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Advanced bioprinting biomaterials for personalized cancer therapy and drug screening: From functional bioinks to precision oncology platforms

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Article ID: IJB026340365

Citation: Li S, Gu R, Feng X, Li P, Bai H. Advanced bioprinting biomaterials for personalized cancer therapy and drug screening: From functional bioinks to precision oncology platforms. *Int J Bioprint*. 2026. doi: 10.36922/IJB026340365

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AccScience Publishing

REVIEW ARTICLE

Volume X Issue X (2026)

doi: 10.36922/IJB026340365

Advanced bioprinting biomaterials for personalized cancer therapy and drug screening: From functional bioinks to precision oncology platforms

Running title: Functional bioinks for precision oncology

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Citation: Li S, Gu R, Feng X, Li P, Bai H. Advanced bioprinting biomaterials for personalized cancer therapy and drug screening: From functional bioinks to precision oncology platforms. *Int J Bioprint*. 2026. doi: 10.36922/IJB026340365

Received: August 21, 2026

Revised: September 16, 2026

Accepted: September 21, 2026

Published online: September 22, 2026

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Abstract

Three-dimensional (3D) bioprinting is increasingly used to construct patient-relevant tumor models, but its value for precision oncology depends on how functional biomaterials connect tissue reconstruction with therapeutic exposure and response measurement. This review presents a function-oriented framework for advanced bioprinting biomaterials in personalized cancer therapy and drug screening. We define functional biomaterials as printable or print-compatible systems that actively regulate cellular behavior, extracellular-matrix cues, transport, release, microenvironmental adaptation, or response reporting, while distinguishing them from patient-derived biological inputs and enabling technologies. We examine how bioink composition, crosslinking, mechanics, degradation, and spatial patterning influence tumor heterogeneity, stromal interactions, vascular, immune, and hypoxic niches, and therapeutic transport. Particular attention is given to localized drug delivery, nanocomposite and stimuli-responsive systems, sequential exposure, and quantitative evaluation of drug distribution and response. Two representative platforms illustrate how material design can couple microenvironment reconstruction with chemoradiotherapy, chemotherapy, and CAR-T response testing. We also assess patient-derived tumor models for personalized drug testing, including model establishment, heterogeneity preservation, assay reproducibility, and the relationship between ex vivo response and clinical decision-making. Bioink-selection principles and study-level reporting benchmarks are summarized without pooling non-equivalent metrics. Finally, we discuss sample attrition, turnaround time, cost, manufacturing variability, quality control, interlaboratory reproducibility, clinical validation, and regulatory requirements. Clinically useful platforms will be those in which each functional component addresses a defined biological or therapeutic question and generates reproducible, interpretable information, rather than those with the greatest material or architectural complexity.

Keywords: 3D bioprinting; Functional biomaterials; Bioinks; Patient-derived tumor models; Tumor microenvironment; Drug screening; Personalized cancer therapy; Precision oncology

1. Introduction

Cancer therapy is increasingly guided by molecular stratification, yet patients with the same histopathological or genomic category can respond differently to the same treatment. This variability reflects not only tumor-cell mutations but also spatial differences in clonal composition, ECM organization, stromal signaling, vascular access, immune infiltration, hypoxia, and drug transport. These factors interact and change during treatment, creating patient-specific therapeutic vulnerabilities and resistance mechanisms that cannot be inferred from genotype alone ^[1,2,3]. Precision oncology therefore requires functional models that preserve relevant patient heterogeneity while allowing controlled and timely evaluation of treatment response.

Existing preclinical models address different parts of this requirement but rarely combine them. Two-dimensional cultures are scalable and experimentally convenient but lack three-dimensional transport barriers and multicellular organization. Spheroids and PDOs better preserve cell-cell interactions and selected patient-specific features, although many systems have limited control over geometry, matrix composition, vascular interfaces, and the positioning of stromal or immune populations. PDX models can retain tumor architecture and heterogeneity but are costly, slow, and difficult to use within a real-time treatment-decision window ^[4,5,6,7,8,9,10,11,12]. The relevant question is therefore not which model is universally superior, but which platform reproduces the biological and transport determinants required for a defined therapeutic decision.

Three-dimensional bioprinting offers a distinctive solution because it can place cells and materials in predefined geometries and generate tumor cores, stromal shells, invasive fronts, perfusable channels, and biochemical or mechanical gradients. Multimaterial and multicellular printing has expanded the range of tumor, fibroblast, endothelial, and immune compartments that can be combined in a single construct ^[2,4,10,13,14,15,16,17]. However, geometric complexity alone does not ensure physiological fidelity. Printing resolution, shear exposure, crosslinking, construct size, culture-induced remodeling, and interface stability determine whether the intended architecture survives and produces a reproducible biological response. The function of the printed model consequently depends on material-process interactions as much as on the printing modality itself.

In this review, functional biomaterials are defined as printable or print-compatible material systems that perform one or more active roles beyond maintaining construct shape and mechanical stability. These roles include instructive regulation of tumor and stromal behavior, recapitulation of tissue-specific ECM cues, spatial or temporal control of therapeutic transport and release, and adaptation to biochemical or physical changes in the TME. Conventional matrices such as GelMA, collagen, hyaluronic-

acid derivatives, alginate, and dECM can become functional when their composition or modification actively determines these outcomes [18,19,20,21,22,23,24,25,26,27,28,29].

Nanoparticles, drugs, cytokines, and immunomodulatory molecules are treated as incorporated functional components, whereas patient-derived cells and PDOs are biological inputs and microfluidics, automated imaging, and AI are external enabling technologies.

This distinction reveals the intrinsic connection among tumor reconstruction, localized therapy, and response evaluation. As a spatial encoder, the biomaterial controls the distribution of tumor, stromal, vascular, and immune compartments and the formation of mechanical or biochemical gradients. As a therapeutic carrier, it regulates cargo loading, retention, diffusion, degradation-coupled release, and regional exposure. As a response modulator, the same matrix properties influence cell phenotype, drug penetration, immune-cell migration, and the survival of resistant niches. Patient-derived cells provide biological specificity, but the material determines how that specificity is organized, challenged by treatment, and converted into a measurable response [30,31,32,33,34,35]. Functional biomaterials therefore act as the continuous interface linking model construction with therapeutic testing rather than as an isolated bioink category.

Two studies illustrate this integration at the mechanism level. Yi et al. bioprinted patient-derived glioblastoma cells, vascular endothelial cells, and brain dECM into a compartmentalized concentric-ring architecture. The material-defined geometry sustained a radial oxygen gradient and reproduced structural, biochemical, and biophysical features of native tumors, while the same platform reproduced clinically observed patient-specific resistance to concurrent chemoradiotherapy and temozolomide [36]. In a complementary vascularized breast tumor model, Dey et al. [37] positioned heterotypic tumor spheroids at defined distances from a perfused vessel, thereby coupling transport and endothelial interactions with therapeutic readouts. Doxorubicin produced a dose-dependent response, whereas perfused HER2-targeted CAR-T cells showed endothelial recruitment, tumor infiltration, and up to approximately 70% reduction in tumor volume [78]. Together, these cases show how a functional material platform can integrate spatial microenvironment reconstruction, controlled therapeutic access, and interpretable response measurement rather than serving only as a printable scaffold.

Several reviews have summarized cancer-bioprinting technologies, bioink formulations, tumor-microenvironment reconstruction, or general applications in drug screening and precision medicine [2,4,7,10,38,39,40,41,42]. Representative reviews compared in Table 1 collectively cover printing modalities, matrix formulations, TME recreation, model applications, and personalized medicine, but their organizing frameworks generally treat these domains as adjacent topics. The present review

instead adopts a function-oriented and critically comparative framework in which biomaterials form the causal interface among model construction, therapeutic exposure, and response interpretation. It evaluates the material as a spatial encoder, therapeutic carrier, and response modulator, and explicitly examines how the same design variables generate trade-offs among printability, biological fidelity, transport, throughput, and reproducibility. It further adds two levels of comparison that remain uncommon in prior reviews: a function-led material-selection matrix and a study-level quantitative benchmark of representative platforms. Clinical translation is assessed through the complete sample-to-report pathway, including specimen adequacy, establishment success, turnaround time, manufacturing, quality control, clinical validation, and regulatory positioning. The novelty of this review therefore lies in integrating these previously separated dimensions into a single biomaterial-mediated analytical chain rather than claiming exclusivity for any one topic.

Table 1. Scope comparison between the present review and representative reviews of 3D bioprinting in oncology.

Review	Primary organizing perspective	Functional-material design	Spatial/TME reconstruction	Localized delivery or nanomedicine	Patient-derived screening	Quantitative benchmarking	Clinical implementation	Principal distinction or remaining gap
Jung et al., 2022 ^[2]	Matrix design through cancer and precision-medicine applications	Central	Covered	Limited	Covered	Limited	Covered	Connects matrix design with cancer applications, but does not benchmark an integrated delivery-to-clinic workflow. Defines TME components and fabrication strategies;
Shukla et al., 2022 ^[4]	Recreation of the multicellular TME by bioprinting	Covered	Central	Limited	Limited	Limited	Limited	therapeutic transport and clinical implementation are not organizing axes.

Germain et al., 2022 ^[38]	Cancer models and personalized-medicine applications	Covered	Covered	Limited	Covered	Limited	Covered	Broad application overview; limited cross-study metrics and material-mediated workflow analysis. Emphasizes TME fidelity and model construction rather than integrated delivery and clinical decision support. Comprehensive technology-to-application survey; functional materials are not used as the
Parodi et al., 2023 ^[41]	Bioprinted recreation of the TME	Covered	Central	Limited	Limited	Limited	Limited	
Yang et al., 2024 ^[10]	Printing categories to biological and biomedical applications	Covered	Covered	Covered	Covered	Limited	Covered	

Dong et al., 2024 [7]	TME applications and challenges of bioprinting	Covered	Central	Limited	Covered	Limited	Covered	continuous analytical axis. Critically discusses TME applications and barriers, with limited quantitative platform comparison. Organizes evidence by model
Yu et al., 2024 [39]	Construction and application of bioprinted tumor models	Covered	Covered	Limited	Covered	Limited	Covered	construction and use; does not center material-controlled transport and response bias.
Yao et al., 2026 [40]	Spatially controlled, multicomponent TME reconstruction	Covered	Central	Limited	Covered	Limited	Covered	Integrates TME complexity and spatial control; localized delivery and

Present review	Functional biomaterials linking reconstruction, delivery, and response assessment	Central	Central	Central	Central	Central	Central	study-level benchmarks remain secondary. Adds material-selection logic, study-level quantitative benchmarks, and a sample-to-report translational framework.
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Notes: Central, primary organizing theme; Covered, dedicated discussion; Limited, selective or secondary discussion. Coding reflects review scope, not methodological quality. TME, tumor microenvironment.

To define the evidence base for this narrative review, structured searches of PubMed were conducted for English-language publications available through August 2026 and were supplemented by reference-list screening of key reviews and representative original studies. Search terms combined "3D bioprinting" or "biofabrication" with "cancer," "tumor model," "tumor microenvironment," "bioink," "functional biomaterial," "decellularized extracellular matrix," "nanomedicine," "drug delivery," "patient-derived organoid," "drug screening," "personalized medicine," or "clinical translation." Priority was given to original studies and reviews published from January 2019 onward, while earlier seminal reports were retained when required to establish core printing modalities or material concepts. Eligible publications addressed a 3D-bioprinted tumor model and at least one of the following dimensions: functional bioink or material design; spatial, multicellular, or TME reconstruction; localized delivery or nanomedicine; patient-derived modeling; treatment-response assessment; or clinical translation. Studies confined to nonbiological 3D printing, nononcological tissue regeneration, or materials without a tumor-modeling or therapeutic-evaluation role were outside the primary scope. Because the aim was critical integration across heterogeneous technologies rather than effect-size estimation, this work was structured as a narrative review rather than a systematic review or meta-analysis. Quantitative values were recorded only when explicitly reported by the source studies, and non-equivalent mechanical, resolution, viability, degradation, or drug-response metrics were not pooled.

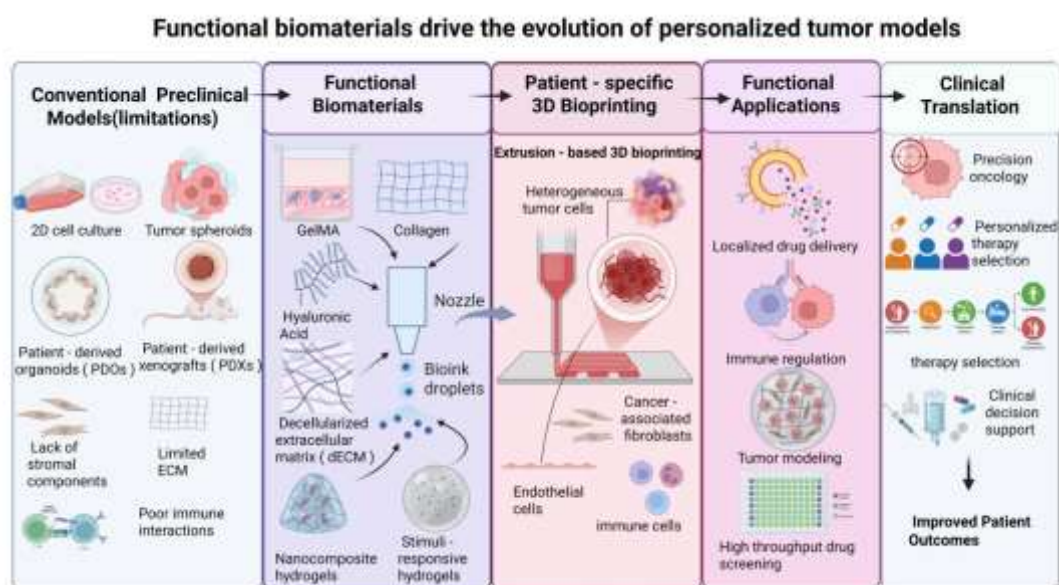


Figure 1. Functional biomaterials drive the evolution of personalized tumor models. Functional biomaterials connect patient-derived biological inputs with spatially programmed tumor reconstruction, localized therapeutic delivery, and multidimensional response assessment. ECM-mimicking and

responsive bioinks organize multicellular tumor compartments and transport barriers, while incorporated therapeutic or nanomedicine components enable controlled exposure and functional testing. The resulting evidence may support drug development and patient-specific treatment prioritization when analytical and clinical validity are established. Created in BioRender. Siqi, L. (2026) <https://BioRender.com/n20jznp>

Figure 1 should be read as a biomaterial-mediated decision chain rather than a linear assembly workflow. Patient-derived information first defines the biological features that must be preserved, including cell composition, ECM phenotype, and clinically relevant treatment options. Material design then converts these inputs into spatial compartments, transport barriers, and local exposure conditions, while the same stiffness, porosity, degradation, and binding properties also influence the response ultimately attributed to the patient. These dual roles make the biomaterial both an experimental control variable and a potential source of bias. For example, increasing crosslink density may improve geometric fidelity but suppress invasion and drug penetration, whereas faster degradation may facilitate remodeling while changing therapeutic release. Consequently, response prediction requires the structural, transport, and biological functions of the material to be characterized together. The central value of Figure 1 is therefore the closed connection among tumor reconstruction, therapeutic delivery, and response interpretation, with functional biomaterials occupying the causal interface between these stages ^[30,31,32,33,34,35].

2. Conceptual Framework and Design Principles of Functional Biomaterials

2.1. Definition, Scope, and Classification of Functional Biomaterials

In this review, functional biomaterials are defined as printable or print-compatible material systems that perform one or more active roles beyond providing structural support. These roles include instructive regulation of tumor-cell and stromal-cell behavior, recapitulation of tissue- or patient-specific extracellular matrix (ECM) cues, spatial or temporal control of therapeutic transport and release, adaptation to changes in the tumor microenvironment (TME), and modulation or reporting of treatment responses ^[18,19,20,21]. This definition distinguishes functional biomaterials from conventional scaffold materials selected primarily for shape retention or mechanical integrity. It also establishes biomaterial function as the central analytical axis of this review, rather than treating bioinks as interchangeable accessories to printing technologies.

Functional biomaterial systems can be organized into four related levels. The first comprises foundational bioink matrices, such as gelatin methacryloyl (GelMA), collagen, hyaluronic acid (HA), alginate, and other natural or synthetic hydrogels, whose crosslinking, stiffness, porosity, and degradation determine printability and the basic cellular microenvironment. The second includes tissue-instructive matrices,

particularly decellularized extracellular matrix (dECM), which retain organ-specific biochemical cues and can support disease-relevant phenotypes ^[26,43,44,45]. The third consists of incorporated functional components, including nanoparticles, liposomes, therapeutic agents, growth factors, and immunomodulatory molecules, which confer drug delivery, imaging, targeting, or immune-regulatory capabilities ^[19,20,24]. The fourth comprises dynamic or stimuli-responsive material systems whose properties or release behavior change in response to pH, reactive oxygen species, enzymes, light, temperature, or cell-mediated remodeling ^[22,23]. These levels may be combined within a single bioink, but they should not be treated as equivalent technological categories.

