# Human-Relevant Non-Animal Methodologies (NAMs)

*Specialised Models Series:* ***Cancer & Haematology***

# Prostate Cancer Models

**Reference 1.4 in Full Scope Roadmap**

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## Legal & Scientific Imperative for Universities

Section 2A of the Animals (Scientific Procedures) Act 1986 imposes a statutory duty to prioritise replacement with human-relevant methods wherever scientifically possible. Traditional animal models for prostate cancer research — particularly xenograft and patient-derived xenograft (PDX) mouse models — have well-documented limitations due to species differences in tumour microenvironment, androgen signalling, immune responses, metastatic patterns (especially to bone), and drug metabolism.

Traditional animal models in prostate cancer research—particularly subcutaneous/orthotopic xenografts and PDX models—exhibit significant limitations. These include profound species differences in prostatic microarchitecture, androgen signalling, immune surveillance, and bone metastatic tropism. These factors contribute to high attrition rates in drug development, rendering these models non-predictive of clinical outcomes. At the cellular and microenvironmental levels, human and rodent systems exhibit critical disparities:

- **Microenvironmental & Stromal Mismatch:** Human prostate tumours are characterised by complex interactions within the prostatic stroma and a distinct microenvironment that supports tumour progression. Rodent models fail to replicate this human-specific stromal complexity, fundamentally altering the mechanical barriers to drug diffusion and the signalling networks that drive tumour growth.
- **Androgen Signalling & Receptor Discrepancies:** The androgen receptor (AR) signalling pathway is the primary driver in prostate cancer. Rodent AR biology and its response to castration differ substantially from human pathways. Consequently, the efficacy of novel androgen-deprivation therapies and AR-targeted agents translates poorly from rodent assays to human clinical practice.
- **Bone Metastatic Tropism:** Bone metastasis is a major clinical challenge in advanced prostate cancer, yet rodent models often fail to replicate the human-specific bone metastatic niche. This leads to ineffective testing of bone-targeted therapies and systemic distribution predictions that remain poorly translatable to the human clinic.
- **High-Severity Surgical & Tumour Burden Models:** Orthotopic implantation and metastatic induction models frequently inflict high-severity suffering. Animals experience significant tumour burden, progressive organ failure, and systemic distress. This high physiological stress acts as a major confounding variable that masks the true safety and efficacy profiles of experimental treatments.

Transitioning to human-relevant NAMs—such as prostate cancer organoids, prostate cancer-on-chip platforms, and multi-organ prostate–bone metastasis MPS—is a dual scientific and statutory mandate.

## Landmark Regulatory & Scientific Momentum

This section details the transition from traditional animal-based prostate cancer assays to high-fidelity, human-relevant NAMs. By leveraging organ-on-a-chip and 3D niche-mimetic platforms, institutions can replicate the intricate dynamics of human tumour heterogeneity, androgen receptor signalling, and metastatic behaviour with unprecedented accuracy.
Landmark regulatory & scientific momentum

- **Patient-derived prostate cancer organoids:** Increasingly used to model hormone-sensitive and castration-resistant prostate cancer, with growing evidence of strong correlation to clinical drug response, particularly for androgen receptor-targeted therapies.
- **Prostate cancer-on-chip platforms:** Systems incorporating tumour microenvironment and stroma to enable dynamic studies of invasion, androgen signalling, and therapy resistance under physiologically relevant flow conditions.
- **Multi-organ prostate–bone metastasis MPS:** Platforms adopted to study the complex mechanisms of bone metastasis, a major clinical challenge in advanced prostate cancer.
- **Growing industry & academic interest:** Increased uptake by pharmaceutical companies and academic centres for drug development, biomarker discovery, and personalised treatment strategies, especially where traditional animal models have demonstrated poor translational success.

## Landmark Regulatory Milestone

In recent regulatory advancements, there is increasing acceptance of qualified human-relevant data for oncology efficacy and drug safety assessments. By moving away from restrictive xenograft and PDX models, this shift demonstrates that human-derived organ-on-a-chip and 3D organoid systems can successfully support regulatory advancement in prostate cancer research, setting a clear precedent for replacement under Section 2A of the *Animals (Scientific Procedures) Act 1986*.

