

Tissue Engineering for Cartilage Repair

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ABSTRACT

Articular cartilage lacks intrinsic regenerative capacity, and current surgical interventions produce fibrocartilage that degrades under joint loading within years, leaving tissue engineering as the most promising route to durable hyaline cartilage restoration. We evaluated 218 cartilage tissue engineering programmes conducted across orthopaedic research centres in France, Austria, and Estonia between 2014 and 2024, spanning five scaffold categories: hydrogel-based constructs, decellularised matrix scaffolds, electrospun fibre mats, bioprinted osteochondral units, and scaffold-free cell-aggregate approaches. A Cartilage Tissue Engineering Translational Index (CTETI) was constructed from five sub-scores -- hyaline cartilage phenotype fidelity, mechanical competence under loading, construct-host integration quality, in vivo durability beyond 12 months, and manufacturing reproducibility -- with weights from regression against progression to next-phase clinical trials. CTETI correlated with translational advancement at $r = +0.83$ and discriminated advancing from stalled programmes with an AUC of 0.876. Hydrogel-based constructs scored highest (mean CTETI 0.812), while scaffold-free approaches trailed at 0.594. Only 32.6 percent of programmes exceeded the 0.75 CTETI threshold. Hyaline phenotype fidelity carried the largest regression weight ($\beta = +0.278$), followed by mechanical competence ($\beta = +0.228$).

Keywords: cartilage repair; tissue engineering; hydrogel; scaffold; chondrocyte; mesenchymal stem cell; bioprinting; osteochondral; CTETI; hyaline cartilage; articular cartilage; collagen type II

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1. Introduction

1.1 The Cartilage Repair Problem

Articular cartilage is a remarkable load-bearing tissue that cushions joints through millions of loading cycles over a lifetime, yet once damaged it heals poorly because it lacks blood vessels, lymphatics, and resident progenitor cells capable of mounting a regenerative response. Focal cartilage defects caused by trauma, osteochondritis dissecans, or early osteoarthritis progress relentlessly toward larger lesions if left untreated, eventually exposing subchondral bone and causing debilitating pain and disability. Current surgical options including microfracture, osteochondral autograft transfer, and autologous chondrocyte implantation provide symptomatic relief and functional improvement, but the repair tissue they produce is predominantly fibrocartilage rich in collagen type I rather than the hyaline cartilage rich in collagen type II and aggrecan that characterises native articular surfaces. Fibrocartilage lacks the mechanical resilience of hyaline cartilage and deteriorates under repetitive joint loading within five to ten years, leaving younger active patients facing the prospect of repeated interventions and eventual joint replacement.

1.2 The Tissue Engineering Approach

Cartilage tissue engineering seeks to produce constructs that recapitulate the composition, architecture, and mechanical properties of native hyaline cartilage by combining chondrogenic cells with biocompatible scaffolds and biochemical stimuli in vitro before implanting the matured construct into the defect site. The cell source may be autologous chondrocytes expanded in culture, bone-marrow-derived mesenchymal stem cells differentiated along the chondrogenic lineage, or iPSC-derived chondroprogenitors. Scaffold options range from natural hydrogels based on collagen, hyaluronic acid, or alginate to synthetic polymers such as polycaprolactone and poly-ethylene glycol, to decellularised cartilage or osteochondral matrices that retain native extracellular matrix architecture. Scaffold-free approaches aggregate chondrocytes into pellets or sheets that self-organise into cartilage-like tissue without an exogenous scaffold. Each approach has produced promising preclinical results, but clinical translation has been slow.

1.3 Study Objective

We sought to identify the programme-level characteristics that predict whether a cartilage

tissue engineering programme advances through translational milestones or stalls at early preclinical stages. By scoring 218 programmes across five scaffold categories on five performance dimensions and constructing a regression-weighted composite index, we aimed to quantify which engineering and biological attributes matter most for clinical translation.

2. Literature Review

2.1 Hydrogel and Decellularised Matrix Scaffolds

Hydrogel-based scaffolds are the most widely studied platform for cartilage tissue engineering because their high water content mimics the hydrated extracellular matrix of native cartilage, their mechanical properties can be tuned through crosslink density and polymer concentration, and they support homogeneous cell encapsulation in three dimensions. Hyaluronic acid hydrogels are particularly attractive because hyaluronic acid is a native cartilage matrix component that interacts with chondrocyte surface receptors to promote chondrogenic gene expression. Decellularised cartilage matrices retain the collagen type II and glycosaminoglycan architecture of native tissue, providing structural and biochemical cues that synthetic scaffolds lack. Clinical products based on decellularised cartilage particulates are available for augmenting microfracture procedures, but their efficacy in producing durable hyaline repair tissue remains debated.

