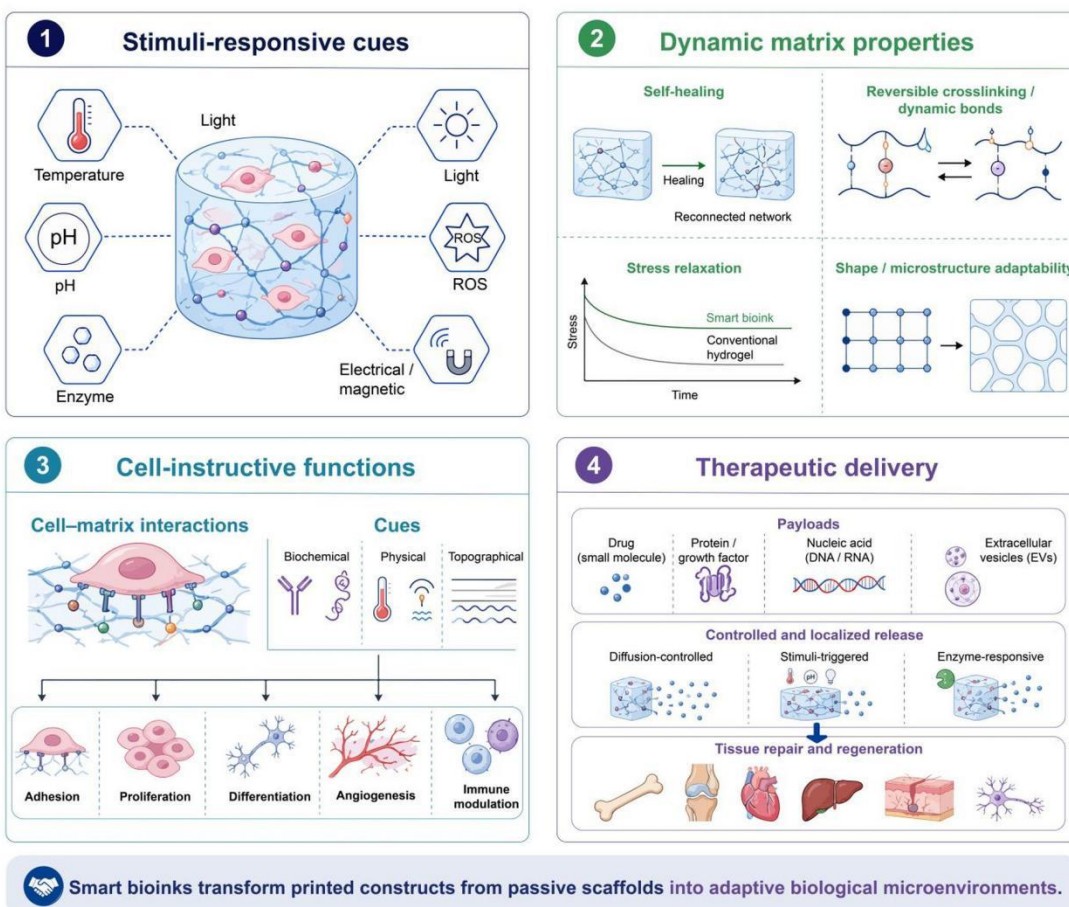


Figure 2. Smart bioinks as candidate responsive and biologically active interfaces. (1) Physical, chemical, and pathological cues can trigger changes in gelation, degradation, stiffness, deformation, or release. (2) Dynamic matrices use self-healing, reversible crosslinking, stress relaxation, and microstructural adaptability to reproduce aspects of extracellular-matrix dynamics. (3) Cell-instructive bioinks translate biochemical, physical, and topographical cues into adhesion, proliferation, differentiation, angiogenic, and immunomodulatory responses. (4) Therapeutic bioinks can localize small molecules, proteins, nucleic acids, or extracellular vesicles and release them through diffusion-, stimulus-, or enzyme-responsive mechanisms. These mechanisms are material-level functions; they should be considered validated adaptive interfaces only when a condition-specific functional benefit and an appropriate comparator are demonstrated, and they do not by themselves constitute a closed-loop intelligent system. Representative quantitative examples discussed in the text include approximately two orders of magnitude tunability in dynamic mechanical behavior and a tenfold post-printing increase in shear elastic modulus in a clickable dynamic bioink system. © The Authors.

Abbreviations: EV, extracellular vesicle; ROS, reactive oxygen species.

Table 2. Representative evidence matrix for smart bioink strategies.

Strategy	Representative evidence / use condition	Functional classification	Readout / comparator needed	Main evidence gap
Tissue-derived biochemical signaling	dECM bioinks preserve tissue-associated matrix cues and support lineage-relevant behavior. ³⁶	Biologically instructive component; no R–O–D–A loop by itself	Composition and tissue-specific function versus a defined synthetic or conventional matrix; batch comparability	Source variability, sterilization, compositional heterogeneity
Stimuli-responsive behavior	Temperature-, light-, pH-, ROS-, enzyme-, electrical-, or magnetic-responsive systems. ^{27,38,41,42}	Responsive component (R); typically preprogrammed	Trigger range, response kinetics, reversibility and task benefit versus a non-responsive control	Trigger specificity, off-target activation, limited cross-condition validation
Dynamic matrix mechanics	Self-healing, reversible crosslinking, and stress-relaxing hydrogels. ^{44-46,55}	Responsive/dynamic component (R); O/D usually absent	Recovery or relaxation metrics plus cell/function outcome versus a static-matrix control	Time-dependent specifications and limited longitudinal validation
Electrical or magnetic functionality	Conductive polymers/carbon materials and magnetic nanoparticles. ^{37,38}	Functional or externally actuated component; not closed-loop without O→D→A	Conductivity/magnetic response and biological function versus filler-free or unstimulated control	Particle distribution, long-term safety, process interference
Therapeutic delivery	Growth factors, nucleic acids, EVs, drugs, and functional nanoparticles. ^{49,51-53}	Passive delivery or responsive component, depending on release mechanism	Loading, spatial distribution, release kinetics, dose-response and benefit versus cargo-free/non-triggered control	Dose definition, cargo stability, release reproducibility, regulatory complexity

Abbreviations: A, actuation; D, decision capability; dECM, decellularized extracellular matrix; EV, extracellular vesicle; O, observability; R, responsiveness; ROS, reactive oxygen species.

Table 2 deliberately separates material-level functionality from system-level intelligence. Most representative bioink studies in this literature set are best classified as biologically instructive or responsive components rather than validated closed loops, because observability, a decision rule, and measurement-driven actuation are usually absent. Smartness should therefore be evaluated as a functional relationship rather than a material label. The relevant question is not whether a bioink contains a responsive chemistry, conductive filler, nanoparticle, or biological cargo, but whether that feature produces a measurable advantage under the conditions in which the construct will be used. This context dependence argues against ranking bioinks on a universal intelligence scale and instead favors indication-specific response profiles with predefined functional readouts.

A second issue is compositional burden. Adding multiple responsive groups, nanoparticles, growth factors, vesicles, or sensors can improve functionality in a proof-of-concept setting while simultaneously increasing batch variability, analytical complexity, sterilization difficulty, and the number of failure modes. Intelligent bioink design should therefore follow an economy-of-function principle: every added component needs a clear role, measurable benefit, and controllable specification. This becomes especially important when a bioink is expected to transition from

exploratory tissue engineering to a regulated product, because material complexity eventually becomes a quality-control problem as well as a biological design problem.

