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International Journal of Bioprinting

ACCEPTED PAPER · MAIN TEXT

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Article ID: IJB026190175

Citation: Alvarez-Lorenzo C, Pérez-Mañanes R, Vallet-Regí M. Clinical maturity of 3D printing and bioprinting technologies: A systematic analysis of clinical trials across medical applications. *Int J Bioprint*. 2026. doi: 10.36922/IJB026190175

AccScience Publishing
REVIEW ARTICLE
Volume X Issue X (2026)
doi: 10.36922/IJB026190175

Clinical maturity of 3D printing and bioprinting technologies: A systematic analysis of clinical trials across medical applications

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Citation: Alvarez-Lorenzo C, Pérez-Mañanes R, Vallet-Regí M. Clinical maturity of 3D printing and bioprinting technologies: A systematic analysis of clinical trials across medical applications. *Int J Bioprint.* 2026. doi: 10.36922/IJB026190175

Received: May 6, 2026
Revised: June 10, 2026
Accepted: June 10, 2026
Published online: June 11, 2026

Abstract

3D printing and bioprinting technologies are increasingly being integrated into clinical research and healthcare, enabling the development of patient-specific medical devices, anatomical models, and bioengineered constructs. This study analyzes registered clinical trials in ClinicalTrials.gov to characterize the current clinical landscape and relative degree of clinical maturity of medical 3D printing and bioprinting technologies across different application domains. Search terms included 3D printing, bioprinting, additive manufacturing, patient-specific devices, surgical guides, scaffolds, and biofabrication. Eligible studies involved human subjects and clinical applications related to diagnosis, treatment, surgical planning, or rehabilitation. The identified trials (ca. 700) were categorized into four main domains: patient-specific anatomical models, disease models, orthoses and assistive devices, and implantable prostheses and regenerative scaffolds. Anatomical models represent the most extensively translated application, with widespread use in surgical planning, procedural simulation, and patient communication across multiple specialties. Orthoses and assistive devices also account for a substantial proportion of studies, reflecting the growing adoption of digital workflows for personalized rehabilitation solutions. Implantable prostheses and scaffolds constitute a rapidly expanding area, particularly in orthopedics and maxillofacial surgery, where customization improves anatomical fit and functional outcomes. In contrast, bioprinting-based disease models and regenerative constructs remain limited to early-stage clinical investigations. Overall, the distribution and design of clinical trials reveal a gradient of translational development, with mechanically driven applications showing broader clinical adoption than biologically complex systems. Continued advances in materials, manufacturing processes, and regulatory frameworks will be critical to support large-scale clinical validation and broader implementation of these technologies in personalized and regenerative medicine.

Keywords: Additive manufacturing; Clinical trial; Personalized medicine; Implantable prostheses; Orthoses; Surgical planning; Regenerative medicine; Bioprinted disease models

1. Introduction

3D printing, also known as additive manufacturing, has emerged as a transformative technology in modern medicine, enabling the fabrication of complex, patient-specific structures directly from digital models. By building objects layer by layer, 3D printing allows unprecedented flexibility in design and customization compared to conventional manufacturing techniques. In parallel, advances in imaging, computer-aided design, and biomaterials have facilitated the integration of these technologies into clinical workflows, supporting applications ranging from anatomical modeling, surgical guides and orthotic devices to implant fabrication and, more recently, bioprinting of living tissues.[1-3] Despite this rapid technological progress, the translation of 3D printing from experimental development to routine clinical practice remains heterogeneous across medical domains. Understanding the extent to which these technologies have been validated in clinical settings is essential to assess their true impact and future potential.

1.1 Emergence of 3D Printing in Medicine

The adoption of 3D printing in medicine has been driven by the convergence of several technological advances. High-resolution imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI), enable the accurate reconstruction of patient-specific anatomy. These data can be optimized using artificial intelligence (AI) tools, processed using segmentation software and translated into digital 3D models, which are then fabricated using additive manufacturing techniques.[4] Concurrently, improvements in printing technologies—including stereolithography, selective laser sintering, semi-solid extrusion, and fused deposition modeling—have expanded the range of printable materials and achievable structural complexity.[5,6] Integration of AI-assisted Quality-by-Design (QbD) and combination with complementary fabrication technologies such as electrospinning or laser processing have notably improved the quality control of printable formulations, model structure, printing process, and final functionality.[7-9]

These developments have enabled the production of customized medical devices and models tailored to individual patients. Early applications focused on anatomical replicas for visualization and surgical planning, particularly in complex cases involving craniofacial, cardiovascular, and

orthopedic structures.[10] Over time, the scope of applications has expanded to include functional devices such as orthoses and prostheses, as well as implantable components with controlled mechanical and structural properties.[11,12] More recently, bioprinting approaches have been introduced, incorporating living cells and biological elements to create tissue-like constructs with potential applications in regenerative medicine.[13-15]

1.2 Clinical Translation of 3D Printing Technologies

The clinical translation of 3D printing technologies reflects a gradual shift from proof-of-concept studies to practical applications with measurable clinical benefits. In surgical disciplines, patient-specific anatomical models are increasingly used to enhance preoperative planning, improve spatial understanding and procedural accuracy, and reduce operative time.[16] Similarly, customized surgical guides and implants have been developed to improve precision and outcomes in procedures such as joint replacement, spinal fusion, osteotomies and maxillofacial reconstruction.[17,18]

Beyond surgical applications, 3D printing has also been applied in rehabilitation, where personalized orthoses and assistive devices can be rapidly designed and fabricated to meet individual patient needs. These devices often offer improved comfort, functionality, and accessibility compared to conventional alternatives. These technologies are increasingly applied in rehabilitation medicine for the fabrication of splints, ankle-foot orthoses, and other assistive devices.[19,20] However, while mechanically driven applications have demonstrated clear clinical utility, more complex technologies—particularly those involving biological components—are still in earlier stages of translation.[21,22] The variability in clinical adoption across these domains highlights the need for systematic evaluation of existing clinical evidence.

In addition, physical anatomical models have been shown to improve communication among professionals and specialists from different fields, patient education and informed consent by enabling clearer visualization of disease and planned interventions.[23]

1.3 Relevance for Personalized and Regenerative Medicine

One of the most significant contributions of 3D printing in healthcare is its alignment with the principles of personalized medicine. By enabling the fabrication of patient-specific devices and implants, additive manufacturing supports tailored therapeutic approaches that account for individual anatomical and functional variability. This capability is particularly relevant in fields where precise anatomical fit is critical, such as orthopedics, dentistry, and reconstructive surgery.[24] Patient-specific implants have been successfully applied in cranio-maxillofacial reconstruction, orthopedic surgery, and spinal interventions, where accurate anatomical matching can improve surgical outcomes and reduce intraoperative adjustments.[25,26]

In addition, 3D bioprinting holds promise for advancing regenerative medicine by enabling the creation of biologically functional constructs that mimic native tissues. Advances in biomaterials and biofabrication technologies are accelerating the development of porous scaffolds designed to support tissue regeneration.[27] Bioprinting technologies aim to replicate the structural and functional characteristics of biological tissues, facilitating the creation of engineered tissue models and potentially implantable living constructs.[28] Although still largely experimental, these approaches aim to address limitations in current treatments, such as the shortage of donor tissues and the challenges of tissue integration. The combination of personalized design with biologically active materials represents a potential paradigm shift in the development of next-generation therapies.

In parallel, bioprinted disease models and organoids have emerged as promising tools for studying disease mechanisms and predicting therapeutic responses. By incorporating patient-derived cells within biomimetic matrices, these constructs can replicate key aspects of the tumor microenvironment or tissue pathology, enabling more accurate evaluation of drug efficacy and personalized treatment strategies.[29-31] Although most of these approaches remain in the experimental or early translational stages, several recent clinical studies have begun exploring their potential applications in precision oncology.

Despite the growing number of studies investigating medical applications of 3D printing, the clinical translation of these technologies remains heterogeneous across different application domains. While anatomical models and orthotic devices are increasingly integrated into clinical practice, implantable devices and bioprinted constructs face additional challenges related to regulatory approval, manufacturing standardization, and long-term safety evaluation.[32]

Understanding the current landscape of clinical research is therefore essential to identify emerging trends and remaining barriers to clinical adoption.

1.4 Objectives of the Review

Earlier reviews of the clinical applications of 3D printing, conducted about a decade ago, highlighted the opportunities and challenges associated with the initial generation of prototypes and clinical products.[33,34] However, given the rapid expansion of 3D printing technologies and their diverse medical applications occurred in the last few years, a comprehensive assessment of their clinical maturity is warranted. This review aims to systematically analyze clinical trials registered in ClinicalTrials.gov involving 3D-printed and bioprinted structures used as anatomical models, disease models, orthoses and assistive devices, and implantable prostheses or regenerative scaffolds. By examining study designs, clinical indications, and reported outcomes, this review seeks to provide an overview of the current state of clinical translation of 3D printing and bioprinting technologies, identify trends across application domains, and highlight key challenges and future directions for research and clinical implementation. Unlike previous reviews that focused on individual medical specialties or specific technological applications, the present work systematically compares the clinical trial landscape across the major domains of medical 3D printing and bioprinting. This cross-domain perspective enables the identification of shared translational barriers, differences in evidentiary maturity, and broader patterns governing clinical adoption. In the present work, the term ‘clinical maturity’ is used qualitatively to describe the relative degree of clinical translation, adoption, and evidentiary development across application domains, rather than as a formal quantitative scoring system.

2. Methods

2.1 Data Source and Search Strategy

A systematic search was conducted in the ClinicalTrials.gov database to identify clinical studies involving 3D printing and bioprinting technologies in medicine. The initial search included the terms “3D printing”, “3D printed”, “3D bioprinting”, and “3D bioprinted”. These terms were

selected to capture the broad spectrum of additive manufacturing applications in clinical research, including both device-based and biologically oriented approaches.

The initial search yielded 308 records for “3D printing”, 635 records for “3D printed”, and 8 records each for “3D bioprinting” and “3D bioprinted” (**Figure 1**). All records were screened and consolidated, and duplicate entries across search terms were removed. The search was limited to studies involving human subjects and clinical applications. No restrictions were applied regarding study status, allowing inclusion of completed, ongoing, and terminated trials to provide a comprehensive overview of the field.

ClinicalTrials.gov was selected as the primary source because it is the largest individual clinical trial registry worldwide, containing studies funded by both public and private organizations and conducted across more than 220 countries and territories. To minimize the possibility of missing relevant studies, supplementary exploratory searches were also performed in ClinicalTrials.gov and in the EU Clinical Trials Register/Clinical Trials Information System (EU-CTR/CTIS). Expanded search terms included “additive manufacturing”, “patient-specific implant”, “customized prosthesis”, “surgical guide”, “printed scaffold”, “CAD/CAM device”, “biofabrication”, “personalized regenerative device”, and “tissue-engineered construct”. These searches yielded a limited number of additional records involving 3D printing or bioprinting technologies: 34 for additive manufacturing, 67 for patient-specific implant, 27 for customized prosthesis, 74 for surgical guide, 15 for printed scaffold, 21 for CAD/CAM device, and 2 for biofabrication. After removal of duplicate records, the expanded search strategy contributed 44 additional studies to the 648 studies retrieved through the initial search.

The nearly 700 records identified reflect the rapid expansion of additive manufacturing in medicine, driven by advances in medical imaging, digital modeling, computer-aided design, and biomaterials that enable the fabrication of patient-specific devices and constructs. Crowns and dentures, although fitting in the prosthesis section, are shown separately in **Figure 1** to highlight the prominence of this application, in good agreement with previous reports.[1,35]

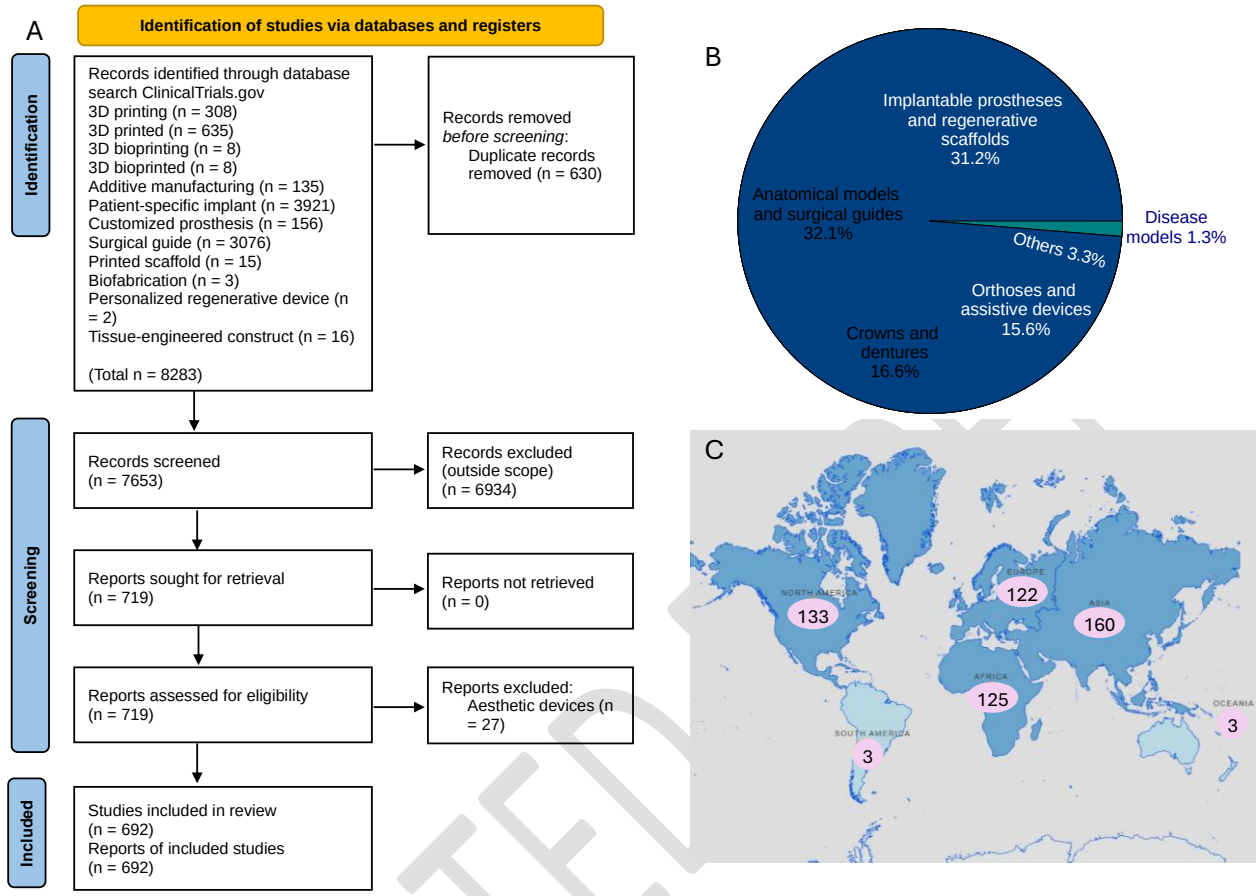

Figure 1. (A) PRISMA 2020 flow diagram for the systematic review of clinical trials involving 3D printing and bioprinting technologies retrieved from ClinicalTrials.gov; (B) pie chart showing the distribution of clinical trials across the main application domains; and (C) geographical distribution of clinical studies by region. Data were retrieved between April and May 2026.

2.2 Study Selection Criteria

Studies were included if they met the following criteria:

- Clinical trials involving the use of 3D-printed or bioprinted structures
- Human studies
- Clinical objectives related to diagnosis, treatment, rehabilitation, surgical planning, procedural simulation, or patient communication

Studies were excluded if they:

- Did not involve 3D printing or bioprinting technologies
- Were preclinical or animal studies
- Focused exclusively on software development, image-processing workflows, segmentation algorithms, or technical validation without a direct clinical application
- Represented duplicate records or incomplete registrations without sufficient information
- Focused on aesthetic, not clinical, outcomes.

The selection process involved screening study titles, summaries, and detailed descriptions to ensure relevance to the clinical applications of additive manufacturing.

2.3 Study Classification

Included studies were categorized into four main application domains according to the principal intended clinical function of the 3D-printed construct:

1. **Patient-specific anatomical models:** Physical replicas of patient anatomy generated from medical imaging data and used primarily for surgical planning, procedural simulation, education, or patient communication. Surgical guides were included in this category because their primary role is procedural assistance.
2. **Disease models:** Constructs designed to replicate pathological tissue environments or disease processes, including bioprinted tumor models, organoids, or biomimetic tissue constructs used for studying disease biology or predicting therapeutic responses.
3. **Orthoses and assistive devices:** Personalized external devices manufactured using additive manufacturing technologies to support rehabilitation, improve functional performance, or enhance patient comfort, such as prosthetic limbs, splints, braces, and rehabilitation aids.

4. **Implantable prostheses and regenerative scaffolds:** Implantable devices fabricated using additive manufacturing to replace or reconstruct damaged tissues, including patient-specific implants and biomaterial scaffolds designed to promote tissue regeneration.