The scope of functional biomaterials also requires clear boundaries. Patient-derived tumor cells, organoids, cancer-associated fibroblasts, endothelial cells, and immune cells are biological inputs rather than biomaterials. Similarly, microfluidics, automated imaging, artificial intelligence, and high-throughput screening systems are enabling technologies that control culture, measurement, or data interpretation but do not themselves constitute functional bioinks. Nanoparticles occupy an intermediate position: they are considered functional material components when incorporated into a printable matrix, whereas independently administered nanoformulations remain therapeutic products evaluated by the model. Four-dimensional bioprinting is included only when time-dependent behavior arises from a programmed material response. This hierarchical distinction prevents materials, cells, therapeutic cargos, and external platforms from being conflated and clarifies how each contributes to a personalized oncology workflow.

Within this framework, functional biomaterials serve as an integration hub across three stages. During tumor reconstruction, they encode spatial organization, ECM composition, mechanical cues, and biochemical gradients. During therapeutic intervention, they regulate drug loading, retention, diffusion, degradation-coupled release, and local exposure. During response assessment, the same material properties influence cell viability, immune infiltration, drug penetration, and the emergence of resistant phenotypes. Consequently, biomaterial selection is not a preliminary fabrication decision but a determinant of both model fidelity and the interpretation of therapeutic efficacy. The following sections therefore evaluate materials according to the biological and therapeutic functions they enable, together with the trade-offs that limit cross-platform comparison and clinical translation.

2.2. Bioprinting Modalities and Material–Process Interactions

Bioprinting modality and bioink design are interdependent. Extrusion-based printing accommodates relatively viscous, cell-dense, and multimaterial formulations and is therefore widely used to construct multicellular tumor models; however, nozzle-induced shear stress, limited feature resolution, and filament deformation can compromise cell viability and spatial fidelity. Droplet-based printing offers rapid and reproducible deposition of small volumes, but requires lower-viscosity inks and is sensitive to nozzle clogging and nonuniform droplet formation. Laser-assisted printing avoids nozzle contact and can achieve precise cell placement, although equipment complexity, limited construct thickness, and throughput remain practical constraints. Vat-photopolymerization methods, including digital light processing, can rapidly generate complex architectures with high geometric fidelity, but depend on photocrosslinkable formulations and require careful control of light dose, photoinitiator concentration, and optical attenuation to protect cells [22,38,46,47]. Thus, no printing modality is universally optimal; each imposes a distinct material-processing window [48,49].

These interactions are particularly important in extrusion bioprinting, where print fidelity depends on viscosity, shear-thinning behavior, yield stress, gelation kinetics, and post-print crosslinking. Increasing polymer concentration or crosslink density generally improves filament stability, but may also increase extrusion pressure, reduce cell migration, restrict molecular diffusion, and alter drug sensitivity. Conversely, highly compliant matrices may better support cell spreading and remodeling yet collapse after deposition or lose the intended spatial organization. Dynamic hydrogel networks and modified alginate systems partly address this conflict by introducing reversible or secondary crosslinks that support extrusion and subsequent stabilization [22,50]. For example, oxidized alginate can form dynamic covalent interactions with gelatin, allowing mechanical and degradation properties to be adjusted while supporting the formation of endothelialized channels. The value of such systems lies not only in improved printability, but also in their ability to coordinate fabrication requirements with biologically relevant remodeling.

Material-process interactions also determine whether a printed architecture remains stable during culture. A high nominal printing resolution does not guarantee long-term spatial fidelity because swelling, degradation, cell-mediated contraction, and ECM deposition can progressively alter feature dimensions and compartment boundaries. Multimaterial printing further introduces interfaces with different crosslinking kinetics and mechanical properties, creating risks of delamination, diffusion across compartments, and batch-dependent misalignment. In multicellular tumor models, these changes may modify tumor-stroma contact, vascular accessibility, immune-cell

Figure 2 illustrates a sequence of coupled design decisions in which errors can accumulate across the workflow. Limited biopsy material and the required cell populations constrain bioink volume and composition; rheology and crosslinking determine the feasible printing modality and spatial resolution; printing pressure, light exposure, and post-print stabilization affect cell state and construct maturation; and these upstream choices shape the reliability of downstream drug-response measurements. The relevant outcome is therefore not printing resolution alone but a performance envelope balancing spatial fidelity, cell viability, biological function, throughput, and reproducibility. A high-resolution construct may be less informative if shear or photochemical exposure alters patient-cell phenotypes, while a highly biomimetic multimaterial model may be impractical if alignment errors, maturation time, or batch variability exceed the clinical testing window. Figure 2 thus provides a dependency framework for selecting the least complex process that preserves the biological feature and therapeutic readout required by the study [22,32,38,46,50,51,52].

2.3. Design Trade-offs and Bioink Selection Principles

The design of functional bioinks requires balancing printability, structural stability, cytocompatibility, biological fidelity, therapeutic transport, and reproducibility. These objectives frequently conflict. Higher stiffness and crosslink density improve shape retention but may suppress invasion, reduce nutrient and drug diffusion, or generate resistance phenotypes that reflect the material rather than the patient's tumor. Greater degradability facilitates cell migration and ECM remodeling but can destabilize long-term cultures and change release kinetics. Increasing cell density improves cell-cell communication and tissue maturation, yet raises viscosity, nutrient demand, and sensitivity to shear stress. Similarly, incorporating nanoparticles or therapeutic cargos may reinforce the hydrogel or enable controlled delivery, but can also alter gelation, cause aggregation or sedimentation, change optical properties, and introduce carrier-related toxicity [18,19,20,21,24,25]. These trade-offs should be treated as experimental variables rather than as secondary technical details.

Bioink selection should therefore be guided by the dominant biological feature and intended readout rather than by cancer type alone. Models of desmoplastic pancreatic cancer require matrices capable of reproducing high stiffness, collagen- and HA-rich stroma, and tumor-CAF reciprocity [32,51]. Brain tumor models may prioritize HA-associated signaling, soft-tissue mechanics, and transport across vascular barriers, whereas breast and bone-metastasis models may require tunable stiffness, tissue-specific ECM, or mineral-associated cues [24,25,26,44]. Immunotherapy models additionally require pore architecture, degradability, and chemokine transport compatible with immune-cell trafficking. Platforms designed for localized drug delivery must characterize cargo-matrix interactions and release kinetics, while high-

throughput screening favors formulations that can be miniaturized, rapidly crosslinked, and reproduced across wells. The same tumor type may therefore require different materials depending on whether the objective is to study invasion, vascularization, immune exclusion, nanomedicine penetration, or patient-specific drug sensitivity.

A fit-for-purpose selection process should begin by defining the biological question, relevant cell populations, target ECM properties, culture duration, therapeutic exposure route, and quantitative endpoint. Candidate materials should then be assessed using comparable metrics, including rheological behavior, crosslinking conditions, filament or feature dimensions, mechanical properties, time-resolved cell viability, degradation, swelling, drug diffusion, and batch-to-batch variability. Importantly, Young's modulus, compressive modulus, and storage modulus describe different material behaviors and should not be compared without specifying the testing method and conditions. Likewise, cell viability must be linked to a defined post-printing time point, and degradation data should identify the medium, enzymatic environment, and observation period. Consistent reporting of these parameters is essential for interpreting whether differences in therapeutic response arise from tumor biology or from the fabrication platform^[48,49].

Taken together, functional biomaterials mediate the relationship between fabrication parameters and biological performance. Their composition and processing determine not only whether a construct can be printed, but also whether spatial compartments remain stable, cells preserve relevant phenotypes, therapeutics reach their targets, and drug-response readouts remain comparable. This design-centered framework provides the basis for the next section, which examines how biomaterials are used to reconstruct spatially organized multicellular architectures and patient-specific tumor microenvironments.

Bioink selection should be driven by the dominant biological feature and the intended readout rather than by tumor name alone. A desmoplastic invasion model may prioritize fibrillar collagen or tissue-specific dECM, whereas a high-throughput cytotoxicity assay may favor a more defined GelMA- or alginate-containing composite. For drug-delivery studies, cargo-matrix interactions and transport kinetics become primary criteria; for immune or vascular models, cell migration, pore architecture, and remodeling capacity are more informative than bulk stiffness alone. Table 2 therefore presents selection logic and practical

Table 2. Functional bioink selection matrix for 3D-bioprinted tumor models.

Bioink category	Functional role	Advantages	Limitations and practical pain points	Selection logic	Representative cancer/model contexts	Refs
GelMA-based	Tunable mechanics and photocrosslinking; amenable to ligand, drug, and particle incorporation	Reproducible formulation; good extrusion or light-based printability; broad mechanical range	Limited tissue-specific signaling unless modified; photoinitiator/light exposure; dense or highly crosslinked networks can restrict migration and drug diffusion	Prioritize when standardized mechanics, geometric fidelity, or multiwell screening is central; tune crosslinking to the transport endpoint Select for invasion fronts,	Breast, ovarian, gastric, and glioblastoma models; standardized drug-screening constructs	[18,22,35,53]
Collagen- or fibrin-based	Native integrin-binding and fibrillar cues; supports remodeling, invasion, and vascular assembly	High biological relevance; permissive cell migration and matrix remodeling	Weak shape fidelity and mechanical strength; temperature-sensitive gelation; contraction and batch variability	desmoplastic interfaces, or endothelial network formation; reinforce only as much as required for printing	Pancreatic and breast tumor-stroma models; vascularized tumor constructs	[32,51,54,55]

Hyaluronic acid-based	HA-CD44 signaling and tissue-relevant glycosaminoglycan cues; tunable by chemical modification	Useful for stemness, migration, and HA-rich microenvironments; compatible with composite networks	Poor standalone printability; molecular weight and substitution strongly affect behavior; insufficient crosslinking can cause cell leakage	Prioritize when HA-CD44 signaling or a brain/gastric-like ECM is mechanistically relevant; report molecular weight and modification degree	Glioblastoma, gastric, breast, ovarian, and selected colorectal models	[4,33,35,56]
Alginate-based	Rapid ionic gelation and rheological support; can serve as a structural matrix or support bath	Low cost; robust shape retention; convenient for extrusion and multiwell formats	Biologically inert without modification; heterogeneous Ca ²⁺ crosslinking; limited remodeling and possible cell escape; ion exchange changes long-term mechanics	Use for short-term, geometry-controlled, or high-throughput assays; combine with adhesive or ECM-rich components for biological fidelity	Colorectal, breast, and gastric models; embedded printing and composite scaffolds	[33,35,43,50]
dECM-based	Retains tissue-specific ECM proteins, glycosaminoglycans, and bound biochemical cues	High organ-specific biochemical fidelity; supports patient-derived phenotypes and heterogeneity	Batch variability and incompletely defined composition; weak printability; xenogeneic-source and sterilization	Prioritize when organ-specific signaling or patient-tissue concordance outweighs manufacturing	Gastric, breast, head-and-neck, liver, and patient-derived tumor models	[26,43,45,55,57,58]

			concerns; difficult quality control	simplicity; document source, decellularization, and lot criteria Select when one matrix cannot		
Composite or microgel-based	Combines structural and instructive phases; can decouple extrusion rheology from post-print biology	Balances printability, mechanics, and bioactivity; supports multicompartment or gradient designs	Complex formulation and crosslinking; interfacial defects; component-specific variability; harder scale-up and attribution of biological effects	simultaneously meet spatial, mechanical, and biological requirements; minimize components to those linked to the study hypothesis Choose according to cargo	Desmoplastic pancreatic, breast tumor-stroma, vascular, and multicellular interface models	[21,24,32,51]
Nanocomposite or drug-loaded	Adds controlled release, imaging, targeting, photothermal, magnetic, or immunomodulatory functions	Integrates therapy and readout; enables localized exposure and combination delivery	Particle aggregation or sedimentation; altered rheology/crosslinking; carrier toxicity; difficult separation of matrix, carrier, and drug effects	physicochemistry, desired exposure profile, and analytical method; include unloaded-material and carrier-only controls	Localized therapy and nanomedicine testing across solid-tumor models	[19,20,24,28,29]

Stimuli-responsive and time-responsive/4D systems	Changes release, mechanics, or structure in response to pH, ROS, enzymes, light, temperature, or time	Spatiotemporal control; can model treatment-evolving niches or sequential therapy	Response thresholds may not match the modeled TME; hysteresis, fatigue, and external-trigger penetration; complex reproducibility and validation	Use only when the trigger is measured in the model and causally linked to the intended function; benchmark against a nonresponsive control	Hypoxic, acidic, oxidative, and treatment-adaptive tumor models	[22,23,24,28,29]
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Note: Representative cancer contexts indicate common modeling priorities, not tumor-specific material prescriptions.

3. Biomaterial-Enabled Reconstruction of Patient-Specific Tumor Microenvironments

3.1. Spatially Programmed Multicellular Architectures

Spatial control is the feature that most clearly distinguishes bioprinted tumor models from conventional spheroids and self-organized organoids. Rather than merely combining several cell types in one hydrogel, bioprinting can position tumor cells, cancer-associated fibroblasts (CAFs), endothelial cells, immune populations, and ECM domains as predefined compartments. Relevant configurations include tumor-core-stromal-shell structures, sea-and-island arrangements, vascular-adjacent and hypoxic regions, invasion fronts, and immune-infiltrated or immune-excluded zones. These architectures are not interchangeable: the distance and interface between compartments determine paracrine signaling, direct cell-cell contact, nutrient transport, drug penetration, and the route available for immune-cell migration [14,15,16,17,32]. Functional biomaterials act as spatial encoders in this process because their rheology, crosslinking, adhesiveness, degradability, and biochemical composition determine whether the programmed organization can be printed and subsequently maintained.

Patient-derived organoids (PDOs) extend this approach by preserving tumor-specific genomic and phenotypic heterogeneity, while printing provides the stromal and geometric organization that conventional PDO culture often lacks. Co-printing PDOs or primary tumor cells with CAFs, endothelial cells, and immune cells can generate patient-specific multicellular constructs for studying immunotherapy and treatment resistance [12,15,17,33,59,60]. For example, bladder cancer models incorporating PDOs, stromal cells, and endothelial components have been used to retain phenotypic diversity while supporting vascular organization. Acoustically patterned colorectal microtissues have spatially positioned tumor and healthy organoids to quantify invasion across a defined interface. These studies illustrate that the value of multicellular printing lies not in maximizing the number of cell types, but in reproducing the specific cellular relationships that control the clinical question under investigation.

Spatial compartmentalization is particularly important in desmoplastic tumors. In pancreatic ductal adenocarcinoma (PDAC), tumor cells and CAFs can be deposited in predefined domains within matrices that reproduce stiffness gradients and permit progressive stromal remodeling [32,35,61,62]. The bioprinted sea-and-island model developed with patient-derived PDAC cells and CAFs separated tumor-rich islands from a surrounding stromal matrix, enabling tumor-CAF metabolic reciprocity to be

examined as a spatially dependent process ^[32]. Similarly, degradable matrices allow fibroblasts to deposit collagen and HA, contract the local matrix, and progressively change mechanical barriers. Spatial gradients can also be introduced through material composition, cell density, pore architecture, oxygen availability, chemokine presentation, or localized drug loading. Such gradients are biologically meaningful only when they are quantitatively characterized and linked to functional outcomes such as invasion distance, immune penetration, regional viability, or differential drug response.

Greater architectural complexity nevertheless introduces technical trade-offs. Higher resolution may require lower-viscosity formulations, stronger photopolymerization, smaller nozzles, or longer printing times, each of which can compromise cell viability, construct thickness, or throughput. High cell density promotes tissue maturation but increases nutrient demand and may destabilize extrusion.

Multimaterial printing enables sharper tumor-stroma interfaces but also creates risks of interfacial delamination, cross-diffusion, and batch-dependent misregistration. Moreover, printing-time fidelity does not ensure long-term fidelity because swelling, degradation, cell migration, and cell-mediated contraction can erase the intended boundaries during culture. Studies should therefore report measured feature dimensions and their temporal stability, rather than relying solely on nozzle diameter or nominal printer resolution. The appropriate architecture should be the simplest configuration that reproduces the spatial mechanism required for the intended biological or therapeutic readout ^[22,32,38,46,50,51,52,63] ^[48,49].

3.2. ECM Composition, Mechanics, and Biochemical Signaling

The ECM is not simply an acellular scaffold surrounding tumor cells; it is a dynamic signaling and transport system that regulates adhesion, proliferation, stemness, invasion, immune exclusion, and therapeutic resistance. Collagen, HA, fibronectin, laminin, proteoglycans, and matrix-bound factors interact with receptors such as integrins and CD44, while crosslinking and remodeling alter tissue stiffness, porosity, and interstitial transport ^[54,64,65,66,67,68,69,70,71,72,73,74]. Functional bioinks reproduce selected elements of this environment through compositional cues, ligand presentation, degradability, and mechanical properties. The resulting material context can change cellular phenotype even when the same tumor cells are used, meaning that drug sensitivity measured in a printed model reflects the interaction between patient biology and the engineered matrix rather than tumor genotype alone ^[75].

Different material classes provide distinct forms of ECM instruction. GelMA offers cell-adhesive motifs, controllable photocrosslinking, and tunable mechanics, but its behavior depends strongly on methacrylation, polymer concentration, light dose, and

photoinitiator conditions ^[18,43]. HA-based matrices are particularly relevant when CD44 signaling, soft-tissue mechanics, or HA-rich stroma contribute to tumor progression, although HA often requires chemical modification or combination with other polymers to achieve printability. Tissue-derived dECM retains organ-specific proteins and biochemical cues and can reproduce disease-relevant phenotypes more faithfully than generic hydrogels, but variability in source tissue, decellularization, digestion, and residual composition complicates standardization ^[23,26,44,45,76,77]. Composite bioinks can combine these biological signals with synthetic control, yet each additional component makes causal interpretation more difficult.

