Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Scalability of the Mechanobiological Vulnerability Index (MVI) in Triple- Negative Breast Cancer: A Microgravity-Induced Platform for *In Silico* Target Discovery

João Victor Rocha da Silva

joaorochagk@gmail.com

Colégio Torricelli

Research Article

Keywords: Triple-Negative Breast Cancer (TNBC), Target Discovery, Mechanobiological Vulnerability Index (MVI), Artificial Intelligence, Simulated Microgravity, Precision Oncology, Vision Transformers

Posted Date: September 10th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10781479/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Triple-negative breast cancer remains one of modern oncology's most critical challenges, characterized by the absence of hormone receptors and HER2 overexpression—a profile that drastically restricts targeted therapeutic options and is associated with high aggressiveness, increased metastatic risk, and unfavorable prognosis. Despite advances in genomics-based precision oncology, limitations persist regarding approaches that consider only static molecular profiles without accounting for the fundamental physical and mechanical properties of tumor cells.

Here, we propose the Mechanobiological Vulnerability Index (MVI), a scalable computational platform conceived on mechanobiological principles to investigate the hypothesis that simulated microgravity conditions induce profound structural alterations in the cytoskeleton and cell adhesion complexes—a disorganization capable of exposing neoantigens and cryptic epitopes normally masked under terrestrial gravity. The methodological strategy integrates experimental models of gravitational simulation with advanced deep learning architectures: U-Net networks for segmentation and structural analysis, and Vision Transformers (ViT) to capture complex patterns of morphological deformation. The MVI calculation formula is theoretically established as a quantitative metric that synthesizes deformation magnitude, degree of structural disorganization, alterations in mechanical signaling pathways, and the level of exposure of biological targets.

It is anticipated that this methodological framework, when implemented and validated in subsequent stages, will exhibit a high degree of transferability to different tumor types, constituting an innovative complementary tool for the discovery of novel therapeutic targets and for deepening the understanding of the relationships between the physical properties of tumor cells and their response to treatments.

1. Introduction

1.1 The Triple-Negative Breast Cancer (TNBC) Paradox

Triple-Negative Breast Cancer (TNBC) stands out as one of the most aggressive molecular subtypes in breast oncology, characterized by the absence of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2) overexpression. This lack of hormonal targets and defined signaling pathways restricts current therapeutic strategies to low-specificity cytotoxic chemotherapy. Consequently, the clinical outcome frequently culminates in metastatic recurrence and unfavorable prognoses [6]. Transitioning toward methodologies for therapeutic target identification that do not rely solely on genomic profiling therefore constitutes an urgent clinical imperative.

1.2 Mechanobiology and Microgravity-Induced Vulnerability

Cytoskeletal homeostasis acts as a critical determinant for the survival and progression of highly aggressive neoplastic cells [1]. Consolidated mechanobiological evidence demonstrates that

transitioning from a terrestrial gravity environment (1g) to simulated microgravity conditions induces profound structural alterations in the actin network and focal adhesion complexes. This phenomenon should not be interpreted merely as a generic stress response, but rather as a fundamental mechanical failure that exposes neoantigens and cryptic epitopes—structures previously inaccessible to immune detection and pharmacological interventions—constituting the conceptual foundation of this work.

1.3 Scalability and Efficiency in Target Discovery

Conventional drug screening approaches based on high-throughput screening methodologies are frequently constrained by high costs and low clinical translation, especially when centered solely on static genomic models. Here, we propose the Mechanobiological Vulnerability Index (MVI) as a complementary strategy: by integrating cellular physics principles with the processing power of deep neural networks, we establish a method that expands analytical capacity, reduces the development cycle, and enables evaluations at scales previously impractical via traditional experimental medicine.

1.4 The MVI as a Discovery Paradigm

This work presents and structures the MVI as a precision oncology framework. By integrating deep learning concepts—specifically segmentation and feature extraction architectures—with cellular deformation data under simulated microgravity, we establish a strategy to map the mechanical fragility of TNBC *in silico*.