Some studies involved multiple applications of 3D printing technologies. In such cases, classification was based on the primary intended clinical use of the printed construct. Although certain applications, such as patient-specific implants, regenerative scaffolds, surgical guides, or hybrid biofabricated constructs, could reasonably be assigned to more than one category, a single-category approach was adopted to facilitate comparative analysis across application domains.

An additional **"Other Applications"** category was included to compile studies involving physical therapies, pharmacological interventions, and miscellaneous clinical uses supported by 3D printing technologies.

This classification framework was designed to reflect both the functional role of the printed construct and its relative level of technological and translational complexity.

2.4 Data Extraction and Analysis

For each included study, data were extracted using standardized criteria, including clinical indication or disease area, type of 3D-printed construct, intended application, intervention type, study design, recruitment status, and available outcome measures.

Studies were analyzed descriptively and subsequently grouped according to the classification framework described above. Particular attention was given to trends in clinical application, study design, technological complexity, degree of personalization, and progression from feasibility studies to comparative clinical investigations. Study screening, eligibility assessment, and classification were performed independently by the three authors. Any uncertainties were discussed collectively, and final inclusion decisions were reached by consensus.

Representative studies within each category were selected to illustrate key applications, clinical achievements, and emerging trends. Because of the substantial heterogeneity in study designs, indications, endpoints, and reporting practices, quantitative meta-analysis was not considered

appropriate. Instead, a qualitative comparative synthesis was conducted to provide an integrated overview of the current state of clinical translation.

The concept of clinical maturity was used qualitatively throughout the analysis to compare the relative degree of clinical translation, adoption, evidentiary development, and integration into clinical practice across application domains. This assessment was based on comparative characteristics observable within the clinical trial landscape, including the volume and diversity of registered studies, progression from feasibility to comparative clinical designs, evidence of recurrent clinical use, and the degree of biological and regulatory complexity associated with each application domain. No formal scoring system, weighting scheme, or technology-readiness framework was applied.

2.5 Limitations of the Methodology

Several limitations should be considered when interpreting the findings of this review. First, the analysis relied primarily on information available in registered clinical trial records, which may provide limited methodological detail and may not reflect final published outcomes. Second, terminology within the field of 3D printing and bioprinting remains heterogeneous, creating the possibility that some relevant studies were not captured despite the expanded search strategy.

Third, because of the substantial heterogeneity of clinical applications, study designs, and reported endpoints, formal meta-analysis and standardized risk-of-bias assessment were not feasible. The analysis was based primarily on registry records rather than completed published studies with standardized outcome reporting, thus formal risk-of-bias assessment using conventional systematic review tools was not feasible. The present work should be interpreted as a systematic registry-based translational analysis with qualitative comparative synthesis rather than a meta-analysis of clinical outcomes. Similarly, the number of registered studies should not be considered as a direct measure of clinical effectiveness, comparative superiority, or routine adoption. Registry activity primarily reflects research interest, developmental progression, and translational efforts within a given application domain.

Finally, the qualitative assessment of clinical maturity should not be interpreted as a formal technology-readiness ranking system. No standardized maturity-assessment framework currently

exists for the diverse clinical applications encompassed by medical 3D printing and bioprinting. Therefore, the conclusions should be interpreted as an analysis of translational progress, evidentiary development, and clinical adoption patterns rather than a quantitative maturity evaluation.

Despite these limitations, ClinicalTrials.gov provides a comprehensive and standardized source for evaluating clinical research activity and translational trends in emerging medical technologies.

2.6 Study Selection Process and PRISMA Flow Description

The study selection process followed the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (**Figure 1**). All records identified through the search strategy were initially screened based on their titles, summaries, and study descriptions. After removal of duplicate entries, the remaining studies were assessed for eligibility according to the predefined inclusion and exclusion criteria.

During screening phase, 6968 studies were excluded because they did not involve 3D (bio)printing technologies or focused exclusively on computational algorithms, software validation, image segmentation workflows, or unrelated aesthetic procedures. Studies involving crowns and dentures were retained because they represent clinically relevant prosthetic applications. The remaining studies were evaluated in detail and included in the qualitative synthesis when they met all eligibility criteria. Each study was subsequently categorized according to its principal clinical application domain.

Classification was based primarily on the principal intended clinical function of the printed construct rather than exclusively on material composition or fabrication route. When studies involved overlapping features, classification priority was assigned according to the dominant translational objective. For example, surgical guides associated with implantation procedures were classified as procedural assistance tools rather than implantable devices, whereas biologically active scaffolds containing cells or regenerative components were distinguished from structurally passive implants and classified within regenerative applications.

3. 3D-Printed Anatomical Models and Surgical Guides

3D printing has been widely adopted for the fabrication of anatomical models, representing one of the earliest and most clinically mature applications of additive manufacturing in medicine. Generated from patient imaging data (mostly CT and MRI), these models provide accurate, tangible representations of individual anatomy, including complex structures and pathological conditions. Their primary function is to support preoperative planning, particularly in cases where spatial relationships are difficult to interpret using conventional imaging alone. By offering a physical, patient-specific reference, these models enhance anatomical understanding and facilitate surgical decision-making. In addition, their use extends to procedural simulation, medical education, and patient communication, including support for informed consent.

Compared with implantable or biologically active constructs, anatomical models have achieved a higher level of clinical translation.[36] This is largely due to their lower regulatory complexity and their seamless integration into established clinical workflows, making them one of the most accessible and widely implemented uses of 3D printing in healthcare.

3.1 Patient-Specific Anatomical Models for Surgical Planning and Procedural Simulation

Patient-specific anatomical models play a central role in surgical planning and intraoperative decision-making, particularly in complex cases involving intricate anatomical relationships. Derived from radiologic datasets, these models are converted into tangible, patient-matched physical replicas that allow surgeons to visualize and manipulate individualized anatomy prior to intervention. This facilitates improved spatial understanding, anticipation of procedural challenges, and refinement of surgical strategies. In the clinical trials reviewed, their primary use is to support anatomical comprehension, procedural rehearsal, and optimization of operative approaches before entering the operating room. Clinical applications span a broad range of surgical disciplines (**Table 1**).

3.1.1 Hepatobiliary surgery

Hepatobiliary surgery represents one of the most advanced areas of application. Several trials (NCT06526754, NCT06006338, NCT03744624, and NCT03074708) evaluate patient-specific liver models for planning resection in primary and secondary liver tumors. These models enable detailed visualization of intrahepatic vascular anatomy, segmental relationships, and resection

planes. More recent developments include reusable, self-healing liver models (NCT06006338, NCT06911086), which allow repeated simulation of surgical maneuvers.

Overall, these studies position 3D-printed liver models as tools to improve planning accuracy, operative efficiency, and surgical confidence, with common endpoints including operative time, blood loss, resection extent, and perioperative recovery.

3.1.2 Cardiovascular interventions

Cardiovascular applications constitute another major area of translation. In left atrial appendage occlusion, patient-specific atrial models are used to optimize transseptal puncture site selection, device sizing, and catheter alignment (e.g., NCT03330210, NCT05743322, and NCT07483008). Similarly, in transcatheter valve procedures, printed aortic models are evaluated for anatomical fidelity and procedural utility (NCT05484713).

Vascular applications extend to angioplasty and aortic aneurysm repair (NCT07000097, NCT06147024), where personalized models support procedural planning and enhance understanding of lesion morphology. Collectively, these studies highlight the growing role of 3D printing in device selection and procedural optimization.

3.1.3 Thoracic surgery

In thoracic surgery, 3D printing is applied to both planning and intraoperative guidance. For pulmonary nodule management, patient-specific localization templates have been evaluated (NCT02952261, NCT04056923) as alternatives to conventional CT-guided techniques, with the potential to streamline workflow and reduce imaging dependence.

Additional studies focus on anatomical lung models for segmentectomy and malformation resection. NCT03913416 evaluates flexible pulmonary models in pediatric surgery, while NCT06507774 explores multi-material, AI-assisted models with detailed subsegmental anatomy. Notably, NCT05695404 suggests that such models may reduce surgeon cognitive load and fatigue, indicating benefits beyond traditional operative metrics.

3.1.4 Urological surgery

Urological applications demonstrate particular value in complex oncologic procedures. In renal tumors with vascular involvement, NCT03738488 assesses whether biomodel-assisted planning

improves surgical precision compared with imaging alone. NCT03656822 evaluates combined 3D-printed and virtual visualization approaches, while NCT05960669 investigates intraoperative use of prostate models to guide selective resection during nerve-sparing prostatectomy.

These studies suggest that 3D-printed models are especially beneficial when surgical outcomes depend on precise differentiation between tumors, vasculature, and adjacent critical structures.

3.1.5 Orthopedic and trauma surgery

In orthopedic and trauma settings, anatomical models are primarily used to optimize reduction strategies and implant preparation. Trials involving acetabular fractures (NCT04660734), distal radius fractures (NCT05739240), distal tibia fractures (NCT02845245), and bone tumor resections (NCT06387485) demonstrate their utility in visualizing fragment orientation, pre-contouring fixation devices, and defining resection margins.

A consistent hypothesis is that improved preoperative planning translates into shorter operative times, reduced blood loss, and more accurate reconstruction. This approach is further reflected in NCT05741892, which evaluates point-of-care printed reposition guides for long bone fractures.

3.1.6 Maxillofacial and craniofacial surgery

Maxillofacial and craniofacial surgery represents one of the most mature domains of application due to its high demand for spatial precision. Trials such as NCT05733221 evaluate the use of printed models for mandibular fracture repair and plate pre-bending, while NCT04662190 examines their role in orbital decompression.

Reconstructive applications (NCT05672056, NCT03550053, NCT06898736) involve mandibular reconstruction and complex fracture fixation using integrated planning and printed guides. In this context, 3D printing enables accurate translation of virtual plans into surgical execution, improving structural alignment and aesthetic outcomes.

3.1.7 From passive anatomical models to active surgical guidance

A key translational trend is the shift from passive anatomical visualization to active surgical guidance. Many studies extend the same digital workflow to produce patient-specific guides, templates, splints, or positioning devices that transfer the preoperative plan directly to the operative field.[37]

This evolution is observed across multiple specialties, including guided endodontic microsurgery (NCT05283252, NCT06643676), spinal instrumentation (NCT02970578, NCT05487690, NCT05403775, NCT05632835), dental implant placement (NCT04061694, NCT06925438, NCT07149987), orthognathic surgery (NCT06132906, NCT04224805, NCT06188403, NCT06933628), and high tibial osteotomy (NCT04000672, NCT07212777, NCT04666571).

These approaches represent a higher level of clinical maturity, as the printed object becomes an interventional tool that constrains surgical actions—such as drilling, cutting, or positioning—thereby improving reproducibility and reducing operator-dependent variability.

3.1.8 Clinical Impact and Emerging Role

Clinical evidence consistently supports the utility of patient-specific anatomical models. In maxillofacial surgery, studies report improved planning accuracy and reduced operative time. The use of customized orbital reconstruction models and patient-specific implants has also been investigated to enhance anatomical precision and reduce complications, as illustrated in NCT03673865. In orthopedic, dental, and spinal procedures, 3D-printed models and guides contribute to improved implant positioning and alignment, resulting in more consistent outcomes.

Beyond preoperative planning, these models are increasingly integrated into surgical simulation workflows, allowing clinicians to rehearse procedures and evaluate alternative strategies. This contributes to procedural standardization and may reduce intraoperative uncertainty.

Overall, reported benefits across clinical trials include improved planning accuracy, enhanced operative efficiency, reduced operative time, and greater reproducibility. In addition, these models facilitate multidisciplinary communication by providing a clear and intuitive representation of patient anatomy, reinforcing their role as decision-support tools rather than direct therapeutic interventions.

Table 1. Representative clinical trials of patient-specific anatomical models and guide-assisted procedures

Clinical domain	Representative trials (NCT)	3D-printed application	Main clinical purpose	Typical endpoints
Hepatobiliary surgery	NCT06526754, NCT06006338, NCT03744624, NCT03074708, NCT06911086, NCT03153332, NCT06911086	Patient-specific liver models, including reusable self-healing models	Planning liver resection; vascular/anatomical understanding; repeated simulation	Operative time, blood loss, resection precision, hospital stay, planning efficiency
Gastric and abdominal surgery planning	NCT03599895	Preoperative visualization and surgical strategy	Radical gastrectomy; complex abdominal procedures	Operative efficiency, decision-making, intraoperative difficulty
Cardiovascular interventions	NCT03330210, NCT05743322, NCT07483008, NCT05484713, NCT07000097, NCT06147024, NCT07039838, NCT05852106	Left atrial appendage, aortic valve, vascular, and aortic lesion models, and congenital heart disease.	Device sizing, transseptal puncture planning, TAVI/LAAO strategy, aneurysm/angioplasty planning	Procedural success, device selection accuracy, complications, operative efficiency
Thoracic surgery	NCT02952261, NCT04056923, NCT03913416, NCT06507774, NCT05695404	Pulmonary anatomy models and navigational templates	Nodule localization, segmentectomy planning, pulmonary malformation resection	Localization accuracy, safety, surgeon workload, procedural efficiency
Urologic surgery	NCT03738488, NCT03656822, NCT05960669	Renal and prostate models	Planning nephron-sparing or oncologic surgery; margin-oriented resection	Planning accuracy, operative metrics, margin status, functional outcomes
Orthopedic and trauma surgery	NCT04660734, NCT05739240, NCT02845245, NCT06387485, NCT05741892	Fracture models and reduction/planning guides	Plate contouring, fracture reduction, tumor resection planning	Reduction quality, operative time, blood loss, complication rates

Clinical domain	Representative trials (NCT)	3D-printed application	Main clinical purpose	Typical endpoints
Maxillofacial and craniofacial surgery	NCT05733221, NCT04662190, NCT05672056, NCT03550053, NCT06898736	Mandibular, orbital, and reconstructive models/guides	Fracture fixation, orbital decompression planning, fibula flap reconstruction	Positioning accuracy, operative time, reconstruction fidelity, healing
Spine and minimally invasive interventions	NCT02970578, NCT05487690, NCT05403775, NCT05632835	Patient-specific guide plates/modules	Pedicle screw insertion and needle trajectory guidance	Accuracy, radiation exposure, procedure duration, safety
Dental and endodontic guided procedures	NCT05283252, NCT06643676, NCT04061694, NCT06925438, NCT07149987	Surgical guides, implant guides, endodontic templates	Improve transfer accuracy of digital planning to surgery	Angular/linear deviation, stability, healing, operative time, complications

3.2. Medical training and surgical education

3D printed anatomical models are also widely used for medical training and surgical education. Traditional training methods often rely on cadaveric specimens or virtual simulations, which may have limitations related to availability, cost, or anatomical variability. In contrast, additive manufacturing enables the production of reproducible and anatomically accurate training models derived from real clinical imaging datasets.

Clinical trials have investigated the use of such models in the training of medical students, residents, and healthcare professionals. These studies report that physical anatomical models can improve spatial understanding of complex anatomy and enhance procedural training in various specialties, including cardiovascular interventions, thoracic surgery, and maxillofacial surgery.[38,39]

For example, 3D-printed models have been used to train clinicians in procedures such as cardiac catheterization, bronchoscopy, and airway management, allowing learners to practice procedural steps in a realistic anatomical context.[40] Although many of these studies focus on educational outcomes, they demonstrate the potential of additive manufacturing technologies to support simulation-based training and skill acquisition in clinical environments.

3.3 Anatomical Models for Patient Communication and Medical Education

Although surgical planning dominates the literature, a substantial group of studies evaluates 3D-printed models as tools for patient understanding, informed consent, and shared decision-making (**Table 2**). In these trials, the value of the model lies not in intraoperative guidance, but in its capacity to make anatomy and pathology easier to grasp than 2D imaging or verbal explanations alone. Physical models provide an intuitive and accessible representation of anatomical structures, which can improve patient understanding of disease conditions and proposed treatments.

Table 2. Representative trials using 3D-printed models for patient communication

Clinical context	Representative trials (NCT)	Intended communication outcome
Orthognathic surgery	NCT07068412	Improve understanding of skeletal movements, reduce anxiety, improve informed consent
Breast cancer	NCT04693364, NCT05755984	Support treatment decision-making, reduce decisional conflict, improve communication
Complex fracture education	NCT04009252	Improve understanding, coping, satisfaction, and rehabilitation engagement
Renal disease / renal tumors	NCT06683573, NCT06379698, NCT06035211	Improve health literacy, understanding of disease and surgery, and reduce anxiety
Colorectal cancer	NCT06625008	Improve shared decision-making and reduce preoperative anxiety
Mohs surgery	NCT03461965	Improve patient understanding and satisfaction, reduce anxiety
Anal fistula	NCT04069728	Improve comprehension of anatomy and confidence in treatment decisions
Otolaryngology (Ear, Nose, Nose and Throat (ENT)) surgery	NCT02905344	Improve understanding of anatomy, disease, and operative plan

Clinical context	Representative trials (NCT)	Intended communication outcome
Brain tumor surgery	NCT04970615	Improve recall of information and satisfaction with consultation
Maternal-fetal attachment	NCT03883971, NCT04541121	Improve maternal behavior, and aid in smoking cessation

In orthognathic surgery, NCT07068412 directly evaluates whether 3D-printed jaw models improve informed consent relative to conventional 2D explanations. Similar patient-centered objectives are seen in breast cancer, where printed models are assessed as decision aids in NCT04693364 and NCT05755984. In colorectal cancer, NCT06625008 focuses explicitly on shared decision-making and anxiety reduction, while NCT04069728 addresses patient understanding and treatment confidence in anal fistula care.