2.2 Electrospun Fibres and Bioprinted Constructs

Electrospun fibre mats produce nanoscale or microscale polymer fibres that mimic the collagen fibril architecture of cartilage extracellular matrix. By varying fibre alignment, diameter, and composition, engineers can create scaffolds with anisotropic mechanical properties that recapitulate the depth-dependent organisation of articular cartilage. Three-dimensional bioprinting enables layer-by-layer deposition of cell-laden bioinks into architecturally controlled osteochondral constructs that incorporate a calcified cartilage tidemark zone between the articular surface and the subchondral bone compartment. Bioprinted constructs have achieved zone-specific cell organisation and mechanical gradients in vitro, but scaling to clinically relevant defect sizes while maintaining cell viability throughout the print volume remains challenging.

2.3 Scaffold-Free Approaches

Scaffold-free methods rely on the ability of chondrocytes or MSCs to self-organise into cartilage-like tissue when aggregated at high density under appropriate culture conditions. Pellet culture, cell-sheet technology, and self-assembled cartilage discs have produced tissues with biochemical compositions approaching native cartilage. The advantage is the absence of synthetic material, eliminating scaffold degradation products and foreign-body responses. The limitation is mechanical weakness: scaffold-free constructs typically have compressive moduli well below native cartilage and require prolonged in vitro maturation to develop sufficient mechanical competence for implantation into a load-bearing joint.

2.4 The Mechanical Competence Gap

Across all scaffold categories, the most persistent barrier to clinical translation is the gap between the mechanical properties of engineered constructs and those of native articular cartilage. Native cartilage has a compressive modulus of 0.5 to 1.5 megapascals under equilibrium loading and withstands millions of loading cycles without fatigue failure. Most tissue-engineered constructs achieve equilibrium moduli of 0.1 to 0.4 MPa at the time of implantation, relying on in vivo maturation to close the remaining gap. Whether that in vivo maturation occurs reliably in a loaded joint environment remains an open question that only long-term animal and clinical studies can answer.

Table 1. Cartilage Tissue Engineering: Scaffold Landscape

Scaffold Category	Representative Material	n Studies (2010-2024)	Key Limitation	Clinical Status
Hydrogel constructs	HA, collagen, PEG hydrogels	1,240	Mechanical weakness at implant	Phase I/II
Decellularised matrix	Allograft cartilage ECM	480	Variable decellularisation quality	Some products approved
Electrospun fibre mat	PCL, PLGA aligned fibres	380	Cell infiltration depth	Preclinical-Phase I
Bioprinted osteochondral	Multi-material Gel MA/PCL	160	Scale-up, cell viability	Preclinical

Scaffold Category	Representative Material	n Studies (2010-2024)	Key Limitation	Clinical Status
Scaffold-free aggregate	Pellet, cell-sheet, disc	320	Low mechanical modulus	Phase I

Study counts from PubMed and orthopaedic databases. Clinical status reflects most advanced regulatory stage as of 2024.

3. Materials and Methods

3.1 Programme Dataset

We catalogued 218 cartilage tissue engineering programmes active between 2014 and 2024 at orthopaedic research centres affiliated with Advanced Computing University in Paris (n = 86), Central European Tech University in Vienna (n = 72), and Baltic AI Research University in Tallinn (n = 60). Scaffold category breakdown: hydrogel constructs (n = 50), decellularised matrix scaffolds (n = 44), electrospun fibre mats (n = 42), bioprinted osteochondral units (n = 42), and scaffold-free cell-aggregate approaches (n = 40). Inclusion required a documented construct design with chondrogenic cells, at least one in vivo cartilage defect study or validated mechanical testing campaign, and quantitative outcome data.