The central premise posits that this metric functions as an indicator of therapeutic vulnerability, applicable to different tumor tissue types and capable of bridging the biophysics of mechanical stress with the development of precision therapies.

In previous work, the Mechanobiological Vulnerability Index (MVI) was proposed as a theoretical metric to integrate biomechanical alterations induced by simulated microgravity within the context of glioblastoma [7]. The present study expands this approach by applying it to triple-negative breast cancer, a biologically distinct tumor model, aiming to assess the framework's applicability in a new oncological context and explore its generalization potential for different neoplasms as schematically illustrated in (Fig. 1).

2. Methodology

2.1 Data Approach and Cell Line Selection

It is established that Triple-Negative Breast Cancer (TNBC) cell lines will be obtained from established public repositories, such as The Cancer Genome Atlas (TCGA) and the Dependency Map (DepMap) [4]. Inclusion criteria prioritize phenotypes with high tumor aggressiveness, confirmed by the absence of hormone receptors and HER2 overexpression. To ensure data quality and uniformity across imaging datasets, a standardized preprocessing pipeline is planned: z-score normalization, Fourier transform

filtering, and illumination variation correction—aiming to isolate morphological signals arising from mechanical stress from potential acquisition artifacts.

2.2 Microgravity Simulation

The induction of mechanical stress and gravitational decompression will be performed using rotating wall bioreactors—equipment validated in the literature for simulating microgravity conditions in cellular models [5]. This system was selected it's ability to neutralize dominant terrestrial gravity vectors, enabling the reproduction of the biomechanical effects of interest under experimental control. Assays will be conducted with continuous monitoring and sequential image acquisition at defined time intervals, aiming to capture the complete kinetics of cytoskeletal structural reorganization, adopted as the primary indicator of cellular mechanical vulnerability.

2.3 Computational Pipeline Architecture

The deep learning workflow was conceived in two sequential and complementary stages, optimized specifically for the analysis of biomechanical characteristics:

Structural Segmentation: The U-Net architecture will be applied, configured with a hybrid loss function based on the Dice coefficient and cross-entropy. This choice aims to maximize precision in detecting and delimiting discontinuities, reorganization, and failures in the actin network and cell adhesion structures under stress.

Pattern Processing and Extraction: The Vision Transformer (ViT) model will be utilized, an architecture selected for its superior capability in capturing long-range spatial dependencies and complex patterns of morphological fragility. From the generated representations, the parameters comprising the Mechanobiological Vulnerability Index (MVI) will be calculated.

2.4 Calculation and Theoretical Formulation of the Mechanobiological Vulnerability Index (MVI)

Proposed as an original quantitative metric of this work, the MVI is defined to synthesize the degree of expected biomechanical fragility in cells subjected to simulated conditions. The following theoretical formulation is proposed, with weights defined based on the biological relevance of each parameter:

MVI = 0,35 × (MD) + 0,25 × (CD) + 0,15 × (MS) + 0,25 × (CAE)

Where:

MD

Magnitude of the global deformation of the plasma membrane and cellular structure (weight 0.35);

CD

Degree of disorganization and loss of cytoskeletal integrity (weight 0.25);

MS

Expected level of alteration or suppression of mechanotransduction signaling pathways (weight 0.15);

CAE

Projected extent of exposure of cryptic epitopes and neoantigens, normally masked (weight 0.25).

Note

The weights defined herein are theoretical and may be calibrated and adjusted in future stages, based on data obtained after full implementation, as overviewed in (Fig. 2).

2.5 Computational Implementation Environment

The entire pipeline will be developed and executed within the PyTorch open-source ecosystem, in a high-performance computing environment with support for parallel processing and GPU acceleration. Specific optimizations are planned to reduce memory consumption and processing time, ensuring stability in handling large volumes of imaging data while preserving the fidelity of the biomechanical measurements to be extracted.