Urologic applications are also prominent. NCT06683573 evaluates kidney models as tools to improve health literacy in patients with hypertension-related chronic kidney disease, while NCT06379698 and NCT06035211 examine personalized kidney models in the preoperative education of renal tumor patients. These studies are particularly relevant because they move beyond satisfaction alone and assess outcomes such as understanding, health literacy, trust, and anxiety.

Other examples include patient education in Mohs surgery (NCT03461965), ENT surgical counseling (NCT02905344), and brain tumor consultation (NCT04970615). Study NCT04541121 evaluates whether 3D models of the fetal face, generated from 3D ultrasound imaging, can enhance maternal–fetal attachment and support smoking cessation. Across these trials, a consistent underlying hypothesis is that tactile, patient-specific models improve the quality of clinical consultations by transforming abstract imaging data into intuitive, spatially comprehensible information.

Overall, this subgroup suggests that 3D-printed models may have meaningful value in communication-intensive specialties, particularly when anatomy is complex, surgery is anxiety-provoking, or patient participation in decision-making is important.

3.4. Limitations of Current Clinical Evidence

Despite the widespread adoption of 3D-printed anatomical models, several limitations affect the strength and generalizability of the current clinical evidence. A major concern is the methodological heterogeneity across studies. Many investigations are based on small sample sizes and single-center designs, often lacking robust control groups. In addition, outcomes are frequently assessed using indirect or surrogate measures—such as operative time, workflow efficiency, or user satisfaction—rather than standardized clinical endpoints, making it difficult to draw definitive conclusions regarding patient benefit.

Another important limitation relates to variability in model production. Differences in imaging quality, segmentation protocols, software workflows, and printing materials can significantly influence model accuracy and fidelity. This lack of standardization reduces reproducibility and complicates comparisons across studies, ultimately limiting the ability to establish consistent evidence-based guidelines.

Economic and practical considerations continue to shape the pace of broader implementation. While anatomical models are widely recognized as valuable tools, further evidence is still needed to fully establish their cost-effectiveness and long-term clinical impact. Factors such as production time, resource requirements, and the need for specialized technical expertise may currently limit routine adoption, particularly in resource-constrained settings. However, emerging evidence is encouraging. For example, recent work on a cost-effective 3D-printed skin model for biopsy training demonstrated significantly higher realism and training suitability compared with traditional fruit and foam models, while achieving comparable objective skill outcomes. Importantly, the model's reusability and low-cost materials support its sustainability, suggesting that well-designed 3D-printed solutions can overcome practical barriers and represent a promising, scalable innovation in medical education.[41]

Beyond surgical planning, anatomical models have demonstrated potential to enhance interdisciplinary communication and patient engagement. By providing a shared, tangible representation of anatomy, they can facilitate discussions among surgeons, radiologists, and other healthcare professionals, as well as improve patient understanding during preoperative counseling.[42] However, despite these advantages, their routine use in patient education remains limited, again due to logistical and economic barriers.

Overall, these considerations highlight both the versatility and the current limitations of patient-specific anatomical models. While their role in surgical planning is well established, further high-quality, multicenter studies with standardized evaluation criteria are needed to better define their clinical value. Importantly, these models should be distinguished from disease models, which aim to replicate pathological tissue environments for research and therapeutic testing. This emerging and more complex application domain is addressed in the following section.

4. Disease Models for Pathophysiological Investigation and Therapeutic Testing

Disease models represent a more advanced and conceptually distinct application of 3D printing, aiming to replicate pathological conditions rather than normal anatomy. In contrast to patient-specific anatomical models, which primarily reproduce structural features for visualization and surgical planning, disease models are designed to capture key biological and pathological characteristics of tissues or organs. These constructs may reproduce aspects of tissue architecture, disease microenvironment, and cellular interactions, enabling investigation of disease mechanisms and evaluation of therapeutic responses.[30,43,44]

Recent advances in 3D bioprinting and tissue engineering have enabled the fabrication of increasingly complex constructs incorporating living cells, biomaterials, and biochemical cues. Compared with conventional two-dimensional cell cultures, these biomimetic systems offer improved physiological relevance and may enhance the predictive value of preclinical testing. However, despite these technological advances, their translation into clinical trials remains limited.

A notable finding from the current registry analysis is the scarcity of true disease-replicating models in clinical studies (1.3%; **Figure 1**). From a translational perspective, disease models can be broadly divided into two categories: non-biological models, which replicate pathological anatomy, and biologically active models, including bioprinted constructs that incorporate living cells and aim to reproduce functional aspects of disease.

4.1 Non-Biological Disease Models

Non-biological disease models currently represent the most common form of disease modeling in clinical trials. These models are typically derived from imaging data and reproduce pathological anatomical features such as deformities, tumors, or vascular abnormalities. Their primary applications include diagnostic validation, procedural planning, and device testing.[45]

For example, in NCT05673473, 3D-printed scoliosis models were used to evaluate radiographic techniques, enabling controlled assessment of imaging parameters such as measurement reliability and radiation exposure. Similarly, NCT03149042 employed patient-specific coronary phantoms to validate computed tomography–derived fractional flow reserve measurements. Although highly valuable for improving diagnostic accuracy and standardization, such models function primarily as experimental or validation platforms rather than as true biological disease models.

In oncology and surgical planning, structural disease models are also used to represent tumor geometry and its spatial relationship with surrounding tissues, as explained in section 3. While these approaches improve understanding of disease extent and support intervention planning, they remain limited to anatomical representation and do not capture disease biology or therapeutic response.[46]

4.2 Bioprinted and Biologically Active Disease Models

Bioprinted disease models represent an emerging frontier in translational medicine, with the potential to replicate not only anatomical structure but also the biological function of diseased tissues. These constructs integrate living cells, extracellular matrix components, and bioactive materials to recreate tissue microenvironments, including tumor niches and organ-specific pathologies.[47-49]

A major area of development is the use of bioprinted tumor models in precision oncology. Several clinical studies (**Table 3**) explore the generation of patient-specific tumor constructs to predict therapeutic responses. For example, NCT06792149 investigates bioprinted gastric cancer models derived from patient tissue samples to evaluate chemotherapy sensitivity. Similarly, NCT05955092 focuses on pancreatic ductal adenocarcinoma, while NCT07437859 and NCT04755907 examine applications in hepatocellular carcinoma and colorectal cancer,

respectively. These models aim to reproduce the structural and biochemical features of the tumor microenvironment, enabling personalized treatment selection.

Beyond solid tumors, organoid-based and biomimetic disease models are also emerging. For instance, NCT03890614 investigates 3D organoid models derived from bone marrow aspirates in hematological malignancies, while NCT07250126 explores a biomimetic spine unit model to study degenerative disc disease. These approaches demonstrate the potential of bioprinting to reproduce complex disease processes by integrating structural, cellular, and molecular components.

Despite their promise, biologically active disease models remain at an early stage of clinical translation. Their potential lies in enabling patient-specific drug screening, treatment optimization, and prediction of therapeutic response, thereby supporting the development of precision medicine approaches.[50,51]

4.3 Clinical Maturity and Current Limitations

Compared with anatomical models, bioprinted disease models exhibit a significantly lower level of clinical maturity. Most registered studies are exploratory and focus on feasibility, technical validation, or methodological development rather than on demonstrating direct clinical benefit. This reflects both the complexity of replicating human disease and the challenges associated with translating bioprinted systems into clinical research.[52]

Several limitations contribute to this gap. First, current models often fail to fully reproduce the biological complexity of human disease, including cellular heterogeneity, dynamic interactions, and systemic influences. Second, substantial variability in fabrication processes, materials, and design strategies limits reproducibility and comparability across studies. Third, standardized clinical endpoints for evaluating the performance and impact of disease models are largely lacking. In addition, the cost, technical expertise, and infrastructure required for advanced bioprinting remain significant barriers to widespread adoption.

From a regulatory perspective, recent developments such as the FDA Modernization Act 2.0 and subsequent initiatives by FDA and EMA in new approach methodologies (NAMs), are expected to play an important role in accelerating the adoption of advanced in vitro models.[53,54] By

promoting the use of human-relevant testing platforms as alternatives to animal models, these frameworks may facilitate the integration of bioprinted disease models into drug development and clinical research pipelines.[55-57]

Despite these advances, the current clinical-trial landscape clearly indicates that true 3D-printed disease models capable of replicating tissue or organ pathology for therapeutic testing remain rare. Most applications continue to focus on anatomical replication or regenerative constructs, rather than on functional disease modeling. Nevertheless, disease models represent a critical bridge between preclinical research and clinical bioprinting applications. Their continued development has the potential to transform drug discovery, improve therapeutic decision-making, and enable more personalized treatment strategies. Achieving this will require further progress in model standardization, validation, scalability, and regulatory alignment to support their transition from experimental platforms to clinically impactful tools.

Table 3. Clinical trials investigating disease-specific 3D-printed or bioprinted models. These studies aim to replicate pathological tissue environments to investigate disease mechanisms, predict therapeutic responses, or develop personalized treatment strategies.

Disease model type	Clinical indication	Representative trials (NCT)	Model type	Primary research objective
Bioprinted gastric tumor models for drug response prediction	Gastric cancer	NCT06792149	Patient-derived 3D bioprinted tumor constructs	Evaluate chemotherapy response and identify personalized treatment strategies
Tumor microenvironment models for personalized therapy	Pancreatic ductal adenocarcinoma	NCT05955092	Bioprinted tumor microenvironment models	Predict treatment response and study tumor–microenvironment interactions
Tumor microenvironment models for hepatocellular carcinoma	Primary liver cancer	NCT07437859	Patient-specific bioprinted tumor constructs	Evaluate individualized therapeutic responses
Bioprinted tumor models for metastatic cancer	Colorectal cancer with/without liver metastases;	NCT04755907; NCT07112989	Bioprinted tumor models derived	Predict tumor progression and chemotherapy

Disease model type	Clinical indication	Representative trials (NCT)	Model type	Primary research objective
	Sarcomas and metastases from solid tumors		from surgical samples	efficacy and guide treatment decisions
Hematologic malignancy organoid models	Multiple myeloma and other hematologic cancers	NCT03890614	3D tumor organoids generated from marrow aspirates	Study disease biology and chemotherapy sensitivity
Biomimetic degenerative tissue models	Degenerative disc disease	NCT07250126	Bioprinted biomimetic spine unit integrating tissue engineering and transcriptomics	Investigate pathophysiology of disc degeneration
Bioprinted airway constructs for regenerative therapy	Tracheal defects after thyroid cancer surgery	NCT06051747	Patient-specific bioprinted tracheal construct	Evaluate feasibility and safety of airway regeneration
Engineered dermo-epidermal skin substitutes	Skin defects requiring reconstructive surgery	NCT04925323	Biofabricated dermo-epidermal tissue substitute	Assess regenerative potential and therapeutic feasibility

5. 3D-Printed Orthoses and Assistive Devices

5.1 Concept and advantages of patient-specific orthoses

Orthoses and assistive devices constitute one of the most active areas of clinical translation for 3D printing. In contrast to anatomical models, which are usually adjunctive tools for visualization or planning, orthoses are directly used by patients in daily life and therefore provide an important window into real-world clinical maturity. Their rapid expansion in clinical trials reflects a favorable combination of factors: relatively low manufacturing complexity, compatibility with surface scanning and digital design workflows, lower regulatory barriers than implantable devices, and immediate relevance to rehabilitation and chronic care.[12]

The core value of additive manufacturing in this domain is personalization. Conventional orthoses are often manually fabricated from plaster casts or thermoformed materials, processes that are labor-intensive and operator-dependent. In contrast, 3D printing allows the use of digital scans, computer-aided design, and reproducible manufacturing to generate devices tailored to the

patient's anatomy and functional needs. This approach has several theoretical and practical advantages: improved fit, reduced weight, better ventilation, easier reproducibility, digital archiving, and potentially lower production burden once workflows are established.[58,59]

Clinical trials repeatedly evaluate similar endpoints across orthotic categories, including comfort, fit, satisfaction, adherence, usability, pain relief, gait or upper-limb function, and feasibility of fabrication. Across the available NCTs, the strongest signal is not yet unequivocal superiority in all clinical outcomes, but rather consistent feasibility and high patient acceptability, especially where conventional devices are bulky, poorly ventilated, or difficult to customize. Thus, orthoses and assistive devices may be considered one of the clearest examples of a clinically maturing 3D-printing application.

5.2 Upper-limb orthoses and hand-related assistive devices

Upper-limb orthoses are among the most frequently studied 3D-printed rehabilitation devices. They include wrist splints, thumb carpometacarpal orthoses, finger splints, dorsal blocking orthoses, and functional splints for neurological rehabilitation. These applications are well suited to additive manufacturing because they require close anatomical conformity, low weight, and user comfort during prolonged wear.

Several trials focus on thumb carpometacarpal osteoarthritis. NCT05896410 compares a 3D-printed thumb orthosis with a conventional thermoplastic orthosis in a crossover design, evaluating pain, usability, function, satisfaction, fabrication time, and weight. Similarly, NCT04297943 examines 3D-printed versus thermoplastic splints for carpometacarpal osteoarthritis, incorporating not only pain relief and function but also adherence monitoring and joint mechanics. These studies are representative of a broader trend: 3D printing is being tested not merely as a substitute manufacturing route, but as a means to improve wearability and compliance.

Hand and wrist splinting has also been studied in more heterogeneous patient groups. NCT05320211 evaluates 3D-printed hand orthoses in chronic hand disorders, with attention to daily functioning, satisfaction, and production efficiency. NCT05597930 investigates the design and validation of a novel low-cost 3D-printed wrist and hand orthosis for conditions such as carpal tunnel syndrome and wrist drop. In fracture care, NCT04306796, NCT05346926, NCT05075135,

NCT05902442, NCT03848702, and NCT06312995 examine 3D-printed splints or braces as alternatives to plaster or conventional splints for distal radius and related fractures. Across these studies, recurring themes include improved comfort, lower weight, better hygiene, and comparable immobilization performance, although large comparative effectiveness datasets remain limited.

Finger splints and smaller assistive devices further illustrate the adaptability of additive manufacturing. NCT05903391 compares customizable 3D-printed finger splints with conventional splints for hypermobility and swan-neck deformity, emphasizing satisfaction and functional status. NCT05589324 assesses 3D-printed writing aids in patients with nerve injury, showing how the same digital personalization paradigm extends beyond classical orthoses to task-specific assistive devices. Likewise, NCT05519891 explores custom 3D-printed assistive devices for mobile device use in people with physical disabilities, highlighting the occupational and participatory dimensions of additive manufacturing.

Neurological rehabilitation is another important subgroup. In stroke survivors, 3D-printed functional splints and dynamic orthoses are under investigation in NCT06979934, NCT07243314, and NCT06271187, where outcomes include upper-limb motor recovery, muscle tone, range of motion, and satisfaction. These studies suggest a gradual transition from static support devices toward more active rehabilitation-oriented orthoses. In home-based rehabilitation, NCT04363944 evaluates a smartphone-supported system using 3D-printed tools for chronic stroke, indicating how printing technologies can be integrated with tele-rehabilitation and digital health platforms.

Pediatric and congenital upper-limb applications expand the scope further. NCT05024409 investigates an upper-extremity orthotic device in children with cerebral palsy, while NCT03122171 reports the use of low-cost 3D-printed upper-limb prosthetic devices combined with occupational therapy in the same population. Although these latter studies border the prosthetics category, they are relevant here because they reflect the same rehabilitative logic of personalized external support.

Overall, upper-limb devices represent one of the most clinically advanced categories in the orthosis literature. The evidence consistently supports feasibility and user acceptance, with growing efforts to demonstrate superiority in function and adherence.

5.3 Lower-limb orthoses, insoles, and gait-related devices

Lower-limb orthoses are another major domain of clinical translation, particularly in foot biomechanics, neurological gait impairment, osteoarthritis, and pressure off-loading. This area is especially rich in clinical trials because 3D printing offers clear practical advantages in the fabrication of insoles and ankle-foot orthoses, which are highly geometry-dependent and traditionally labor-intensive to produce.[60]

Foot orthoses are the most represented subgroup. NCT05896917 compares 3D-printed foot orthoses with prefabricated orthoses in flexible flatfoot, focusing on comfort, function, durability, and pain relief. NCT07022093 compares 3D-printed insoles with CNC-manufactured custom insoles in pes planus, using biomechanical and patient-reported endpoints. NCT05306886 and NCT05163418 similarly evaluate customized plantar orthoses in flat or high-arched feet. In runners, NCT06034210 studies personalized 3D-printed insoles for pain reduction and performance. For plantar fasciitis, NCT05707013 compares 3D-printed orthotics with traditional orthotics. Together, these studies show that 3D printing is becoming a practical route for delivering individualized insoles across both therapeutic and sports-related indications.