Matrix mechanics should likewise be treated as a biological variable rather than a fabrication endpoint. Tunable-stiffness breast cancer, glioblastoma, and PDAC models have shown that changes in stiffness or HA content can modify invasion, macrophage polarization, stemness, and therapeutic resistance ^[25,53,56,77,78]. However, stiffness cannot be interpreted independently of ligand density, pore size, viscoelasticity, swelling, and degradation, all of which may change when polymer concentration or crosslinking is adjusted. Furthermore, Young's modulus, compressive modulus, and storage modulus describe different mechanical responses and should not be compared as equivalent values. Mechanistic claims therefore require reporting of the testing mode, strain or frequency, hydration state, culture time, and whether mechanical measurements were performed before or after cell-mediated remodeling ^[75].

ECM properties also evolve after printing. CAFs can deposit and reorganize collagen, secrete matricellular proteins, degrade the initial hydrogel, and increase local stiffness, thereby changing tumor invasion and treatment response over time ^[79,80,81,82]. Protease-degradable HA matrices have demonstrated that tumor-fibroblast interactions alter spheroid growth through spatially controlled remodeling ^[81], while more complex breast tumor models develop progressive collagen deposition, hypoxia, and altered radiosensitivity during maturation ^[82]. Consequently, the printed formulation should be regarded as an initial condition rather than a fixed representation of the mature TME. Longitudinal measurements of composition, mechanics, degradation, and cellular remodeling are needed to distinguish genuine tumor-driven evolution from passive material aging.

3.3. Vascular, Immune, and Hypoxic Niches

Vascular, immune, and hypoxic niches are tightly coupled determinants of therapeutic response. Tumor vessels are structurally abnormal and functionally heterogeneous, producing uneven perfusion, oxygenation, nutrient supply, drug exposure, and immune-cell access. The presence of endothelial cells or CD31-positive structures

alone does not establish a functional vascular model; clinically relevant platforms require lumen continuity, barrier properties, perfusability, and measurable transport [35,59,70,71,72]. Sacrificial, embedded, coaxial, and microgel-based printing strategies can generate perfusable channels, while seamless vessel-microenvironment printing enables direct study of contact-dependent communication between endothelial cells, tumor cells, and CAFs [37,83,84,85]. Nevertheless, channel formation must be distinguished from mature microvasculature, and flow conditions should be selected according to the drug-delivery or cell-trafficking question being modeled [86].

Immune behavior is similarly dependent on spatial context. TAMs, T cells, neutrophils, and other immune populations respond to local cytokines, ECM density, antigen distribution, oxygen tension, and their distance from tumor and stromal compartments [65,69]. Bioprinted neuroblastoma and glioblastoma models have enabled immune-cell chemotaxis, infiltration depth, cytokine release, and tumor killing to be measured as linked processes rather than as endpoint viability alone [87,88,89]. Spatially arranged fibroblast-tumor constructs further show that intermixed and barrier-like stromal distributions can produce different levels of TGF-beta-periostin signaling, immune suppression, and response to PD-1 blockade [90]. For adoptive cell therapies, model architecture also affects CAR-T or NK-cell access, persistence, and cytotoxicity [91,92,93]. These findings indicate that immune competence depends on the geometry and material permeability of the construct, not simply on adding immune cells to the culture [94,95].

Hypoxia arises from the combined effects of cellular oxygen consumption, diffusion distance, vascular insufficiency, and matrix density. Stabilization of HIF-1 α can enrich cancer stem-like populations, alter metabolism, promote angiogenic signaling, and increase chemoresistance [67,68]. High-cell-density and vascularized bioprinted models allow oxygen gradients to be generated more reproducibly, but the location and severity of hypoxia remain sensitive to construct dimensions, medium exchange, flow, and material diffusivity [82,96,97]. Hypoxic regions should therefore be validated using spatial measurements rather than inferred from construct thickness alone. Because oxygen tension also modifies macrophage phenotype, immune-cell function, and drug metabolism, vascular and hypoxic modules should be analyzed together rather than presented as independent features [86].

The functional consequence of these coupled niches is most evident in drug-response studies. In the multicellular 3DM-7721 liver cancer model, the addition of fibroblasts and endothelial cells increased the expression of MRP1, BCRP, and MDR-1 and raised the IC₅₀ values of doxorubicin, cisplatin, and luteolin by approximately 2.3-, 1.9-, and 2.7-fold, respectively, compared with a single-cell printed model [98]. In a patient-derived gastric cancer platform constructed from 33 tumors, drug-response

measurements were associated with clinical neoadjuvant chemotherapy outcomes and distinguished responders from nonresponders [35,99,100]. These examples demonstrate why vascular, stromal, immune, and hypoxic features must be connected to quantitative endpoints. Adding biological complexity is justified only when it measurably improves mechanistic insight or predictive performance.

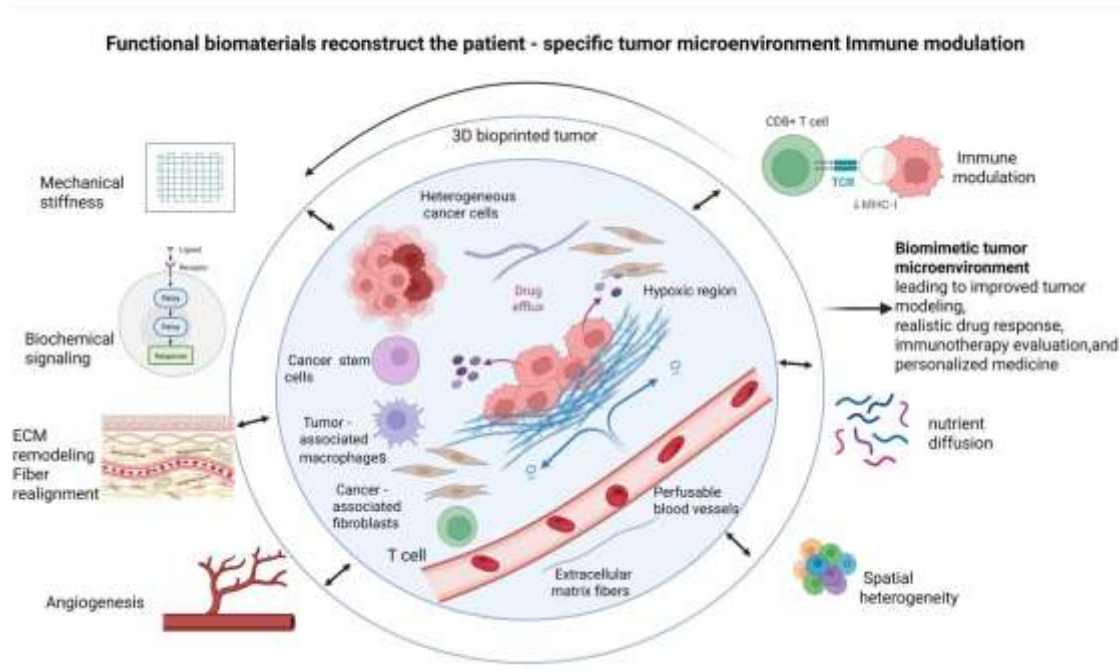


Figure 3. Functional biomaterials enable reconstruction of patient-specific tumor microenvironment immune modulation. Functional biomaterials enable reconstruction of patient-specific tumor microenvironments by coordinating mechanical stiffness, biochemical signaling, ECM remodeling, vascularization, hypoxia, and immune regulation, thereby improving the physiological relevance of drug-response and immunotherapy assessment. Created in BioRender. siqi, L. (2026) <https://BioRender.com/kpn50tz>

Figure 3 represents the TME as a coupled niche network rather than a collection of independently reproduced components. Matrix composition and stiffness regulate tumor and stromal phenotypes; degradability and pore architecture govern remodeling and immune-cell access; vascular functionality changes oxygenation, nutrient transport, and drug delivery; and hypoxia reciprocally alters angiogenic, metabolic, and immune responses. A single material adjustment can therefore improve one dimension while distorting another. Increasing matrix density may reproduce desmoplastic resistance but simultaneously restrict immune infiltration and drug diffusion, whereas adding perfusion may relieve hypoxia while changing cytokine clearance and therapeutic exposure. This coupling also defines the appropriate validation strategy: structural evidence such as compartment geometry or endothelial

staining should be paired with functional measurements of permeability, oxygen gradients, migration, immune killing, or regional drug response. Biological complexity is justified only when the added niche produces a measurable mechanistic or predictive gain. Figure 3 should therefore be interpreted as a design-dependency map linking biomaterial properties to interacting TME functions and quantitative treatment endpoints [65,69,82,90,91,92,93,96,98].

3.4. Dynamic and Treatment-Evolving Tumor Microenvironments

Native tumors evolve continuously during growth and treatment, whereas many bioprinted models are evaluated at a single time point. Tumor progression is accompanied by changes in stromal phenotype, ECM organization, vascular networks, metabolic stress, immune state, and clonal composition. Next-generation platforms should therefore move from static structural resemblance toward spatiotemporal reconstruction, in which the TME can mature, remodel, and respond to intervention during culture [37,40,79,80,81,82,96,101,102]. Remodelable bioinks, perfusable vascular systems, and spatially organized stromal and immune compartments provide the physical basis for this transition [86,94,103].

Longitudinal studies already demonstrate the value of dynamic assessment. Vascularized breast cancer models have enabled doxorubicin transport and HER2-targeted CAR-T-cell activity to be evaluated in relation to vascular accessibility [37]. Neurovascular glioblastoma models combining longitudinal imaging with single-cell profiling have captured changes in tumor growth, vascular phenotype, and cytokine secretion [96]. Increasing stromal complexity in bioprinted lung tumor models has also been shown to progressively suppress CAR-NK-cell infiltration, cytotoxicity, and cytokine release [101]. These observations reveal treatment response as an evolving interaction among tumor cells, matrix barriers, vasculature, and immune populations rather than as a fixed property measured by terminal viability.

Dynamic models are particularly valuable for investigating treatment-induced adaptation and acquired resistance. Repeated or sequential exposure can be used to track regional cell death, surviving clones, ECM remodeling, efflux-pump expression, immune exhaustion, and tumor regrowth. Relevant readouts may include live imaging, secreted factors, spatial transcriptomics, single-cell sequencing, matrix mechanics, and repeated functional drug testing. However, time-resolved measurement must minimize destructive sampling and distinguish biological adaptation from changes caused by hydrogel degradation, nutrient depletion, or declining cell viability. Baseline characterization and untreated time-matched controls are therefore essential [94,103].

The main challenge is to balance temporal fidelity with reproducibility and clinical feasibility. Highly remodelable constructs may better reproduce disease evolution but become difficult to standardize across patients and laboratories. Long maturation periods may capture vascular and stromal development yet exceed the treatment-decision window. Conversely, rapidly fabricated models may support screening but fail to reproduce the adaptive states responsible for relapse. A fit-for-purpose platform should therefore define which stage of tumor evolution it intends to predict, which dynamic features are indispensable, and whether those features improve prediction beyond a simpler static model. This critical distinction links TME reconstruction to the drug-delivery and personalized screening applications discussed in the following sections.

4. Functional Biomaterials for Localized Drug Delivery and Nanomedicine

4.1. From Passive Tumor Models to Therapeutic Platforms

Most bioprinted tumor constructs remain passive disease models in which a therapeutic agent is added to the culture medium after tissue fabrication. This design is useful for comparing intrinsic drug sensitivity, but it treats exposure as an external variable and therefore leaves out material-dependent determinants of local pharmacology, including retention, matrix binding, diffusion distance, concentration gradients, degradation-coupled release, and regional transport barriers [39,47,104,105,106,107,108]. Functional biomaterials can bridge this gap by incorporating therapeutic cargos or delivery functions into defined spatial domains of the printed construct. The key advance is therefore not simply drug loading, but the conversion of the biomaterial from a structural scaffold into a controllable interface between tumor architecture and therapeutic exposure.

This distinction is important because two related applications are often discussed as if they were equivalent. In one, the printed construct is an *in vitro* tumor model for comparing free drugs, nanoparticles, or other formulations under controlled transport barriers. In the other, the printed material itself acts as a localized delivery depot, analogous to an injectable hydrogel, implantable patch, or spatially patterned reservoir [18,19,20,21,24,47]. The first primarily asks how tumor architecture modifies drug exposure and response; the second asks whether the material can generate a desired therapeutic concentration-time profile. Similar materials may serve both purposes, but the experimental endpoints and translational claims are different. A model that reproduces diffusion through a tumor-like matrix should not be presented as evidence of *in vivo* pharmacokinetic equivalence, and a sustained-release depot should not automatically be regarded as a patient-specific efficacy model.

The central analytical link between these applications is that material properties simultaneously determine tissue fidelity and therapeutic exposure. ECM composition, stiffness, porosity, charge, degradation, and water content can influence cell phenotype while also controlling drug partitioning, nanoparticle mobility, uptake, and retention. Consequently, changing the bioink to improve printability or mechanical stability may unintentionally change the therapeutic response being measured. Conversely, patient-specific differences in stromal density or matrix composition may reveal whether an apparent treatment failure reflects tumor-intrinsic resistance or insufficient delivery. Functional biomaterials should therefore be evaluated as coupled architecture-transport-response systems rather than as independent scaffolds plus drugs ^[75].

4.2. Drug-Loaded and Nanocomposite Bioinks

Therapeutic cargos can be incorporated through direct molecular encapsulation, affinity-based retention, adsorption to matrix components, covalent or degradable linkages, or secondary carriers such as liposomes, polymeric nanoparticles, micelles, microgels, and inorganic nanomaterials ^[19,20,24,47]. These strategies are not interchangeable. Direct encapsulation is simple and minimizes formulation complexity, but printing may expose labile cargos to photoinitiators, crosslinking reactions, shear stress, or reactive groups. Secondary carriers can protect cargos and add release control, but they introduce a second material phase with its own size, surface chemistry, stability, uptake, and toxicity. Selection should therefore start from the intended biological question—transport testing, localized delivery, or both—then match cargo stability, solubility, exposure duration, and required spatial precision to the loading mechanism.

Hydrogel network properties provide a first layer of release control, but they also create a major source of confounding. Increasing polymer concentration or crosslink density generally decreases mesh size and slows diffusion, while simultaneously increasing stiffness and potentially altering cell phenotype or nutrient transport. Degradation can accelerate release, yet cell-mediated degradation is spatially heterogeneous and may differ markedly from passive hydrolysis. Electrostatic or hydrophobic interactions can improve retention but reduce the freely available concentration. Accordingly, cumulative release curves alone cannot establish controlled delivery. Release data should be interpreted together with swelling, degradation, mechanics, cargo stability, and the concentration that actually reaches viable tumor cells; otherwise, an apparent therapeutic benefit may arise from altered matrix biology rather than improved drug delivery ^[18,22,23,24,47,109].

Nanocomposite bioinks add a second functional layer by integrating hydrogels with nanoclays, liposomes, polymeric nanoparticles, metallic or magnetic particles, or other nanoscale components ^[19,20,24,28,29]. Their value lies in coupling structural properties with sustained release, imaging, photothermal, magnetic, or targeting functions. However, the nanoparticle is no longer an isolated nanomedicine once it enters a printable matrix. Aggregation, sedimentation, adsorption to polymer chains, attenuation of curing light, uneven filament distribution, altered gelation kinetics, increased nozzle pressure, and optical interference can all emerge at the particle-matrix interface. Therefore, performance cannot be inferred by simply combining characterization data from the nanoparticle and the hydrogel; the printed composite must be characterized as a new material system.

Carrier-free nanodrug delivery systems provide a complementary nanomedicine strategy in which therapeutic molecules self-assemble with one another or with small coordinating species, potentially increasing drug loading while reducing inert carrier content ^[110,111,112,113]. Reported pH-, redox-, and light-responsive assemblies illustrate opportunities for high-loading and triggerable delivery ^[114,115,116,117]. Nevertheless, most such systems have been studied outside bioprinted patient-derived tumors. Their presence in the literature should therefore not be interpreted as evidence of an established integrated bioprinting platform. A more rigorous framing is to regard carrier-free nanodrugs as candidate cargos whose compatibility with printing, spatial retention, penetration, release, and patient-derived response remains to be demonstrated.

Imaging-functionalized materials can connect delivery with longitudinal response monitoring. For example, dECM-supported plasmonic SERS structures have been printed within breast-derived matrices to monitor chemotherapy while retaining spatial tumor organization ^[118]. The important criterion is not whether a material is imageable, but whether the signal provides quantitative information that changes interpretation of therapeutic exposure or response. Signal intensity must therefore be calibrated against cargo concentration, tissue depth, material degradation, cellular uptake, and optical interference. Where possible, imaging-derived exposure should be cross-validated with an orthogonal chemical or biological measurement ^[103].

4.3. Stimuli-Responsive and Sequential Drug Delivery

Stimuli-responsive bioinks are designed to alter permeability, degradation, swelling, or cargo binding in response to defined endogenous or exogenous triggers. Endogenous signals include acidic pH, reactive oxygen species, glutathione, tumor-

associated enzymes, and hypoxia; external triggers include light, temperature, ultrasound, magnetic fields, and electrical stimulation ^[28,29,119]. Their conceptual advantage is temporal and spatial control of exposure. Their major limitation is that trigger behavior measured in acellular gels may not persist in the complete printed construct, where cells, serum proteins, ECM components, buffering, oxygen gradients, and fluid flow can shift the effective threshold. Responsiveness should therefore be quantified under the biological conditions in which therapeutic efficacy is claimed.