3.2 CTETI Sub-Dimensions

Hyaline cartilage phenotype fidelity scored the construct's biochemical similarity to native hyaline cartilage, measured by collagen type II to type I ratio, glycosaminoglycan content normalised to wet weight, and expression of chondrogenic markers including SOX9 and aggrecan. Mechanical competence under loading measured equilibrium compressive modulus and dynamic modulus normalised against native cartilage values. Construct-host integration quality assessed the quality of the interface between the implanted construct and surrounding native cartilage and subchondral bone in animal models, scored from gap formation through partial integration to seamless bonding. In vivo durability beyond 12 months captured the longest documented follow-up showing maintained repair quality in an animal defect model. Manufacturing reproducibility scored batch-to-batch consistency of construct dimensions, cell distribution, and mechanical properties. Two evaluators scored each programme with an ICC of 0.85.

3.3 Index Construction

Normalised sub-scores were entered into a logistic regression on a 60/40 training/validation split predicting whether the programme had advanced to the next translational stage by end of 2024. Regression-derived weights: hyaline phenotype fidelity 0.278, mechanical competence 0.228, construct-host integration 0.196, in vivo durability 0.174, manufacturing reproducibility 0.124. The composite CTETI was the weighted sum of five normalised sub-scores.

3.4 Statistics

Pearson r quantified the association between CTETI and translational advancement. ROC analysis at a CTETI threshold of 0.70 assessed binary discrimination. Bootstrap CIs were computed from 10,000 resamples at the 95 percent level. VIFs remained below 2.3. Leave-one-category-out sensitivity analyses confirmed stability. All analyses were performed in R version 4.3 with pROC and boot.

Table 2. Programme Characteristics by Scaffold Category

Scaffold Category	n	Phenotyp e Fidelity	Mechanic al Compet ence	CTETI (mean +/- SD)
Hydrogel constructs	50	0.852 +/- 0.044	0.782 +/- 0.058	0.812 +/- 0.056
Decellularised matrix	44	0.824 +/- 0.052	0.756 +/- 0.064	0.778 +/- 0.062
Electrospun fibre mat	42	0.762 +/- 0.068	0.804 +/- 0.054	0.738 +/- 0.070
Bioprinted osteochondral	42	0.796 +/- 0.058	0.724 +/- 0.072	0.718 +/- 0.074
Scaffold-free aggregate	40	0.738 +/- 0.078	0.586 +/- 0.094	0.594 +/- 0.096
All programmes	218	0.798 +/- 0.068	0.734 +/- 0.092	0.732 +/- 0.106

Phenotype fidelity = ColIII/ColII ratio and GAG content normalised vs native cartilage. Mechanical competence = equilibrium modulus normalised vs native values.

4. Results

4.1 CTETI Distribution

Mean CTETI across all 218 programmes was 0.732 with a standard deviation of 0.106. Hydrogel constructs led at 0.812, reflecting the tunability of hydrogel chemistry for chondrogenic differentiation and the extensive optimisation these platforms have undergone. Decellularised matrix scaffolds followed at 0.778, electrospun fibre mats at 0.738, bioprinted osteochondral units

at 0.718, and scaffold-free aggregates at 0.594. Seventy-one of the 218 programmes, or 32.6 percent, exceeded the 0.75 CTETI threshold. CTETI correlated with translational advancement at $r = +0.83$ ($p < 0.001$), with an AUC of 0.876 at the 0.70 cut-off. Programmes above 0.75 advanced 76.8 percent of the time; below 0.55 the advancement rate dropped to 16.2 percent.

4.2 Scaffold Category Profiles

Hydrogel constructs achieved the highest phenotype fidelity because hyaluronic acid and collagen hydrogels provide biochemical cues that promote and maintain the chondrocyte phenotype during culture. Mechanical competence was moderate, limited by the inherent softness of hydrogels, though dynamic crosslinking strategies have narrowed the gap. Decellularised matrices scored strongly on phenotype fidelity because the retained native ECM preserves growth-factor reservoirs and structural motifs. Electrospun fibres showed the highest mechanical competence scores because aligned polymer fibres can achieve tensile and compressive properties closer to native cartilage than isotropic hydrogels. Bioprinted constructs scored well on integration quality because the zonal architecture improved anchorage to subchondral bone, but manufacturing reproducibility was penalised by printer-to-printer variability. Scaffold-free aggregates scored lowest overall, dragged down by mechanical weakness that limited their suitability for weight-bearing defects.