A particularly relevant translational theme is diabetic foot prevention.[61] NCT05301478 assesses patient-specific 3D-printed insoles designed to reduce plantar pressure in individuals at risk of ulceration. NCT03958539, NCT04630795, and NCT05843929 extend this concept to ulcer prevention and perfusion monitoring, reflecting an effort to link patient-specific geometry with measurable biomechanical risk reduction. These studies are important because they move beyond comfort and preference toward prevention-oriented endpoints with potentially high clinical and economic relevance.

Lower-limb orthoses for neurological conditions and gait disorders also feature prominently.[62] NCT05122949, NCT03770949, and NCT03965715 evaluate 3D-printed ankle-foot orthoses in stroke, cerebral palsy, spinal cord injury, and nerve palsy. Typical outcomes include gait performance, satisfaction, usability, and quality of life. NCT05947630 is particularly relevant from a health systems perspective, as it studies 3D-printed ankle foot orthosis (AFO) and knee ankle foot orthosis (KAFO) in low-resource settings and in relation to tele-rehabilitation access. These trials reinforce the idea that additive manufacturing may be particularly useful where conventional orthotic services are scarce or centralized.

Knee and spinal orthoses have also been investigated. NCT02873403 compares a 3D-printed knee brace with a standard brace in medial knee osteoarthritis, while NCT05814471 examines a brace fastening system incorporating 3D-printed components in gonarthrosis. For spinal deformity and posture, NCT03365804, NCT04282408, NCT06785207, and NCT06988046 study 3D-printed scoliosis or hyperkyphosis braces. These investigations repeatedly address comfort, compliance, correction efficacy, and patient experience—key issues in brace therapy, where treatment success often depends as much on wear tolerance as on biomechanical design.

Additional lower-limb or locomotor-related assistive devices broaden the category. NCT05878652 and NCT06524349 assess 3D-printed knee extenders in anterior cruciate ligament-related rehabilitation. NCT04668755 evaluates a 3D-printed sole in a Charcot restraint orthotic walker. NCT03900052, although not strictly a printed orthosis, illustrates the broader assistive-device logic by assessing a haptic biofeedback cane for unloading the arthritic knee.

Taken together, lower-limb applications show a relatively advanced stage of clinical maturity. They combine strong technical fit with clinically meaningful endpoints such as gait, pain, pressure redistribution, and functional mobility.[63] However, definitive long-term comparative data and cost-effectiveness analyses remain limited.

5.4 Orthoses and devices for burn, scar, craniofacial, and airway management

A particularly interesting subgroup includes orthoses developed for burn rehabilitation, scar management, airway interfaces, and craniofacial support. These applications showcase the ability of 3D printing to address complex surface geometries that are difficult to manage with conventional fabrication methods.

In burn and scar management, NCT06487910 evaluates a differential-pressure orthosis produced through 3D scanning and printing for post-burn hypertrophic scarring, while NCT04884789 investigates a transparent customized facial orthosis with silicone interface for post-burn facial scars. Although evidence remains early and includes withdrawn or pilot studies, the rationale is compelling: digital workflows may improve conformity over irregular facial contours and support more reproducible pressure therapy.[64]

Microstomia and maxillofacial rehabilitation provide additional examples. NCT06801535 studies a 3D-printed mouth splint in patients with microstomia, and NCT06413628 evaluates a 3D-printed threaded screw appliance for radiation-induced trismus. These devices are clinically meaningful because they respond to anatomically specific restrictions where standard devices may fit poorly or offer limited adjustability.

Airway and ventilation-related interfaces are another active area. Personalized non-invasive ventilation or continuous positive airway pressure (CPAP) masks are assessed in NCT02896751, NCT06224816, NCT06215391, NCT03519880, NCT04179123, and NCT02261857. Across pediatric sleep apnea, prematurity, chronic obstructive pulmonary disease (COPD), and craniofacial anomalies, the consistent clinical problem is poor fit of standard masks leading to leakage, skin injury, and poor adherence. These trials collectively suggest that patient-specific 3D-printed masks may be particularly valuable where facial anatomy deviates from standard commercial designs.

Further examples of anatomically personalized support include NCT07349433, which evaluates a 3D-printed airway fixation device in obese patients, and NCT04021095 and NCT06899711, which investigate 3D-printed external cranial protection devices after decompressive craniectomy. Although these are not orthoses in the narrow musculoskeletal sense, they belong to the broader category of personalized external supportive devices enabled by additive manufacturing.

This subgroup illustrates one of the strongest advantages of 3D printing in medicine: the capacity to fabricate patient-matched external devices for anatomically complex or non-standard body regions where industrially standardized products are often inadequate.

5.5 Dental, orthodontic, and oral appliance applications as assistive/orthotic systems

A substantial number of trials involve oral appliances that function as orthotic or assistive devices (16.6%; **Figure 1**). These include occlusal splints, retainers, aligners, mandibular advancement devices, maxillary expanders, myofunctional appliances, Twin Block appliances, space maintainers, and nasoalveolar molding systems. Although some of these overlap with dentistry and orthodontics rather than rehabilitation per se, they are relevant to this section because they are

patient-specific, externally worn or removable, and manufactured through digital additive workflows.[65,66]

Occlusal splints for temporomandibular disorders and bruxism are among the best represented. NCT06781138, NCT07433725, NCT04455672, NCT07371078, NCT04591899, NCT06138535, and NCT06652217 compare 3D-printed or digital splints with conventional appliances, addressing pain relief, patient satisfaction, clinical performance, adjustment burden, and durability. These studies suggest that digital splints are clinically viable and may improve fabrication efficiency and reproducibility, though long-term durability remains an important point of comparison.

Orthodontic aligners, retainers, and bonding trays represent another dense area of investigation. Trials such as NCT07496892, NCT07420777, NCT05018234, NCT07143370, NCT06823310, and NCT07098325 explore direct-printed aligners, shape-memory aligners, microbial colonization, and biological performance. Retainers and transfer trays are assessed in NCT05968625, NCT03572179, NCT03585881, NCT03363607, NCT06167278, NCT03564717, and NCT07318857. These trials collectively show that orthodontics has become a major translational environment for additive manufacturing, driven by digital workflows and the demand for patient-specific appliances.

Pediatric craniofacial orthoses are also notable. NCT06683560, NCT04334590, NCT04369638, NCT05940389, NCT06451276, NCT02845193, and NCT06970158 investigate 3D-printed nasoalveolar molding devices, aligners, or passive plates for cleft lip and palate. Here, the value proposition includes customization, reduction of conventional impression burden, and potential facilitation of repeated appliance adjustment during early growth.

Mandibular advancement devices for obstructive sleep apnea, such as NCT05461417, NCT05018234, and NCT06352658, extend oral orthotic applications into sleep medicine. These studies highlight another clinically mature use case for personalized fabrication, where comfort and adherence are central to therapeutic effectiveness.

Thus, oral and orthodontic appliances should be recognized as an important and rapidly growing subfield of medical 3D printing. Their high trial density reflects both technical readiness and an efficient interface between digital design and everyday clinical care.

5.6 Clinical outcomes evaluated across orthoses and assistive devices

Across the orthosis and assistive-device literature, several outcome domains recur consistently. The most common are comfort, fit, usability, and patient satisfaction, reflecting the central importance of wearability in external devices. Pain reduction is another frequent endpoint, especially in osteoarthritis, plantar fasciitis, temporomandibular disorders, and fracture immobilization. Functional outcomes vary by indication and include gait performance, balance, hand function, total active motion, bite stability, oral aperture, and device adherence.

Biomechanical and imaging endpoints are increasingly incorporated, particularly in insoles, braces, and craniofacial appliances. Examples include plantar pressure distribution, motion analysis, postural alignment, bone thickness, cone-beam computed tomography (CBCT)-based tooth movement, and radiographic correction.[67] Production-related variables such as fabrication time, need for adjustments, and feasibility of digital or remote workflows are also common, underscoring that clinical maturity in this field depends not only on therapeutic effectiveness but also on practical deployability.

This pattern suggests that orthosis trials often evaluate a composite notion of value: not simply whether the printed device works, but whether it is more comfortable, easier to produce, better tolerated, and more compatible with personalized care.

5.7 Challenges for clinical adoption

Despite the large number of trials (**Table 4**), important barriers remain before 3D-printed orthoses can be considered fully mature across all indications. First, clinical evidence is heterogeneous. Many studies are small, pilot, crossover, or feasibility trials, and endpoints are often non-uniform, which limits meta-analytic synthesis and strong comparative conclusions.[59] Second, long-term durability remains insufficiently studied in several appliance categories, especially where repeated loading, humidity, friction, or cleaning may alter material properties.[68]

Third, digital workflow advantages are not universal. Although scanning and printing may reduce manual labor, they require infrastructure, software expertise, and post-processing capabilities that are not yet evenly distributed. In some settings, cost savings may depend on scale, local

manufacturing organization, and reimbursement structures. Fourth, regulatory pathways vary depending on whether a device is categorized as a custom-made medical device, rehabilitation aid, or dental appliance, which can complicate implementation.[69]

Finally, personalization itself introduces challenges of standardization. While customized designs are a core strength of additive manufacturing, they also make inter-study comparison more difficult and require robust quality control. Thus, the field is clinically promising and already advanced in selected applications, but broader translation will require standardized manufacturing protocols, stronger comparative trials, durability studies, and cost-effectiveness data.

Table 4. Relevant clinical trials of 3D-printed orthoses

Orthosis category	Main indication	Representative trials	Comparator	Typical endpoints
Hand/wrist/thumb orthoses and splints	Thumb osteoarthritis, hand injuries, post-fracture immobilization, nerve injury	NCT05896410 hand orthosis vs thermoplastic; NCT04306796 made-to-measure hand splints; NCT05320211 hand orthoses; NCT05075135 wrist-based splints; NCT05902442 distal radius fracture splints; NCT05597930 wrist orthosis	Thermoplastic splints, plaster cast, standard splint	Comfort, fit, function, satisfaction, safety, acceptability
Finger splints	Swan-neck deformity, interphalangeal hypermobility	NCT05903391 custom finger splints	Conventional finger splints	Satisfaction, function, usability
Upper-limb stroke rehabilitation splints	Stroke rehabilitation and upper-limb recovery	NCT06979934 functional hand splints after stroke; NCT07243314 post-stroke upper-limb splints	Functional or conventional splints	Function, ADL, motor recovery, satisfaction
Assistive devices rather than immobilizing splints	Writing aid, universal cuff, pillbox	NCT05302141 assistive device for nerve injury; NCT05589324 writing assistive device; NCT03353038 pillbox; NCT03861845 pillbox adherence	Universal cuff, standard devices	Feasibility, ADL, adherence, satisfaction
Ankle-foot orthoses (AFOs)	Stroke, spinal cord injury, nerve palsy, cerebral palsy, neurological conditions	NCT05122949 customized 3D-printed AFO; NCT03965715 AFO improves gait; NCT05947630 access to telerehabilitation with AFO/KAFO; NCT03770949	Thermoformed or off-the-shelf AFOs	Gait, comfort, satisfaction, adherence, tele-rehab feasibility

Orthosis category	Main indication	Representative trials	Comparator	Typical endpoints
		pediatric AFOs; NCT06828653 digital vs traditional AFOs		
Knee orthoses/extenders	ACL surgery and rehabilitation	NCT06524349 customized knee extender; NCT05878652 Playmaker knee extender	Standard prehabilitation/rehab	Function, rehab adherence, postoperative outcomes
Spinal braces	Adolescent idiopathic scoliosis, hyperkyphosis	NCT03365804 new spinal brace concept; NCT06217510 automatic design/3D printing scoliosis braces; NCT06785207 varying flexibility scoliosis brace; NCT04282408 back braces for spinal deformity; NCT06988046 hyperkyphosis orthosis	Conventional brace/orthosis	Comfort, correction, wearability, function
Orthotic insoles/foot orthoses	Diabetes, flatfoot, foot deformity, plantar pressure	NCT05301478 diabetic insoles; NCT07022093 CAD/CAM insoles in flexible flatfoot; NCT04381039 insoles and biomechanics; NCT02895139 orthotic insoles; NCT07136649 custom insoles for foot deformities; NCT05163418 plantar orthoses validation; NCT05896917 flatfoot insoles	Standard care insole, molded, milled, other custom insole	Pressure redistribution, pain, gait, biomechanics, satisfaction
Burn/scar orthoses	Hypertrophic scar, microstomia	NCT06487910 differential pressure distribution orthosis; NCT07264218 microstomia orthosis	Standard care/conventional treatment	Scar control, fit, tolerance, function
Dental or craniofacial orthotic appliances	Myofunctional appliance, nasoalveolar molding, orthodontic devices, obturators	NCT04810286 myofunctional appliances; NCT04369638 for cleft lip and palate; NCT06683560 printed aligners for nasoalveolar treatment; NCT04422847/NCT04422964 3D obturator pilot	Prefabricated or conventional devices	Fit, comfort, treatment success, workflow efficiency
CPAP/NIV masks and facial interfaces	Sleep apnea, premature infants, ALS, ventilatory support	NCT02261857 3D-printed CPAP masks in children; NCT04179123 PAP therapy masks; NCT02972970 Aveera patient-matched CPAP mask; NCT06215391 customized NIV masks; NCT06224816 neonate nasal masks;	Traditional masks/interfaces	Fit, leakage, tolerance, feasibility, safety

Orthosis category	Main indication	Representative trials	Comparator	Typical endpoints
		NCT03519880 ALS printed masks		
Other personalized orthotic appliances	Ostomy appliance, toe spacer, hearing aid ear tips	NCT06310070 personalized ostomy appliance; NCT07267156 toe spacer; NCT07216937/NCT07228845 ear tip comfort	Standard appliance	Comfort, leakage, satisfaction, usability

6. Implantable Prostheses and Regenerative Scaffolds

6.1 From external personalization to implantable reconstruction

Implantable prostheses and regenerative scaffolds represent the most ambitious frontier of clinical translation in medical 3D printing. Unlike anatomical models or external orthoses, these applications place additively manufactured structures directly into the human body, where they must satisfy demanding requirements for sterility, mechanical reliability, biocompatibility, anatomical precision, and long-term clinical safety. As a result, this section provides the clearest view of where 3D printing has already achieved meaningful clinical maturity and where bioprinting remains emergent but strategically important.

The available clinical trials show that implantable applications have expanded rapidly across orthopedics, craniomaxillofacial surgery, spinal surgery, chest wall reconstruction, breast reconstruction, airway surgery, and dental/maxillofacial bone regeneration (**Table 5**). Most mature studies involve patient-specific metallic implants, especially porous titanium,[70] or polyetheretherketone (PEEK)-based devices designed to improve anatomical fit and osseointegration.[71] A second major group includes biodegradable or biomimetic scaffolds intended to support tissue regeneration rather than act solely as permanent structural substitutes. A smaller but particularly significant subgroup comprises true bioprinting-related studies, in which living cells, biological matrices, or tissue-engineered constructs are combined with printing technologies to produce regenerative implants.

Taken together, the trials in this section reflect a gradient of maturity. Permanent structural implants are the most clinically advanced; resorbable and regenerative scaffolds are expanding but still heterogeneous; and living bioprinted constructs remain few in number but are

disproportionately important because they signal the transition from additive manufacturing of devices to biofabrication of functional tissues.

6.2 Patient-specific metallic and polymeric implants: the most mature implantable category

The largest body of evidence concerns patient-specific or porous implants fabricated from titanium alloys, PEEK, magnesium alloys, or composite biomaterials. In these studies, the main translational advantage of 3D printing is the ability to match complex anatomy, create porous architectures favorable to tissue integration, and streamline reconstruction in anatomically difficult defects.

6.2.1 Orthopedic oncology and large bone defect reconstruction

One of the most established clinical niches for 3D-printed implants is reconstruction after tumor resection or major segmental bone loss. NCT05794594 evaluates a 3D-printed personalized extendable prosthesis for limb salvage in pediatric osteosarcoma, while NCT05616195, NCT06269354, NCT04466397, NCT03941028, and NCT04449211 address 3D-printed bone prostheses or individualized porous implants for long bone defects and limb salvage. These trials deal with situations in which conventional implants are often suboptimal due to unusual defect geometry, skeletal immaturity, or the need for personalized load-bearing reconstruction.