Responsive nanomedicines provide useful design concepts, including acid-sensitive assemblies, glutathione-responsive metal-organic systems, and near-infrared-triggered prodrug platforms ^[114,115,116,117]. However, many reported examples remain nanomedicine studies rather than integrated bioprinted tumor platforms. The translational question is consequently not whether the nanosystem can respond to a trigger in isolation, but whether the trigger reaches the relevant spatial compartment, whether penetration and release remain adequate in a cell-dense patient-derived matrix, and whether the trigger itself perturbs the model. These controls are essential when attributing improved efficacy to stimulus-responsive delivery rather than to nonspecific light-, heat-, redox-, or metal-associated effects.

Sequential delivery is particularly relevant to combination therapy because efficacy may depend on treatment order, interval, and local concentration rather than total dose alone. Printed constructs can spatially separate cargos into layers, particles, or hydrogel domains and exploit different diffusion or degradation mechanisms to generate staged exposure. Potential applications include stromal modulation before cytotoxic therapy, vascular normalization before nanoparticle delivery, immune activation after chemotherapy, or sensitization before radiotherapy. The critical design criterion is a clinically meaningful exposure sequence, not simply co-encapsulation of several agents. Each component should therefore be quantified for loading, recovery, release, stability, and biological activity and compared with simultaneous-delivery, free-drug, and order-reversed controls where relevant.

Personalization in this setting concerns both therapeutic selection and the delivery conditions under which a therapy is tested. Dense desmoplastic tumors may require penetration-enhancing or matrix-remodeling strategies, whereas highly vascularized or immune-infiltrated tumors may require different spatial and temporal exposure patterns. Functional materials can reproduce these barriers and test alternative delivery schedules within the same patient-derived background. Yet every additional responsive element also increases formulation complexity, manufacturing variability, and attribution difficulty. The most informative personalized platform is therefore not

the one with the greatest number of functions, but the one in which each material function addresses a defined patient-specific therapeutic question and can be independently validated.

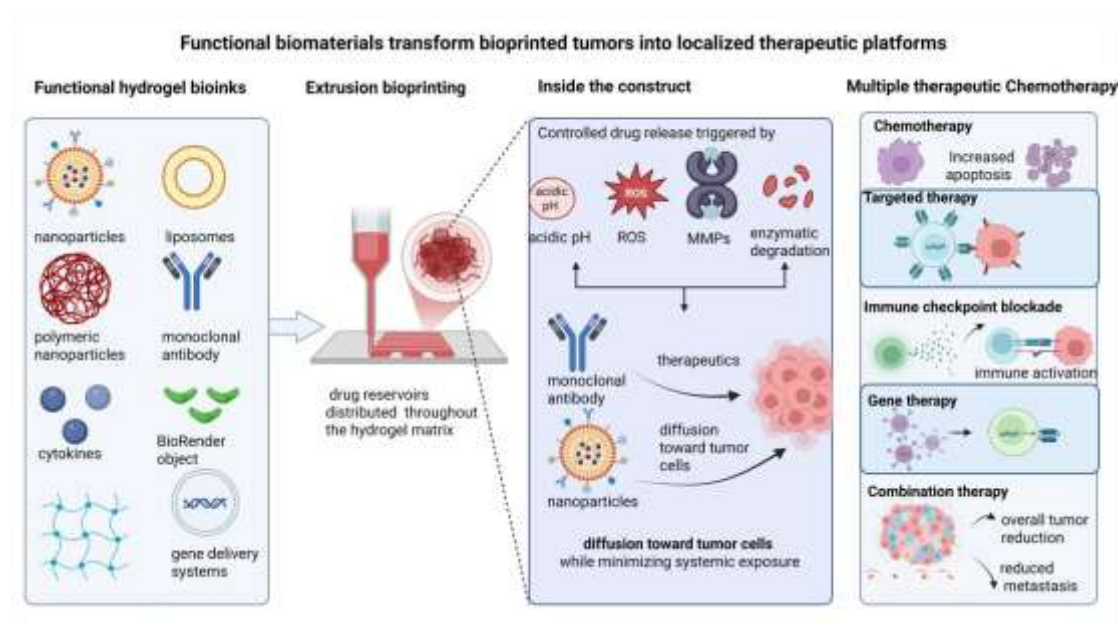


Figure 4. Functional biomaterials transform bioprinted tumors into localized therapeutic platforms. Functional hydrogel bioinks incorporating nanoparticles, liposomes, antibodies, gene-delivery systems, and other therapeutic cargos enable spatial loading and stimuli-responsive release for chemotherapy, targeted therapy, immunotherapy, and combination treatment. Created in BioRender. siqi, L. (2026) <https://BioRender.com/19otf2j>

Figure 4 summarizes the progression from cargo incorporation to localized therapeutic action. The critical relationship is not simply that a hydrogel contains a drug: material composition and crosslinking control cargo retention and diffusion; nanoparticles or affinity interactions modify stability and cellular uptake; endogenous or external triggers determine release timing; and the surrounding tumor architecture governs penetration and response. These variables must be interpreted together. For example, slower release may prolong exposure but also lower the effective concentration, while stronger matrix retention may improve localization yet prevent the drug from reaching deeper tumor compartments. Figure 4 therefore represents a coupled delivery-evaluation pathway rather than a catalogue of therapeutic agents.

4.4. Evaluation Criteria and Current Bottlenecks

Quantitative evaluation should begin with a complete mass balance rather than a single release curve. At minimum, studies should report nominal and recovered loading, encapsulation efficiency, spatial loading distribution, burst release,

cumulative release, release duration, cargo stability, and residual material-associated drug. Nanocomposite systems additionally require particle size and distribution before and after printing, aggregation or sedimentation assessment, and characterization of changes in rheology and crosslinking ^[19,24,47,109]. Release conditions—including medium volume, exchange frequency, temperature, pH, enzymes, serum proteins, and flow—must be reported because they directly shape apparent kinetics. Mathematical fitting can facilitate comparison, but fitted parameters should not be treated as mechanistic evidence unless the underlying transport and degradation assumptions are experimentally justified.

Bulk release does not establish spatial drug exposure within a heterogeneous tumor construct. Relevant endpoints include penetration depth, regional concentration, intracellular uptake, target engagement, and distance-dependent cell death. Dense ECM, interstitial resistance, hypoxia, and stromal binding can generate a large difference between the amount released from the material and the amount reaching viable tumor cells ^[39,104,105,106,120]. Fluorescent analogues are useful for spatial mapping but may not reproduce the physicochemical behavior of the native drug, and optical scattering, quenching, or material autofluorescence can distort apparent concentration. Imaging should therefore be calibrated whenever possible against an orthogonal chemical or biological measurement.

The relationship between in vitro release and clinical exposure remains a major translational limitation. Static culture can behave as a large sink, whereas tumors in vivo are shaped by blood flow, lymphatic drainage, protein binding, metabolism, clearance, and systemic redistribution. Conversely, an injectable or implantable depot may interact with host immune and stromal compartments that are absent from a tumor-only construct. Bioprinted systems are consequently well suited to comparative and mechanistic evaluation of local exposure, but should not be presented as reproducing clinical pharmacokinetics unless perfusion, clearance, and relevant tissue barriers are explicitly modeled. The appropriate output is often a relative ranking of formulations or exposure-response relationships rather than direct clinical dose conversion ^[86,121].

Nanomedicine studies require controls that separate therapeutic activity from carrier and matrix effects. Empty nanoparticles, unloaded bioinks, free-drug controls, carrier-only controls, and equivalent total-dose conditions are needed to identify toxicity arising from the vehicle, photothermal activation, reactive species, or altered matrix mechanics. Uptake should be resolved across tumor, stromal, endothelial, and immune populations because sequestration by one compartment may alter both efficacy and toxicity. Longitudinal assessment is also necessary: an early viability reduction does not exclude delayed regrowth, selection of resistant subclones, or persistent immune suppression after the release phase.

Cross-platform comparison remains difficult because studies vary in construct size, cell density, release medium, mechanical metrics, viability time points, imaging methods, and therapeutic endpoints. Miniaturization improves throughput and reduces reagent use, but can shorten diffusion distances and flatten the very gradients that motivate three-dimensional modeling. A critical bottleneck is therefore not simply the lack of more sophisticated materials, but the lack of agreed performance criteria linking print fidelity, material stability, spatial exposure, biological preservation, and response reproducibility. Future studies should report these parameters in a fit-for-purpose manner and define acceptance ranges before comparing formulations. This would allow functional biomaterials to be judged as integrated delivery-and-evaluation systems and provide a clearer evidentiary basis for assessing clinical translation ^[48,49,121,122].

5. Patient-Derived Bioprinted Platforms for Personalized Drug Screening

5.1. Patient-Derived Cells, Organoids, and Biological Inputs

Patient specificity can enter a bioprinted tumor model through several biological inputs, including freshly isolated tumor cells, short-term primary cultures, patient-derived organoids (PDOs), tissue fragments, and matched stromal or immune populations. These inputs should be distinguished from the functional biomaterial that organizes and regulates them. Freshly isolated cells minimize culture-induced selection but may be scarce and heterogeneous, whereas expanded primary cells and PDOs provide more material for printing but can undergo clonal selection, phenotypic drift, or loss of nonmalignant cell populations during propagation ^[6,30,31,34,43,123]. The appropriate source therefore depends on the clinical question, the amount and quality of available tissue, and the time permitted for model establishment ^[124,125].

Surgical resections generally provide more cells and permit spatial sampling of distinct tumor regions, but they are available only for selected patients and may not represent metastatic or treatment-refractory lesions. Core-needle biopsies are clinically accessible and can sample the lesion being treated, yet low tumor cellularity, necrosis, fibrosis, and dissociation-associated cell loss may leave insufficient material for a complex printed construct. Material and process choices must consequently be adapted to sample constraints. Miniaturized constructs, lower-volume bioinks, gentle crosslinking, and parallel quality-control aliquots can conserve cells, but excessive miniaturization may eliminate the diffusion distances and spatial gradients that motivate three-dimensional modeling in the first place ^[125,126].

Patient-derived tumor cells can be combined with cancer-associated fibroblasts, endothelial cells, macrophages, lymphocytes, or other stromal populations to reconstruct tumor-cell interactions that influence invasion, vascular permeability, immune exclusion, and drug response^[17,33,59,60,87,88,89,127]. Autologous accessory cells offer the strongest patient-specific context but are not always recoverable in sufficient numbers and may be altered by isolation or expansion. Standardized allogeneic cells improve availability and interexperiment reproducibility, but they cannot reproduce the patient's immune compatibility or stromal history. Studies should therefore report the provenance, matching status, passage number, and mixing ratio of every cell population rather than labeling a model patient-derived when only the malignant compartment originates from the patient.

The biomaterial determines whether these biological inputs retain clinically relevant behavior after printing. Tissue-specific dECM may preserve native biochemical cues, whereas GelMA, collagen, hyaluronic-acid derivatives, and composite matrices provide greater control over mechanics, degradation, and printability^[21,22,23,26,100]. No matrix is intrinsically patient-specific merely because it contains patient-derived cells. Fidelity should be tested against the parental tumor using fit-for-purpose measurements such as histology, lineage markers, genomic alterations, transcriptional states, ECM features, and treatment-response patterns. Likewise, PDO integration does not automatically make a bioprinted model superior to an unprinted organoid assay; the added value must arise from controlled spatial organization, defined transport barriers, or inclusion of cellular compartments that materially change the therapeutic readout^[123,128,129,130,131,132] ^[124,125].

5.2. High-Throughput and Automated Drug Screening

High-throughput screening requires more than printing many constructs. A scalable workflow must coordinate sample processing, bioink preparation, automated dispensing, crosslinking, culture, drug addition, imaging, and data analysis within a clinically relevant time window. Compatibility with multiwell plates and robotic liquid handling can reduce reagent use and operator variability, but only if construct position, volume, geometry, cell density, and crosslinking are reproducible across wells. Print failure, nozzle obstruction, settling of cells or particles, and edge effects during culture can otherwise create well-to-well differences that are misinterpreted as drug responses^[31,35,105,106] ^[126].

Miniaturization improves throughput and conserves scarce patient material, yet it changes the biology being measured. Small constructs equilibrate oxygen and drugs rapidly and may not develop the hypoxic, nutrient, or penetration gradients observed in larger tumors. Conversely, increasing cell types, spatial compartments, or maturation time improves biological fidelity but reduces the number of conditions that can be tested and increases batch variability. Platform design should therefore begin with the decision being supported. A focused panel of clinically actionable regimens may justify a more complex patient-specific model, whereas early discovery screening may prioritize simpler, robust constructs that provide a consistent ranking of many compounds ^[126].

Automated readouts are equally important. Plate-reader measurements and endpoint viability assays are inexpensive but collapse spatially heterogeneous responses into a single value. High-content imaging can quantify tumor-cell burden, morphology, invasion, apoptosis, immune-cell infiltration, and regional drug effects over time, while label-free or nondestructive imaging preserves constructs for repeated measurements ^[35,105,106,133,134]. Image-analysis and machine-learning pipelines can accelerate segmentation and response classification, but their performance depends on representative training data, transparent preprocessing, and external validation. Changes in construct size, matrix autofluorescence, cell density, or imaging depth can bias an algorithm even when the underlying treatment response is unchanged ^[103].

Reproducibility must be assessed at both technical and biological levels. Replicate wells from one print run measure dispensing and assay variability, whereas independent bioink preparations, print runs, and patient specimens capture manufacturing and biological variation. Reporting only within-plate replicates can therefore overstate platform robustness. Reference compounds, untreated and vehicle controls, predefined acceptance thresholds, and randomized plate layouts should be incorporated into screening workflows. At the screening stage, the essential question is whether the platform can deliver an interpretable result within the relevant clinical decision window ^[48,49,126].

5.3. Drug-Response and Resistance Readouts

Drug response should be defined using endpoints that match the intended therapeutic claim. Metabolic activity or live-dead staining provides a rapid measure of acute cytotoxicity but cannot distinguish growth arrest from irreversible cell death and may be confounded by stromal cells or material-dependent assay interference. More informative panels combine tumor-cell-specific viability with proliferation, apoptosis, target engagement, three-dimensional tumor burden, invasion, and post-treatment regrowth. Spatial analysis is particularly important because a stable whole-construct

average can conceal elimination of peripheral cells together with survival of a protected hypoxic or stem-like compartment [94,103].

Bioprinted models are well suited to separating several forms of resistance. Baseline nonresponse may reflect tumor-intrinsic alterations, whereas matrix stiffness, dense ECM, stromal signaling, hypoxia, impaired penetration, and preferential uptake by nonmalignant cells can generate microenvironment-mediated resistance [55,67,68,79,98,102,134]. Acquired resistance requires longitudinal or repeated-exposure designs that track surviving populations after treatment and recovery. A single short-term viability measurement should not be described as a resistance assay unless the model demonstrates persistence or regrowth under an exposure schedule that is relevant to the therapy being tested.

Immunotherapy requires a distinct set of readouts. Tumor killing should be evaluated together with immune-cell migration, infiltration depth, cell-cell contact, activation or exhaustion phenotype, cytokine release, and tumor-antigen dependence [37,87,88,89,90,91,92,93,101]. Autologous immune cells are preferable for patient-specific claims, while allogeneic systems are more appropriately used to study general mechanisms or material effects. Materials can influence immune behavior through stiffness, pore structure, degradation products, cytokine binding, and nonspecific sequestration of antibodies; unloaded-material and immune-cell-only controls are therefore needed to distinguish therapeutic activity from biomaterial-mediated immunomodulation.

Combination and sequential treatments should be assessed against clinically meaningful doses, exposure durations, and orders of administration. Apparent synergy may arise from prolonged local retention or overlapping toxicity rather than a true interaction between therapeutic mechanisms. Dose matrices, single-agent controls, temporal sampling, and a prespecified synergy model improve interpretation. Where feasible, orthogonal measurements such as imaging, molecular biomarkers, flow cytometry, or recovered-cell sequencing should confirm the primary readout. These approaches turn the printed construct from a binary sensitive-or-resistant assay into a platform for identifying why a patient-derived tumor responds, fails to respond, or relapses after treatment [124,125].

5.4. Evidence for Clinical Predictive Value

The clinical predictive value of a patient-derived bioprinted model should be judged by the level of evidence supporting it. Technical feasibility demonstrates that a patient's cells can be printed and remain viable. Biological concordance shows that the construct retains selected features of the parental tumor. Retrospective association links an ex vivo response with an observed clinical outcome, whereas prospective

prediction requires the assay result to be generated before treatment and evaluated against a predefined endpoint. The strongest evidence would come from prospectively designed, adequately powered, multicenter studies that measure model-establishment success, uninterpretable results, and predictive performance in consecutive patients rather than only in successfully cultured samples ^[124,125].

Early studies provide encouraging but still limited evidence. Patient-derived gastric cancer models have reproduced histopathological characteristics and generated drug-response patterns associated with clinical outcomes; one reported cohort included 33 patients and found a significant association between model response and patient outcome ($p = 0.004$) ^[35,99,100]. Such findings support further validation, but small cohorts, heterogeneous treatments, selective model establishment, and incomplete blinding can inflate apparent predictive performance. Correlation in a feasibility cohort should therefore not be equated with demonstrated clinical utility.