4. Data-driven and closed-loop biofabrication

4.1. Computational design and inverse design

The computational component of intelligent bioprinting begins before material deposition. Medical images, microscopy, histology, and biological data can be used to define patient-specific anatomy, spatial cell requirements, pore architectures, or target mechanical and transport properties. Automated segmentation and image reconstruction can reduce operator dependence, while generative and optimization methods can explore architectures that would be difficult to design manually.^{11,12,14,15}

The more consequential shift is from forward design to inverse design. In forward design, a material and geometry are chosen and their performance is measured. In inverse design, the desired outcome - for example permeability, stiffness, diffusion distance, degradation profile, or anisotropy - is specified first, and computational methods search for material and structural combinations that satisfy those objectives. This approach is particularly well suited to bioprinting because geometry, formulation, and process settings are strongly coupled. However, biological objectives are noisy and multiscale; therefore, inverse design models are only as reliable as the experimental datasets and mechanistic constraints used to train or calibrate them.

4.2. Bioink formulation and process optimization

Bioink formulation and printing parameters create a high-dimensional design space. Viscosity, shear thinning, yield stress, recovery, crosslinking kinetics, cell density, nozzle diameter, pressure, speed, temperature, and layer height interact nonlinearly. Conventional one-factor-at-a-time optimization is inefficient and can miss interactions. Supervised learning, response-surface approaches, surrogate models, Bayesian optimization, and active-learning strategies can reduce the number of experiments required to identify acceptable print windows.²⁸⁻³¹

Recent work in machine-learning-guided bioink optimization, Bayesian search, and process-parameter modeling illustrates the emerging direction: measured material behavior is converted into a model that predicts printing performance rather than being treated as a descriptive post hoc variable.⁵⁶⁻⁵⁸

The practical benefit of predictive formulation and process models is not simply faster optimization. A validated model can define operating boundaries, quantify uncertainty, and support transfer of a process between batches or devices.⁵⁶⁻⁵⁸ Those functions are more relevant to manufacturing than a single model that reports high accuracy on a small internal dataset.

4.3. Intelligent selection of bioprinting strategies for microstructural control

Between bioink formulation and real-time process monitoring lies a distinct strategy-selection layer: the choice of printing modality determines which geometries, material states, cell densities, and microstructural features are physically achievable before numerical parameter optimization begins. Intelligent bioprinting should therefore optimize not only material formulation and numerical process parameters but also the manufacturing strategy itself. Coaxial and sacrificial approaches can facilitate lumenized or perfusable architectures; embedded or freeform printing can enable fabrication with soft, weakly self-supporting, or high-cell-density bioinks; multimaterial and gradient printing can reproduce zonal or interfacial heterogeneity; directional extrusion can introduce controlled anisotropy and cellular alignment; vat-photopolymerization-based approaches can provide high spatial resolution; and in situ bioprinting can conform fabrication to patient-specific anatomical surfaces.⁵⁹ These strategies differ not only in achievable geometry but also in material compatibility, shear exposure, cell density, resolution, fabrication speed, crosslinking requirements, and clinical deployability.

A future decision-support system should map desired structural and biological attributes to a feasible combination of printing modality, toolpath, material window, cell density, spatial resolution, and viability constraints rather than optimizing pressure or speed in isolation. Strategy selection should be treated as a multi-objective decision problem. Microstructure governs diffusion distance, pore connectivity, cell alignment, local mechanics, interfacial organization, and vascular access; consequently, the strategy that maximizes geometric resolution may not maximize biological function. Intelligent selection should expose trade-offs explicitly, including resolution versus cell density, shear exposure versus filament stability, and fabrication speed versus structural complexity. In this framework, formulation defines the available material design space, strategy selection determines how that design space is converted into tissue architecture, and subsequent monitoring and feedback maintain the selected process within its intended operating window.

4.4. In-line monitoring, biosensing, and label-free readouts

A closed loop requires observability. During printing, machine vision can identify deviations in filament width, strand placement, continuity, layer alignment, or embedded-print geometry. Integrated microscopy has demonstrated in situ assessment of embedded bioprinting, while thermal imaging can detect geometrical changes even when transparent materials complicate visible-light monitoring.^{32,33,60} These approaches convert defects from an end-point discovery into a process signal that can potentially trigger corrective action.

Recent biosensing analyses reinforce the need to connect in situ measurements to actionable process or biological states rather than to data acquisition alone.^{61,62}

Structural monitoring is only one layer of observability. Biological performance depends on oxygenation, nutrient transport, metabolic activity, barrier integrity, mechanical loading, and cell state. Oxygen-sensing nanoparticles can report spatial oxygen gradients in printed constructs; co-printed impedimetric fibers can provide electrical readouts related to local biological behavior; and printed glucose sensors have been integrated with liver-on-a-chip systems.⁶³⁻⁶⁵ Such biosensors are important because a construct can be geometrically accurate yet biologically compromised.

Label-free optical technologies are attractive for longitudinal and manufacturing-oriented monitoring because they avoid introducing reporter molecules. Raman imaging can characterize cells and matrix components within bioinks, while OCT provides depth-resolved structural information. Multimodal Raman-OCT strategies combine biochemical and morphological information.⁶⁶⁻⁶⁸ For clinical manufacturing, however, sensor selection must be driven by decision relevance: a measurement is useful only if it links to a defined quality attribute, process action, or release decision.

4.5. Feedback control and adaptive quality assurance

Monitoring becomes intelligent manufacturing when observations are used to change the process. A representative closed-loop extrusion platform used convolutional neural networks to classify over-extrusion, under-extrusion, and acceptable printing in real time, then coupled classification to a controller that adjusted extrusion behavior during the run. The platform reached 90% accuracy for single-line classification and corrected extrusion errors across several ink types within approximately 10 s.^{13,34} The significance of this study lies less in the specific network architecture than in the integration of sensing, classification, and actuation into a single control loop.

Earlier adaptive manufacturing studies established complementary concepts. Computer vision-guided printing on moving and deformable surfaces showed that deposition paths can be updated relative to a changing target, a capability relevant to in situ bioprinting.⁶⁹ In OCT-based iterative feedback bioprinting, mismatch between designed and printed morphological parameters was reduced from roughly 40% to within 7% after feedback-based redesign, with parallel improvements in cell viability, proliferation, morphology, and hepatocyte-marker expression.³⁵ Flow-sensor studies similarly emphasize that reproducibility is improved by measuring delivered process output rather than assuming commanded pressure or flow equals the material actually deposited.⁷⁰

For translation, closed-loop quality assurance should be organized around a hierarchy of CQAs. Geometry and pore architecture may be monitored by vision or OCT; process consistency by pressure, flow, or rheology; biological state by oxygen or metabolic signals; and maturation by functional assays. Not every variable needs continuous measurement, but the selected variables should be linked to product risk. This risk-based framing is more useful than maximizing the number of sensors or algorithms.

Geometric and biological feedback also operate on different time scales. Filament width or layer position can be detected and corrected within seconds, whereas changes in cell viability, differentiation, matrix deposition, or tissue maturation may unfold over hours to weeks. A single controller cannot be assumed to manage both domains in the same way. Near-term closed-loop systems are therefore most credible when they control fast manufacturing variables with well-defined targets, while slower biological feedback is used to adjust culture, perfusion, stimulation, or dosing schedules. Recognizing these nested time scales prevents the concept of closed-loop bioprinting from becoming unrealistically broad and provides a practical route toward staged automation.

Sensor integration creates its own engineering constraints. Embedded probes can perturb local mechanics, diffusion, or cell organization; optical readouts can be affected by scattering and matrix composition; and electrochemical or impedance sensors may undergo biofouling, baseline drift, cross-sensitivity, or loss of calibration during long cultures. Sterilization can alter sensor coatings or calibration, whereas sensor footprint and wiring can complicate perfusion, containment, and scale-up.^{71,72} Long-term use therefore requires biocompatibility testing, matrix-specific calibration, drift and latency limits, interference testing against the biological process being

measured, and predefined recalibration or replacement rules. A signal should trigger a defined quality, process, or biological action rather than simply add another data stream.