Similarly, NCT06180525 assesses osseointegration of 3D-printed porous collars in hip and knee resection prostheses, and NCT07072832 evaluates a custom 3D-printed shelf implant for adult hip dysplasia. In theses cases, the clinical value of additive manufacturing lies not only in shape matching but also in structural optimization at the bone–implant interface. This is especially relevant in oncologic and revision settings, where standard implants may not adequately restore anatomy or fixation.[72]

6.2.2 Craniomaxillofacial and cranial reconstruction

Craniofacial reconstruction is another highly mature field. NCT05291754 and NCT06782711 evaluate patient-specific 3D-printed PEEK skull implants in cranioplasty, with emphasis on safety, complication rates, functional recovery, and aesthetics. NCT02828306 complements these studies by examining a computer-based algorithm for improving design accuracy of patient-specific

cranial implants, highlighting that translational maturity depends not only on fabrication but also on robust digital planning.

In maxillofacial surgery, personalized fixation and reconstructive systems have been extensively investigated. NCT04635865, NCT03057223, and NCT03905005 evaluate 3D-printed patient-specific titanium plates in jaw reconstruction and orthognathic or mandibular surgery, comparing them with conventional plates or pre-flexed systems. NCT05348434 studies 3D-printed PEEK facial implants for maxillofacial deformities, and NCT06940115 compares CAD/CAM PEEK plates with titanium plates in subcondylar fractures. These trials consistently address reconstruction accuracy, surgical efficiency, fit, postoperative stability, and complication profiles, underscoring that maxillofacial surgery has become one of the most operationally advanced environments for patient-specific implantable devices.

Orbital reconstruction offers another example of a clinically mature implant application. NCT03608280, NCT04271137, NCT03673865, and NCT05438784 compare patient-specific porous titanium implants, PEEK onlays, or pre-adapted orbital implants with autografts, stock meshes, or prebent alternatives. These studies are notable because orbital reconstruction requires millimetric accuracy and therefore represent rigorous test cases for whether digital customization translates into better functional and esthetic outcomes.

6.2.3 Spinal and joint implants

Spinal implants form one of the densest bodies of implantable 3D-printing evidence. Trials such as NCT03647501, NCT04086784, NCT05696470, NCT05237908, NCT05023733, NCT04418817, NCT04566874, NCT05981222, and NCT06940453 evaluate 3D-printed titanium interbody cages or related spinal implants across lumbar fusion, XLIF, TLIF, ALIF, and multi-level anterior cervical discectomy and fusion (ACDF). Across these studies, the main questions are whether porous printed cages improve fusion, reduce subsidence, enhance screw stability, and produce better clinical outcomes than PEEK or titanium-coated alternatives.

This is one of the clearest examples of additive manufacturing reaching advanced clinical maturity: the implants are load-bearing, commercially deployed or under post-market study in several cases, and evaluated using clinically meaningful radiographic and patient-reported endpoints. The rationale is also strong from a materials perspective, as porous architectures can be tuned to

promote osseointegration and potentially reduce stiffness mismatch.[73] Studies such as NCT04167878 on biodegradable cervical cages and NCT05396222 on non-rigid biomimetic spinal implants indicate that innovation is now moving beyond shape customization toward mechanical and biological optimization.

Joint reconstruction trials further support this trend. NCT06287021 compares a 3D-printed highly porous titanium acetabular cup with a conventional cup in total hip arthroplasty, while NCT05773261 and NCT05651009 examine porous or 3D-printed components in hip and knee arthroplasty. NCT04963491 and NCT04950348 investigate personalized total knee arthroplasty prostheses and matching guides, reflecting the convergence of implant customization with surgical instrumentation.

Despite the high level of clinical maturity observed in patient-specific metallic and polymeric implants, emerging evidence highlights important challenges related to manufacturing consistency and quality control. A recent multi-company evaluation of powder bed fusion–fabricated titanium pelvic implants demonstrated substantial variability across manufacturers, even among certified medical device companies. While some producers achieved defect-free implants, others exhibited clinically relevant issues, including geometric deviations, lattice structure failures, and internal or surface defects that could compromise mechanical performance and long-term safety.[74] These findings underscore that the successful clinical translation of 3D-printed implants depends not only on design and indication, but also on strict control of process parameters, postprocessing, and microstructural integrity. Importantly, the study also confirms that, when appropriately managed, additive manufacturing can reliably produce high-quality implants, reinforcing its potential as a robust fabrication strategy. However, the observed variability highlights the urgent need for standardized manufacturing protocols and regulatory frameworks to ensure consistent safety and performance across providers.

6.3 Regenerative scaffolds and bioactive implants: toward biologically integrated reconstruction

A second major category includes biodegradable scaffolds, bioactive meshes, porous matrices, and customized bone substitutes designed not only to replace missing structure but to promote tissue

regeneration. These studies are particularly relevant because they bridge traditional 3D printing and regenerative medicine.

6.3.1 Bone regeneration and alveolar/maxillofacial reconstruction

Bone regeneration is one of the most active scaffold-based areas. NCT04773847 evaluates the patient-specific biomimetic bone substitute MimetikOss 3D in maxillofacial defects. NCT06773923 compares a 3D-printed PCL scaffold with conventional PTFE plus xenograft bone regeneration in elderly edentulous jaws. NCT03735199 studies ridge preservation using a PCL-TCP scaffold after tooth extraction, while NCT05241548 evaluates bone marrow aspirate concentrate seeded onto a PCL scaffold for ridge augmentation. These trials assess not only clinical healing but also histology, micro-CT, bone quality, and tissue integration.

Related studies explore customized shells and membranes. NCT06559605 compares a 3D-printed zirconia barrier with titanium mesh; NCT06186232 studies customized polymethylmethacrylate (PMMA) membranes for guided bone regeneration; NCT06227455 compares zirconia and polytetrafluoroethylene (PTFE) non-resorbable barriers; NCT04075942 evaluates a customized xenograft bone shell; and NCT05624697 assesses a patient-specific PEEK shell that functions both as barrier and implant housing. Collectively, these studies illustrate a clinically meaningful transition from generic membranes toward digitally matched regenerative compartments tailored to defect morphology.

In alveolar cleft and craniofacial bone regeneration, NCT07137975 evaluates patient-specific autogenous bone plugs designed with 3D printing, and NCT05971914 studies an autogenous tooth-derived particulate graft with a novel flap technique. These trials show that additive manufacturing is increasingly integrated into reconstructive workflows even when the implanted material itself is biological or autogenous rather than printed as the final implant.

6.3.2 Breast, chest wall, and soft tissue scaffolds

Soft-tissue scaffolds are particularly important from a regenerative medicine perspective. NCT03348293 and NCT06993714 evaluate 3D-printed biodegradable breast implants for reconstruction after breast cancer surgery, while NCT07365267 studies a 3D-printed biodegradable biological mesh used together with implant-based reconstruction after radical

mastectomy. These studies are representative of a strategy in which a printed scaffold provides shape and support while promoting host tissue integration over time.

An illustrative example of translational progression is provided by the clinical development of patient-specific polycaprolactone (PCL) breast scaffolds combined with autologous fat grafting for soft-tissue regeneration. The initial first-in-human study (NCT05437757) was conducted at a single center and enrolled 19 patients undergoing breast implant revision or correction of congenital breast defects. In this trial, a resorbable 3D-printed PCL scaffold served as a temporary structural framework that was populated intraoperatively with autologous adipose tissue, aiming to promote endogenous soft-tissue regeneration while gradually replacing conventional silicone implants. Although limited in size, this study is particularly noteworthy because it subsequently generated a structured clinical development program. A multicenter clinical investigation (NCT07367698) was designed to enroll 73 patients and evaluate long-term safety and effectiveness across a broader population. In parallel, an additional long-term follow-up study (NCT07383012) was initiated to monitor the original cohort for up to five years after implantation and to assess imaging surveillance strategies, including mammographic evaluation. This sequence of studies illustrates an important characteristic of clinical translation in medical 3D printing. Many registered trials are necessarily small during the early stages of development because they evaluate novel patient-specific devices with limited prior clinical experience. However, successful pilot studies may serve as the foundation for larger multicenter investigations and extended post-implantation surveillance. Consequently, the predominance of small early-phase studies within the registry should not necessarily be interpreted as evidence of limited clinical relevance, but rather as a reflection of the staged translational pathway through which innovative 3D-printed implants progress toward broader clinical adoption.

Pectus excavatum correction is a closely related application. NCT05451108 and NCT05634070 investigate patient-specific PCL scaffolds combined with autologous fat grafting. These trials also sit at the interface between scaffold-based structural correction and soft tissue engineering. The scaffold is not simply a passive implant: it is intended to support tissue regeneration, volume maintenance, and gradual remodeling.

Chest wall reconstruction provides another regenerative-structural hybrid indication. NCT06977022 evaluates biodegradable 3D-printed implants for chest wall tumor surgery, while

NCT07018960 and NCT05057143 address patient-specific titanium chest wall prostheses. The biodegradable studies are of special interest because they test whether personalized scaffolds can provide temporary support while the host tissues recover and integrate.

6.3.3 Cartilage and osteochondral repair

Cartilage regeneration remains less represented than bone, but there are notable examples. NCT07312175 evaluates a 3D-printing-assisted strategy for knee cartilage repair using scaffold-assisted autologous periosteum-bone grafting with or without platelet-rich plasma (PRP). Although not a living bioprinted construct in the strict sense, it demonstrates how additive manufacturing is being used to improve defect-matched osteochondral reconstruction. This is a significant translational step because cartilage repair requires not only structural fill but restoration of a highly specialized surface geometry.

6.3.4 Biodegradable metals and infection-related spacers

Additional scaffold-like strategies include biodegradable metallic or antimicrobial implants.[75] NCT06349629 evaluates a 3D-printed WE43 magnesium alloy prosthesis with controlled degradation in periarticular bone defects. NCT07031999 studies a vancomycin-impregnated thermoplastic spacer for infected orthopedic implants. These applications broaden the regenerative scaffold concept to include controlled degradation, antimicrobial delivery, and temporary support rather than permanent implantation.

Overall, regenerative scaffold trials are clinically promising but more heterogeneous than permanent implant studies. They often include richer biological endpoints, but are usually smaller, less standardized, and more dependent on defect type, biomaterial behavior, and local surgical technique.

6.3.5. Dental and oral implantable restorations as a parallel translational stream

A large parallel stream involves dental and oral implantable restorations, including 3D-printed dentures, inlays, onlays, abutments, retainers, and root-analogue implants. These applications demonstrate a clinically mature additive-manufacturing workflow for patient-specific intraoral devices.[76]

Examples include NCT06103019 on complete dentures, NCT06774560 and NCT07195201 on onlay restorations, NCT06092697 and NCT04532671 on 3D-printed PEEK restorations, NCT05350293 on printed abutments, and NCT06449391 on personalized root-analogue implants. These studies show how additive manufacturing is becoming normalized in prosthodontic practice, often through comparison with milled or conventional workflows. While these devices are not usually the conceptual centerpiece of regenerative medicine, they contribute to the overall maturity profile of medical 3D printing by showing that patient-specific additive manufacturing can become routine in high-volume clinical contexts.

Table 5. Representative clinical trials on implantable prostheses and regenerative scaffolds

NCT Number	Implant/scaffold type	Clinical indication	Main material/biological component	Main comparator	Core translational question
NCT05794594	Personalized extendable prosthesis	Pediatric osteosarcoma	3D-printed metallic prosthesis	Observational	Feasibility and early effectiveness for limb salvage in growing children
NCT05616195	Limb-salvage bone prosthesis	Bone tumors	3D-printed bone prosthesis	Observational	Long-term safety and function of printed prosthetic reconstruction
NCT04466397	Individualized porous implant	Large bone defects	Porous 3D-printed implant	Observational	Bone repair without conventional bone grafting
NCT03941028	Porous titanium implant	Large segmental bone defect	3D-printed titanium	Interventional	Bone regeneration and recovery without grafts or growth factors
NCT05291754	Custom cranioplasty implant	Skull defect	3D-printed PEEK	Conventional approaches	Safety and feasibility of in-house printed cranial implants
NCT06782711	Customized skull implant	Cranial defects	3D-printed PEEK	Single-arm/clinical follow-up	Safety, function, and aesthetics in cranioplasty
NCT04635865	Patient-specific surgical plates	Jaw reconstruction	3D-printed titanium plate	Conventional commercial plates	Reconstruction accuracy and surgical efficiency
NCT03057223	Printed titanium plates	Jaw surgery	Patient-specific titanium plates	Historical/conventional plates	Feasibility and precision of

NCT Number	Implant/scaffold type	Clinical indication	Main material/biological component	Main comparator	Core translational question
					personalized fixation
NCT03608280	Porous titanium orbital implant	Orbital defects	3D-printed porous titanium	Bone autograft	Functional and esthetic reconstruction vs autologous grafting
NCT05348434	Facial implant	Maxillofacial deformities	3D-printed PEEK	Observational	Fit, precision, and reconstructive utility
NCT03647501	Lumbar interbody cage	Lumbar fusion	3D-printed porous titanium	PEEK cage	Fusion and clinical outcomes in spine surgery
NCT05696470	Multi-level ACDF cage	Cervical fusion	3D-printed porous titanium cage	Retrospective allograft control	Fusion performance in 3–4 level ACDF
NCT05237908	TLIF cage	Degenerative lumbar disease	3D-printed cage	Titanium-coated PEEK cage	Fusion rate and patient outcomes
NCT04167878	Biodegradable cervical cage	Cervical disc disease	PCL/TCP 3D-printed cage	PEEK cage	Non-inferiority of biodegradable printed cages
NCT05396222	Non-rigid biomimetic spinal implant	Spinal tumor reconstruction	Custom 3D-printed biomimetic implant	Single-arm	Safety, fusion, subsidence, and functional outcomes
NCT06287021	Acetabular cup	Total hip arthroplasty	Highly porous 3D-printed titanium	Conventional sprayed cup	Bone remodeling and osseointegration
NCT05651009	Cementless knee implant	Knee osteoarthritis	Includes 3D-printed implant design	Alternative cementless TKA design	In vivo stability and fixation
NCT04773847	Biomimetic bone substitute	Maxillofacial bone defects	Patient-specific printed bone substitute	Post-market open label	Stable bone regeneration and surgical handling

NCT Number	Implant/scaffold type	Clinical indication	Main material/biological component	Main comparator	Core translational question
NCT06773923	PCL scaffold	Jaw atrophy	3D-printed PCL scaffold	PTFE + xenograft	Histologic and volumetric bone regeneration
NCT03735199	Socket/ridge preservation scaffold	Post-extraction ridge preservation	PCL-TCP scaffold	Natural healing / membrane strategy	Bone preservation and implant site development
NCT05241548	Cell-augmented scaffold	Ridge augmentation	BMAC + PCL scaffold	Single-arm	Whether marrow concentrate enhances scaffold-mediated bone regeneration
NCT06559605	Customized barrier	Alveolar ridge defect	3D-printed zirconia barrier	Titanium mesh	Bone gain and complication reduction
NCT03348293	Biodegradable breast implant	Breast reconstruction	Personalized biodegradable scaffold	Single-arm	Safety, integration, and cosmetic outcomes
NCT05437757	Biodegradable scaffold + fat grafting	Breast defect and/or deformity	3D-printed PCL scaffold + autologous fat	Single-arm	Feasibility and safety
NCT06993714	Degradable breast implant	Breast restoration	3D-printed degradable implant	Breast-conserving/silicone approaches	Aesthetics, QoL, and safety
NCT07365267	Biodegradable mesh	Immediate breast reconstruction	3D-printed biological mesh	Prospective single-arm	Cosmetic outcomes and tissue support
NCT05451108	Pectus scaffold + fat grafting	Pectus excavatum	3D-printed PCL scaffold + autologous fat	Single-arm	Soft tissue regeneration and chest wall correction
NCT05634070	Pectus scaffold + fat grafting	Pectus excavatum	3D-printed PCL scaffold + autologous fat	Single-arm	Long-term integration and resorption behavior

NCT Number	Implant/scaffold type	Clinical indication	Main material/biological component	Main comparator	Core translational question
NCT06977022	Biodegradable chest wall implant	Chest wall tumor	Custom biodegradable implant	Single-arm	Structural reconstruction with degradable printed implant
NCT06051747	Bioprinted trachea	Airway defects/thyroid cancer	Biopolymers, hydrogels, stem cells	Early clinical single-arm	Safety and function of patient-specific bioprinted tracheal implantation
NCT06587633	Bioprinted GI scaffold + cells	Chronic GI fistula	3D bioprinted scaffold + autologous stromal vascular fraction	Early single-arm	Tissue regeneration and fistula closure with cell-enriched bioprinting
NCT04399239	Bioprinted ear construct	Microtia	Patient-specific bioprinted auricular implant	Early clinical study	Safety and preliminary efficacy of bioprinted ear reconstruction
NCT06406452	Bioresorbable airway splint	Tracheobronchomalacia	3D-printed bioresorbable splint	Pivotal single-arm	Airway stabilization in pediatric collapse
NCT06349629	Biodegradable metallic implant	Periarticular bone defects	3D-printed WE43 magnesium alloy	Single-arm	Controlled degradation with new bone regeneration
NCT07031999	Antimicrobial temporary spacer	Orthopedic implant infection	Vancomycin-loaded PLA spacer	Feasibility	Infection control with customized printed spacers

6.4 Bioprinting-related and cell-containing clinical studies: early but strategically pivotal

The most conceptually significant studies identified in this review are those that move beyond the fabrication of inert devices toward the creation of living or biologically active constructs. Although

these trials remain relatively few, they represent the clinical frontier of bioprinting. Unlike conventional 3D-printed models or implants, these approaches aim to integrate cells, biomaterials, and bioactive environments to produce constructs capable of regeneration, integration, and functional restoration (**Table 6**).