The range of cancers modeled by bioprinting is expanding. Examples include colorectal cancer constructs designed to reproduce ECM-dependent drug gradients, high-grade serous ovarian cancer models based on GelMA/hyaluronic-acid systems, head-and-neck and liver cancer models incorporating patient-derived cells, lung cancer platforms for invasion and barrier studies, and glioblastoma or melanoma constructs used for therapeutic screening ^[128,129,130,131,132,135,136,137,138,139,140,141]. This breadth demonstrates adaptability of the technology, but cancer-type coverage is not itself evidence of prediction. Many platforms have been tested with a small number of samples, established cell lines, or experimental agents and have not yet been compared with the patient's actual treatment response.

Bioprinting must also demonstrate incremental value over less complex patient-derived assays. PDOs, spheroids, tumor slices, and microfluidic cultures may provide faster or more economical response measurements, whereas bioprinting offers potential advantages when spatial organization, matrix-defined transport, multicellular interfaces, or regional treatment delivery are central to the question ^[123,131,142]. Comparative studies should test whether these additional features improve discrimination, calibration, or decision impact rather than assuming that greater architectural complexity produces greater clinical accuracy. A complex model that cannot be established consistently or reported in time may be less useful than a simpler assay with validated performance ^[121,124,125].

Accordingly, patient-derived bioprinted tumor models should presently be viewed as emerging complementary functional-testing platforms rather than established diagnostic methods. Their near-term value lies in mechanistic stratification, prioritization of a focused treatment panel, evaluation of delivery barriers, and hypothesis generation alongside pathology, genomic profiling, and organoid-based

testing. Demonstrating clinical utility will require evidence that the result changes a treatment decision and improves an outcome relative to existing care. The practical requirements for achieving that standard, including sample adequacy, turnaround time, cost, quality control, interlaboratory reproducibility, and regulation, are considered in Section 6 ^[124,125].

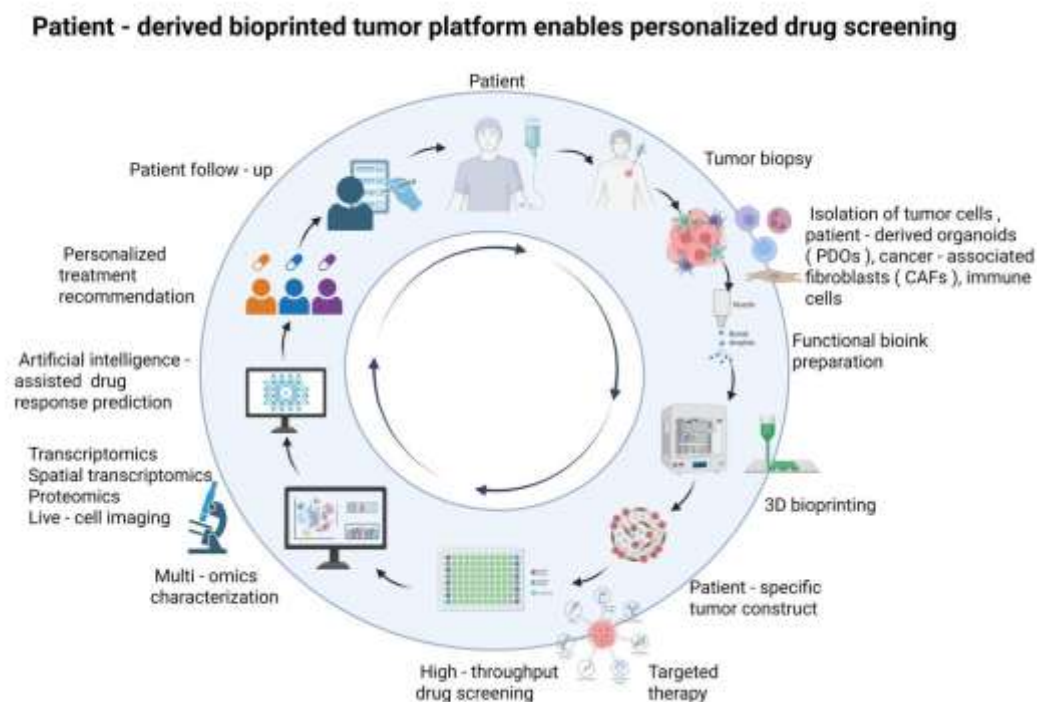


Figure 5. Patient-derived bioprinted tumor platform enables personalized drug screening. A patient-derived bioprinted tumor platform links specimen acquisition, biological input preparation, functional bioink design, automated drug screening, multimodal response analysis, and clinical feedback. The workflow emphasizes iterative validation rather than a one-directional transition from printing to treatment recommendation. Created in BioRender. siqi, L. (2026) <https://BioRender.com/sbgzm6n>

Figure 5 depicts a conditional clinical decision-support pathway rather than a routine workflow already achieved. Attrition can occur at every transition: a biopsy may provide insufficient viable or representative cells; expansion and printing may select subclones or alter stromal and immune composition; miniaturization may improve throughput while reducing spatial fidelity; analytical pipelines may generate uncertain sensitivity classifications; and ex vivo activity may not capture systemic pharmacology or host toxicity. Accordingly, clinical feasibility must be evaluated across the complete sample-to-report interval rather than by assay time alone. Model-establishment success rate, usable sample fraction, manufacturing failures, turnaround time, cost, predefined quality-control thresholds, and concordance with patient outcomes should all be reported, including failed models and discordant predictions. The feedback arrow is therefore essential: it supports recalibration of model design and decision thresholds rather than merely confirming successful cases. Until prospective studies demonstrate added decision impact, patient-derived bioprinted models are best positioned as complementary functional tests alongside pathology, genomics, organoids, and other ex vivo assays ^[35,99,100,123,131,142].

6. Clinical Translation: Feasibility, Standardization, and Regulation

6.1. Sample Adequacy and Model Establishment

Clinical translation begins before bioink formulation or printing. As discussed in Sections 3 and 5, the fidelity of a patient-derived bioprinted model depends not only on material and spatial design but also on whether the clinical specimen contains sufficient viable and representative information. Surgical resections may provide abundant tissue and permit regional sampling, but they are unavailable for many patients with unresectable, metastatic, or recurrent disease. Core biopsies are more compatible with routine care, yet low tumor cellularity, necrosis, fibrosis, prior treatment, and dissociation-associated loss can prevent construction of complex multicellular models ^[30,31,34,35]. Thus, sample adequacy should be treated as a measurable entry condition of the platform rather than as an implicit prerequisite.

Sample handling can introduce additional selection. Ischemic time, transport temperature, dissociation method, cryopreservation, red-blood-cell removal, and microbial contamination affect cell recovery and phenotype. Expansion of primary tumor cells or patient-derived organoids increases the number of printable units but may favor selected clones and deplete stromal or immune populations; direct printing of fresh cells better preserves the sampled state but leaves less material for replicate constructs and quality-control assays ^[6,30,123,143]. A clinically relevant workflow should therefore record tissue source, tumor-cell fraction, viability, passage number, culture duration, and the origin of accessory cells. For specimens that do not meet

predefined criteria, the appropriate endpoint should be a simpler validated assay or a classified no-result outcome, rather than forced construction or interpretation.

Establishment success should be reported against the full clinical denominator. A technically successful model derived from selected high-cellularity specimens does not indicate how often the workflow will succeed in consecutive patients. Studies should record attrition during transport, isolation, expansion, printing, maturation, and drug-response analysis, together with the reason for failure and the time at which it occurred. This connects the sample-level problem identified here with the clinical validity framework in Section 6.4: an assay that frequently produces delayed or uninterpretable results may have limited clinical utility even when its successful models show high biological fidelity ^[35,57].

Fit-for-purpose entry criteria and stop rules can reduce wasted tissue and false confidence. Before printing, the workflow should confirm sample identity, sterility, minimum viable tumor-cell content, recovery of required accessory populations, and compatibility with the planned number of treatment conditions. After printing, predefined gates should assess construct geometry, immediate and time-resolved viability, retention of key tumor features, and baseline growth or stability. Failure to meet these criteria should trigger repeat preparation, a simpler validated assay, or a no-result classification rather than forced interpretation. Such triage links sample adequacy to downstream analytical validity and prevents model complexity from masking an uninformative specimen ^[35,57].

6.2. Turnaround Time, Cost, and Scalability

Turnaround time should be measured from specimen acquisition to an interpretable report, not from the start of printing. Tissue transport, dissociation, cell or organoid expansion, bioink preparation, printing, construct maturation, drug exposure, imaging, analysis, and multidisciplinary interpretation all contribute to the total interval. The clinically acceptable interval depends on the decision being supported: a model intended to inform an immediate treatment choice faces a much narrower window than one used to investigate resistance before a later line of therapy. Studies should therefore report the duration and range of each step, the proportion of samples yielding an interpretable result, and the proportion of results returned before the relevant treatment decision ^[31,35,57,143,144].

Cost is distributed across the same workflow. Major drivers include skilled personnel, printer and imaging infrastructure, patient-specific reagents, dECM or specialty polymers, quality-control testing, culture duration, data analysis, and failed model attempts. Automation, acoustic or droplet-based deposition, microarrays, and

miniaturized multiwell formats can reduce labor and reagent consumption and increase screening capacity [34,58,134,144,145,146]. However, throughput should not be equated with efficiency: miniaturization may remove relevant spatial gradients, complex imaging may require extensive manual correction, and a high failure rate can make a low cost per well misleading. Cost per clinically interpretable result is therefore a more meaningful translational metric than cost per printed construct.

Scalability requires a controlled balance between standardization and patient specificity. Centralized facilities can provide specialized equipment, trained operators, and harmonized analytics but add specimen-transport time and may complicate integration with local clinical teams. Distributed hospital-based workflows shorten transport and feedback loops but require instrument equivalence, operator training, external proficiency testing, and robust digital quality records. A modular strategy may offer a practical compromise: standardized matrix or plate formats, reference controls, and analytical pipelines can be combined with patient-specific cells and a focused treatment panel. The objective is not maximum model complexity for every patient, but the minimum reproducible complexity that answers the intended clinical question within the available time and resources [147,148,149,150,151].

6.3. Quality Control and Interlaboratory Reproducibility

Quality control should connect manufacturing performance to biological and analytical validity. Material attributes include composition, lot identity, sterility, rheology, crosslinking behavior, stiffness, swelling, degradation, and the identity and loading of incorporated drugs or nanoparticles. Process attributes include cell density, deposition accuracy, construct dimensions, crosslinking dose, printing time, temperature, and shear exposure. Biological attributes include immediate and longitudinal viability, identity of each cell population, retention of clinically relevant tumor features, spatial organization, and phenotypic stability. Analytical attributes include assay dynamic range, reference-drug responses, imaging performance, repeatability, and predefined criteria for sensitivity, resistance, and uninterpretable results [40,147,149,152]. This framework directly operationalizes the material- and process-level variables discussed in Sections 2–4 [48,49,122].

Lot-to-lot, run-to-run, operator-to-operator, and laboratory-to-laboratory variability should be evaluated separately. Natural polymers and dECM may vary in composition and gelation, while photoinitiators, nanoparticles, and biochemical ligands can alter curing, transport, and assay signals. Printer hardware, nozzle geometry, calibration, software path generation, operator technique, and ambient conditions introduce additional variation. Complete reporting of these parameters is necessary but insufficient; studies should quantify precision using shared reference materials and predefined acceptance ranges. Longitudinal control charts or equivalent drift-

monitoring approaches can help identify process changes before they alter patient classification ^[48,49].

Interlaboratory reproducibility remains a major unresolved requirement. A round-robin study involving 12 laboratories showed that extrusion-bioprinting outcomes remained sensitive to equipment- and operator-dependent factors even under substantially standardized conditions, whereas automated image analysis improved the objectivity of quality assessment ^[148]. This supports the use of shared reference bioinks, standardized test geometries, benchmark cell materials, and external proficiency programs. Quantitative reporting should also distinguish nozzle diameter from measured filament width, specify the mechanical modulus being reported, state the viability time point, and define degradation and drug-response conditions; otherwise, apparently similar constructs cannot be meaningfully compared.

Acceptance criteria should be fit for purpose rather than universal. A mechanistic invasion model, a high-throughput discovery screen, and a patient-specific response assay require different levels of structural fidelity and measurement precision. Tiered qualification is therefore preferable: basic manufacturing qualification for exploratory models; assay validation for comparative drug screening; and more stringent analytical and clinical validation for results intended to influence care. Reference compounds, positive and negative controls, blinded analysis, and prespecified uncertainty zones should accompany higher validation tiers. Table 3 provides a useful study-level reporting benchmark, but community reporting standards and multicenter performance studies are still required to define clinically acceptable thresholds ^{[57,147,148,149,152] [48,49,122]}.

Table 3. Study-level quantitative reporting benchmark for representative 3D-bioprinted tumor platforms.

Notes: NR, not reported in the source article. Resolution is listed as an actual feature size only when explicitly measured; nozzle gauge or diameter and designed line width are labeled separately. Mechanical values retain the metric used by the original study, and cell-viability results retain the reported measurement time. These distinctions prevent inappropriate direct comparison of non-equivalent endpoints.

Study [Ref]	Bioink composition	Crosslinking	Printing technique	Resolution	Mechanical properties	Cell viability	Degradation	Tumor type	Cell populations	Drug-response readout	Major limitations
Xu et al., 2023 [43]	6% gelatin + 3% sodium alginate + 1% porcine liver dECM (6G3S1d representative)	3% CaCl ₂ followed by EDC/NHS double crosslinking	Extrusion; 0.20 MPa; 8 mm/s; 0.2-mm layers	1.0-mm designed strand spacing; nozzle/actual filament width NR	Compression modulus 29.64 +/- 0.41 kPa (6G3S1d)	Live/dead and CCK-8 on days 1, 4, and 7; exact percentage NR	Serum-enzyme degradation assessed qualitatively; quantitative kinetics NR	Metastatic breast cancer	4T1 cells; L929 fibroblasts as a material-control cell line	No therapeutic drug test; tumor-sphere growth and viability	Post-print cell seeding rather than cell-laden printing; murine cells; no drug-response validation; incomplete quantitative degradation reporting
Gonzalez-Callejo et	Porcine breast dECM bioink;	Thermal gelation; detailed	Extrusion into 48-well plates	Nozzle/feature size NR	NR	Viability assessed after printing;	NR	Breast cancer	MDA-MB-231 or MCF-7 tumor cells	Doxorubicin and paclitaxel; 72-h response;	Cell-line-based tumor compartment; animal-derived

al., 2023 [55]	spatially separated tumor core and stromal compartm ent	crosslinking metric NR					exact value/time- point harmonizat ion NR			with human breast fibroblasts; endothelial component evaluated	subtype- dependent viability	dECM; mechanics, degradation, and printing resolution incompletely reported for cross-platform comparison Single cell line and single drug;
Shukla et al., 2024 [58]	3% caprine decellular ized adipose- tissue hydrogel	Thermal gelation; additional stabilization NR	Extrusio n biprinti ng in 96- well plates	150- micron nozzle; actual feature size NR	Rheology reported; numeric modulus NR		Live/dead and functional characteriz ation; exact percentage /time point NR	NR	Breast cancer	MDA- MB-231 cells	5-fluorouracil viability response in bioprinted microtumors	xenogeneic dECM; limited clinical validation; several benchmark metrics not reported quantitatively
Li et al., 2024 [32]	GelMA- collagen tumor- island bioink	GelMA photocrossli nking plus collagen	Multimat erial extrusion ; sea- and-	Island/inte rface feature size NR	NR		Post-print viability reported; harmonize d	NR	PDAC	Human PDAC cells with cancer-	Metabolic adaptation and tumor- stroma response;	Model optimized for mechanism rather than throughput;

	within collagen-rich interstitial ECM	thermal assembly	island architecture			percentage /time point NR			associated fibroblasts	therapeutic cytotoxicity not the primary endpoint	quantitative resolution, mechanics, degradation, and standardized drug-response metrics incomplete
Han et al., 2025 [33]	50% Geltrex + 32.5 mg/mL gelatin + 6 mg/mL HA; printed into 1.5% alginate support bath	~30 min cooling, then 40 mM CaCl2 for ~15 min	Embedded extrusion of PDO ink; PCL wall and alginate bath deposition	~200-micron PDO dots (measured); 200-micron PCL nozzle; 300-micron bath nozzle	Alginate-bath compressive modulus ~7.5 kPa	CellTiter-Glo used for drug response; baseline post-print percentage NR	NR	Colorectal cancer	Patient-derived colorectal organoids with retained tumor-associated stromal features	5-fluorouracil survival/AUC ; morphology, CEACAM5, transcriptomics, and label-free response prediction	Small patient cohort; support-bath workflow adds manufacturing complexity; degradation and direct construct-mechanics data NR
Choi et al., 2025 [57]	10% (w/v) porcine gastric dECM	Thermal gelation/culture at 37 degrees C; explicit	Extrusion into 24-well plates; 18G	18G nozzle; printed tissue size/feature	NR	Cancer/stromal cell viability maintained through	NR	Gastric cancer	Patient- or PDX-derived tumor fragments;	5-FU, oxaliplatin, docetaxel and combinations; CCK-8 after	Porcine dECM and tissue-content-dependent behavior;

	with minced patient- or PDX-derived gastric tumor tissue	quantitative gelation endpoint NR	nozzle; 35 kPa	e resolution NR		day 28; exact percentage NR			endogenous stromal cells; optional human gastric fibroblasts	3-day exposure	mechanics, degradation, and actual feature resolution NR; limited prospective outcome validation 33/40 models established
Du et al., 2025 [35]	6.25% GelMA + 0.5% HAMA (150 kDa) + 0.125% LAP; 5 x 10 ⁶ primary cells/mL	405-nm light, 15 mW/cm ² for 20 s	Light-assisted extrusion in 48-well plates; 23G nozzle	6 x 6 x 0.8 mm grid; 0.2-mm layer height; 1.0-mm designed line width; actual width NR	Rheology/compression curves reported; numeric modulus NR	>80% through day 15	Enzymatic recovery demonstrated; degradation kinetics NR	Gastric cancer	Patient-derived gastric-cancer cell suspension retaining epithelial and stromal/immune markers	CellTiter-Glo 3D after 72 h; FLOT/XELO X/SOX components, CPT-11, and targeted agents; clinical correlation	(82.5%); surgical samples; retrospective/matched-outcome evidence; standardized cost and multicenter reproducibility not established

6.4. Clinical Validation and Regulatory Pathways

Regulatory requirements depend on intended use rather than on the label '3D bioprinting' itself. A construct used for exploratory research differs from an assay that reports patient-specific drug sensitivity, a software-assisted decision-support system, or an implantable therapeutic product. These applications may involve different expectations for manufacturing control, analytical validation, software oversight, biosafety, and clinical evidence. Authors should therefore state the intended use of each platform and avoid implying an established approval pathway where one has not been demonstrated ^[149,150,151,153] ^[121,122].