4.6. Digital twins and autonomous workflows

Digital twins provide a conceptual bridge between monitored manufacturing and prediction, but the term should be used more strictly than a static computational model. We propose five minimum criteria for a genuine bioprinting digital twin: (1) explicit correspondence between a physical construct/process and its digital representation; (2) dynamic assimilation of data from the physical system; (3) predictive capability for future process or biological states; (4) quantified predictive accuracy, uncertainty, and domain of validity; and (5) decision or control relevance, such that twin outputs can inform a predefined manufacturing or maturation action. Bidirectional traceability, version control, and change logging are additional requirements when the twin enters a regulated workflow. Models that are not updated by physical-process data are more accurately described as digital models rather than digital twins.

The long-term vision is a self-driving bioprinting laboratory that integrates cell expansion, formulation, design, printing, maturation, monitoring, and decision-making with minimal manual intervention.^{10,18} Such systems should be viewed as a staged engineering roadmap rather than a near-term clinical reality. Autonomy increases the need for traceable datasets, version-controlled models, interpretable control policies, fault detection, and human override. In other words, greater autonomy does not reduce the burden of quality assurance; it redistributes that burden from operator skill toward validated data and control infrastructure.

4.7. Intelligent optimization of post-printing tissue maturation

Digital twins and predictive process models should ultimately extend beyond fabrication to the post-printing maturation phase, where the relevant objective shifts from maintaining geometric fidelity to steering a living construct toward a desired functional state. A major gap between current manufacturing feedback and truly adaptive tissue engineering therefore lies in post-printing maturation. Whereas geometric variables can often be measured within seconds and linked directly to corrective printing actions, cell differentiation, extracellular-matrix deposition, vascular maturation, electrophysiological coupling, and tissue-specific function evolve over hours to weeks and often vary across donors and batches. Useful ground truth still frequently depends on destructive histological, molecular, or mechanical assays.

A maturation loop would require non-destructive observables—such as oxygen, pH, glucose/lactate, electrophysiological activity, force, barrier function, or imaging-derived matrix features—linked to bounded actuators such as perfusion rate, oxygenation, medium composition, growth-factor dosing, mechanical loading, or electrical stimulation. Bioreactor and tissue-maturation platforms provide the physical basis for such interventions.⁷³ Biological feedback remains immature because biomarkers are often indirect, cellular responses are delayed and nonlinear, donor- and batch-dependent variability is large, and the correct control action is not always identifiable from a single abnormal signal. Progress will therefore require validated non-destructive functional CQAs, multimodal longitudinal sensing, quantitative stimulus-response models, adaptive bioreactors with bounded actuation, and model-predictive or uncertainty-aware control. These requirements explain why fast geometric control can be relatively mature while biological closed loops remain early within the same fabrication platform.

4.8. AI-specific limitations, multimodal models, and failure modes

AI can accelerate design and control, but its failure modes are distinct from those of the printer or material. Current datasets are commonly small, class-imbalanced, generated on a single device or material family, and inconsistently annotated. Domain shift can occur when the printer, nozzle, illumination, imaging pipeline, bioink batch, or cell source changes. Black-box predictions can obscure the reason for a control action, and poorly calibrated uncertainty can lead to overconfident extrapolation. Data leakage, hidden correlations, automation bias, model drift, and software-version changes are additional risks. These issues make external validation, standardized metadata, explainable or physics-informed modeling, out-of-distribution detection, and locked-version change control essential for clinical manufacturing.^{17,74}

Multimodal and foundation-model approaches are emerging in adjacent biomaterials and biological-design domains, where image, sequence, mechanical, chemical, and textual information can be fused for candidate generation or prioritization.^{74,75} Their relevance to bioprinting remains prospective rather than established. Near-term value is more likely to come from domain-constrained multimodal models operating within validated design spaces than from unrestricted general-purpose autonomy. Automated laboratory platforms and self-driving workflows provide a complementary path through iterative design-build-test-learn cycles, but model predictions must remain traceable to standardized experiments and auditable decisions.

Apparently contradictory results should also be interpreted as condition-specific success–failure boundaries rather than collapsed into a single ranking. A model can achieve high internal accuracy yet fail on a different printer or bioink; an added sensor can improve observability while increasing integration burden and biological interference; and a highly functional bioink can improve a selected biological endpoint while reducing reproducibility or manufacturability. Differences in material chemistry, cell density, hardware, validation split, comparator, endpoint definition, and culture duration can therefore produce results that appear inconsistent without being mutually exclusive. Critical evaluation should identify the operating boundary, failure context, and external-validity gap of each approach rather than reporting only its best-performing condition.

Figure 3 presents the closed-loop architecture proposed in this review, and Table 3 summarizes the enabling technologies and their current evidence gaps. © The Authors.