6.4.1 Bioprinted skin substitutes

One of the earliest translational approaches in clinical bioprinting involves engineered dermo-epidermal substitutes (NCT04925323). This study describes the generation of GMP-compliant skin constructs using autologous keratinocytes and fibroblasts derived from surgical waste tissue, assembled into layered structures through sequential culture and bioprinting. The process, completed within a few weeks, includes evaluation of genetic stability across production stages. This trial highlights key translational challenges, including cell sourcing, scalability, and quality control, and reflects the shift toward biologically active, cell-laden constructs.

In terms of clinical maturity, bioprinted skin occupies an intermediate position between acellular devices and fully established regenerative treatments, while also posing regulatory challenges as advanced therapy due to its hybrid nature combining cells, biomaterials, and patient-specific manufacturing. A major limitation remains the achievement of adequate vascularization, which is essential for graft survival and integration. Despite progress, no standardized or fully effective approach has yet emerged. The addition of multiple cell types improves biological relevance, but the recreation of complex skin appendages such as hair follicles and sebaceous glands remains unresolved. Similarly, while melanocytes have been incorporated to enable pigmentation, this does not ensure uniformity or accurate matching to patient skin tone. These limitations highlight the gap between structural reconstruction and full functional and aesthetic restoration.[77,78]

6.4.2 Bioprinted tracheal constructs

Airway reconstruction represents one of the most advanced clinical applications of bioprinting. The trial NCT06051747 evaluates a patient-specific bioprinted trachea designed for implantation in patients requiring partial or segmental airway resection. This approach combines biopolymers, hydrogel-based bioinks, and autologous cells—including stem cells and cartilage-forming cells—to create a construct that mimics both the structural and biological properties of native tracheal tissue.

The bioprinting process enables precise spatial organization of materials and cells, resulting in a customized graft capable of supporting cartilage regeneration, mucosal lining formation, and mechanical stability. Following implantation, patients undergo comprehensive follow-up, including endoscopic evaluation, imaging, and laboratory monitoring to assess airway patency, tissue integration, and inflammatory responses.

Related earlier studies using similar combinations of biomaterials and regenerative cells reinforce the relevance of airway reconstruction as a leading translational domain.[79,80] Collectively, these trials represent a critical step toward the development of functional, implantable, tissue-engineered organs and illustrate the potential of bioprinting to provide personalized alternatives to conventional reconstructive techniques.

6.4.3 Bioprinted auricular constructs

Bioprinted ear reconstruction is exemplified by NCT04399239, which evaluates a patient-specific auricular implant (AuriNovo) for the treatment of microtia. This construct is designed as a living, cell-based implant tailored to the patient's anatomy. Although the study was terminated, it remains a landmark example of clinical bioprinting, demonstrating both the transformative potential and the challenges of early-stage translation.

From a clinical perspective, this trial underscores the feasibility of producing anatomically precise, biologically active implants for reconstructive surgery, while also highlighting the fragility of early clinical development pathways in this field.

6.4.4 Cell-combined and hybrid biofabricated systems

A broader category of studies involves hybrid systems that combine 3D-printed scaffolds with autologous cells or cell-derived products. While not always classified as "bioprinting" in a strict sense, these approaches represent important intermediate steps toward fully biological constructs.

A notable example is NCT06587633, which investigates the treatment of chronic gastrointestinal fistulae using patient-specific bioprinted scaffolds enriched with stromal vascular fraction derived from adipose tissue. These constructs integrate structural biomaterials with regenerative cellular components, enabling minimally invasive delivery and promoting tissue repair through cell-mediated processes such as proliferation, differentiation, and cytokine signaling. The study also

explores interactions between the scaffold–cell system and the intestinal microbiota, reflecting an increasing focus on complex biological environments.

Other studies, including NCT05241548 (bone marrow aspirate concentrate on printed scaffolds for ridge augmentation) and trials such as NCT06977022, NCT03348293, NCT05451108, and NCT05634070, similarly combine printed structures with biologically active components. In these cases, the printed scaffold serves not merely as a structural support but as a biointeractive platform that facilitates tissue regeneration.

6.4.5 Translational significance and current position

Although the number of bioprinting-related clinical trials remains small compared with the extensive body of work on conventional implants and anatomical models, their significance is outsized. These studies directly address the central promise of bioprinting: the fabrication of patient-specific, living constructs capable of integration, remodeling, and functional restoration.

At the same time, they clearly illustrate the current limitations of clinical maturity in this field. Most trials are early-phase and focused on feasibility and safety rather than comparative effectiveness. Applications are concentrated in highly specialized indications—such as airway, auricular, or gastrointestinal reconstruction—and remain technically demanding.

Taken together, these findings indicate that clinical bioprinting is transitioning from a purely experimental domain toward early human application. While still emergent, the presence of these trials confirms that the field has moved beyond preclinical research, establishing a foundation for future development of regenerative, patient-specific therapies.

Table 6. Bioprinting-related and biologically integrated implant trials of special relevance

NCT Number	Category	Biological component	Target tissue/organ	Relevance
NCT06051747	True bioprinted implant	Patient-derived cells, hydrogels, biopolymers	Trachea	One of the clearest clinical examples of patient-specific bioprinted tissue implantation
NCT06587633	Bioprinted scaffold + autologous cells	Stromal vascular fraction micro-emulsion	Gastrointestinal fistula defects	Combines printed scaffold with patient-derived cellular therapy

NCT Number	Category	Biological component	Target tissue/organ	Relevance
NCT04399239	Bioprinted tissue construct	Living auricular construct	External ear (microtia)	Landmark early trial in reconstructive bioprinting
NCT05241548	Cell-enhanced regenerative scaffold	Bone marrow aspirate concentrate	Alveolar ridge/bone regeneration	Illustrates translational bridge between scaffold printing and cell-based regeneration
NCT05451108	Scaffold + autologous tissue engineering	Autologous fat grafting	Chest wall soft tissue contour	Personalized scaffold used as regenerative template
NCT05634070	Scaffold + autologous tissue engineering	Autologous fat grafting	Pectus excavatum correction	Soft-tissue regenerative reconstruction rather than simple prosthetic replacement
NCT03348293	Biodegradable scaffold reconstruction	Host tissue integration expected	Breast reconstruction	Personalized scaffold designed to support tissue regeneration
NCT06993714	Biodegradable implant reconstruction	Host tissue remodeling expected	Breast restoration	Tests whether printed biodegradable constructs can replace conventional reconstruction paradigms
NCT06977022	Biodegradable implant	Regenerative structural support	Chest wall	Transitional category between structural implant and regenerative scaffold
NCT06349629	Degradable metallic implant	Bone regeneration around degrading magnesium	Periarticular bone defect	Important example of printed implants designed to disappear while healing progresses

6.5 Clinical Maturity and Barriers to Translation in Implantable and Bioprinted Applications

When implantable applications are considered as a whole, a clear gradient of clinical maturity emerges, reflecting both technological complexity and degree of clinical integration.

At the most advanced level are patient-specific structural implants, including devices manufactured from titanium, porous titanium, and PEEK. These applications are supported by the largest number of clinical studies and are frequently evaluated in comparative or post-market settings. They address well-defined reconstructive needs in areas such as orthopedic oncology, spinal surgery, cranioplasty, and maxillofacial reconstruction. Their relative maturity is driven by

established manufacturing workflows, regulatory familiarity, and predictable mechanical performance.

An intermediate level of maturity is represented by regenerative scaffolds and biodegradable implants. These approaches incorporate increasing biological sophistication, often aiming to support tissue regeneration rather than simply replace damaged structures. Although the number of clinical trials in this category is growing, they remain heterogeneous in design and objectives. Most studies focus on feasibility, bone regeneration, or quality-of-healing outcomes, with limited long-term data on durability and clinical effectiveness.

At the most emerging end of the spectrum are bioprinted and cell-containing constructs. These studies are comparatively few but represent the most forward-looking direction of the field. Trials such as NCT06051747, NCT06587633, and NCT04399239 demonstrate that bioprinting has entered early-stage human clinical experimentation, particularly in airway reconstruction, soft tissue repair, and complex regenerative applications. However, these efforts should still be regarded as pioneering translational studies rather than established clinical practice.

Across all three categories, several barriers continue to limit broader clinical translation. For permanent structural implants, key challenges include the need for robust long-term comparative data, standardization of design parameters such as porous architectures, and demonstration of cost-effectiveness beyond technical feasibility. In the case of biodegradable scaffolds, uncertainties persist regarding degradation kinetics, mechanical stability over time, inflammatory responses, and reproducibility across manufacturing processes.

Bioprinting introduces an additional layer of complexity. Major challenges include reliable cell sourcing, manufacturing under Good Manufacturing Practice (GMP)-like conditions, sterility assurance, vascularization of constructs, and successful integration with host tissues. Regulatory classification of living constructs and the need for long-term monitoring further complicate clinical implementation.

An additional cross-cutting issue is the convergence of multiple innovations within single studies. Many trials simultaneously introduce patient-specific design, novel biomaterials, porous architectures, biological augmentation, and modified surgical workflows. While this reflects the

multidisciplinary nature of the field, it makes it difficult to isolate the contribution of individual components to clinical outcomes.

Taken together, the current evidence indicates that implantable applications of 3D printing are no longer uniformly exploratory. Instead, the field comprises a mature segment focused on structural implants, an expanding and heterogeneous domain of regenerative scaffolds, and an early but clearly emerging clinical bioprinting segment.

7. Other clinical applications

In addition to the core domains of anatomical modeling, implantable devices, and bioprinting, a heterogeneous group of clinical trials illustrates the broader integration of 3D printing and related technologies into therapeutic workflows. In these studies, 3D printing is often not the primary intervention but rather a complementary or enabling tool within multimodal treatment strategies, reflecting an expanding clinical ecosystem in which additive manufacturing supports patient care.

A first subset of studies is associated with radiotherapy-related interventions, primarily focusing on the management of treatment-induced complications and optimization of long-term monitoring. For example, NCT06413628 evaluates therapeutic strategies for radiation-induced trismus in head and neck cancer patients, comparing a 3D-printed screw-based oral appliance, low-level laser therapy, and their combination. Outcomes include mouth opening, pain reduction, and functional recovery, demonstrating how customized printed devices can function as adjunct therapeutic tools. Similarly, NCT05002751 investigates radiation-induced vaginal stenosis through patient-reported outcomes, contributing to the understanding of long-term toxicity and unmet therapeutic needs. Other studies, such as NCT05673473, assess low-dose imaging techniques in scoliosis to reduce cumulative radiation exposure, while NCT05427656 explores radiotracer-based neuroimaging to monitor neuroplasticity and disease progression. Although not directly therapeutic, these approaches have important implications for treatment planning, safety, and longitudinal patient management.

A second group focuses on personalized pharmacological strategies, particularly for populations with unmet formulation needs such as pediatric patients. The lack of age-appropriate dosage forms frequently compromises adherence and treatment effectiveness, as conventional approaches rely

on tablet splitting or poorly accepted liquid formulations. Early clinical studies have demonstrated the feasibility of 3D printing for personalized drug delivery. A first clinical trial in pediatric patients with maple syrup urine disease (MSUD) showed that 3D-printed chewable tablets were both acceptable and effective, supporting the use of this technology for on-demand manufacturing.[81] Subsequent work further demonstrated the feasibility of combining multiple active components into a single chewable printlet, reducing treatment burden and improving quality of life in children with rare metabolic disorders.[82]

More recent trials continue to expand this field. The NCT07424495 study evaluates the acceptability of placebo 3D-printed chewable tablets in children and adolescents, focusing on palatability, flavor preference, and dose personalization using child-friendly designs. Similarly, the NCT06435481 trial compares 3D-printed chewable hydrocortisone tablets with a conventional oral suspension in pediatric patients with endocrine disorders, while the CTIS2024-519378-37-00 trial investigates 3D-printed chewable biotin formulations for children with methylcrotonylglycinuria or biotinidase deficiency. Using randomized crossover designs, these studies assess tolerability, patient acceptance, and treatment adherence, with the ultimately goal of improving clinical outcomes through age-appropriate and personalized dosage forms.

Together, these studies reflect a broader shift toward point-of-care manufacturing, where 3D printing enables the production of individualized medicines within hospital settings. This approach offers advantages in dose flexibility, rapid adaptation, and improved adherence, particularly for chronic conditions requiring frequent dose adjustments. However, clinical translation remains at an early stage. Key challenges include the establishment of robust regulatory frameworks, validation of manufacturing processes, and implementation of quality control systems in decentralized environments. Emerging initiatives from regulatory bodies such as the EMA and FDA aim to support safe implementation, although harmonized guidance is still evolving.[83]

Overall, pharmacological applications represent one of the most promising and rapidly advancing areas of clinical 3D printing, with significant potential to enhance personalization, adherence, and therapeutic effectiveness, particularly in vulnerable patient populations.

8. Cross-Cutting Analysis of Clinical Evidence and Translational Trends

Whereas the preceding sections summarize representative studies within individual application domains, the purpose of this section is to synthesize cross-cutting patterns emerging across the entire dataset. Rather than focusing on specific technologies or indications, this comparative analysis examines the relationships among clinical adoption, evidentiary development, biological complexity, manufacturing requirements, regulatory burden, and translational progression across the spectrum of medical 3D printing and bioprinting applications. It should also be recognized that the boundaries between application domains are not always absolute. Certain technologies combine structural, regenerative, and procedural functions simultaneously, and alternative classification frameworks could redistribute a limited number of studies among categories. However, such reclassification would be unlikely to alter the major translational patterns observed across the dataset.

When the clinical trial landscape is considered across all application domains, 3D printing in medicine does not appear as a single unified field progressing at the same speed. Rather, it is a spectrum of technologies with markedly different levels of clinical maturity, evidentiary depth, regulatory complexity, and translational readiness. The trials reviewed in this work collectively show that the medical use of 3D printing has already moved beyond proof-of-concept, but that this progress is unevenly distributed. Some applications are now clinically routine or close to routine, whereas others remain exploratory, small-scale, or early-phase despite their high conceptual promise (**Table 7**).

A first cross-cutting observation is that **clinical maturity tends to decrease as biological and regulatory complexity increase**. Since no standardized maturity-assessment framework currently exists for this field, the conclusions should be interpreted as a systematic registry-based analysis of translational progress and clinical adoption patterns rather than as a quantitative maturity evaluation. Applications involving no implantation and minimal biological interaction, such as anatomical models for surgical planning or external orthoses, show the broadest clinical adoption and the most consistent growth in clinical evaluation. These applications rely on relatively straightforward workflows involving imaging acquisition, digital segmentation, computer-aided design, manufacturing, and clinical deployment. Because the printed construct is either external to the body or not intended as a long-term implant, requirements related to biocompatibility, sterility

assurance, long-term safety, and regulatory approval are generally less demanding. Consequently, development cycles are shorter, manufacturing is more reproducible, and clinical studies can focus on practical endpoints such as accuracy, comfort, operative time, or user satisfaction. By contrast, implantable devices, regenerative scaffolds, and especially bioprinted living constructs face substantially greater translational challenges. These technologies require more stringent control of materials, manufacturing processes, and product consistency, while also addressing issues such as host integration, tissue remodeling, long-term functionality, and safety. For biologically active constructs, additional challenges arise from cellular viability, vascularization, scalability, storage, and compliance with advanced manufacturing and regulatory requirements. These factors increase development time, cost, and evidentiary burden, which is reflected in the smaller number of registered trials, the predominance of early-phase studies, and the limited use of large-scale comparative clinical designs within the bioprinting domain.

A second major trend is that **the dominant value proposition of 3D printing remains personalization**. Across anatomical models, orthoses, surgical guides, implants, and regenerative scaffolds, the most recurrent rationale is the ability to tailor geometry to patient anatomy. This feature is central to the field's translational identity. In surgical planning studies, personalized models are expected to improve anatomical understanding, operative confidence, and simulation. In orthoses and assistive devices, customization is linked to comfort, adherence, function, and production efficiency. In implantable prostheses, patient-specific design is used to improve fit, restore complex anatomy, reduce intraoperative adjustment, and optimize load transfer or fixation. Even in regenerative scaffold studies, geometric matching of the defect site is often presented as a prerequisite for predictable tissue regeneration. Thus, while different studies vary in indication and sophistication, patient specificity serves as the common translational thread that connects the whole field.