## Core Specialised Prostate Cancer Models & Enabling Platforms

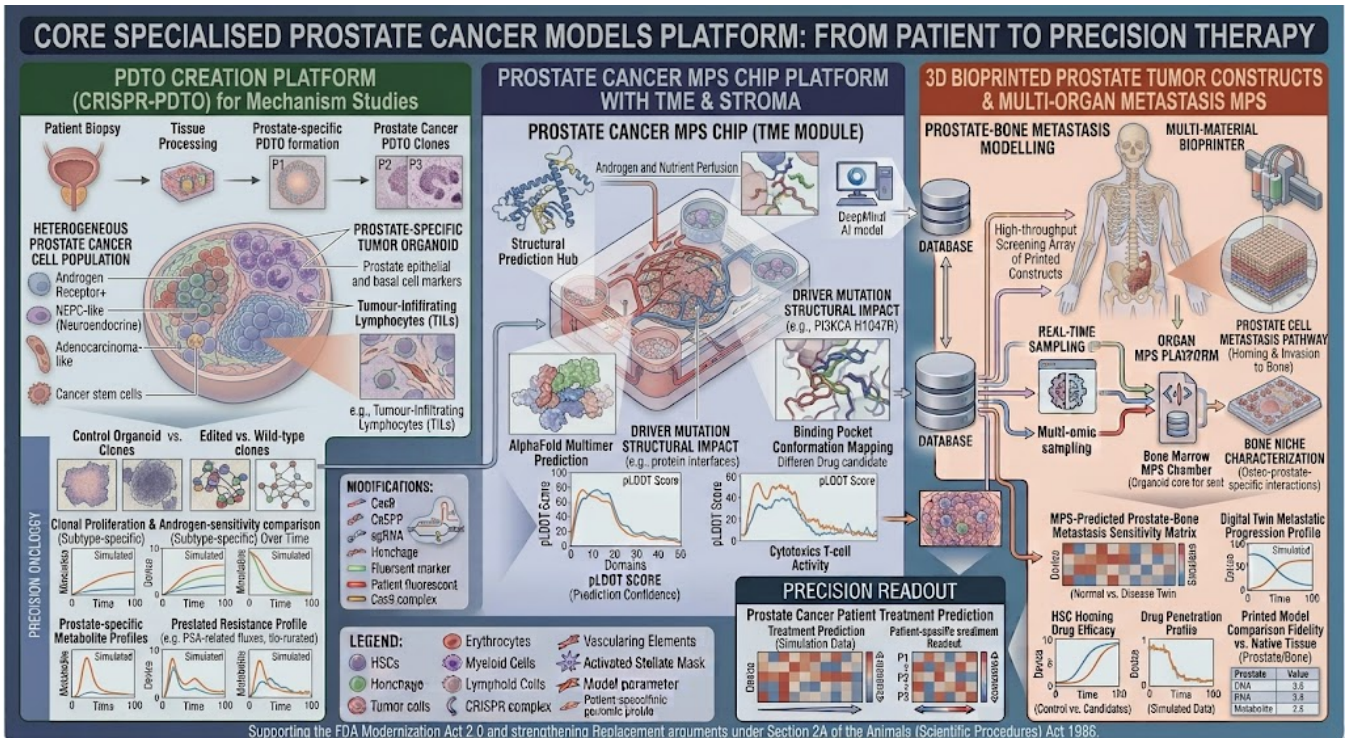


**Figure 1: Core Specialised Prostate Cancer Models** — *Prostate cancer organoids / patient-derived prostate tumour organoids (left), prostate cancer-on-chip with tumour microenvironment and stroma (center), and 3D bioprinted prostate tumour constructs plus multi-organ prostate–bone metastasis MPS (right). These platforms support the FDA Modernization Act 2.0 and strengthen Replacement arguments under Section 2A of the Animals (Scientific Procedures) Act 1986.*

### Table 1: Core Specialised Prostate Cancer Models

| Platform | Key Applications | Benefits for 3Rs |
|---|---|---|
| **Prostate Organoids** | AR-targeted therapy & drug screening | Preserves patient-specific tumour heterogeneity |
| **Prostate-on-Chip** | Invasion & androgen signalling | Replaces invasive xenograft models |
| **Multi-Organ Metastasis MPS** | Bone metastatic niche studies | Bypasses high-severity metastatic induction |
| **3D Bioprinted Constructs** | High-throughput therapeutic testing | High experimental control & reproducibility |

## Cross-Cutting & Enabling Platforms for Prostate Cancer Research

These platforms support multiple Prostate research areas and are widely applicable across various blood disorders and cell therapies. While specialised models focus on specific disease states, these enabling platforms are essential for validating the high-maturity NAMs and ensuring they meet the high standards required for regulatory-accepted, "fit-for-purpose" research.