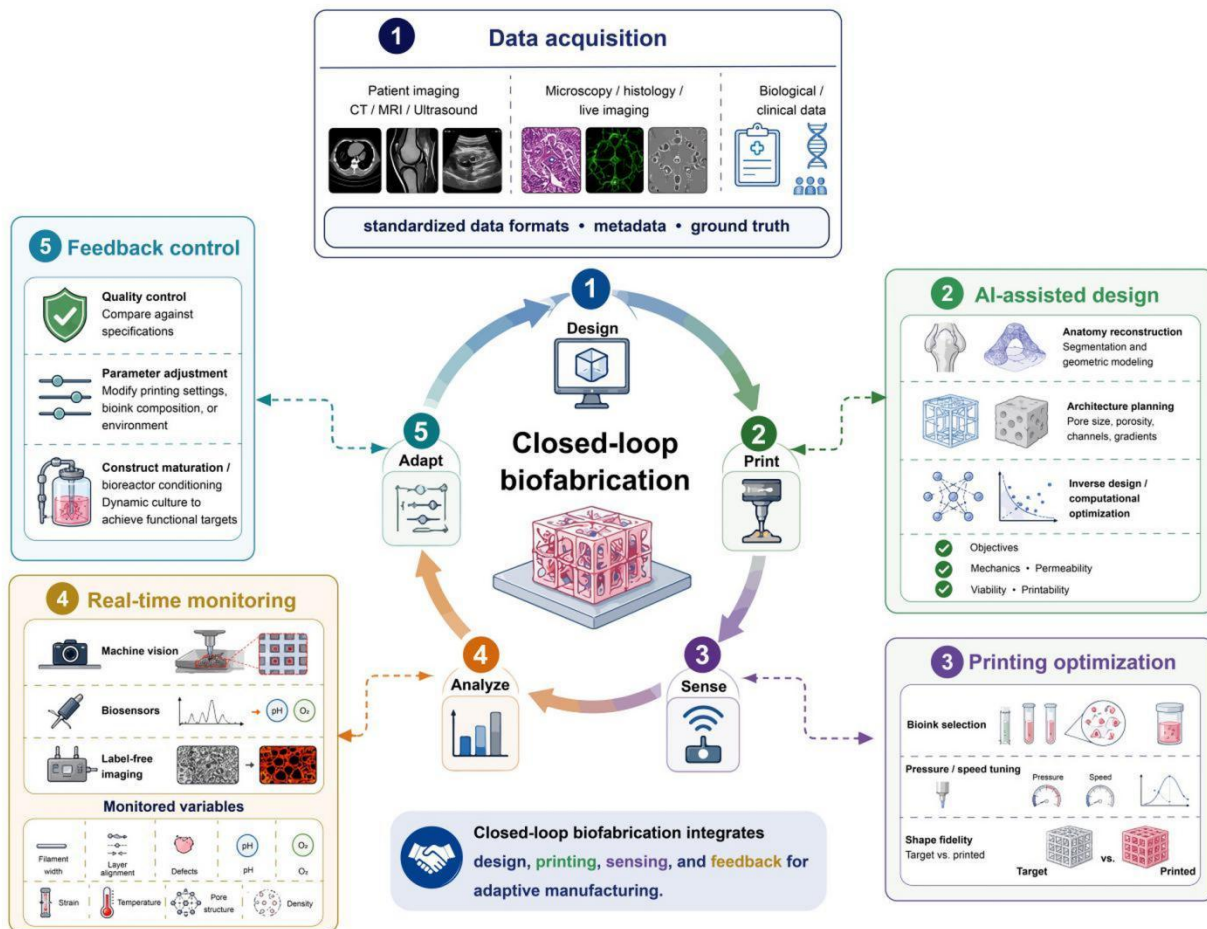


Figure 3. Data-driven closed-loop biofabrication. The proposed mature workflow links (1) standardized multimodal data acquisition, (2) AI-assisted or computational design, (3) printing optimization, (4) real-time process and biological monitoring, and (5) feedback control. The central design–print–sense–analyze–adapt loop distinguishes closed-loop biofabrication from open-loop automation. In the taxonomy used here, monitoring alone is observational and computational prediction alone is intelligence-assisted; closed-loop status requires measured information to trigger a defined actuation around a prespecified target, with benefit demonstrated against an appropriate baseline or control. Representative closed-loop examples include approximately 90% single-line defect classification with extrusion correction within about 10 s, and OCT-guided iterative feedback that reduced morphological mismatch from roughly 40% to within 7%. © The Authors.

Abbreviations: AI, artificial intelligence.

Table 3. Representative evidence matrix for data-driven and closed-loop biofabrication.

Workflow element	Representative evidence	Functional level	Readout / comparator	Cross-condition validation / main gap
Design	Medical-image segmentation, patient-specific reconstruction, and computational/inverse design. ^{11,12}	Intelligence-assisted; offline decision support (D)	Reconstruction/prediction error versus ground truth or held-out data	External validation and multimodal-data transfer remain limited
Formulation/process optimization	Supervised learning, surrogate modeling, Bayesian optimization, and predictive rheology. ^{28,30,56,58}	Intelligence-assisted; offline decision support (D)	Printability/fidelity/viability versus baseline settings or conventional optimization	Small datasets; platform- and formulation-specific models
Machine vision / thermal monitoring	Integrated microscopy, defect detection, and thermal imaging. ^{32,33,60}	Observational (O) unless linked to actuation	Detection accuracy, localization, latency versus annotated/reference measurements	Generalization across illumination, materials, geometries, and devices
Biosensing	Oxygen probes, impedimetric fibers, and metabolite sensors. ⁶³⁻⁶⁵	Observational (O) unless a decision rule and actuation are connected	Accuracy, drift, response time versus reference assay in the intended matrix	Calibration, integration burden, and long-term stability
Label-free optical monitoring	Raman imaging and OCT. ^{66,67}	Observational (O)	Correlation with structural/biochemical reference measurements	Throughput, spectral complexity, standardized interpretation
Feedback control	Layer-by-layer correction and real-time extrusion correction. ^{34,35}	Validated closed loop (O→D→A) in representative fast manufacturing tasks	Target deviation, defect/failure rate, or fidelity before versus after feedback	Robustness across inks, geometries, hardware, and failure modes
Flow/process sensing	Flow-sensor-based assessment of extrusion reproducibility. ⁷⁰	Observational or supervised control depending implementation	Delivered flow/reproducibility versus commanded settings and reference flow	Closed-loop actuation and cross-printer qualification remain limited
Digital twins / autonomy	Continuously updated process models and self-driving workflow concepts. ^{11,18}	Early intelligence-assisted to aspirational autonomous; O/D/A linkage inconsistent	Update fidelity, predictive calibration, control benefit versus static model	Definitions, qualification, change control, traceability, and human oversight

The representative evidence matrix supports a narrower maturity claim than a field-wide ranking: design, optimization, and sensing are mostly open-loop or observational, whereas the clearest measurement–decision–actuation demonstrations in the cited set address rapid manufacturing variables such as extrusion and geometry. Slow biological feedback and multi-stage autonomy remain substantially less validated. Abbreviations: A, actuation; AI, artificial intelligence; D, decision capability; O, observability; OCT, optical coherence tomography.

5. Intelligent bioprinting for regeneration and precision therapeutics

5.1. Regenerative medicine: intelligence must solve tissue-specific constraints

Regenerative medicine is the most intuitive destination for intelligent bioprinting, but tissue applications should not be evaluated by anatomical resemblance alone. Each tissue presents a different dominant constraint, and the value of intelligence lies in addressing that constraint through materials, spatial design, monitoring, or adaptive culture. Musculoskeletal tissues require regional mechanics and interface control; neural tissues require directional and electrophysiological function; skin requires rapid conformal coverage and wound-responsive behavior; and cardiac tissues require vascularization, electromechanical coupling, and high metabolic support.

In bone and osteochondral engineering, developmentally inspired bioprinting and gradient design have moved the field beyond uniform scaffolds. Endochondral templates and graded constructs can assign different compositions and architectures to cartilage and bone regions.⁷⁶⁻⁷⁹

Large-animal regenerative studies and cell-recruitment strategies further illustrate how local composition can be linked to tissue-specific repair goals.^{80,81} Spatially heterogeneous collagen constructs show how regional mechanics and composition can be engineered within one printed system.⁸² The intelligent step is not simply adding more layers, but linking local composition to a measurable requirement such as mineralization, chondrogenic matrix production, permeability, or interface integrity.

Tendon and ligament interfaces present a related gradient problem in which aligned fibrous tissue transitions to mineralized insertion zones. Recent bioprinting strategies emphasize anisotropy, graded mechanics, multiple cell types, and spatially patterned biological signals rather than a homogeneous scaffold.⁸³ This application is well suited to intelligent manufacturing because regional requirements can be translated into design rules and monitored during maturation.

Neural applications require directional guidance and functional connectivity. Conductive bioinks containing PEDOT:PSS or carbon-based materials can support electrical interactions, while

oriented architectures can guide neurite extension.³⁷ Some influential 3D-printed spinal cord scaffolds were not bioprinted with living cells at fabrication and therefore sit at the boundary of the strict bioprinting definition, but they provide important design evidence for channel geometry and directional regeneration.⁸⁴ Future intelligent neural constructs should integrate architecture with longitudinal electrophysiological or metabolic readouts rather than relying only on end-point histology.

Skin and wound repair provide one of the clearest opportunities for adaptive and in situ bioprinting because the target is accessible and changes over time. Handheld and in situ systems have deposited cell-containing materials directly onto wounds, reducing the separation between fabrication and implantation.^{85,86} Current reviews of in situ bioprinting increasingly frame control as a transition from open-loop deposition toward reconstruction, conformal path planning, sensing, and closed-loop adjustment.⁸⁷ Responsive hydrogels that react to oxidative stress, infection-associated signals, or pH could add a second level of adaptation after deposition, provided that trigger-response relationships are quantitatively characterized.