At the same time, the collected information shows that **personalization alone is no longer sufficient as a marker of innovation**. The more advanced clinical studies increasingly combine patient-specific geometry with additional layers of functional design. In orthopedic and spinal implants, porous architectures are introduced to promote osseointegration and tune mechanical stiffness. In breast, chest wall, and pectus scaffolds, degradable polymers are used not only to match anatomy but to support progressive tissue remodeling. In airway and tracheal applications,

printing is integrated with hydrogels, stem cells, or bioactive matrices in an effort to move from structural substitution toward biological restoration. This indicates a broader translational shift: the field is moving from "customized shape" toward "customized function," where printed constructs are expected not only to fit the patient but also to interact with tissues in a biologically or mechanically optimized way.

A third cross-cutting feature is the **predominance of device-centered and workflow-centered endpoints over long-term clinical endpoints**. A large proportion of trials evaluate immediate or short-term measures such as positional accuracy, operative time, planning efficiency, comfort, production feasibility, user satisfaction, bone gain at early follow-up, or radiographic surrogate markers. These outcomes are entirely appropriate in an emerging field, particularly during the early stages of clinical translation. However, they should be distinguished from patient-centered clinical endpoints such as long-term functional recovery, complication rates, implant survival, quality of life, or cost-effectiveness. Consequently, while many studies demonstrate improvements in procedural efficiency, usability, or technical performance, the strength of evidence supporting durable clinical benefit remains comparatively limited in several application domains. This distinction is particularly relevant when comparing clinical maturity across applications, as evidence of successful workflow integration does not necessarily equate to evidence of superior long-term patient outcomes.

Many studies are still testing whether 3D printing can be implemented effectively, rather than whether it changes major patient outcomes in a durable and clinically meaningful way. For example, a customized guide may improve drilling precision, but fewer trials demonstrate whether that precision translates into lower revision rates, better function, or superior long-term survival. Similarly, an orthosis may be lighter or more comfortable, but evidence for sustained superiority in rehabilitation outcomes is often less robust. This gap between technical performance and long-term effectiveness remains one of the central translational bottlenecks. Across application domains, most registered studies remain early-stage investigations characterized by small sample sizes, single-center recruitment, and limited follow-up periods. Consequently, although the volume of clinical activity is substantial, the overall strength of evidence remains heterogeneous and, in many cases, insufficient to support definitive conclusions regarding clinical superiority, long-term functional benefit, implant survival, or cost-effectiveness.

Closely related to this is the **heterogeneity of trial design**. The reviewed studies include randomized controlled trials, crossover designs, single-arm feasibility studies, observational registries, pilot studies, and post-market evaluations. This diversity reflects the breadth of clinical applications but complicates cross-study comparison. In orthoses and dentistry, crossover designs are common because devices can be tested in the same patient over defined periods. In surgical planning and implantable reconstruction, single-arm or observational designs are more frequent, often because patient numbers are limited and anatomical variability is high. In highly innovative areas such as bioprinting, early feasibility and safety designs dominate. As a result, the field contains many promising signals but relatively few harmonized datasets. This heterogeneity limits meta-analytic synthesis and makes it difficult to identify universally accepted standards of benefit.

Another important translational trend is the **strong influence of specialty-specific adoption patterns**. Certain disciplines have emerged as particularly fertile environments for 3D printing. Maxillofacial surgery, orthopedics, spine surgery, dentistry, and rehabilitation account for a large proportion of the reviewed NCTs. These specialties share several enabling features: high reliance on imaging, anatomically complex procedures, a need for personalization, and well-defined interfaces between digital planning and physical intervention. Conversely, some fields with obvious theoretical relevance to 3D printing still show comparatively limited clinical trial activity. Disease modeling is the clearest example. Despite enormous scientific interest in organoids, tumor models, microphysiological systems, and 3D bioprinted constructs for drug testing, relatively few registered clinical studies directly evaluate these technologies in patient-centered clinical contexts. This suggests that translational barriers are higher when the printed construct is not itself the therapeutic device but part of a diagnostic, modeling, or precision-medicine workflow whose clinical utility is more indirect.

The review also highlights a gradual but notable shift from **adjunctive tools to therapeutic systems**. Early and mature applications alike often begin as supports to existing care: a model to help planning, a guide to improve placement, a splint to facilitate rehabilitation, a custom plate to replicate a conventional implant more precisely. However, the more recent trial landscape increasingly includes technologies that are not merely adjunctive but potentially transformative. Relevant examples are printed porous implants intended to alter bone integration dynamics, biodegradable scaffolds for tissue restoration, root-analogue implants tailored to extraction sockets,

and bioprinted tracheal or auricular constructs designed as new therapeutic entities. This change matters because it marks a deeper level of clinical translation. Once a printed construct becomes the therapeutic core rather than a procedural aid, the scientific, manufacturing, and regulatory expectations increase dramatically. The field is now entering this more demanding stage.

Within this context, the application of 3D printing to bone regeneration in large segmental defects provides a particularly informative case study of current translational barriers. Despite the clear clinical need and the conceptual advantages of patient-specific implants, progress remains constrained by structural rather than purely technological limitations. The CoMBI (Consensus Meeting on 3D-printed patient-specific Bone Implants) initiative highlights that challenges span the entire translational continuum.[32] At the level of fundamental research, there is still no unified consensus on key implant design requirements, including osteoinductive capacity, biodegradability, antimicrobial functionality, and mechanical performance under physiological loading. At the preclinical stage, variability in experimental models and limited standardization—despite the widespread use of large animal segmental defect models—complicate cross-study comparability and translational validity. Clinically, the need for interdisciplinary coordination, feasibility-driven trial design, and multicenter evidence generation remains a major limiting factor. In parallel, emerging models such as point-of-care manufacturing introduce opportunities for rapid personalization but also add layers of regulatory and quality assurance complexity. Altogether, this example underscores a broader conclusion of the present review: the main bottleneck for advanced implantable and regenerative applications lies in the fragmentation of standards, evidence generation strategies, and regulatory pathways, rather than in the absence of enabling technologies.

Within this broader pattern, **bioprinting remains the least mature but most strategically significant frontier**. The number of NCTs involving living cells, stem-cell-containing scaffolds, or true tissue-engineered printed constructs is still very small compared with the volume of studies on static devices. Yet these few studies carry disproportionate conceptual weight. Trials such as NCT06051747 on patient-specific bioprinted tracheal implantation, NCT06587633 on 3D bio-structures for gastrointestinal post-surgical defects using autologous stromal vascular fraction, and NCT04399239 on the AuriNovo bioprinted ear construct are not simply incremental improvements in digital fabrication. They represent attempts to clinically restore living tissue architecture using

customized, biologically active constructs. Their small number, early-phase design, and concentration in highly specialized indications show that this part of the field is still in its infancy. Most bioprinting-related studies remain focused on feasibility and safety rather than efficacy, reflecting the early developmental stage of biologically active constructs and the substantial manufacturing, regulatory, and validation challenges associated with their clinical implementation.

Another recurring theme is the **co-evolution of printing technologies with advances in imaging, digital planning, and simulation**. Clinical translation is rarely driven by the printer alone. Most successful workflows depend on the combined maturation of volumetric imaging, segmentation software, CAD tools, computational design, and increasingly automated or AI-assisted planning. In several studies, the most important innovation is not simply the printed object itself but the entire digital chain that enables reproducible personalization. This is especially evident in cranioplasty algorithms, patient-specific guides, CAD/CAM barriers, and complex reconstructions based on mirrored anatomy or virtual planning. For bioprinting and regenerative medicine, this systems-level view is even more important because cell handling, scaffold design, biomaterial formulation, and quality control must all be integrated. Thus, clinical maturity should be understood not as the maturity of a printer or a material in isolation, but as the maturity of a complete translational platform.

A further cross-cutting issue is the **relationship between additive manufacturing and conventional alternatives**. Many studies are designed not to show dramatic superiority, but rather non-inferiority combined with practical benefits such as faster production, reduced waste, improved access, lower cost, simplified workflow, or better customization. This is particularly clear in dentures, splints, sockets, insoles, and several implant studies comparing 3D-printed constructs with milled, molded, or manually fabricated comparators. The implication is that clinical translation may proceed not only through clearly superior efficacy, but through improved logistics and scalability. In real-world healthcare systems, this may be one of the strongest drivers of adoption. A device that performs similarly but is more reproducible, faster to fabricate, easier to personalize, or more accessible in low-resource settings may still have substantial translational value. Collectively, these observations suggest that successful clinical translation is driven not only by technological innovation but also by manufacturing reproducibility, regulatory feasibility,

scalability, and the ability to demonstrate clinically meaningful value through robust and measurable endpoints.

The evidence base also reveals a persistent **geographic and institutional concentration of innovation**. Many studies originate from specialized academic centers or high-volume surgical units with strong engineering collaboration. This concentration is understandable in a technically intensive field, but it raises questions about generalizability. A workflow that performs well in a center with advanced imaging, in-house design expertise, and close manufacturing support may be difficult to reproduce in routine practice. Consequently, one hallmark of the next translational phase will be movement from expert-center feasibility to multicenter standardization. Registries, post-market surveillance studies, and multicenter comparative trials will become increasingly relevant in determining whether promising results can be generalized across health systems.

Viewed across the entire dataset, a distinction emerges between applications supported primarily by workflow-related evidence and those evaluated using direct clinical outcomes. Anatomical models, surgical guides, and many orthotic devices are frequently assessed through measures such as operative time reduction, planning efficiency, procedural accuracy, comfort, or user satisfaction. By contrast, implantable devices, regenerative scaffolds, and bioprinted constructs are more often expected to demonstrate outcomes related to tissue integration, functional restoration, long-term safety, or therapeutic efficacy. Consequently, comparisons across application domains should consider not only the quantity of available evidence but also the nature and clinical significance of the endpoints being evaluated.

Importantly, the framework proposed here should be interpreted as a qualitative synthesis of translational patterns observed across the dataset rather than as a formal classification system derived from predefined quantitative criteria. Taken together, the clinical trial landscape supports a **three-tier translational continuum** for medical 3D printing and bioprinting (**Figure 2**). The first tier includes highly mature applications such as anatomical models, surgical guides, and external orthoses, where technical feasibility is largely established and the main challenges now concern standardization, evidence quality, and reimbursement. The second tier includes permanent implantable prostheses and porous structural devices, where clinical use is already substantial, but long-term comparative effectiveness and wider adoption remain active questions. The third tier includes regenerative scaffolds and true bioprinted constructs, where translation has clearly begun

but remains early, indication-specific, and heavily dependent on advances in biomaterials, manufacturing controls, and regulatory frameworks.

Applications described here as relatively more clinically mature are those characterized by broader clinical adoption, larger and more diverse bodies of clinical evidence, greater integration into routine clinical workflows, and a higher degree of regulatory and manufacturing standardization. Notably, some of the most clinically mature applications are relatively simple from an engineering perspective, such as splints, insoles, or anatomical models. Conversely, the most technologically ambitious applications, particularly cell-containing or organ-like bioprinted constructs, remain at an early stage of clinical translation. This pattern does not reflect a limitation of the technology itself; rather, it illustrates how medical innovation tends to progress first in areas where implementation is more straightforward, risks are lower, and benefits can be demonstrated through reproducible and measurable outcomes. The progression from external devices to implantable constructs and ultimately to living engineered tissues therefore represents not only a technological gradient but also a translational one.

Overall, the reviewed NCTs show that 3D printing in medicine has entered a phase of broad clinical relevance, although its development remains highly heterogeneous across application domains. Personalized medical 3D printing is no longer a niche experimental practice but a distributed technological ecosystem that has already substantial clinical integration in several application areas and is progressively extending toward regenerative and bioprinted therapies. The next challenge is not simply to increase the number of clinical trials, but to improve their comparability, strengthen the quality and clinical relevance of outcome measures, clarify which indications derive the greatest benefit, and establish clearer translational pathways connecting current device-based applications with future biologically integrated therapeutic strategies.

Table 7. Major translational trends identified across the reviewed clinical trials

Translational trend	Interpretation	Examples
Personalization as the central driver	Most trials justify 3D printing through anatomical customization and patient-specific fit	Customized sockets, implants, guides, airway splints, orthoses

Translational trend	Interpretation	Examples
Shift from shape to function	Newer studies optimize porosity, degradation, mechanics, or biological performance, not just geometry	Porous titanium cages, biodegradable meshes, magnesium implants
Faster maturity in low-risk applications	External or non-implantable uses have progressed faster than implanted or cell-based constructs	Splints, insoles, models vs bioprinted trachea or ear constructs
Workflow value often precedes outcome superiority	Many studies aim to show equal clinical performance plus lower cost, time, or complexity	Digital dentures, sockets, guides, custom obturators
Surrogate endpoints dominate	Accuracy, fit, bone gain, comfort, and satisfaction are more common than long-term hard outcomes	Implant position, operative time, user satisfaction scores, radiographic fusion
Specialty clustering	Maxillofacial surgery, orthopedics, spine, dentistry, and rehabilitation dominate the trial landscape	Multiple jaw, spine, orthosis, and dental restoration NCTs
Bioprinting remains niche but pivotal	Few NCTs, but strong strategic relevance because they represent true regenerative translation	NCT06051747, NCT06587633, NCT04399239
Digital ecosystem dependence	Clinical translation depends on imaging, CAD, simulation, and workflow integration as much as on printing itself	Cranioplasty planning algorithms, CAD/CAM barriers, PSI workflows

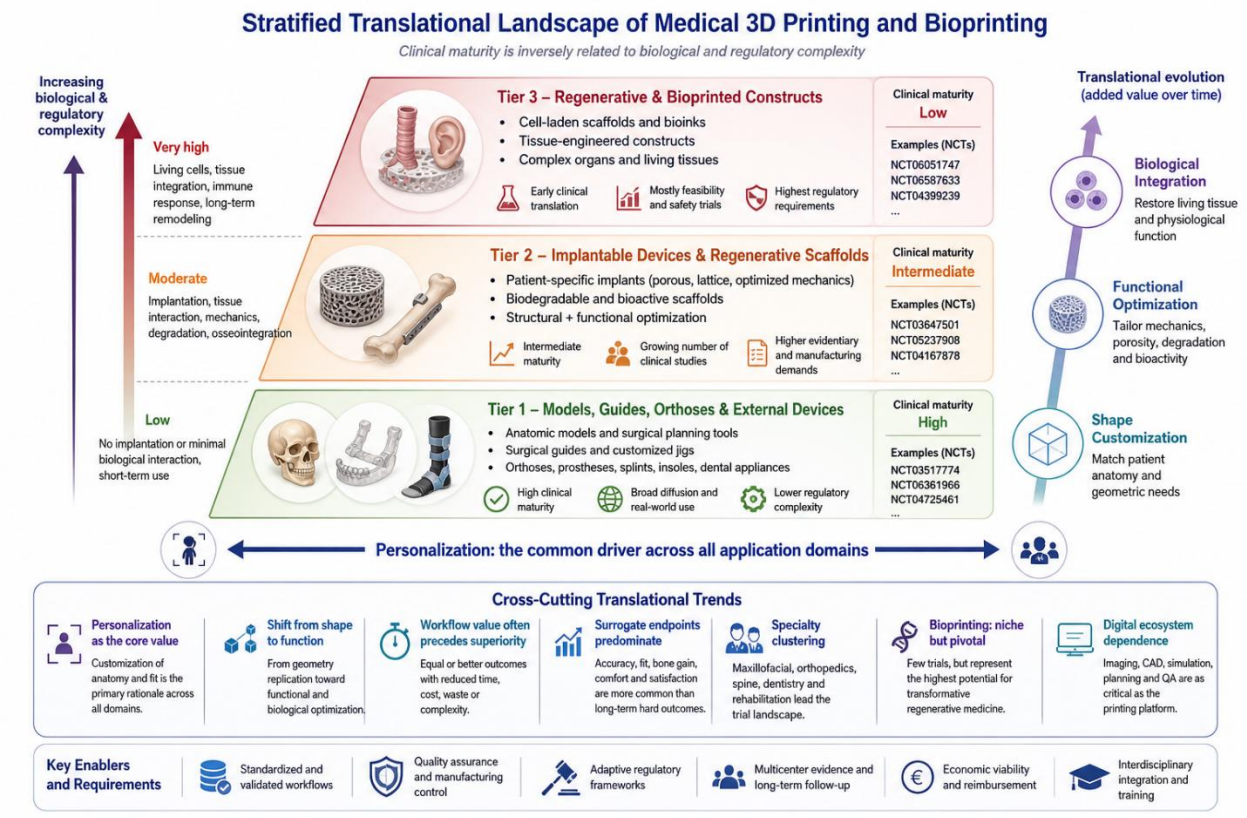

Figure 2. Stratified translational landscape of medical 3D printing and bioprinting. Clinical applications of additive manufacturing can be viewed as a continuum characterized by an inverse relationship between the degree of clinical translation and biological/regulatory complexity. The relative position of each application domain was qualitatively inferred from multiple indicators observed across the clinical trial landscape, including the number of registered studies, diversity of clinical indications, integration into routine clinical workflows, regulatory requirements, biological complexity, and evidentiary development. Highly translated applications, such as anatomical models, surgical guides, and orthoses, occupy the lower-complexity end of the spectrum, whereas implantable devices and regenerative scaffolds represent intermediate stages. Cell-containing bioprinted constructs remain at an early stage of clinical translation despite their high transformative potential. Across all domains, personalization acts as a common driver of innovation, while recent developments reflect a progression from geometry-based customization toward functional and biological integration. The framework is conceptual and intended to illustrate relative trends observed across the clinical trial landscape rather than a formalized quantitative maturity-assessment model.