Translation of a patient-specific assay requires three linked forms of evidence. Analytical validity asks whether the platform measures response accurately and reproducibly; clinical validity asks whether the measured response is associated with patient outcome; and clinical utility asks whether use of the result changes treatment selection or improves outcomes relative to existing care. Much of the current literature establishes technical feasibility or biological concordance, while a smaller subset reports retrospective clinical associations ^[35,57]. These evidence levels are valuable but should not be presented as proof of readiness for routine clinical decision-making ^[121,122,124,125].

Prospective validation should enroll consecutive patients, prespecify treatment panels and response thresholds, and include failed or delayed models in the analysis. Where feasible, laboratory assessment and clinical outcome evaluation should be blinded or independently adjudicated. Performance should be reported using discrimination, calibration, uncertainty, and decision-impact measures rather than correlation alone. Multicenter studies are needed to test stability across laboratories, tumor types, sample sources, and treatment contexts, with direct comparison against PDO assays, molecular biomarkers, pathology, and current clinical decision pathways to establish the incremental value of bioprinting ^[121,122,124,125].

Governance must also address informed consent, sample provenance, return of research results, genomic and imaging data security, algorithm updates, and responsibility for discordant recommendations. If AI contributes to response classification, the model version, training population, external validation, preprocessing pipeline, and human oversight should be documented. These considerations support a cautious near-term position: patient-derived bioprinted models are best developed as complementary functional-testing platforms and drug-development tools while prospective evidence accumulates, rather than being described as conventional clinical diagnostic methods ^[121,122,124].

6.5. Enabling Technologies and Future Integration

Microfluidics, spatial profiling, multi-omics, automated imaging, and AI can extend the capabilities of bioprinted models, but they are enabling technologies rather than

functional biomaterials. Their value should be judged by a defined gain in perfusion control, biological measurement, analytical robustness, or clinical decision value. This distinction is important because increasing technological complexity can also increase cost, parameter uncertainty, and sources of variability^[154,155]. Integration should therefore be justified by an explicit performance gain rather than by technological novelty alone^[121,122].

Microfluidic perfusion can introduce dynamic drug supply and clearance, endothelial barriers, interstitial flow, and immune-cell trafficking that static cultures cannot reproduce. Recent bioprinted tumor-on-chip systems demonstrate that perfusion can alter drug availability and treatment response and can support real-time analysis of chemotaxis, infiltration, and multicellular communication^[131,156,157]. Nevertheless, tubing absorption, channel geometry, flow instability, bubble formation, and differences between imposed flow and human tumor perfusion complicate interpretation. Multi-organ configurations may capture systemic interactions, but each additional compartment increases parameter uncertainty and can reduce throughput^[158,159]^[86,121].

Spatial and single-cell profiling can identify which tumor, stromal, immune, and ECM features should be reconstructed and can reveal regional responses after treatment. AI may assist with bioink optimization, print-path selection, image segmentation, multimodal integration, and response classification^[133,154,155,160,161]. However, the current evidence base remains limited by low external-validation rates and sensitivity to changes in matrix, imaging system, tumor type, and laboratory conditions^[162]. Prospective use therefore requires representative training data, locked preprocessing, uncertainty reporting, external validation, and monitoring for model drift.

Time-responsive or 4D materials provide a distinct future direction when their shape, mechanics, permeability, or biochemical presentation changes after printing in response to a controlled stimulus^[163]. Such systems could model evolving fibrosis, treatment-induced matrix remodeling, or scheduled therapeutic release, but material responsiveness must be distinguished from ordinary culture-driven tissue change. A realistic translational roadmap is therefore staged: near-term efforts should prioritize standardized patient-derived workflows, quantitative reporting, and focused prospective validation; medium-term development can add perfusion and longitudinal molecular profiling; and longer-term platforms may combine validated AI with adaptive materials in closed-loop systems. This staged progression is more credible than assuming that all emerging technologies will converge immediately into routine care.

7. Conclusion and Outlook

This review proposes a function-oriented framework for 3D-bioprinted tumor platforms in which functional biomaterials are evaluated not as passive printable supports, but as interfaces that couple spatial tissue reconstruction, local therapeutic exposure, and measurable drug response. The central premise is that material composition, crosslinking, mechanics, degradation, and spatial patterning simultaneously influence biological fidelity and therapeutic transport. This perspective connects three activities that are often considered separately—patient-specific tumor reconstruction, localized or nanomedicine-enabled treatment, and functional drug-response assessment—while distinguishing the material matrix and incorporated functional components from patient-derived biological inputs and external enabling technologies.

Across the reviewed literature, the major opportunity is also the major challenge: increasing functional complexity does not necessarily produce a more clinically useful model. Spatially organized tumor-stroma, vascular, immune, and hypoxic niches can improve biological representation, but added compartments and responsive functions may increase printing difficulty, maturation time, batch variability, assay interference, and cost. Drug-loaded and stimuli-responsive materials can better reproduce local exposure, yet release behavior measured in simplified culture cannot be equated with clinical pharmacokinetics. Patient-derived constructs can retain clinically relevant heterogeneity, but establishment success, model attrition, and ex vivo response concordance remain incompletely characterized. These limitations indicate that platform quality should be judged by whether each added function improves a predefined biological or therapeutic decision, rather than by architectural complexity alone [35,40,57,147,148,149,152].

The translational priority is therefore to establish fit-for-purpose models with explicit performance criteria. Material and process characterization should be linked to measurable quality attributes, including print fidelity, mechanics, degradation, spatial drug distribution, time-resolved viability, and assay precision. Studies should also report the full clinical denominator, including failed or delayed patient-derived models, because establishment failure is part of real-world platform performance rather than an exception to be omitted. For personalized drug testing, turnaround time and cost should be calculated to an interpretable result, not merely to fabrication of a construct. These principles provide a direct bridge from the technical advances discussed in Sections 2–5 to the clinical feasibility, standardization, and validation framework in Section 6 [48,49,121,122,124,125].

Future progress will depend on disciplined integration of enabling technologies rather than indiscriminate accumulation of functions. Microfluidic perfusion, spatial and single-cell profiling, automated imaging, AI-assisted analysis, and time-responsive or

4D materials may improve selected workflows when their incremental value is demonstrated and independently validated [150,151,154,155,156,162,163]. In particular, AI-supported prediction should be evaluated as a clinical decision-support component with defined training populations, external validation, model-version control, uncertainty reporting, and human oversight, rather than as an automatic extension of image analysis. Likewise, nanomedicine should be integrated with bioprinting when the material architecture adds a demonstrable advantage in spatial exposure, delivery control, or response measurement—not simply because nanoparticles or responsive cargos are present.

Ultimately, 3D-bioprinted patient-derived tumor platforms are most appropriately positioned, at the current evidence stage, as complementary functional systems for mechanistic studies, therapeutic development, and treatment prioritization rather than as universally validated replacements for established clinical assays. Their contribution to precision oncology will depend on reproducible manufacturing, transparent quality control, clinically relevant turnaround, prospective multicenter evidence, and demonstration of clinical utility. The field should move from asking how complex a tumor can be printed to asking which material functions are necessary to answer a specific clinical question, how reliably that answer can be obtained, and whether acting on it improves patient-relevant outcomes [121,122,124,125].

Acknowledgments

None.

Funding

This work was supported by the Natural Science Foundation of Jiangsu Province (Grant No. BK20240738), the Basic Science (Natural Science) Research General Program of Jiangsu Provincial Colleges and Universities (Grant No. 24KJB360004) and Natural Science Foundation Project of Nanjing University of Chinese Medicine (No. XZR2024010).

Conflict of interest

The authors declare no conflicts of interest.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

References

- [1] Abuwatfa WH, Pitt WG, Hussein GA. Scaffold-based 3D cell culture models in cancer research. *J Biomed Sci.* 2024;31:7. doi:10.1186/s12929-024-00994-y.
- [2] Jung M, Ghamrawi S, Du EY, Gooding JJ, Kavallaris M. Advances in 3D bioprinting for cancer biology and precision medicine: from matrix design to application. *Adv Healthc Mater.* 2022;11(24):2200690. doi:10.1002/adhm.202200690.
- [3] Huang Z, Duan X, Ji J, et al. Deconstructing cancer in 3D: models, mechanisms, and personalized solutions. *Mol Cancer.* 2026;25(1). doi:10.1186/s12943-026-02704-8
- [4] Shukla P, Yeleswarapu S, Heinrich MA, Prakash J, Pati F. Mimicking tumor microenvironment by 3D bioprinting: 3D cancer modeling. *Biofabrication.* 2022;14(3):032002. doi:10.1088/1758-5090/ac6d11.
- [5] Branco F, Cunha J, Mendes M, Sousa JO, Vitorino C. 3D bioprinting models for glioblastoma: from scaffold design to therapeutic application. *Adv Mater.* 2025;37(18):2501994. doi:10.1002/adma.202501994.
- [6] Lv J, Du X, Wang M, Su J, Wei Y, Xu C. Construction of tumor organoids and their application to cancer research and therapy. *Theranostics.* 2024;14(3):1101-1125. doi:10.7150/thno.91362.
- [7] Dong Y, Zhou X, Ding Y, Luo Y, Zhao H. Advances in tumor microenvironment: applications and challenges of 3D bioprinting. *Biochem Biophys Res Commun.* 2024;730:150339. doi:10.1016/j.bbrc.2024.150339.
- [8] Yang Y, Kong Y, Cui J, Hou Y, Gu Z, Ma C. Advances and applications of cancer organoids in drug screening and personalized medicine. *Stem Cell Rev Rep.* 2024;20(5):1213-1226. doi:10.1007/s12015-024-10714-6.
- [9] Arani RM, Yousefi N, Hamidieh AA, Gholizadeh F, Sisakht MM. Tumor organoid as a drug screening platform for cancer research. *Curr Stem Cell Res Ther.* 2024;19(9):1210-1250. doi:10.2174/011574888X268366230922080423.

- [10] Yang J, Wang L, Wu R, et al. 3D Bioprinting in Cancer Modeling and Biomedicine: From Print Categories to Biological Applications. *ACS Omega*. 2024;9(44):44076-44100. doi:10.1021/acsomega.4c06051.
- [11] Qu J, Kalyani FS, Liu L, Cheng T, Chen L. Tumor organoids: synergistic applications, current challenges, and future prospects in cancer therapy. *Cancer Commun (Lond)*. 2021;41(12):1331-1353. doi:10.1002/cac2.12224.
- [12] Wang Y, Zhang L, Wang LZ, et al. The application of organoids in treatment decision-making for digestive system cancers: progress and challenges. *Mol Cancer*. 2025;24:222. doi:10.1186/s12943-025-02429-0.
- [13] Banerjee D, Singh YP, Datta P, et al. Strategies for 3D bioprinting of spheroids: A comprehensive review. *Biomaterials*. 2022;291:121881. doi:10.1016/j.biomaterials.2022.121881.
- [14] Li Y, Liu J, Xu S, Wang J. 3D Bioprinting: An Important Tool for Tumor Microenvironment Research. *Int J Nanomedicine*. 2023;18:8039-8057. doi:10.2147/IJN.S435845.
- [15] Wang X, Luo Y, Ma Y, Wang P, Yao R. Converging bioprinting and organoids to better recapitulate the tumor microenvironment. *Trends Biotechnol*. 2024;42(5):648-663. doi:10.1016/j.tibtech.2023.11.006.
- [16] Xie R, Yang J, Lu X, et al. Physiologically relevant 3D tumor models for therapeutic screening. *Biomaterials*. 2026;334:124231. doi:10.1016/j.biomaterials.2026.124231.
- [17] Mazzaglia C, Shery Huang YY, Shields JD. Advancing tumor microenvironment and lymphoid tissue research through 3D bioprinting and biofabrication. *Adv Drug Deliv Rev*. 2025;217:115485. doi:10.1016/j.addr.2024.115485.
- [18] de Barros NR, Gomez A, Ermis M, et al. Gelatin methacryloyl and laponite bioink for 3D bioprinted organotypic tumor modeling. *Biofabrication*. 2023;15(4):045005. doi:10.1088/1758-5090/ace0db.
- [19] Chakraborty A, Roy A, Ravi SP, Paul A. Exploiting the role of nanoparticles for use in hydrogel-based bioprinting applications: concept, design, and recent advances. *Biomater Sci*. 2021;9(19):6337-6354. doi:10.1039/D1BM00605C.
- [20] Fernandes PD, Silva FC, Magalhães FOD, Pereira RBF, Santos SG, Pinto AM. 3D printing of nanoparticle-containing scaffolds for cancer phototherapy, magnetic hyperthermia therapy, and tissue regeneration. *Acta Biomater*. 2026;210:221-279. doi:10.1016/j.actbio.2025.11.043.
- [21] Iyer KS, Bao L, Zhai J, et al. Microgel-based bioink for extrusion-based 3D bioprinting and its applications in tissue engineering. *Bioact Mater*. 2025;48:273-293. doi:10.1016/j.bioactmat.2025.02.003.
- [22] Hull SM, Lou J, Lindsay CD, et al. 3D bioprinting of dynamic hydrogel bioinks enabled by small molecule modulators. *Sci Adv*. 2023;9(13):eade7880. doi:10.1126/sciadv.ade7880.
- [23] Zhang C, Shen Y, Huang M, et al. Dynamic hydrogel mechanics in organoid engineering: from matrix design to translational paradigms. *Bioact Mater*. 2026;55:144-170. doi:10.1016/j.bioactmat.2025.09.021.

- [24] Wang Y, Duan Y, Yang B, Li Y. Nanocomposite hydrogel bioinks for 3D bioprinting of tumor models. *Biomacromolecules*. 2024;25(8):5288-5299. doi:10.1021/acs.biomac.4c00671.
- [25] Jeong W, Kim D, Wajih N, et al. The effect of stiffness on cell behavior and drug resistance in patient-derived breast cancer organoids. *Acta Biomater*. 2026;210:27-39. doi:10.1016/j.actbio.2025.12.026.
- [26] Blanco-Fernandez B, Bagci G, Perez-Amodio S, et al. A bioprinted breast cancer model using bioinks of decellularized breast tissue for studying cancer stemness, invasion, and drug efficacy. *Acta Biomater*. 2025;203:306-321. doi:10.1016/j.actbio.2025.07.054.
- [27] Yang R, Yu Y. Patient-derived organoids in translational oncology and drug screening. *Cancer Lett*. 2023;562:216180. doi:10.1016/j.canlet.2023.216180.
- [28] Fang T, Cao X, Ibnat M, Chen G. Stimuli-responsive nanoformulations for CRISPR-Cas9 genome editing. *J Nanobiotechnology*. 2022;20:354. doi:10.1186/s12951-022-01570-y.
- [29] Wei D, Sun Y, Zhu H, Fu Q. Stimuli-Responsive Polymer-Based Nanosystems for Cancer Theranostics. *ACS Nano*. 2023;17(23):23223-23261. doi:10.1021/acsnano.3c06019.
- [30] Vaskovich-Koubi D, Green Buzhor M, Krinsky A, et al. Patient-derived 3D-bioprinted models of pancreatic cancer: toward personalized therapy and overcoming tumor microenvironment challenges. *Adv Drug Deliv Rev*. 2025;225:115670. doi:10.1016/j.addr.2025.115670.
- [31] Jung M, Poltavets V, Skhinas JN, et al. High-throughput 3D engineered paediatric tumour models for precision medicine. *Mol Syst Biol*. 2025;21(12):6. doi:10.1038/s44320-025-00152-y.
- [32] Li M, Freeman S, Franco-Barraza J, et al. A bioprinted sea-and-island multicellular model for dissecting human pancreatic tumor-stroma reciprocity and adaptive metabolism. *Biomaterials*. 2024;310:122631. doi:10.1016/j.biomaterials.2024.122631.
- [33] Han J, Jeong HJ, Choi J, et al. Bioprinted patient-derived organoid arrays capture intrinsic and extrinsic tumor features for advanced personalized medicine. *Adv Sci (Weinh)*. 2025;12(20):2407871. doi:10.1002/advs.202407871.
- [34] Chen H, Wu Z, Gong Z, et al. Acoustic bioprinting of patient-derived organoids for predicting cancer therapy responses. *Adv Healthc Mater*. 2022;11(13):e2102784. doi:10.1002/adhm.202102784.
- [35] Du L, Zheng Z, Zhang K, et al. Exploring personalized prediction of clinical chemotherapy efficacy and revealing tumor heterogeneity using patient-derived 3D bioprinting gastric cancer models. *Mol Cancer*. 2025;24(1):259. doi:10.1186/s12943-025-02466-9.
- [36] Yi HG, Jeong YH, Kim Y, et al. A bioprinted human-glioblastoma-on-a-chip for the identification of patient-specific responses to chemoradiotherapy. *Nat Biomed Eng*. 2019;3(7):509-519. doi:10.1038/s41551-019-0363-x.