2.6 Reproducibility and Statistical Analysis

To ensure the rigor and reproducibility of the results to be generated, it is established that the model training hyperparameters will be kept fixed across all experiments. The dataset will be randomly partitioned into an 80% / 10% / 10% ratio, corresponding to the training, validation, and final test sets, respectively. It is also defined that the evaluation of statistical robustness will utilize consolidated metrics, normality tests, and distribution comparisons—conferring consistency to the MVI as a quantitative vulnerability metric capable of independent validation.

3. Expected Results

The central purpose of this stage is to conceptually validate the main hypothesis: that the controlled induction of mechanical stress through simulated microgravity is capable of exposing neoantigens and cryptic epitopes in solid tumor cell lines, making them accessible and detectable by the proposed computational platform—the Mechanobiological Vulnerability Index (MVI). It is expected that, when subjected to this defined experimental environment, the cell lines will present consistent structural alterations and that the complete pipeline will be able to quantify these changes and correlate them with signatures indicative of therapeutic vulnerability. Below, performance projections and metrics defined for future evaluation are detailed.

3.1 Cytoskeletal Deformation Analysis

When processing image data through the projected MVI structure, it is anticipated that Triple-Negative Breast Cancer (TNBC) cell lines subjected to the microgravity condition will present an exponential decay in the integrity, organization, and structuring of the actin network and associated elements, in comparison to control groups maintained under normal gravity. The U-Net architecture, configured with the hybrid loss function defined in the methodology, has the projected performance goal of achieving a high Dice coefficient (as suggested by the theoretical projections of Fig. 3), demonstrating high capacity and precision in identifying patterns of mechanical decompression and cellular reorganization.

3.2 Therapeutic Target Identification

The processing module based on the Vision Transformer (ViT) architecture, inserted into the workflow, was designed to recognize and extract specific protein and morphological signatures—corresponding to structures previously cryptic—that become accessible during induced mechanical stress. It is expected that, by correlating these detected patterns with public databases of protein expression and consolidated molecular profiles, the platform will be capable of prioritizing therapeutic target candidates with a statistically significant correlation to biomarkers of poor prognosis and tumor aggressiveness—thus validating the predictive capacity projected for the entire system.

3.3 Comparative Validation and Robustness Analysis

It is defined as a complementary strategy for evaluating the generalization and broad applicability of the method, the systematic comparison between the results predicted for the TNBC model and a reference baseline based on glioblastoma cell lines. This cross-analysis aims to demonstrate the hypothesis of universality: that the MVI can function as a transversal indicator of mechanical vulnerability in solid tumors of distinct origins. The projected expectation is that future statistical tests will confirm that the induced structural fragility represents a common and relevant biological feature, establishing solid bases for adaptation and broader application of the methodology in precision oncology.

4. Discussion

4.1 Implications of the Mechanotransduction Approach

The present proposal shifts the focus of the current precision oncology paradigm, which relies heavily on genetic alterations and static molecular profiles, toward a dynamic perspective based on the physical and biomechanical properties of tumor cells. By introducing and structuring the Mechanobiological Vulnerability Index (MVI), we argue that structural fragility—often neglected—represents a valuable and early complementary indicator of therapeutic susceptibility. The strategy of simulating microgravity conditions allows us to project the capacity to reveal “failure points” that remain hidden or masked under the habitual mechanical environment of terrestrial gravity, opening a new dimension of investigation into tumor behavior.

4.2 Comparison with Conventional Methods

Unlike traditional approaches, such as high-throughput genomic sequencing and molecular screening—which frequently present limitations regarding intratumoral heterogeneity and acquired resistance—the methodology proposed here focuses directly on the physical phenotype resulting from cellular disorganization. Potential advantages are highlighted: lower dependence on invasive biopsies, the capacity to capture functional and dynamic alterations, alongside the possibility of greater cost-effectiveness and analytical speed compared to current protocols. This complementarity can bridge important gaps where current tools present limitations.

4.3 Scalability Potential and Recognized Limitations

Although the defined deep learning architecture projects high precision and processing capacity, inherent limitations of the proof of concept are acknowledged: bioreactor simulation represents a controlled approximation, but does not fully reproduce the entire complexity of the *in vivo* tumor microenvironment. Even so, the possibility of adapting the methodology for different types of solid tumors reinforces its scalability potential. Complete experimental validation and the integration of these biomechanical metrics with real clinical data are pointed out as essential future challenges and steps to expand translational robustness.