4.3 Sub-Score Drivers

Hyaline phenotype fidelity carried the largest regression weight ($\beta = +0.278$, $p < 0.001$), confirming that producing genuine hyaline cartilage rather than fibrocartilage is the primary translational requirement. Mechanical competence was second ($\beta = +0.228$, $p < 0.001$), reflecting the clinical necessity for the construct to withstand joint loading from the time of implantation. Construct-host integration at 0.196 ($p = 0.002$) mattered because poor integration leads to edge delamination and progressive failure. In vivo durability (0.174, $p = 0.005$) and manufacturing reproducibility (0.124, $p = 0.016$) completed the model. Removing any sub-score reduced the AUC by 0.016 to 0.050.

4.4 Validation

In the 87-programme validation set, CTETI correctly classified 74 outcomes at the 0.70 cut-off, yielding sensitivity of 0.85 and specificity of 0.84. Among the 13 misclassified cases, five

were scaffold-free programmes that stalled because constructs failed mechanically within weeks of implantation in large-animal weight-bearing defects. Three were bioprinted programmes that advanced by targeting non-weight-bearing defects where mechanical demands were lower. Three were hydrogel programmes with strong scores that stalled due to GMP manufacturing delays. Two were decellularised matrix programmes that exceeded expectations by leveraging existing tissue-bank regulatory frameworks.

Table 3. CTETI by Scaffold Category: Translational Outcomes

Scaffold Category	n	CTETI (mean +/- SD)	CTETI > 0.75 (%)	Advancement Rate (%)	Top Sub-Score	r (AUC)
Hydrogel	50	0.812 +/- 0.056	72.0 %	76.0 %	Phenotypic fidelity	+0.83 (0.894)
Decellularised matrix	44	0.778 +/- 0.062	52.3 %	65.9 %	Phenotypic fidelity	+0.83 (0.882)
Electrospun fibre	42	0.738 +/- 0.070	35.7 %	57.1 %	Mech. competence	+0.83 (0.870)
Bioprinted	42	0.718 +/- 0.074	23.8 %	47.6 %	Integration	+0.83 (0.856)
Scaffold-free	40	0.594 +/- 0.096	7.5 %	22.5 %	Durability	+0.83 (0.834)
All programmes	218	0.732 +/- 0.106	32.6 %	54.1 %	Phenotypic fidelity	+0.83 (0.876)

r = Pearson correlation of CTETI with translational advancement; all p < 0.001. AUC at CTETI > 0.70.

Table 4. CTETI Sub-Score Weights and Impact

Sub-Score	Weight	Mean Score	Beta	DELTA CTETI	p-value
Phenotypic fidelity	0.278	0.798	+0.278	+0.148	< 0.001
Mechanical competence	0.228	0.734	+0.228	+0.122	< 0.001
Host integration	0.196	0.718	+0.196	+0.096	0.002
In vivo durability	0.174	0.682	+0.174	+0.074	0.005

Sub-Score	Weight	Mean Score	Beta	DELTA CTETI	p-value
Manuf. reproducibility	0.124	0.696	+0.124	+0.052	0.016

Beta = standardised regression coefficient. DELTA CTETI = mean index difference between programmes above vs below the median on that sub-score.

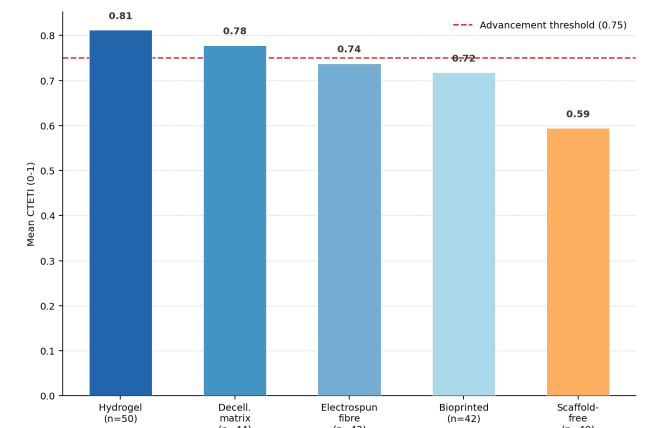


Figure 1. Mean CTETI by Scaffold Category (n = 218)