Cardiac and vascular tissues expose the scale limits of current biofabrication. Cardiac-specific extracellular-matrix and progenitor-cell patches have demonstrated functional potential in preclinical models, while recent reviews summarize complementary repair-material strategies.^{88,89}

For larger tissues, vascular architecture remains decisive. Perfusable heterogeneous constructs, multivascular networks, and high-cell-density embedded vascular channels have established increasingly sophisticated structural solutions.⁹⁰⁻⁹² These remain enabling architectures rather than proof of clinically mature vascular integration.

Visceral tissues such as liver, kidney, and pancreas illustrate an additional boundary between regenerative ambition and near-term utility. Their functions depend on dense vascularization, multiple interacting cell types, polarized epithelia, and organ-level transport. Current bioprinting and organoid platforms are therefore often more mature as disease models or screening systems than as implantable organs.^{4,93-95}

5.2. Disease modeling and precision therapeutics

The second major application pathway does not require implantation. Bioprinted disease models can combine patient-derived cells, extracellular matrix, stromal compartments, vascular elements, and defined spatial architecture to create experimental systems for drug testing and mechanistic

studies. Cancer models are particularly advanced because tumor behavior depends strongly on cell-cell interactions, matrix composition, oxygen gradients, and perfusion.^{96,97}

Glioblastoma models illustrate this potential. A patient-derived glioblastoma-on-a-chip recreated cancer-stroma organization and an oxygen gradient, and reproduced patient-specific responses to chemoradiation.⁹⁸ A perfusable 3D-bioprinted glioblastoma model incorporating patient-derived tumor cells and multiple microenvironmental cell types showed phenotypic and treatment-response features closer to in vivo disease than simplified culture systems.⁹⁹ These platforms support the concept of ex vivo therapeutic testing, but the clinical claim should remain prospective unless treatment selection based on the model has been validated in sufficiently powered patient cohorts.

Patient-derived colorectal cancer and liver-metastasis models have provided stronger translational signals by linking printed-model drug responses with clinical chemotherapy outcomes.¹⁰⁰ Bioprinted acute myeloid leukemia niches have reproduced interactions among leukemic blasts, stromal cells, and endothelial components and have been used to investigate chemoresistance.¹⁰¹ High-throughput multiwell bioprinting using tissue-derived hydrogels is also improving the scalability of cancer models for screening.¹⁰² The key transition for precision therapeutics is therefore from visually realistic disease models to analytically validated models with reproducible turnaround time, assay performance, and clinically meaningful predictive accuracy.

Multi-organ and body-on-a-chip systems further extend this logic by linking tissues through controlled fluidic circuits. Integrated platforms can reveal metabolism-dependent toxicity and inter-organ effects that single tissues miss.^{93,94} In principle, intelligent sensing could provide continuous oxygen, metabolite, electrical, and barrier readouts across these modules.

In practice, increased model complexity also increases the number of failure modes and complicates validation. Precision-medicine applications therefore need a fit-for-purpose balance between biological complexity and assay robustness.^{95,97,103}

The evidence hierarchy for precision therapeutics should be explicit. Reproducing a patient's histology or drug-response phenotype is an important validation step, but clinical utility requires more: the model must be generated within a clinically relevant time window, produce repeatable results across technical replicates and sites, and improve a treatment decision beyond available clinical information. Retrospective concordance can support analytical plausibility, whereas prospective studies are needed to demonstrate predictive value. This distinction is especially

important for cancer models, where a visually convincing tumor microenvironment can still fail as a decision tool if assay variability or turnaround time exceeds the clinical window.

Figure 4 integrates regenerative and precision therapeutic applications, while Table 4 highlights the dominant biological problem and the intelligent function most likely to add value in each setting. © The Authors.

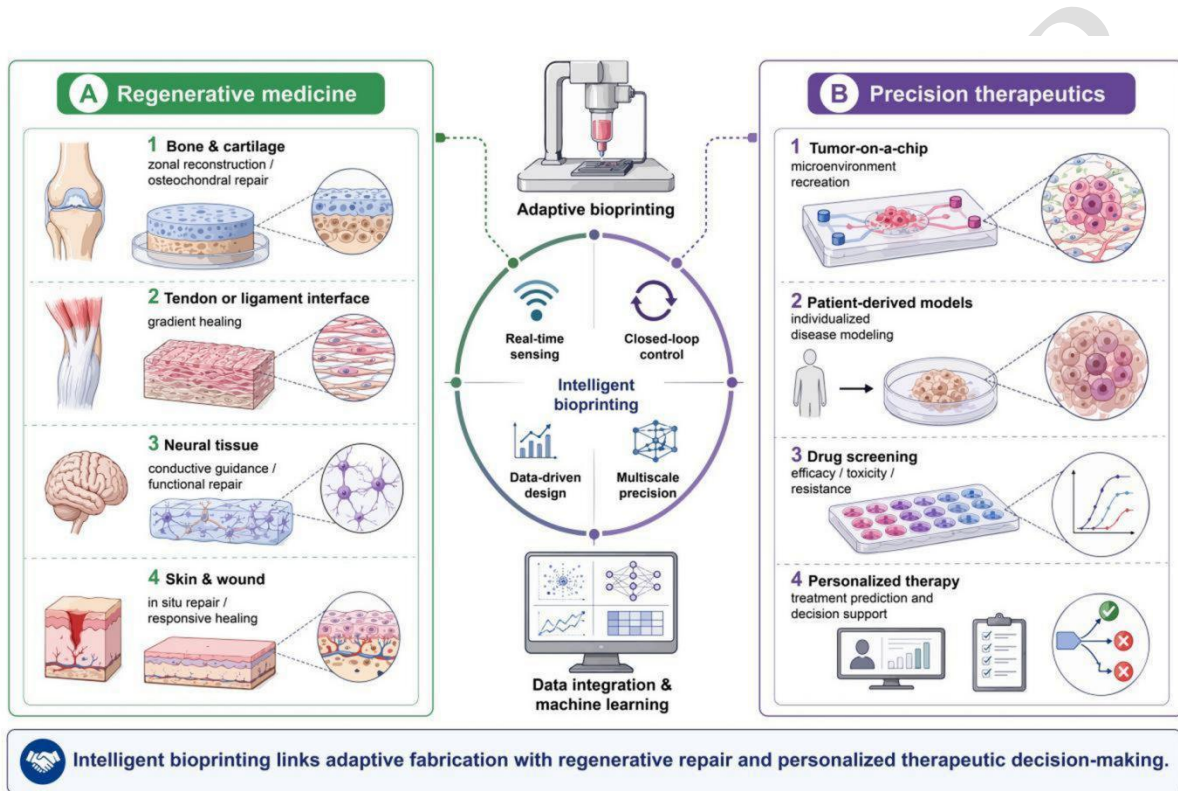


Figure 4. Intelligent bioprinting for regeneration and precision therapeutics. (A) In regenerative medicine, intelligent strategies are most useful when they address tissue-specific constraints such as osteochondral zonation, tendon/ligament interface gradients, directional neural repair, or dynamic wound environments. (B) In precision therapeutics, patient-derived disease models, tumor-on-a-chip systems, high-throughput drug screening, and treatment-prediction workflows provide an experimental pathway toward individualized decision support. Evidence maturity should be interpreted as a progression from biological resemblance to analytical reproducibility, clinically relevant turnaround, and finally prospective predictive utility. The last step—using a model to improve or change a treatment decision—remains a validation target rather than an established capability across the field. The central hub highlights sensing, feedback control, data-driven design, and multiscale precision as cross-cutting capabilities. © The Authors.

Table 4. Application-specific roles of intelligent bioprinting and the evidence needed for translation.