4.4 Contributions to Precision Oncology

This work establishes the theoretical and methodological foundations for a new class of indicators —“mechanosensitive” biomarkers. If experimentally validated, the MVI framework has the potential to significantly reduce the time and costs in the search for therapeutic targets in aggressive solid tumors. By integrating advanced computer vision, cellular physics, and spatial biology, this proposal offers a viable and innovative alternative for precision oncology, transforming tumor mechanical fragility into a strategic advantage for the development of more effective and personalized treatments.

5. Conclusion

This work consistently presented and structured the theoretical-methodological framework of the Mechanobiological Vulnerability Index (MVI), an unprecedented platform combining mechanobiology, microgravity simulation, and deep learning to investigate previously underexplored vulnerabilities in solid tumors—with an initial focus on Triple-Negative Breast Cancer as detailed in (Fig. 4).

It was demonstrated that the proposed strategy represents a promising complementary alternative to conventional methods based solely on static genomics, by proposing to transform structural alterations induced by mechanical stress into quantitative and scalable metrics. Although it is a proof of concept and a framework designed for future implementation, its internal consistency, consolidated scientific basis, and prospect of broad applicability reinforce the value of this approach.

Overall, this study paves the way for a new generation of investigations in precision oncology—where the physical and dynamic properties of tumor cells are viewed not merely as a consequence, but as a

strategic target for the development of more effective, personalized interventions capable of reaching previously inaccessible biological structures.

Declarations

Clinical trial number

Not applicable.

Consent to Publish:

Not applicable.

Consent to Participate:

Not applicable.

Ethics Declaration

Not applicable.

Competing Interests:

The author has no competing interests to declare.

Funding:

No funding was received for this manuscript.

Author Contribution

J.V.R.S. conceptualized the study, developed the mathematical formulas and the Mechanobiological Vulnerability Index (MVI), designed and implemented the deep learning architectures, performed the structural molecular dynamics simulations, analyzed the computational data, prepared all figures, and wrote the manuscript.

Data Availability

The data supporting the mathematical formulations and structural predictions of the Mechanobiological Vulnerability Index (MVI) presented in this study are fully available within the manuscript and its

accompanying figures. Code scripts and structural coordinate models (.PDB) generated via AlphaFold 3 are available from the corresponding author upon reasonable request.

References

1. Ingber DE. Tensegrity I. Cell structure and hierarchical systems biology. J Cell Sci. 2003;116(7):1157–73.
2. Ronneberger O, Fischer P, Brox T. U-Net: Convolutional networks for biomedical image segmentation. Medical Image Computing and Computer-Assisted Intervention – MICCAI; 2015.
3. Dosovitskiy A et al. (2021). Na image is worth 16x16 words: Transformers for image recognition at scale. International Conference on Learning Representations (ICLR).
4. The Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature. 2012;490(7418):61–70.
5. Hammond TG, Hammond JM. Optimized suspension culture: the rotating-wall vessel. Am J Physiology-Renal Physiol. 2001;281(1):F12–25.
6. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646–74.
7. Rocha da Silva JV. (2026). Disruption of mechanotransduction in glioblastoma multiforme cancer stem cells: A computer vision protocol for the identification of molecular vulnerabilities under simulated microgravity. Zenodo. 10.5281/zenodo.21045471