- [37] Dey M, Kim MH, Dogan M, et al. Chemotherapeutics and CAR-T Cell-Based Immunotherapeutics Screening on a 3D Bioprinted Vascularized Breast Tumor Model. *Adv Funct Mater.* 2022;32(52):2203966. doi:10.1002/adfm.202203966.
- [38] Germain N, Dhayer M, Dekiouk S, Marchetti P. Current advances in 3D bioprinting for cancer modeling and personalized medicine. *Int J Mol Sci.* 2022;23(7):3432. doi:10.3390/ijms23073432.
- [39] Yu J, Zhang Y, Ran R, et al. Research progress in the field of tumor model construction using bioprinting: a review. *Int J Nanomedicine.* 2024;Volume 19:6547-6575. doi:10.2147/IJN.S460387.
- [40] Yao L, Xie P, Huang T, et al. 3D Bioprinting for Tumor Microenvironment Reconstruction: Advances, Challenges, and Future Perspectives. *Biotechnology Journal.* 2026;21(6). doi:10.1002/biot.70267
- [41] Parodi I, Di Lisa D, Pastorino L, Scaglione S, Fato MM. 3D bioprinting as a powerful technique for recreating the tumor microenvironment. *Gels.* 2023;9(6):482. doi:10.3390/gels9060482.
- [42] Aoun J, de Oliveira H, Fennell S, Diab-Assaf M, Caldefie-Chezet F, Delort L. 3D bioprinting for reproducing the tumor microenvironment in cancer research models. *Current Research in Biotechnology.* 2026;11:100385. doi:10.1016/j.crbiot.2026.100385
- [43] Xu J, Yang S, Su Y, et al. A 3D bioprinted tumor model fabricated with gelatin/sodium alginate/decellularized extracellular matrix bioink. *Int J Bioprint.* 2023;9(1):630. doi:10.18063/ijb.v9i1.630.
- [44] Wang H, Yu H, Zhou X, et al. An overview of extracellular matrix-based bioinks for 3D bioprinting. *Front Bioeng Biotechnol.* 2022;10:905438. doi:10.3389/fbioe.2022.905438.
- [45] Chen Q, Zhou R, Xu Q, Li Z, Tao J. dECM bioinks for 3D bioprinted tumor models: Advances, challenges, and drug screening. *iScience.* 2026;29(8):117085. doi:10.1016/j.isci.2026.117085
- [46] Tiwari AP, Thorat ND, Pricl S, Patil RM, Rohiwal S, Townley H. Bioink: a 3D-bioprinting tool for anticancer drug discovery and cancer management. *Drug Discov Today.* 2021;26(7):1574-1590. doi:10.1016/j.drudis.2021.03.010.
- [47] Xu H, Zhang S, Song K, Yang H, Yin J, Huang Y. Droplet-based 3D bioprinting for drug delivery and screening. *Adv Drug Deliv Rev.* 2025;217:115486. doi:10.1016/j.addr.2024.115486.
- [48] Gillispie G, Prim P, Copus J, et al. Assessment methodologies for extrusion-based bioink printability. *Biofabrication.* 2020;12(2):022003. doi:10.1088/1758-5090/ab6f0d.
- [49] Miri AK, Mirzaee I, Hassan S, et al. Effective bioprinting resolution in tissue model fabrication. *Lab Chip.* 2019;19(11):2019-2037. doi:10.1039/C8LC01037D.
- [50] Murab S, Gupta A, Włodarczyk-Biegun MGK, et al. Alginate based hydrogel inks for 3D bioprinting of engineered orthopedic tissues. *Carbohydr Polym.* 2022;296:119964. doi:10.1016/j.carbpol.2022.119964.

- [51] Ermis M, Falcone N, Roberto de Barros N, et al. Tunable hybrid hydrogels with multicellular spheroids for modeling desmoplastic pancreatic cancer. *Bioact Mater.* 2023;25:360–373. doi:10.1016/j.bioactmat.2023.02.005.
- [52] Dai X, Liu L, Ouyang J, et al. Coaxial 3D bioprinting of self-assembled multicellular heterogeneous tumor fibers. *Sci Rep.* 2017;7(1):1457. doi:10.1038/s41598-017-01581-y.
- [53] Gugulothu SB, Joseph JP, Chatterjee K. A 3D-bioprinted hydrogel platform with tunable matrix stiffness reveals mechanical adaptation and doxorubicin resistance in triple-negative breast cancer. *J Mater Chem B.* 2026;14(27):8460–8474. doi:10.1039/d6tb00892e
- [54] Kataki AD, Gupta PG, Cheema U, et al. Mapping tumor-stroma-ECM interactions in spatially advanced 3D models of pancreatic cancer. *ACS Appl Mater Interfaces.* 2025;17(11):16708–16724. doi:10.1021/acsami.5c02296.
- [55] González-Callejo P, Vázquez-Aristizabal P, García-Astrain C, et al. 3D bioprinted breast tumor-stroma models for pre-clinical drug testing. *Mater Today Bio.* 2023;23:100826. doi:10.1016/j.mtbio.2023.100826.
- [56] Yu IS, Li YCE, Chen PY, Chen KT, Lee IC. 3D bioprinted silk fibroin- and hyaluronic acid-based biomimetic extracellular matrices with tunable stiffness regulate glioblastoma invasion and macrophage polarization. *International Journal of Biological Macromolecules.* 2026;379:153883. doi:10.1016/j.ijbiomac.2026.153883
- [57] Choi YM, Na D, Yoon G, et al. Prediction of Patient Drug Response via 3D Bioprinted Gastric Cancer Model Utilized Patient-Derived Tissue Laden Tissue-Specific Bioink. *Adv Sci (Weinh).* 2025;12(10):e2411769. doi:10.1002/advs.202411769.
- [58] Shukla P, Bera AK, Yeleswarapu S, Pati F. High Throughput Bioprinting Using Decellularized Adipose Tissue-Based Hydrogels for 3D Breast Cancer Modeling. *Macromol Biosci.* 2024;24(8):e2400035. doi:10.1002/mabi.202400035.
- [59] Devarasetty M, Mazzocchi AR, Skardal A. Applications of bioengineered 3D tissue and tumor organoids in drug development and precision medicine: current and future. *BioDrugs.* 2018;32(1):53–68. doi:10.1007/s40259-017-0258-x.
- [60] Mierke CT. Bioprinting of cells, organoids and organs-on-a-chip together with hydrogels improves structural and mechanical cues. *Cells.* 2024;13(19):1638. doi:10.3390/cells13191638.
- [61] Bidan NG, Dunsmore G, Ugrinic M, et al. Multicellular tumor spheroid model to study the multifaceted role of tumor-associated macrophages in PDAC. *Drug Deliv Transl Res.* 2024;14(8):2085–2099. doi:10.1007/s13346-023-01479-5.
- [62] Ju M, Jin Z, Yu X, et al. Gastric Cancer Models Developed via GelMA 3D Bioprinting Accurately Mimic Cancer Hallmarks, Tumor Microenvironment Features, and Drug Responses. *Small.* 2025;21(8):e2409321. doi:10.1002/smll.202409321.
- [63] Immohr MB, Dos Santos Adrego F, Teichert HL, et al. 3D-bioprinting of aortic valve interstitial cells: impact of hydrogel and printing parameters on cell viability. *Biomed Mater.* 2023;18(1):015004. doi:10.1088/1748-605X/ac9f91.
- [64] Chang TW, Huang MW, Dong GC, Lee IC. Construction of a 3D bioprinted microfluidic platform to study breast cancer bone metastasis and tumor

- microenvironmental influences. *ACS Appl Mater Interfaces*. 2025;17(45):61718-61730. doi:10.1021/acsami.5c15529.
- [65] Li J, Parra-Cantu C, Wang Z, Zhang YS. Improving bioprinted volumetric tumor microenvironments In vitro. *Trends Cancer*. 2020;6(9):745-756. doi:10.1016/j.trecan.2020.06.002.
- [66] Bilotta MT, Antignani A, Fitzgerald DJ. Managing the TME to improve the efficacy of cancer therapy. *Front Immunol*. 2022;13:954992. doi:10.3389/fimmu.2022.954992.
- [67] Zhou B, Sun M, Yang M, Cui W, Yang H. Construction and application of multicellular tumor microenvironment models based on three-dimensional bioprinting technology. *Hepatobiliary Surg Nutr*. 2025;14(4):692-696. doi:10.21037/hbsn-2025-504.
- [68] Wu Y, Zhang F, Du F, Huang J, Wei S. Combination of tumor organoids with advanced technologies: a powerful platform for tumor evolution and treatment response (review). *Mol Med Rep*. 2025;31(6):140. doi:10.3892/mmr.2025.13505.
- [69] Bocheng X, França R. Innovative 3D bioprinting approaches for advancing brain science and medicine: a literature review. *Biomed Phys Eng Express*. 2024;10(6):062002. doi:10.1088/2057-1976/ad795c.
- [70] Choi J, Lee EJ, Jang WB, Kwon SM. Development of biocompatible 3D-printed artificial blood vessels through multidimensional approaches. *J Funct Biomater*. 2023;14(10):497. doi:10.3390/jfb14100497.
- [71] Albritton JL, Miller JS. 3D bioprinting: improving in vitro models of metastasis with heterogeneous tumor microenvironments. *Dis Model Mech*. 2017;10(1):3-14. doi:10.1242/dmm.025049.
- [72] Bertassoni LE. Bioprinting of complex multicellular organs with advanced functionality—recent progress and challenges ahead. *Adv Mater*. 2022;34(3):2101321. doi:10.1002/adma.202101321.
- [73] Tayler IM, Stowers RS. Engineering hydrogels for personalized disease modeling and regenerative medicine. *Acta Biomater*. 2021;132:4-22. doi:10.1016/j.actbio.2021.04.020.
- [74] Plava J, Cehakova M, Kuniakova M, et al. The third dimension of tumor microenvironment—the importance of tumor stroma in 3D cancer models. *Exp Biol Med* (Maywood). 2023;248(15):1347-1358. doi:10.1177/15353702231198050.
- [75] Pedron S, Wolter GL, Chen JWE, Laken SE, Sarkaria JN, Harley BAC. Hyaluronic acid-functionalized gelatin hydrogels reveal extracellular matrix signals temper the efficacy of erlotinib against patient-derived glioblastoma specimens. *Biomaterials*. 2019;219:119371. doi:10.1016/j.biomaterials.2019.119371.
- [76] Domingues MF, Carreira MC, Santos MS, et al. A 3D Bioprinted Spheroid-Laden dECM-Enriched Osteosarcoma Model for Enhanced Drug Testing and Therapeutic Discovery. *Adv Healthc Mater*. 2026;15(15):e03633. doi:10.1002/adhm.202503633.
- [77] An S, Jo S, Kim G. A mechanobiology-driven cell-derived ECM bioink for engineering 3D glioblastoma tumor microenvironment models. *Theranostics*. 2026;16(14):8361-8384. doi:10.7150/thno.137729

- [78] Stecher S, Schenk J, Cianciosi A, et al. 3D Bioprinted Breast Cancer-Stroma Model with Tailored Migration-Permissive Bioink Reveals Impact of Adipose-Derived Stromal Cells on Cancer Cell Migration and Invasion Dynamics. *Adv Healthcare Materials*. 2026;15(30). doi:10.1002/adhm.71353
- [79] Chen Y, Xue Y, Yan C, et al. Bioprinted Fibroblast Mediated Heterogeneous Tumor Microenvironment for Studying Tumor-Stroma Interaction and Drug Screening. *Adv Healthc Mater*. 2025;14(7):e2404642. doi:10.1002/adhm.202404642.
- [80] Xu K, Huang Y, Wu M, Yin J, Wei P. 3D bioprinting of multi-cellular tumor microenvironment for prostate cancer metastasis. *Biofabrication*. 2023;15(3). doi:10.1088/1758-5090/acd960.
- [81] Rasti Boroojeni F, Naeimipour S, Lifwergren P, et al. Proteolytic remodeling of 3D bioprinted tumor microenvironments. *Biofabrication*. 2024;16(2). doi:10.1088/1758-5090/ad17d1.
- [82] Desigaux T, Comperat L, Dusserre N, et al. 3D bioprinted breast cancer model reveals stroma-mediated modulation of extracellular matrix and radiosensitivity. *Bioact Mater*. 2024;42:316-327. doi:10.1016/j.bioactmat.2024.08.037.
- [83] Krajewska U, Chechlińska M, Kurzyk A. Vascularisation in 3D bioprinted models: emerging solutions engineering functional tissues and tumour models. *Biofabrication*. 2026;18(2):022001. doi:10.1088/1758-5090/ae2f02.
- [84] Zhao Y, Peng Y, Hu R, et al. Seamless vessel-microenvironment bioprinting reveals contact-dependent vascular communications. *Trends Biotechnol*. 2026;44(7):2140-2169. doi:10.1016/j.tibtech.2026.02.003.
- [85] Gao Q, Guo Z, Zhang S, et al. Coaxial bioprinting of microsphere bioink to engineer heterogeneous vascularized lung cancer model. *Biomater Adv*. 2026;183:214741. doi:10.1016/j.bioadv.2026.214741.
- [86] Neufeld L, Yeini E, Reisman N, et al. Microengineered perfusable 3D-bioprinted glioblastoma model for in vivo mimicry of tumor microenvironment. *Sci Adv*. 2021;7(34):eabi9119. doi:10.1126/sciadv.abi9119.
- [87] Grunewald L, Lam T, Andersch L, et al. A reproducible bioprinted 3D tumor model serves as a preselection tool for CAR T cell therapy optimization. *Front Immunol*. 2021;12:689697. doi:10.3389/fimmu.2021.689697.
- [88] Tang M, Xie Q, Gimple RC, et al. Three-dimensional bioprinted glioblastoma microenvironments model cellular dependencies and immune interactions. *Cell Res*. 2020;30(10):833-853. doi:10.1038/s41422-020-0338-1.
- [89] Zimmer J, Castriconi R, Scaglione S. Editorial: recent 3D tumor models for testing immune-mediated therapies. *Front Immunol*. 2021;12:798493. doi:10.3389/fimmu.2021.798493.
- [90] Naoi Y, Inukai Y, Izumikawa T, et al. Close Spatial Interactions between Cancer Cells and Cancer-Associated Fibroblasts Suppress Antitumor Immunity. *Cancer Immunol Res*. 2025;13(9):1471-1484. doi:10.1158/2326-6066.cir-24-1144.
- [91] Andersch L, Grunewald L, Stecklum M, et al. Investigating genetic modifications to enhance L1CAM-CAR T cell migration in solid tumors in a 3D bioprinted neuroblastoma model. *Front Immunol*. 2025;16:1677361. doi:10.3389/fimmu.2025.1677361.