9. Challenges for Clinical Translation

Despite the rapid growth of clinical research in medical 3D printing, the transition from technical feasibility to routine clinical implementation remains incomplete. The studies reviewed here demonstrate the broad applicability of additive manufacturing across multiple medical fields but also reveal persistent barriers that continue to limit translation. These challenges recur across anatomical models, orthoses, implantable devices, regenerative scaffolds, and bioprinted constructs, although their magnitude generally increases with biological complexity, manufacturing demands, and regulatory requirements.

A central challenge is **the lack of standardization across the entire workflow**. Most applications rely on multistep processes—image acquisition, segmentation, digital modeling, design optimization, material selection, printing, post-processing, sterilization, and clinical deployment—where variability can arise at each stage. Differences in imaging quality, software platforms, printing parameters, or finishing procedures may alter the accuracy or performance of the final construct.[74] This is particularly critical for surgical guides and patient-specific implants, where small geometric deviations can affect fit or precision. In orthoses, such variability influences comfort and adherence. In bioprinting, additional sources of variability include cell origin, bioink composition, cell density, crosslinking, and post-print maturation. Until workflows are more reproducible across centers, widespread adoption will remain uneven.

A second major obstacle is **the heterogeneity of materials and the limited comparability of material-specific evidence**. The reviewed NCTs span a wide range of materials, including polymers, metals, ceramics, composites, and cell-containing hydrogels. While this diversity is a strength, it complicates translation: each material has distinct mechanical, biological, and regulatory profiles. As a result, evidence cannot easily be generalized across materials, even within the same indication. Findings from porous titanium implants, for example, are not directly transferable to biodegradable polymers or biomimetic scaffolds. This fragmentation slows the emergence of unified clinical standards.

A third challenge is **the predominance of small, single-center, and early-phase studies**. Much of the current evidence derives from feasibility cohorts, pilot trials, or exploratory interventions

rather than large multicenter randomized studies. While expected in a rapidly evolving field, this limits generalizability. Workflows that perform well in specialized centers may not translate easily to routine practice. Even in mature indications, many studies remain underpowered for endpoints such as long-term complications, revision rates, or cost-effectiveness. For regenerative scaffolds and bioprinted constructs, trials are few and typically focused on safety or proof of concept.

Closely related is the **reliance on surrogate or intermediate endpoints**, including operative time, positional accuracy, early bone gain, radiographic fit, comfort, or satisfaction. These metrics are appropriate early in translation but do not necessarily demonstrate durable clinical benefit. Improved technical performance does not always translate into better long-term outcomes such as reduced revision rates, improved function, or enhanced quality of life. Bridging this gap will require more consistent use of patient-centered and long-term outcome measures.

Regulatory uncertainty remains another major barrier, particularly for highly customized and biologically active products. While external devices can often be accommodated within existing frameworks, patient-specific implants, degradable scaffolds, and bioprinted constructs challenge conventional regulatory paradigms designed for standardized mass production. Authorities must evaluate not only the final product but also the reproducibility of individualized design and manufacturing processes. This complexity is amplified for cell-containing constructs, which combine characteristics of devices, biologics, and tissue-engineered products, requiring stringent oversight of cell sourcing, manufacturing quality, sterility, and long-term safety. A particularly illustrative example of how these challenges converge is bone regeneration in large segmental defects. Despite strong clinical need and promising patient-specific solutions, translation remains limited by systemic barriers rather than technological constraints. Insights from the CoMBI consensus highlight persistent gaps in standardized implant design criteria, variability in preclinical models, and the need for coordinated, multicenter clinical evidence.[32]

Manufacturing scale-up and quality assurance represent additional challenges. Most current trials rely on low-volume, highly controlled production settings, whereas routine adoption requires consistent quality, traceability, and scalable workflows. Point-of-care manufacturing has emerged as a promising model, enabling rapid, patient-specific production within healthcare institutions. However, it introduces distinct regulatory and operational demands compared with centralized manufacturing. In Europe, Regulation (EU) 2017/745 (MDR) provides a framework for hospital-

based custom device production under Article 5.5, allowing in-house manufacturing for specific patient needs under defined conditions, including quality management systems and regulatory oversight.[84] While this pathway has enabled specialized centers to establish certified manufacturing units, broader implementation remains limited. Requirements for infrastructure, validated workflows, material traceability, sterilization, and clinical follow-up create substantial barriers, particularly for institutions without dedicated engineering expertise. Responsibility for device safety also shifts to the healthcare provider, with implications for liability and post-market surveillance. Variability in manufacturing outcomes, even among certified producers, further highlights the need for robust and harmonized quality standards.[74]

Taken together, these findings suggest that while point-of-care manufacturing represents a promising and increasingly structured regulatory trend, its broader adoption will depend on the development of robust validation frameworks, harmonized quality standards, and clear delineation of clinical and manufacturing responsibilities. As trial activity expands, the field will increasingly need robust standards for dimensional verification, mechanical testing, sterilization validation, post-processing control, and, where relevant, biological assays. Bioprinting adds further layers, including batch variability in bioinks, cell viability checks, functional assays, and storage or transport constraints.

Economic and reimbursement barriers also remain significant. Although 3D printing is often associated with cost savings, real-world evidence remains limited and highly context-dependent. While additive manufacturing may reduce operative time or material waste in some cases, it also introduces costs related to imaging, software, equipment, and specialized personnel. Reimbursement systems frequently do not account for the design and manufacturing steps involved in personalized devices, limiting adoption even when clinical benefits are evident.

Another major translational issue is **the need for interdisciplinary integration**. Successful clinical use of 3D printing rarely depends on a single professional group. It requires collaboration among surgeons, rehabilitation specialists, radiologists, dentists, engineers, material scientists, manufacturing technicians, and increasingly data scientists and regulatory specialists. In bioprinting, cell biologists and tissue engineers are also essential. This interdisciplinary dependence is one of the field's strengths, but it can also slow implementation because clinical systems are not always organized around such collaborative workflows. The challenge is therefore

organizational as much as technical. Institutions that lack integrated digital planning pathways, dedicated manufacturing teams, or validated communication protocols may struggle to translate promising technologies into routine practice even when the underlying science is sound.

Clinical translation is also constrained by **the learning curve and usability burden for clinicians**. New workflows may improve personalization but at the cost of increased planning complexity. Surgeons and therapists must learn to interpret digital models, engage with virtual planning systems, evaluate print quality, and understand the limitations of printed devices. If these technologies are perceived as cumbersome or time-consuming, adoption may remain confined to enthusiasts. Several NCTs indicate that 3D-printed tools can reduce cognitive burden or facilitate execution, but this benefit must outweigh the preparatory effort required to design and produce them. The same is true for prosthetic or orthotic workflows, where digital customization may streamline fabrication only if scanning, design, and fitting are well integrated into clinical routines.

For regenerative and bioprinted applications, **biological integration remains the most demanding translational hurdle**. Printing a structure with the correct geometry is only the beginning. A clinically successful regenerative construct must also support cell survival, vascularization, host integration, immune compatibility, controlled degradation if biodegradable, and long-term functional remodeling. These requirements are difficult even in relatively simple avascular tissues and far more complex in dynamic organs such as the airway. While early trials demonstrate feasibility, robust evidence of that living or bioactive constructs can function safely in the human body over time is still limited.

A related challenge is **the scarcity of true clinical disease models**. Although 3D bioprinting is often promoted as a platform for precision medicine, personalized drug testing, and tumor modeling, very few registered human studies directly evaluate such disease-replicating constructs in clinical decision-making. This is an important translational gap. It suggests that the bridge between laboratory disease modeling and formal patient-facing clinical trials is still weak. Regulatory uncertainty, unclear endpoint selection, and the indirect nature of benefit likely all contribute. For this reason, disease models remain conceptually central to bioprinting but clinically underrepresented relative to anatomical models and implantable devices.

Additional challenges include **limited long-term surveillance data and inconsistent terminology** across studies, all of which hinder evidence synthesis and comparison. Many 3D-

printed implants and external devices are relatively new compared with conventional alternatives, and the long-term behavior under repeated stress, biological exposure, or degradation is not always known. This is particularly relevant for porous implants, load-bearing prostheses, sockets, scoliosis braces, and oral appliances exposed to repeated mechanical or chemical stresses. For degradable scaffolds, another difficulty is matching scaffold resorption to the timing of tissue regeneration. Long-term registries and post-market surveillance will therefore be essential, especially for implantable products.

Finally, one of the most important challenges is **avoiding technological enthusiasm without sufficient clinical proof**. Additive manufacturing has a natural visual and conceptual appeal. Personalized devices, digital planning, and bioprinted constructs are compelling innovations, and many early studies show promise. However, clinical maturity requires more than novelty. It requires evidence that a printed solution is not merely possible, but preferable under defined circumstances. This means demonstrating not just technical sophistication but reproducibility, safety, patient benefit, and value within real healthcare systems. The field now stands at a stage where this distinction is becoming increasingly important. The next phase of translation will depend less on showing that 3D printing can be done, and more on showing when it should be used, for whom, and with what measurable advantage.

In summary, the principal challenges for clinical translation can be grouped into several broad domains: workflow standardization, material and manufacturing control, interdisciplinary implementation and organizational integration, evidence quality, regulatory complexity, economic implementation, and long-term biological or mechanical validation (**Table 8**). These challenges are not signs of failure. Rather, they are characteristic of a field moving from technical innovation toward clinical consolidation. The trajectory is already visible across several mature application areas, while regenerative and bioprinting-based therapies remain at an earlier but highly significant stage. Addressing these barriers systematically will determine whether medical 3D printing remains a collection of promising niche innovations or evolves into a deeply integrated platform for personalized and regenerative healthcare.

Table 8. Main challenges for clinical translation across 3D printing and bioprinting applications

Challenge domain	Description	Most affected applications	Representative examples
Workflow standardization	Variability in imaging, segmentation, design, printing, post-processing, and sterilization limits reproducibility	All domains; especially surgical guides, implants, bioprinting	NCT04635865, NCT05291754, NCT06051747
Material heterogeneity	Different materials have distinct mechanical, biological, and regulatory properties, limiting cross-study comparability	Implants, scaffolds, orthoses, dental devices	NCT03647501, NCT04167878, NCT04773847, NCT06940115
Manufacturing scale-up and quality assessment	Transition from bespoke low-volume production to reproducible clinical manufacturing remains difficult	Point-of-care printing, in-house implants, bioprinting	NCT05291754, NCT02828306, NCT03517774
Interdisciplinary implementation and organizational integration	Clinical adoption requires close collaboration across engineering and medical teams	All domains	Seen broadly across maxillofacial, orthopedic, spine, and rehabilitation studies
Small and single-center studies	Many trials are pilot, feasibility, or observational, limiting generalizability	Most domains, especially regenerative and bioprinted constructs	NCT04399239, NCT06587633, NCT05451108
Surrogate endpoints	Accuracy, fit, comfort, and short-term radiographic outcomes often dominate over long-term patient benefit	Models, guides, orthoses, implants	NCT05896410, NCT06361966, NCT03673865, NCT05237908
Regulatory complexity	Personalized and biologically active constructs challenge traditional device and biologic pathways	Implantable devices, degradable scaffolds, bioprinting	NCT06051747, NCT04399239, NCT06406452
Cost and reimbursement	Economic benefits are promising but often not rigorously demonstrated or reimbursed	Orthoses, prosthetics, implants, assistive devices	NCT06648798, NCT04725461, NCT06361966
Long-term durability and surveillance	Many devices lack extensive long-term data on wear, failure, degradation, or integration	Load-bearing implants, prostheses, degradable scaffolds	NCT05773261, NCT05981222, NCT05451108, NCT06993714

Challenge domain	Description	Most affected applications	Representative examples
Biological integration	Living or bioactive constructs must support cell survival, vascularization, remodeling, and safe host integration	Regenerative scaffolds and bioprinting	NCT06051747, NCT06587633, NCT04399239
Limited disease-model translation	Few clinical trials use disease-replicating printed constructs in direct patient-facing workflows	Disease models, precision medicine	Relative scarcity compared with anatomic models, orthoses, and implants

10. Conclusion and Future Perspectives

This systematic analysis of clinical trials shows that 3D printing technologies have achieved substantial clinical translation in several application domains, particularly in anatomical modeling, surgical planning, and patient-specific orthoses and prosthetic devices. These areas are supported by a growing body of interventional and observational studies demonstrating consistent benefits in procedural preparation, device customization, workflow integration, and patient engagement. In contrast, implantable prostheses and regenerative scaffolds represent a rapidly evolving but still consolidating field, in which additive manufacturing enables complex, individualized designs with encouraging early clinical outcomes. The most transformative frontier—bioprinting of living, cell-containing constructs—remains at an early stage of clinical translation, with only a limited number of exploratory studies providing initial evidence of feasibility and safety. Importantly, the relative maturity of different application domains should be interpreted in the context of the available evidence. Many clinically established applications are primarily supported by studies demonstrating procedural utility, workflow improvements, technical performance, or user-related benefits, whereas robust evidence demonstrating long-term patient-centered outcomes, comparative effectiveness, cost-effectiveness, or durable clinical benefit remains more limited across several domains. Consequently, the current clinical trial landscape reflects not only differences in technological sophistication but also differences in evidentiary development, regulatory complexity, and translational readiness.

Across the clinical landscape, trial design and distribution mirror different stages of technological and translational development. Some indications, including spinal and maxillofacial applications, are beginning to transition toward comparative and effectiveness-oriented studies, while others remain centered on feasibility, safety, or pilot-scale investigations. This uneven progression reflects persistent challenges related to material diversity, workflow variability, endpoint selection, and regulatory and manufacturing constraints. These factors continue to limit standardization, comparability, and large-scale implementation, even as the number of registered trials steadily increases, indicating sustained momentum toward broader clinical integration.

Future progress will depend on coordinated advances across several domains. The development of standardized, validated digital workflows will be essential to ensure reproducibility and enable scalability beyond specialized centers. At the same time, the generation of high-quality multicenter clinical evidence, supported by long-term follow-up, will be necessary to establish clear and durable advantages over conventional approaches. Regulatory frameworks must continue to evolve to accommodate patient-specific and biologically complex products, particularly in the context of regenerative medicine and bioprinting. Advances in biomaterials, including bioactive, degradable, and hybrid systems, are expected to support the transition from structural replacement toward functional tissue restoration. In parallel, emerging regulatory instruments such as the EU AI Act (Regulation 2024/1689) and the European Health Data Space (EHDS, Regulation 2025/327) are likely to play an important role in shaping the next phase of clinical translation.[85,86] The former establishes requirements for artificial intelligence systems integrated into medical device workflows, including image segmentation, digital planning, and biofabrication control, while the latter creates new opportunities for the secondary use of clinical data, potentially facilitating large-scale, multicenter evidence generation for personalized 3D-printed technologies.

Concurrently, the integration of AI, advanced imaging, and automated design tools is expected to streamline personalization and reduce the technical burden on clinical teams. Models such as point-of-care manufacturing and distributed digital workflows may expand access to customized solutions, including in resource-constrained environments. More broadly, the continued convergence of engineering, biological sciences, and clinical practice will define the next phase of innovation in this field. If current translational barriers are systematically addressed, 3D printing

and bioprinting technologies are well positioned to become integral components of precision and regenerative medicine, enabling more individualized, effective, and accessible healthcare.

Acknowledgements

We acknowledge support from the PTI FAB3D, Consejo Superior de Investigaciones Científicas (CSIC), Spain.

Funding

The work was supported by Spain Ministerio de Ciencia, Innovación y Universidades MICIU/AEI/ 10.13039/501100011033 [grant PID2023-150422OB-I00 to CAL], ERDF A way of making Europe, cofunded by the European Union, Xunta de Galicia [ED431C 2024/09], Instituto de Salud Carlos III (ISCIII) through the Biomodels and Biobanks Platform and co-funded by the European Union [grant PT23/00116 to RPM].

Conflict of interest

The authors declare they have no competing interests to disclose.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

Further disclosure

AI-assisted technologies (chat-GPT) were used during the preparation of this manuscript both for language editing of the text and for the generation of visual elements of Figure 2. The conceptual design and content of all figures and text were defined by the authors, who reviewed and edited the content as needed and took full responsibility for the content of the published article.

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