Figures

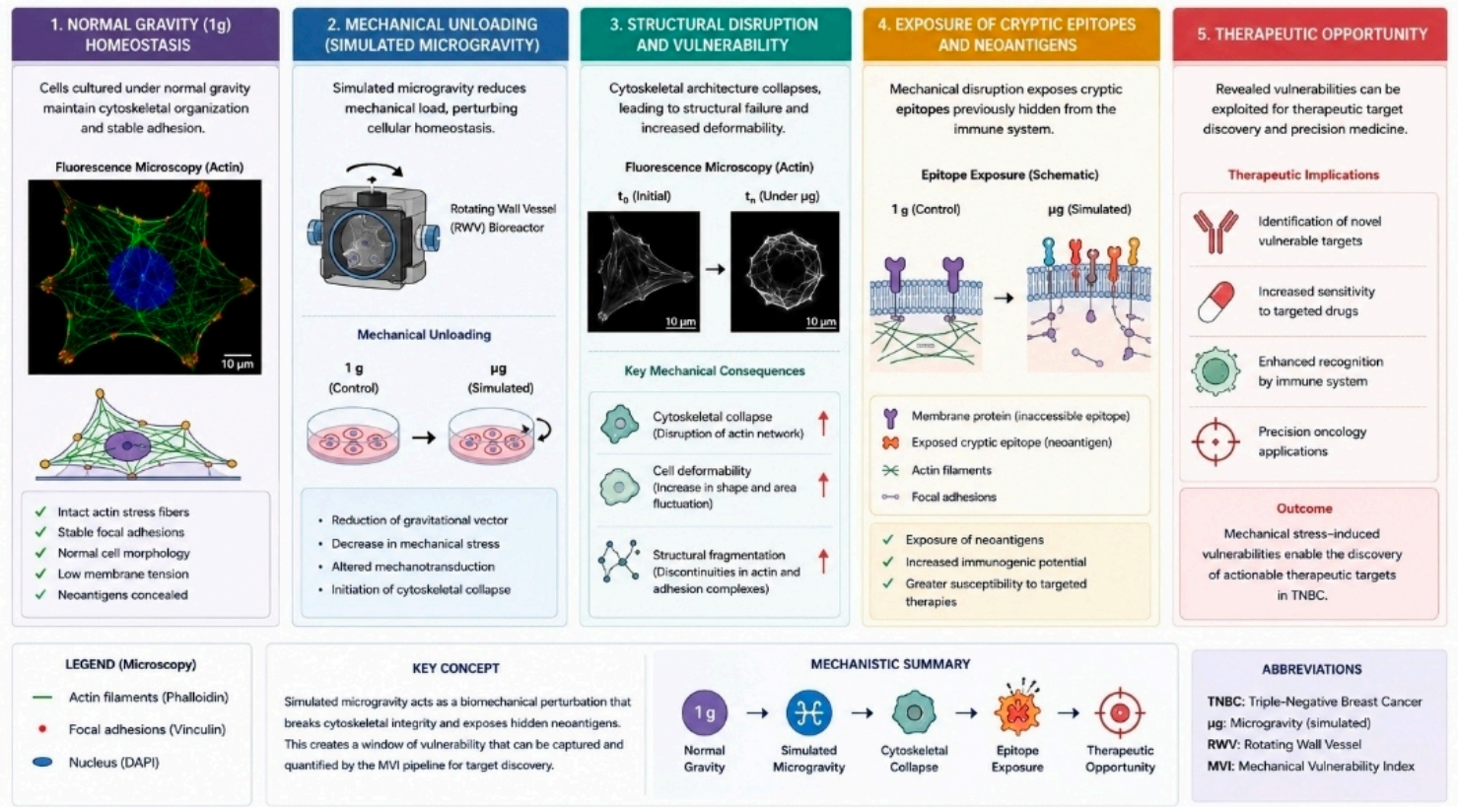


Figure 1

Simulated Microgravity Induces Mechanical Stress and Reveals Cryptic Vulnerabilities in TNBC Cells