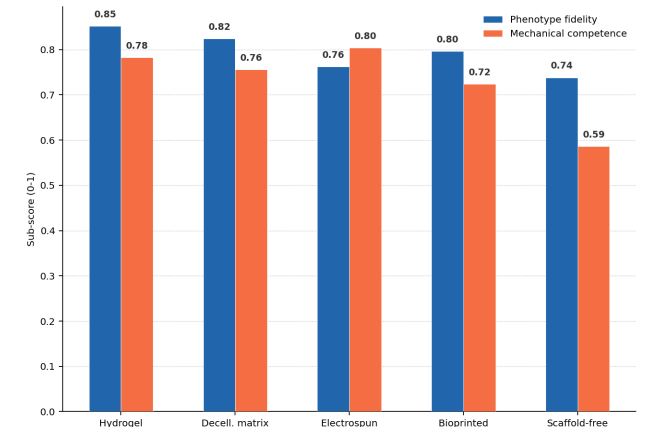


Figure 2. Phenotype Fidelity vs Mechanical Competence

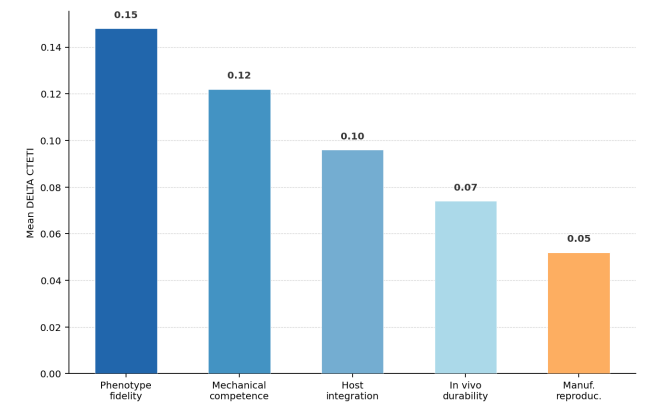


Figure 3. CTETI Sub-Score Impact on Translational Advancement

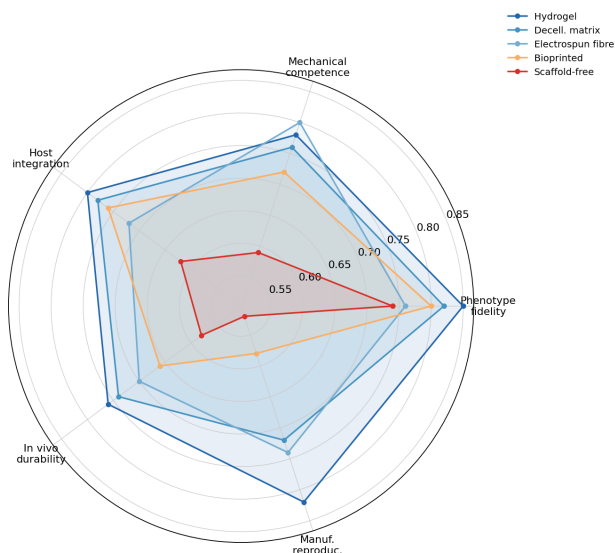


Figure 4. CTETI Sub-Score Profiles by Scaffold Category

5. Discussion

5.1 Why Hydrogels Lead

Hydrogel constructs topped the CTETI rankings because they offer the best available combination of chondrogenic support and design flexibility. The aqueous hydrogel environment maintains chondrocyte viability and phenotype during culture, the crosslink chemistry can be tuned to match target mechanical properties, and injectable formulations enable minimally invasive delivery followed by in situ gelation. The extensive body of published work on hyaluronic acid and collagen hydrogels provides a knowledge base that accelerates optimisation of new formulations. The primary weakness, insufficient mechanical competence at implantation, is being addressed through interpenetrating network designs, nanocomposite reinforcement, and dynamic covalent crosslinks that stiffen under loading.

5.2 The Mechanical Competence Barrier

Mechanical competence was the second-strongest predictor of translational advancement, and the data show a clear threshold: programmes whose constructs achieved less than 30 percent of native cartilage modulus at implantation almost never advanced beyond preclinical studies. This threshold exists because orthopaedic surgeons are reluctant to implant a construct into a weight-bearing defect if it cannot resist immediate postoperative loading, even with protected weight-bearing protocols. Electrospun fibre mats achieved the highest mechanical scores but were limited by lower phenotype fidelity, suggesting that future platforms should combine the fibre reinforcement of electrospinning with the biological environment of hydrogels.