Application	Dominant biological/clinical problem	Intelligent function	Evidence needed / principal gap
Bone/cartilage	Regional mechanics, osteochondral interfaces, vascularization. ^{76,77,82}	Gradient/multimaterial design; instructive bioinks; monitored maturation	Functional integration, long-term mechanics, host vascularization
Tendon/ligament interface	Anisotropy and graded enthesis structure. ⁸³	Aligned deposition, regional material/cell cues, mechanical conditioning	Interface mechanics and reproducible regional maturation
Neural tissue	Axonal guidance and electrophysiological function. ^{37,84}	Conductive bioinks, oriented microarchitecture, functional sensing	Long-distance connectivity, safety, functional integration
Skin/wound	Dynamic geometry, inflammation, infection, rapid coverage. ⁸⁵⁻⁸⁷	In situ printing, responsive materials, wound sensing	Conformal control, sterility, healing-quality endpoints
Cardiac/vascular	Perfusion, electromechanical coupling, high metabolic demand. ^{88,91,92}	Perfusable networks, tissue-specific bioinks, in-line functional monitoring	Microvascular maturation, anastomosis, arrhythmia/safety testing
Visceral microphysiological models	Oxygen/metabolite exchange, barrier or secretory function, multicellular zonation. ^{65,93,94}	Perfusion, metabolic/biosensor readouts, adaptive culture or dosing	Organ-specific functional benchmarks, longitudinal sensor validation, reproducibility
Patient-derived cancer models	Heterogeneity and treatment-response prediction. ⁹⁸⁻¹⁰⁰	Patient-derived cells, spatial microenvironment, drug-response analytics	Clinically relevant turnaround, inter-site repeatability, prospective predictive utility
High-throughput drug-screening models	Scale, throughput, and assay consistency. ¹⁰²	Automated multiwell printing and standardized drug-response readouts	Batch-to-batch assay stability, throughput metrics, cross-platform reproducibility
Multi-organ/body-on-a-chip systems	Inter-organ metabolism, systemic toxicity, and fluidic coupling. ^{93,94}	Controlled inter-module flow, multiplexed sensing, organ-interaction analysis	Flow scaling, module-to-module validation, systemic endpoint standardization

6. Translation and future directions

6.1. Biological scale, vascularization, and maturation

The primary biological barriers remain scale and maturation. Thick constructs require perfusion early enough to prevent diffusion-limited cell loss, yet engineered vessels must also acquire appropriate barrier function, supporting cells, branching hierarchy, and host integration. Perfusable channels are therefore an enabling architecture rather than a complete vascular solution.^{91,92} Maturation is similarly tissue dependent: cartilage requires matrix deposition, bone requires mineralization and vascular integration, muscle and cardiac tissues require electromechanical function, and epithelial barriers require polarity and junctional integrity. Bioreactor culture, perfusion, mechanical loading, and biochemical conditioning can accelerate these processes but add time and manufacturing complexity.¹⁰⁴

6.2. Standardization, CQAs, and manufacturability

For intelligent bioprinting to become a manufacturing platform, the field must move from descriptive demonstrations toward defined process and product specifications. GMP-compatible translation requires qualified raw materials and cell sources, controlled or closed aseptic processing where appropriate, standardized bioink preparation, calibrated hardware, in-process controls, defined CQAs, potency/performance assays, release criteria, and traceable deviation and change-control procedures. The ASTM F3659-24 Standard Guide for Bioinks Used in Bioprinting provides a bioprinting-specific reference for bioink properties, printability, biological considerations, aseptic processing, and downstream testing.^{2,105,106} Reproducibility must be demonstrated across batches, operators, devices, and sites rather than inferred from repeated printing on one platform.

In-line sensors and automated quality systems should be prioritized according to risk. A flow sensor that prevents batch failure may be more valuable than a sophisticated sensor without a release criterion. Similarly, a computational model should be treated as part of the manufacturing process when its output changes a material, toolpath, parameter, or disposition decision. This implies model version control, documented training data, pre-specified performance thresholds, and change-management procedures.

For living or therapeutically active constructs, release testing will also need to move beyond cell viability or nominal geometry toward measures linked to intended function. A construct designed for cartilage repair may require regional matrix mechanics and chondrogenic function; a vascular model may require barrier integrity and perfusability; a tumor model may require reproducible drug-response behavior. These indication-specific potency or performance assays should be defined early enough to guide material selection and process development. Otherwise, sophisticated manufacturing can yield a product that is reproducible in appearance but poorly characterized in function.

6.3. Data quality, interoperability, and model validation

Data scarcity remains a major limitation of computational bioprinting. Most datasets are generated on one printer, one material family, and a narrow parameter range, while differences in image acquisition, rheological protocols, environmental conditions, and post-processing reduce portability between laboratories.^{14,28,30,31}

The problem is therefore not only sample size; it is the lack of standardized metadata and shared outcome definitions. Models that perform well internally may fail when material batches, devices, imaging systems, or geometry change.^{56,57}

Future datasets should pair raw measurements with machine-readable metadata describing material composition, cell type and density, hardware, nozzle, calibration state, temperature, pressure or flow, speed, crosslinking, geometry, and downstream functional outcomes. External validation across platforms is more informative than repeatedly increasing model complexity on one dataset. FAIR-compatible data structures, multimodal fusion, transfer learning, federated learning, and physics-informed modeling may help, but they do not remove the need for representative data, transparent validation, and uncertainty reporting.⁷⁴

6.4. Regulatory and clinical evidence requirements

Intelligent bioprinted products can combine living cells, biomaterials, active molecules, sensors, software, and device functions. This creates a regulatory challenge because the manufacturing process and the product may be inseparable, and classification depends on intended use, composition, biological activity, and primary mode of action. Current translation must therefore be mapped to existing regulatory frameworks rather than assuming a dedicated bioprinting pathway. Relevant examples include the US FDA guidance for additive-manufactured medical devices, the European Union regulation for advanced-therapy medicinal products, ATMP-specific GMP guidance, and recent bioprinting-focused regulatory analysis.^{105,107-109} A change in an algorithm may alter geometry; a change in sensor calibration may alter process decisions; and a change in bioink or cell source may alter biological potency.

Clinical evidence should also be application specific. For implantable constructs, safety, sterility, tumorigenicity where relevant, integration, long-term function, manufacturing consistency, storage, transport, and operating-room or point-of-care compatibility are essential. For patient-derived drug-testing models, analytical validity, turnaround time, repeatability, inter-site transferability, and prospective prediction of treatment response are more relevant than implantability. A technically sophisticated patient-derived model may have limited clinical utility if cell expansion, bioprinting, maturation, and testing exceed the therapeutic decision window, regardless of its biological fidelity. Intelligent monitoring and automation can reduce operator variability, support traceability, define validated design spaces, and maintain CQAs, but they also

introduce obligations for software validation, cybersecurity and data integrity, sensor qualification, algorithm versioning, controlled updates, and change management.

Economic and workflow feasibility should be evaluated alongside technical performance. The relevant metric is not simply the cost of printing, but the total cost required to deliver a reproducible and clinically usable product or actionable result. This includes qualified cells and biomaterials, specialized equipment, controlled manufacturing environments, labor, quality-control and release testing, failed-batch risk, storage and transport, and, where applicable, patient-specific imaging, design, and cell-expansion steps. Centralized manufacturing may improve standardization but increase logistics and transport burdens, whereas point-of-care production may shorten delivery times while transferring greater requirements for equipment qualification, operator training, aseptic processing, and local quality systems to the clinical site. Cost-effectiveness should ultimately be evaluated against the existing standard of care or diagnostic workflow, incorporating time to treatment, failure or revision avoidance, clinical benefit, and—for patient-derived testing platforms—the cost per actionable result and incremental value of improved therapeutic decision-making.