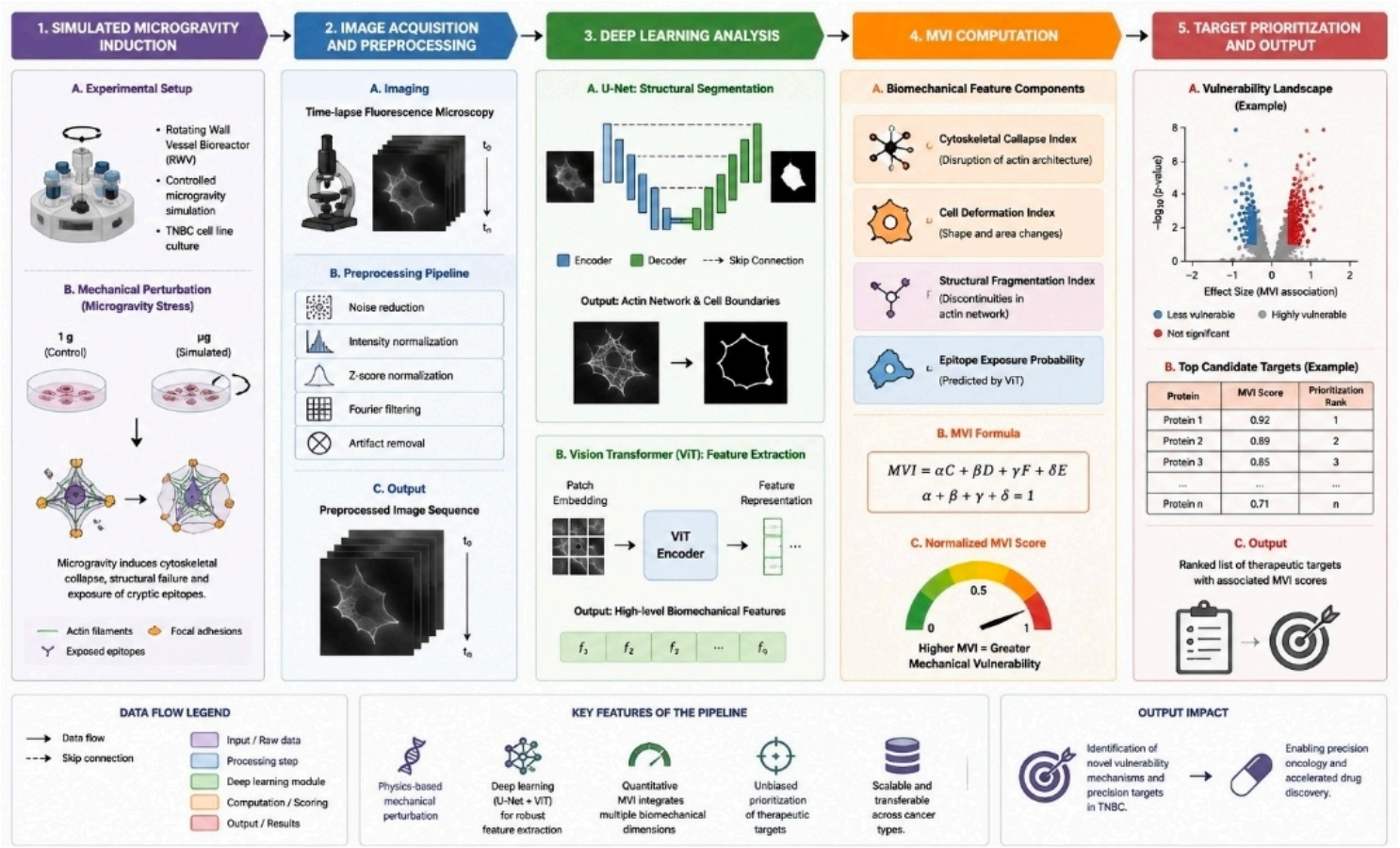