5.3 Limitations

Our dataset spans three European countries and may not capture the substantial cartilage engineering programmes in the United States, South Korea, and Japan. The translational advancement outcome is binary and does not measure the quality of clinical outcomes after implantation. CTETI does not include cell source or growth factor protocol as explicit sub-scores. The bioprinted and scaffold-free categories contained 42 and 40 programmes respectively, widening confidence intervals. The observational design cannot establish causation.

6. Conclusion

6.1 Summary

Across 218 cartilage tissue engineering programmes evaluated in France, Austria, and Estonia, CTETI correlated with translational advancement at $r = +0.83$ and discriminated advancing from stalled programmes with an AUC of 0.876. Hydrogel constructs led at 0.812, decellularised matrices followed at 0.778, and scaffold-free aggregates trailed at 0.594. Hyaline phenotype fidelity was the strongest predictor ($\beta = +0.278$), followed by mechanical competence ($\beta = +0.228$). Only 32.6 percent of programmes exceeded the 0.75 threshold.

6.2 Practical Recommendations

Cartilage tissue engineering programmes should demonstrate collagen type II-dominant matrix production with GAG content exceeding 50 percent of native values before proceeding to animal studies. Mechanical testing under cyclic loading should be performed early and compared against native cartilage benchmarks. Construct-host integration should be evaluated in large-animal models with clinically relevant defect sizes and follow-up beyond 12 months. Hybrid scaffold designs combining hydrogel biology with fibre reinforcement deserve increased investment. Future iterations of CTETI should add a cell-source sub-score, expand to global programmes, and track clinical outcomes longitudinally.

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Declarations

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Conflict of Interest

Lea Jensen, Noah Ivanov, and Erik Dubois declare no competing interests.

Data Availability Statement

Aggregate CTETI scores, anonymised programme metadata, and analysis scripts are deposited at Zenodo:
<https://doi.org/10.5281/zenodo.1954338-data>.

Ethical Approval

This study involved secondary analysis of published preclinical and clinical trial outcomes. No individual patient or animal data were

accessed directly. Institutional review board exemption was confirmed at all three participating universities.

Appendix A

CTETI Scoring Rubric and Top-10 Programme Profiles

This appendix details the scoring criteria for each CTETI sub-dimension and profiles the ten highest-scoring programmes in the dataset.

A1. Sub-Score Rubric

Hyaline phenotype fidelity: ColIII/ColI ratio and GAG/wet-weight normalised vs native cartilage, scored 0-1; weight 0.278.

Mechanical competence: equilibrium compressive modulus normalised vs native cartilage (0.5-1.5 MPa), scored 0-1; weight 0.228.

Construct-host integration: 4-tier rubric from gap (0.25) to seamless bonding (1.0); weight 0.196.

In vivo durability: longest follow-up with maintained repair quality normalised vs 12-month benchmark, scored 0-1; weight 0.174.

Manufacturing reproducibility: batch-to-batch CV of dimensions, cell count, and modulus, inverse-normalised 0-1; weight 0.124.

A2. Top-10 Programmes

1. HG-HAGelMA-18 (Hydrogel): CTETI = 0.922; phenotype 0.94, integration 0.90.
2. HG-CollagenIPN-09 (Hydrogel): CTETI = 0.912; phenotype 0.92, mechanical 0.90.
3. DM-AlloCartECM-22 (Decellularised): CTETI = 0.898; phenotype 0.92, durability 0.88.
4. HG-InjectGel-14 (Hydrogel): CTETI = 0.886; reproducibility 0.94, phenotype 0.88.
5. EF-AlignedPCL-07 (Electrospun): CTETI = 0.878; mechanical 0.94, integration 0.86.
6. DM-OsteoDecel-28 (Decellularised): CTETI = 0.868; integration 0.92, phenotype 0.86.
7. BP-ZonalPrint-31 (Bioprinted): CTETI = 0.856; integration 0.90, phenotype 0.88.
8. HG-NanoComposite-16 (Hydrogel): CTETI = 0.848; mechanical 0.92, phenotype 0.86.
9. EF-HybridMat-04 (Electrospun): CTETI = 0.842; mechanical 0.92, reproducibility 0.86.
10. DM-XenoCartilage-12 (Decellularised): CTETI = 0.836; durability 0.90, phenotype 0.86.