6.5. Change control, revalidation, and autonomy gates

Accountable autonomy requires explicit entry and exit criteria rather than a continuous increase in algorithmic complexity. A practical staged framework is: Stage 0, open-loop or manual operation; Stage 1, supervised feedback for one bounded manufacturing variable, entered only after the sensor, target, action range, comparator benefit, and immediate human override are qualified; Stage 2, qualified adaptive manufacturing across multiple process variables, requiring validation across intended material/device ranges, drift and fault detection, version-controlled models and hardware, and a tested safe-state transition; and Stage 3, biological or digital-twin orchestration across longer time scales, which additionally requires longitudinal biological CQAs, uncertainty-aware model updating, predefined model-change controls, prospective utility evidence where clinically relevant, and fail-safe boundaries. On current evidence, Stage 3 should be treated as a development target rather than a generally demonstrated capability.

Table 5. Change–risk–revalidation framework for accountable intelligent bioprinting.

Change domain	Risk to validated state	Minimum revalidation	Override / out-of-bounds trigger	Safe state / next action
Algorithm, model, or training-data version	Shifted predictions or control behavior; hidden domain drift	Locked version; regression and hold-out testing; intended-use validation; uncertainty/drift assessment	Performance below preset threshold, out-of-distribution input, missing or inconsistent data	Revert to last qualified model or manual decision; quarantine update
Sensor, probe, or calibration	Bias, drift, latency, dropout, or altered interaction with the construct	Matrix- and device-specific accuracy, precision, drift, response-time, and reference-method comparison	Calibration limit exceeded, signal loss, implausible cross-sensor disagreement	Suspend automated actuation; alarm and manual verification/recalibration
Bioink, raw material, cell source, or batch	Changed rheology, print window, viability, potency, or biological response	Identity, rheology, cell-state/viability, functional assay, and process-window confirmation	Critical attribute outside validated range or unexpected interaction with sensing/control	Quarantine batch; do not compensate autonomously for unqualified material change
Printer, nozzle, actuator, or control hardware	Changed flow, geometry, latency, or control stability	Calibration, flow/fidelity benchmark, hardware–software compatibility, controller stability	Abnormal pressure/flow, actuator error, repeated target deviation, communication fault	Pause or safe stop; inspect hardware and requalify before restart
Imaging or data-acquisition system	Domain shift in features used by models or quality decisions	Acquisition SOP, image/data QC, domain-shift testing, model-performance confirmation	Low-quality acquisition, distribution shift, failed preprocessing or metadata checks	Route to human review; block automated decision until data quality is restored
Culture, perfusion, stimulation, or bioreactor environment	Slow biological drift or off-target maturation	Environmental sensor qualification plus longitudinal biological CQA/performance assay	Hypoxia, temperature/metabolite deviation, loss of perfusion, functional readout outside bounds	Alarm, bounded fallback condition, manual intervention and biological reassessment

Abbreviations: CQA, critical quality attribute; QC, quality control; SOP, standard operating procedure.

This framework also defines when autonomy should not escalate. A system should remain at the lower qualified stage whenever its sensing, model, material, device, or biological state moves outside the validated operating space. In that circumstance, preserving a known safe state and routing the decision to a human operator is preferable to allowing the controller to extrapolate beyond evidence.

6.6. Divergent translational roadmaps for implants and decision tools

The translational pathway should diverge early according to intended use. For implantable regenerative constructs, the practical sequence is material and cell-source qualification → reproducible manufacturing and CQA control → preclinical safety and functional integration → scalable GMP production and release testing → clinical feasibility and long-term effectiveness. For patient-derived decision tools, the sequence is analytical validity → technical and inter-site reproducibility → clinically acceptable turnaround → retrospective clinical concordance → prospective prediction → demonstration that model-informed decisions improve care. Retrospective agreement should not be interpreted as decision-level clinical utility.

Table 6. Separate translational roadmaps for intelligent regenerative implants and patient-derived decision tools.

Application pathway	Early validation	Process qualification / analytical validation	Clinical evidence endpoint	Key implementation constraint
Implantable regenerative construct	Material and cell-source identity; biocompatibility; function-relevant potency	GMP-compatible manufacturing; CQA control; sterility; release criteria; batch- and site-level reproducibility	Clinical feasibility; safety; host integration; long-term function; comparative effectiveness	Scale-up; logistics; cost; operating-room or point-of-care compatibility
Patient-derived drug-testing / decision-support model	Biological fidelity; analytical response characteristics; predefined assay endpoints	Technical repeatability; inter-site reproducibility; assay stability; clinically acceptable turnaround time	Retrospective concordance followed by prospective predictive validity and evidence that model-informed decisions improve care	Clinical decision window; sample adequacy; assay failure rate; reimbursement and cost-effectiveness

6.7. Toward autonomous but accountable biofabrication

Self-driving laboratories represent a plausible long-term architecture for integrating the elements reviewed here, but autonomy should be introduced incrementally.^{10,13,18} Near-term priorities are closed-loop control of well-defined printing variables, automated formulation and print-window optimization, standardized sensing, and data capture across the design-build-test cycle. More ambitious systems could then integrate digital twins, adaptive bioreactors, automated biological assays, and robotic handling.

The central design principle should be accountable autonomy. Every automated decision should have a defined input, model or rule, output, uncertainty estimate where appropriate, and human override pathway. This requirement becomes especially important when intelligence extends beyond manufacturing into implanted or patient-facing systems. In that setting, sensing and therapeutic actuation would need fail-safe boundaries and clinical evidence comparable to other adaptive medical technologies.

Accordingly, the most realistic trajectory is not a sudden transition from conventional printing to autonomous tissue factories. It is a sequence of increasingly connected capabilities: responsive materials; standardized data collection; predictive design; in-line monitoring; validated feedback control; automated maturation; and, only after those components are reliable, higher-level orchestration. This staged view preserves the ambition of intelligent bioprinting while keeping claims aligned with current evidence.

7. Perspective: staged milestones toward intelligent bioprinting

Short term (1–3 years). The priority should be reproducible manufacturing rather than full autonomy: ASTM-aligned terminology, standardized machine-readable metadata, qualified sensors, robust closed-loop control of bounded extrusion and geometry variables, external validation of printability models, and GMP-compatible CQA frameworks. Automated experimentation can accelerate design-space definition, but human oversight and predefined safe states should remain explicit.

Medium term (3–7 years). The field should move toward multimodal sensing, adaptive bioreactors, cross-platform validated models, qualified digital twins, and multicenter evaluation of patient-derived disease models. Foundation-model and multimodal-AI approaches may assist material or biological design, but only after task-specific validation, transparent provenance, uncertainty reporting, and controlled model updates.^{74,75} Biological feedback should initially target a small number of non-destructive functional biomarkers with bounded actuators rather than attempting unrestricted autonomy.

Long term (>7 years). Higher-level orchestration may connect automated cell expansion, on-demand bioink formulation, strategy selection, fabrication, maturation, quality release, and patient-specific decision support. The decisive milestone will not be the number of AI modules but whether end-to-end systems remain traceable, fail-safe, economically viable, regulatorily acceptable, and clinically beneficial across sites and patient populations. Fully autonomous biological control should remain a conditional endpoint, not an assumed trajectory, until prospective utility and safe failure handling are demonstrated.

8. Conclusion

Intelligent bioprinting is best understood as a transition from structure-centered fabrication toward measurable and adaptive biofabrication, but the technological ingredients of that transition are not themselves new. The contribution of this review is a cross-domain functional classification that separates preprogrammed responsiveness, intelligence-assisted design/monitoring, and validated closed loops; distinguishes rapid manufacturing feedback from slower biological feedback; and aligns evidence requirements with the intended use of regenerative implants or patient-derived decision tools. The R–O–D–A rubric is a structured narrative aid rather than an independently validated maturity scale.