- [92] Sun X, Zhang Z, Zhao W, et al. Prediction of CAR-T Therapy In Vitro: Development of Biomimetic Models for CAR-T Killing Effect Assessment. *Small*. 2025;21(37):e2503384. doi:10.1002/sml.202503384.
- [93] Kim D, Jo S, Lee D, et al. NK cells encapsulated in micro/macropore-forming hydrogels via 3D bioprinting for tumor immunotherapy. *Biomater Res*. 2023;27(1):60. doi:10.1186/s40824-023-00403-9.
- [94] Morley CD, Flores CT, Drake JA, Moore GL, Mitchell DA, Angelini TE. Spatiotemporal T cell dynamics in a 3D bioprinted immunotherapy model. *Bioprinting*. 2022;28:e00231. doi:10.1016/j.bprint.2022.e00231.
- [95] Heinrich MA, Bansal R, Lammers T, Zhang YS, Michel Schiffelers R, Prakash J. 3D-bioprinted mini-brain: a glioblastoma model to study cellular interactions and therapeutics. *Adv Mater*. 2019;31(14):e1806590. doi:10.1002/adma.201806590.
- [96] Tung YT, Chen YC, Derr K, Wilson K, Song MJ, Ferrer M. A 3D Bioprinted Human Neurovascular Unit Model of Glioblastoma Tumor Growth. *Adv Healthc Mater*. 2024;13(15):e2302831. doi:10.1002/adhm.202302831.
- [97] Yao EJ, Lu GY, Vadla R, et al. Forming a Precise and Reproducible Hypoxic Tumor Microenvironment in Glioblastoma by High Cell Density Bioprinting. *Adv Healthcare Materials*. 2026;15(26). doi:10.1002/adhm.71322
- [98] Wang X, Yang X, Liu Z, et al. 3D bioprinting of an in vitro hepatoma microenvironment model: Establishment, evaluation, and anticancer drug testing. *Acta Biomater*. 2024;185:173-189. doi:10.1016/j.actbio.2024.07.019.
- [99] Devarasetty M, Wang E, Soker S, Skardal A. Mesenchymal stem cells support growth and organization of host-liver colorectal-tumor organoids and possibly resistance to chemotherapy. *Biofabrication*. 2017;9(2):021002. doi:10.1088/1758-5090/aa7484.
- [100] Zhang Z, Chen X, Gao S, Fang X, Ren S. 3D bioprinted tumor model: a prompt and convenient platform for overcoming immunotherapy resistance by recapitulating the tumor microenvironment. *Cell Oncol (Dordr)*. 2024;47(4):1113-1126. doi:10.1007/s13402-024-00935-9.
- [101] Kim D, Jo S, Jang I, et al. Bioprinted Tumor Microenvironment Models Reveal Immune Evasion and Guide CAR-NK Therapeutic Strategies. *Advanced Science*. 2026;13(36). doi:10.1002/advs.202521188
- [102] Wang P, Sun L, Li C, et al. Study on drug screening multicellular model for colorectal cancer constructed by three-dimensional bioprinting technology. *Int J Bioprint*. 2023;9(3):694. doi:10.18063/ijb.694.
- [103] Ozturk MS, Lee VK, Zou H, Friedel RH, Intes X, Dai G. High-resolution tomographic analysis of in vitro 3D glioblastoma tumor model under long-term drug treatment. *Sci Adv*. 2020;6(10):eaay7513. doi:10.1126/sciadv.aay7513.
- [104] Liu C, Shi C, Wang S, et al. Bridging the gap: how patient-derived lung cancer organoids are transforming personalized medicine. *Front Cell Dev Biol*. 2025;13:1554268. doi:10.3389/fcell.2025.1554268.
- [105] Uwimana A, Gnecco G, Riccaboni M. Artificial intelligence for breast cancer detection and its health technology assessment: a scoping review. *Comput Biol Med*. 2025;184:109391. doi:10.1016/j.combiomed.2024.109391.

- [106] Chen H, Zhang B, Huang J. Recent advances and applications of artificial intelligence in 3D bioprinting. *Biophys Rev.* 2024;5(3):031301. doi:10.1063/5.0190208.
- [107] Wang J, Wang F, Jiang Y, Bai L, Chen X, Su J. Organoid-driven nanomedicine platform development. *Biomaterials.* 2026;325:123611. doi:10.1016/j.biomaterials.2025.123611.
- [108] Shboul SA, DeLuca VJ, Dweiri YA, Saleh T. Can 3D bioprinting solve the mystery of senescence in cancer therapy?. *Ageing Res Rev.* 2022;81:101732. doi:10.1016/j.arr.2022.101732.
- [109] Masoumi Shahrbabak S, Jalali SM, Fathabadi MF, et al. Modified alginates for precision drug delivery: Advances in controlled-release and targeting systems. *Int J Pharm X.* 2025;10:100381. doi:10.1016/j.ijpx.2025.100381.
- [110] Fu Y, Bian X, Li P, Huang Y, Li C. Carrier-Free Nanomedicine for Cancer Immunotherapy. *J Biomed Nanotechnol.* 2022;18(4):939-956. doi:10.1166/jbn.2022.3315.
- [111] Liu JY, Zheng YY, Wang SY, et al. Advances in carrier-free nanodrug delivery systems. *Drug Deliv and Transl Res.* 2026;16(8):2603-2621. doi:10.1007/s13346-026-02118-5
- [112] An J, Zhang Z, Zhang J, Zhang L, Liang G. Research progress in tumor therapy of carrier-free nanodrug. *Biomed Pharmacother.* 2024;178:117258. doi:10.1016/j.biopha.2024.117258.
- [113] Zhang X, Hu S, Huang L, et al. Advance Progress in Assembly Mechanisms of Carrier-Free Nanodrugs for Cancer Treatment. *Molecules.* 2023;28(20):7065. doi:10.3390/molecules28207065.
- [114] Guo Q, Lai L, Huang L, et al. Microfluidic fabrication of peptide modified carrier-free self-assembled crizotinib-metal nanodrugs for NIR fluorescence imaging and dual-pathway therapy of non-small cell lung cancer. *J Colloid Interface Sci.* 2026;711:140086. doi:10.1016/j.jcis.2026.140086.
- [115] Fu N, Guo L, Zhou S, et al. Cinnamaldehyde-Based Self-Assembled Nanodrugs with GSH Depletion for Antitumor through Photodynamic Therapy Enhanced Ferroptosis and Immunotherapy. *ACS Appl Mater Interfaces.* 2026;18(14):20247-20264. doi:10.1021/acsami.6c01928.
- [116] Zhao H, Yang C, Bao S, et al. Fe³⁺ loaded mastoparan M - ICG nanoassemblies for synergistic breast cancer therapy via photothermal and chemodynamic therapy-assisted oxidation stress. *iScience.* 2026;29(8):116740. doi:10.1016/j.isci.2026.116740
- [117] Cai S, Zhao J, Liu H, et al. Near-infrared light-triggered, self-amplifying targeted drug-delivery platform achieves precision treatment of retinoblastoma. *International Journal of Pharmaceutics.* 2026;701:127076. doi:10.1016/j.ijpharm.2026.127076
- [118] Troncoso-Afonso L, Vázquez-Aristizabal P, Vinnacombe-Willson GA, et al. dECM-Supported Printing of Plasmonic Pillars for SERS Monitoring of Chemotherapy in 3D Tumor Models. *ACS Sens.* 2025;10(9):7114-7123. doi:10.1021/acssensors.5c02344.

- [119] Shahpouri M, Adili-Aghdam MA, Mahmudi H, et al. Prospects for hypoxia-based drug delivery platforms for the elimination of advanced metastatic tumors: From 3D modeling to clinical concepts. *J Control Release*. 2023;353:1002-1022. doi:10.1016/j.jconrel.2022.12.009.
- [120] Zhang J, Luo X, Sun Z, Jin B, Zhao Y. Tumor Assembloids as Three-Dimensional Platforms for Modeling Drug Delivery Barriers: Construction Strategies, Applications, and Translational Challenges. *DDDT*. 2026;Volume 20:1-16. doi:10.2147/dddt.s618870
- [121] Ingber DE. Human organs-on-chips for disease modelling, drug development and personalized medicine. *Nat Rev Genet*. 2022;23(8):467-491. doi:10.1038/s41576-022-00466-9.
- [122] Marx U. Biology-inspired microphysiological systems to advance patient benefit and animal welfare in drug development. *ALTEX*. 2020;37(3):365-394. doi:10.14573/altex.2001241.
- [123] Herranz-Ors C, Bhosle SG, Beck AE, et al. A tumour-derived organoid biobank maps cancer gene dependencies. *Nature*. 2026;657(8132):765-774. doi:10.1038/s41586-026-10830-y
- [124] Letai A, Bhola P, Welm AL. Functional precision oncology: testing tumors with drugs to identify vulnerabilities and novel combinations. *Cancer Cell*. 2022;40(1):26-35. doi:10.1016/j.ccell.2021.12.004.
- [125] Vlachogiannis G, Hedayat S, Vatsiou A, et al. Patient-derived organoids model treatment response of metastatic gastrointestinal cancers. *Science*. 2018;359(6378):920-926. doi:10.1126/science.aao2774.
- [126] Maloney E, Clark C, Sivakumar H, et al. Immersion bioprinting of tumor organoids in multi-well plates for increasing chemotherapy screening throughput. *Micromachines (Basel)*. 2020;11(2):208. doi:10.3390/mi11020208.
- [127] Yang R, Wang S, Li Z, Yin C, Huang W, Huang W. Patient-derived organoid co-culture systems as next-generation models for bladder cancer stem cell research. *Cancer Lett*. 2025;625:217793. doi:10.1016/j.canlet.2025.217793.
- [128] Liu B, Cheng H, Yu K, et al. Biomimetic 3D-Bioprinted organoids of thymic epithelial tumors for translational drug screening and biomarker identification. *Mater Today Bio*. 2026;37:102878. doi:10.1016/j.mtbio.2026.102878.
- [129] Zhao Y, Li Y, Zhang W, et al. 3D-bioprinted liver cancer models derived from primary hepatocytes for simulating cancer initiation and drug screening. *Hepatol Commun*. 2025;9(11). doi:10.1097/hc9.0000000000000823.
- [130] Rizwan M, Mei X, Cai L, et al. A 3D-bioprinted head and neck cancer model for drug screening. *Biomed Mater*. 2026;21(4):045004. doi:10.1088/1748-605x/ae8069
- [131] Kremneva E, Smolander J, Peltokangas M, et al. Precision tumor-on-chip for personalized assessment of drug efficacy and immune cell delivery. *Cell Reports Methods*. 2026;6(8):101475. doi:10.1016/j.crmeth.2026.101475
- [132] Tong F, Nie R, Wu Z, et al. Construction of 3D bioprinted colorectal cancer models and evaluation of their efficacy and drug sensitivity. *APL Bioengineering*. 2026;10(3). doi:10.1063/5.0320497

- [133] Tang M, Jiang S, Huang X, et al. Integration of 3D bioprinting and multi-algorithm machine learning identified glioma susceptibilities and microenvironment characteristics. *Cell Discov.* 2024;10:39. doi:10.1038/s41421-024-00650-7.
- [134] Diosdi A, Toth T, Harmati M, et al. HCS-3DX, a next-generation AI-driven automated 3D-oid high-content screening system. *Nat Commun.* 2025;16:8897. doi:10.1038/s41467-025-63955-5.
- [135] Becceneri AB, Liu S, Yildirim S, et al. Advancing photocytotoxicity evaluation of nitric oxide derivative-ruthenium complex in 3D biofabricated breast cancer models. *Materials Today Bio.* 2026;39:103348. doi:10.1016/j.mtbio.2026.103348
- [136] Scrocciolani C, Caserio L, Grillo S, et al. 3D Bioprinting of High-Grade Serous Ovarian Cancer Cells: Workflow for Gelatin-Based Bioink Formulation with Hyaluronic Acid and Printability Assessment. *ACS Appl Bio Mater.* Published online June 26, 2026. doi:10.1021/acsabm.6c00299
- [137] Kirac MK, Bilge B, Ozdil CC, Tugcu T, Ulgen KO. 3D bioprinted melanoma constructs reveal delivery-dependent efficacy of phytochemical-gold nanoparticle formulations. *Biomed Mater.* 2026;21(3):035004. doi:10.1088/1748-605x/ae5ee7
- [138] Xu K, Wu J, Li Z, Chen W, Wei P, Wu M. The application of 3D cell culture for melanoma in vitro models. *Acta Biomater.* 2026;209:148-166. doi:10.1016/j.actbio.2025.11.039.
- [139] Kim GM, Lee Y, Park S, Kim I, Lee HR, Jung S. 3-Layer lung cancer invasion model for evaluating MMP-targeted anti-metastatic therapeutics. *Biomed Mater.* Published online June 26, 2026. doi:10.1088/1748-605x/ae834f
- [140] Si W, Zhou J, Jiang M. Lung cancer organoids for functional precision oncology: from disease modeling to clinical decision support. *Front Oncol.* 2026;16. doi:10.3389/fonc.2026.1864153
- [141] Majumder R, Datta P, Moolayadukkam S, Puri IK. Repurposing Alzheimer's and ovarian cancer drugs as sonosensitizers for glioblastoma via a positive-unlabeled learning and 3D bioprinting-based new approach methodology (NAM). *PLoS One.* 2026;21(8):e0354981. doi:10.1371/journal.pone.0354981
- [142] du Plessis J, Omar A. Patient-Derived Organoid-Based CRISPR Screens in Cancer Research: Applications, Advances, and Challenges. *Cancer Med.* 2026;15(8):e72112. doi:10.1002/cam4.72112
- [143] Mao S, Xie R, Shou J, Pang Y, Sun W. Bioprinting of patient-derived heterogeneous renal cell carcinoma organoids for personalized therapy. *Biofabrication.* 2025;17(4). doi:10.1088/1758-5090/adecc5.
- [144] Dai R, Chen W, Chen Y, et al. 3D bioprinting platform development for high-throughput cancer organoid models construction and drug evaluation. *Biofabrication.* 2024;16(3). doi:10.1088/1758-5090/ad51a6.
- [145] Mazzocchi A, Soker S, Skardal A. 3D bioprinting for high-throughput screening: drug screening, disease modeling, and precision medicine applications. *Appl Phys Rev.* 2019;6(1):011302. doi:10.1063/1.5056188.
- [146] Xia Y, Chen H, Li J, et al. Acoustic Droplet-Assisted Superhydrophilic – Superhydrophobic Microarray Platform for High-Throughput Screening of

- Patient-Derived Tumor Spheroids. *ACS Appl Mater Interfaces*. 2021;13(20):23489-23501. doi:10.1021/acsami.1c06655.
- [147] Ali ASM, Wu D, Bannach-Brown A, et al. 3D bioprinting of liver models: a systematic scoping review of methods, bioinks, and reporting quality. *Mater Today Bio*. 2024;26:100991. doi:10.1016/j.mtbio.2024.100991.
- [148] Grijalva Garces D, Strauß S, Gretzinger S, et al. On the reproducibility of extrusion-based bioprinting: round robin study on standardization in the field. *Biofabrication*. 2024;16(1):015002. doi:10.1088/1758-5090/acfe3b.
- [149] Agarwal T, Onesto V, Banerjee D, et al. 3D bioprinting in tissue engineering: current state-of-the-art and challenges towards system standardization and clinical translation. *Biofabrication*. 2025;17(4). doi:10.1088/1758-5090/ade47a.
- [150] Yang K, Wang L, Vijayavenkataraman S, Yuan Y, Tan ECK, Kang L. Recent applications of three-dimensional bioprinting in drug discovery and development. *Adv Drug Deliv Rev*. 2024;214:115456. doi:10.1016/j.addr.2024.115456.
- [151] Zhang Y, Huang Z, Wang B, Li B, Yang Y. Three-dimensional bioprinted organoids: advances and clinical translation. *Regenerative Biomaterials*. 2026;13. doi:10.1093/rb/rbag142
- [152] Li Y, Shi J, Zhang Q, Huang H, Zhou S. Three-Dimensional Bioprinting-Enabled Organoids for Engineering the Tumor Microenvironment. *Tissue Engineering Part B: Reviews*. Published online July 22, 2026. doi:10.1177/19373368261469463
- [153] Michael B, Jayaprakash N, Munivel N, Jaisankar D. 3D printing in drug delivery: emerging technologies, clinical translation, and the future of personalized medicine. *Med Drug Discov*. 2026;29:100242. doi:10.1016/j.medidd.2025.100242.
- [154] Piotrowska U, Tsoi J, Singh P, Banerjee A, Sobczak M. 3D bioprinting and artificial intelligence for tumor microenvironment modeling: a scoping review of models, methods, and integration pathways. *Mol Pharm*. 2025;22(10):5801-5823. doi:10.1021/acs.molpharmaceut.5c01062.
- [155] Zhang Z, Zhou X, Fang Y, Xiong Z, Zhang T. AI-driven 3D bioprinting for regenerative medicine: from bench to bedside. *Bioact Mater*. 2025;45:201-230. doi:10.1016/j.bioactmat.2024.11.021.
- [156] Jaiswal C, Dey S, Prasad J, Gupta R, Agarwala M, Mandal BB. 3D bioprinted microfluidic based osteosarcoma-on-a chip model as a physiomic mimetic pre-clinical drug testing platform for anti-cancer drugs. *Biomaterials*. 2025;320:123267. doi:10.1016/j.biomaterials.2025.123267.
- [157] Zhang C, Yang J, Xiao X, Yu W, Cai X. Spatial architecture and dynamic surveillance: 3D bioprinting and microfluidics converge to overcome digestive malignancies. *Hepatobiliary Surg Nutr*. 2026;15(4):115-115. doi:10.21037/hbsn-2026-0598
- [158] Strepì K, Koppenol RF, Jonkers J, Houthuijzen JM. Beyond the traditional dish: Advanced 3D ex vivo culture platforms for tumor modelling. *Seminars in Cancer Biology*. 2026;125:62-74. doi:10.1016/j.semcancer.2026.07.002

- [159] Murucci MD, Onikanni SA, da Cunha Goldstein A, et al. 3D bioprinted connections in Liver–Pancreas crosstalk: Lessons learned and future directions. *Molecular and Cellular Endocrinology*. 2026;618:112806. doi:10.1016/j.mce.2026.112806
- [160] Ibrahim MS, Kim M. Artificial Intelligence-Aided Microfluidic Cell Culture Systems. *Biosensors (Basel)*. 2025;16(1):16. doi:10.3390/bios16010016.
- [161] Xie T, Huang A, Yan H, Ju X, Xiang L, Yuan J. Artificial intelligence: illuminating the depths of the tumor microenvironment. *J Transl Med*. 2024;22(1):799. doi:10.1186/s12967-024-05609-6.
- [162] Lee JS, Cha JH, Kim BS. Artificial intelligence in 3D bioprinting and biofabrication: a validation-stringency assessment. *Biofabrication*. 2026;18(3):032003. doi:10.1088/1758-5090/ae7b07
- [163] Ashique S, Garg A, Islam A, et al. Exploring the role of 4D printing materials, techniques, and characteristics for personalized oncology. *Translational Oncology*. 2026;70:102818. doi:10.1016/j.tranon.2026.102818