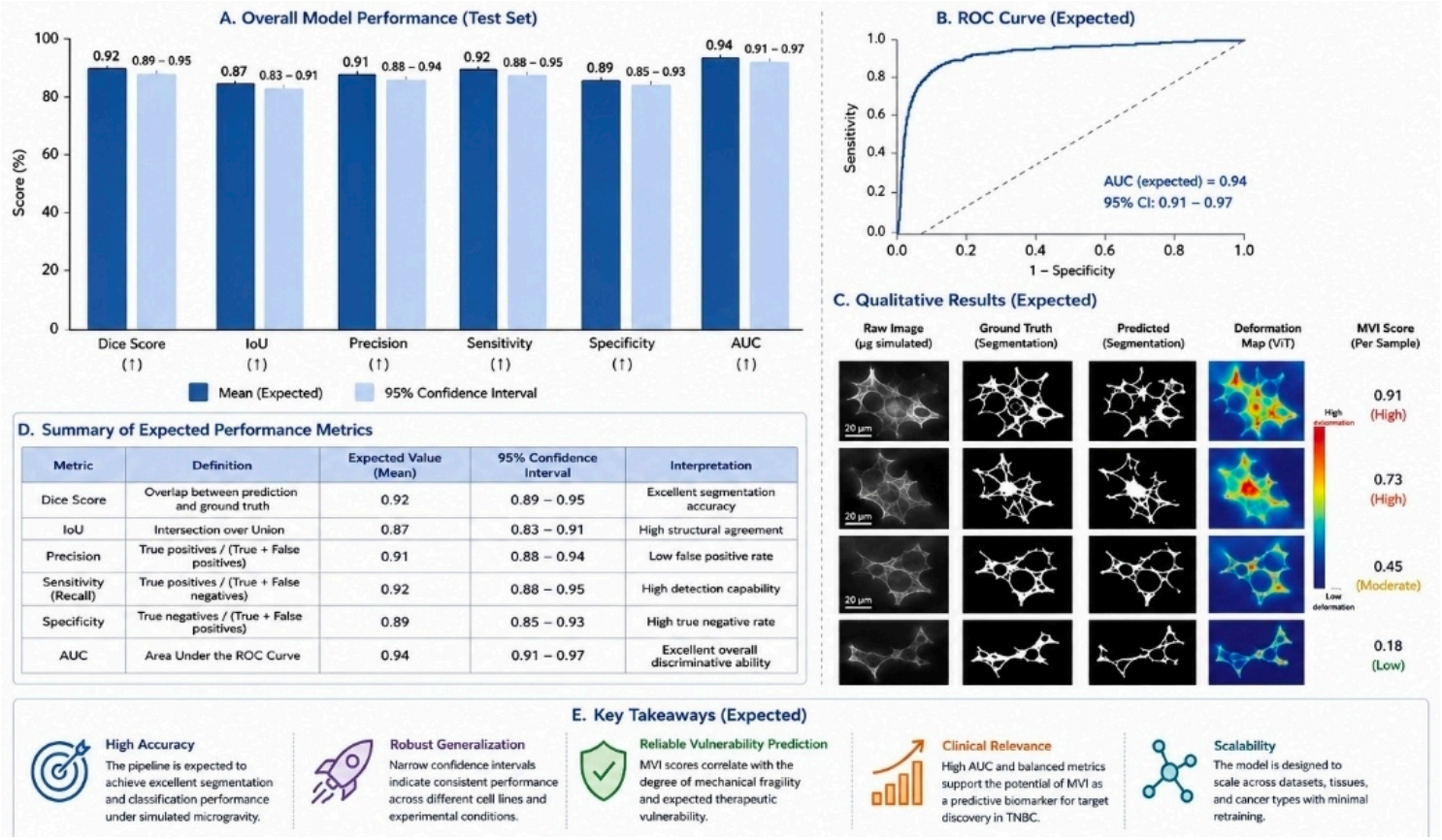