Smart bioinks provide material-level responsiveness and biological instruction; computational design and strategy selection improve prediction and microstructural control; sensors and label-free imaging create observability; and feedback can convert measured states into bounded manufacturing or maturation actions. Current evidence is strongest for closed-loop correction of well-defined, fast process variables, whereas longitudinal biological feedback, continuously updated digital twins, and high-level autonomous orchestration remain early. Translation will require standardized CQAs, GMP-compatible manufacturing, sensor and software qualification, external model validation, traceable change control, realistic cost and workflow integration, and application-specific clinical evidence. With these foundations, intelligent bioprinting can progress toward living systems that are designed, monitored, and adapted according to function without overstating the maturity of current autonomous capabilities.

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Conflict of interest

The authors declare they have no competing interests.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Not applicable.

Further disclosure

OpenAI ChatGPT was used under author supervision solely for English-language polishing and improvement of manuscript readability. All scientific content, literature selection, interpretations, conclusions, references, and final figures were independently reviewed and approved by the authors, who take full responsibility for the manuscript.

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Appendix

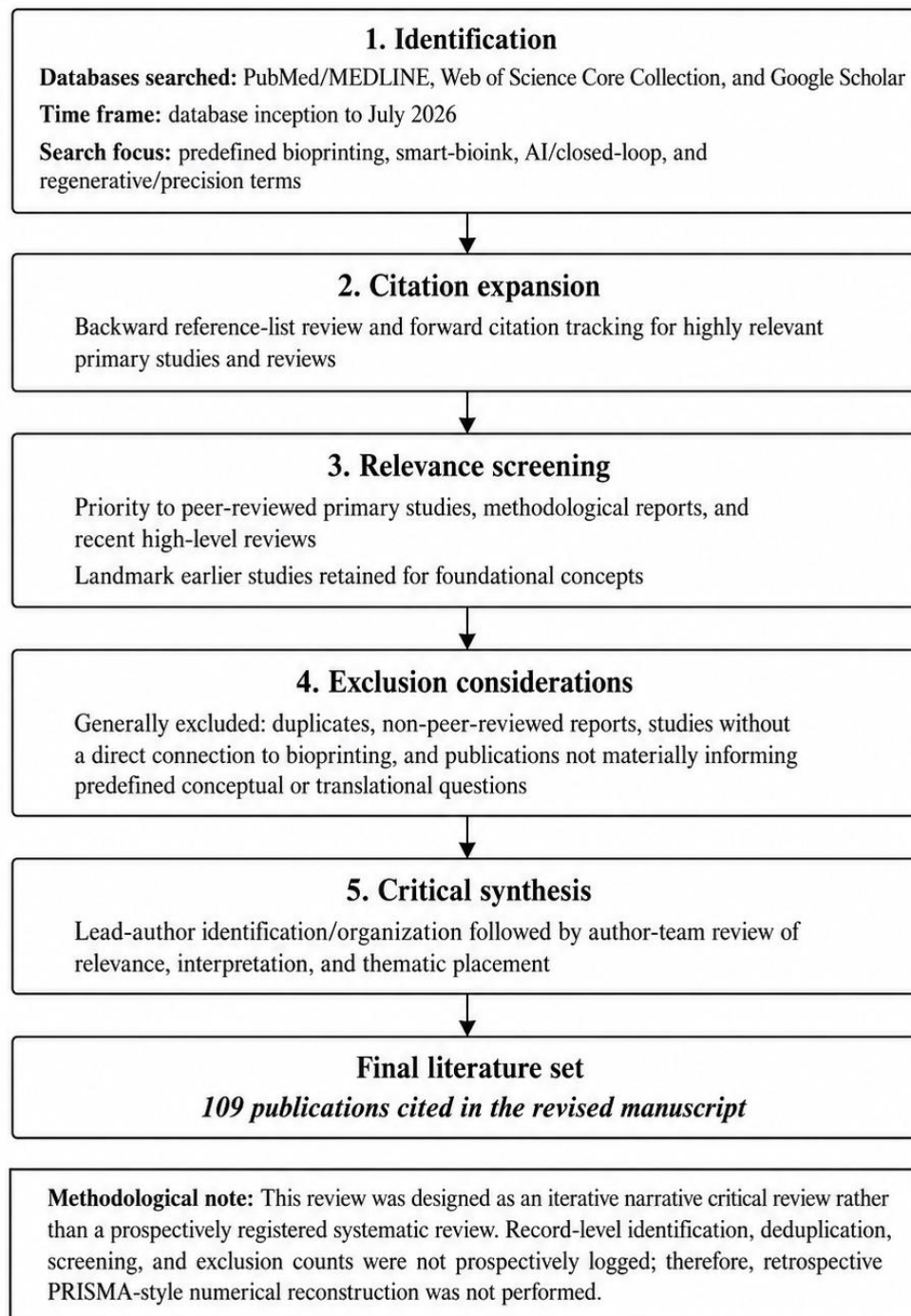


Figure A1. Literature identification and selection workflow. © The Authors.

Table A1. Comparison of representative prior reviews with the scope and functional framework of the present review.

Representative review	Primary emphasis	Functional/closed-loop framework	Feedback-timescale stratification	Translation/evidence pathway	Distinction from present review
Amukarimi et al. (2022) ¹⁶	Smart biomaterials and the transition from 3D to 4D printing; material responsiveness	Closed-loop operation is not the primary focus	Not explicitly stratified	Limited	Primarily addresses material responsiveness and the 3D-to-4D transition rather than a cross-domain functional architecture linking responsiveness, observation, decision, and actuation.
An et al. (2021) ¹¹	Machine learning, big data, and digital twins in bioprinting	Conceptual	Not explicitly stratified	Limited	Primarily emphasizes computational and digital tools, without explicitly formalizing minimum functional connectivity among observation, decision, and actuation.
Zhang et al. (2025) ⁴³	AI-driven bioprinting within a Quality-by-Design framework	Includes in-line process control	Feedback is considered, but not explicitly separated into fast and slow loops	Strong; QbD-oriented	AI/QbD-centered framework; comparatively less emphasis on AI-independent responsiveness, cross-domain functional classification, and application-specific evidence hierarchies.
Liu et al. (2026) ¹⁸	Self-driving bioprinting laboratories and end-to-end autonomy	Explicit autonomous closed-loop vision	Predominantly rapid/autonomous feedback; not formalized as a fast-versus-slow stratification	Strong; autonomy-oriented	Focuses on autonomous future architectures rather than a cross-domain comparison of implementation maturity and evidence requirements across current applications.
Perin et al. (2026) ¹⁰⁵	Regulatory landscape for bioprinted constructs	Closed-loop operation is not the primary focus	Not explicitly addressed	Regulatory focus	Primarily addresses regulatory translation rather than an integrated material-sensing-decision-actuation framework linked to application-specific endpoints.
Present review	Cross-domain R-O-D-A functional taxonomy spanning smart bioinks, strategy selection, sensing, feedback, maturation, and applications	Operational minimum rule: O->D->A around a defined target with demonstrated benefit	Explicit fast-versus-slow feedback stratification	Separates implant and decision-tool pathways with application-specific evidence requirements	Integrates cross-domain functional classification, feedback timescale, implementation maturity, and application-specific evidence pathways within a unified framework.

Note: The comparison summarizes the primary organizing framework of each representative review rather than every topic mentioned within it. Terms such as "not explicitly stratified" therefore indicate that the feature was not formalized as a central comparative framework.