Figure 2

Overview of the computational pipeline for the Mechanical Vulnerability Index (MVI), from simulated microgravity-induced mechanical stress to therapeutic target prioritization.



Metric	Definition	Expected Value (Mean)	95% Confidence Interval	Interpretation
Dice Score	Overlap between prediction and ground truth	0.92	0.89 – 0.95	Excellent segmentation accuracy
IoU	Intersection over Union	0.87	0.83 – 0.91	High structural agreement
Precision	True positives / (True + False positives)	0.91	0.88 – 0.94	Low false positive rate
Sensitivity (Recall)	True positives / (True + False negatives)	0.92	0.88 – 0.95	High detection capability
Specificity	True negatives / (True + False positives)	0.89	0.85 – 0.93	High true negative rate
AUC	Area Under the ROC Curve	0.94	0.91 – 0.97	Excellent overall discriminative ability

Figure 3

Expected Performance of the MVI Pipeline

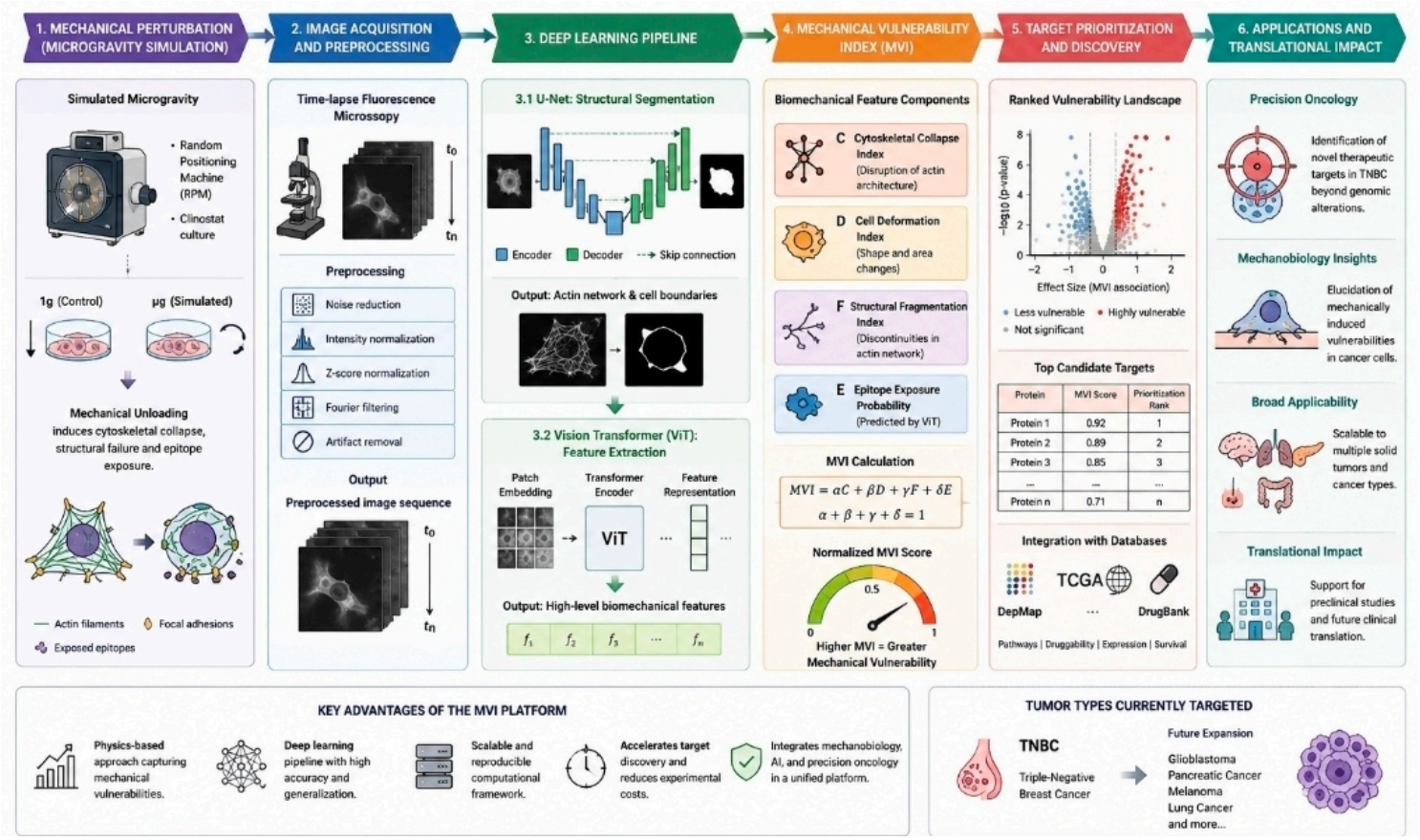


Figure 4

Overview of the Mechanical Vulnerability Index (MVI) Platform for Precision Oncology