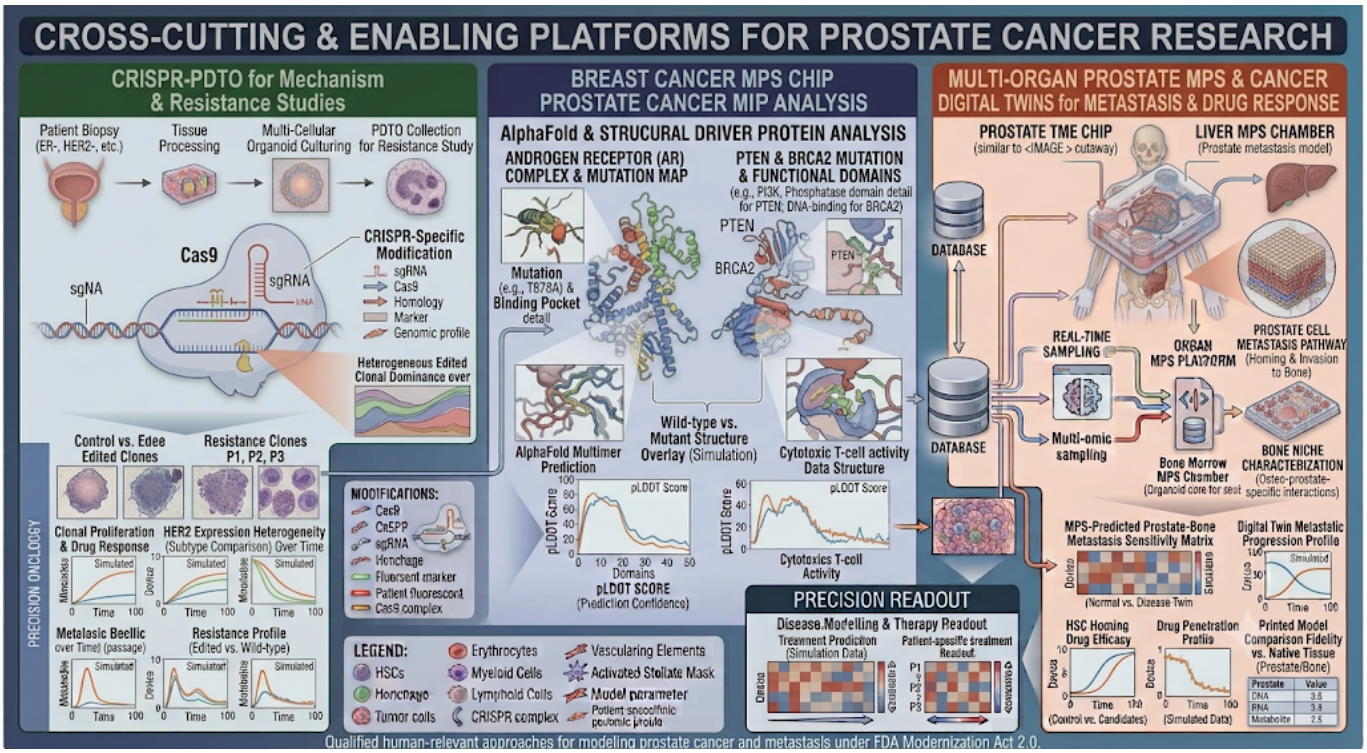


**Figure 2: Cross-Cutting & Enabling Platforms for Prostate Cancer Research —** CRISPR gene editing in prostate cancer organoids for mechanism and resistance studies (left), AlphaFold (DeepMind) predicting structures of prostate cancer-related proteins such as AR, PTEN, and BRCA2 (center), and prostate cancer digital twins or multi-organ prostate–bone / prostate–liver MPS for metastasis and drug response prediction (right). These enabling technologies support qualified human-relevant approaches under the FDA Modernization Act 2.0.

**Table 2: Advanced Computational & Functional Platforms for Prostate Cancer Research**

| Platform / Model | Description | Key Applications | Benefits for Universities & 3Rs |
|---|---|---|---|
| **CRISPR-Based Functional Genomics in Prostate Cancer Organoids** | Gene editing applied in prostate cancer organoids and PDOs to model oncogenic drivers, study resistance mechanisms, or validate therapeutic targets. | Mechanistic studies of prostate cancer drivers (e.g. AR, PTEN, BRCA2), synthetic lethality screening, castration resistance research, target validation. | Directly addresses animal model limitations in genetic modelling. Powerful for mechanistic prostate cancer and precision oncology research. |
| **AlphaFold & Structural Biology for Prostate Cancer Targets** | Use of AlphaFold and related tools to predict structures of prostate cancer-related proteins (e.g. androgen receptor, PTEN, BRCA2) for drug design and mutation impact analysis. | Structure-based drug design for prostate cancer, mapping resistance mutations, accelerating discovery of targeted therapies, personalised oncology. | Accelerates target discovery and drug design while minimising animal use. Ideal for computational + experimental prostate cancer workflows. |
| **Prostate Cancer Digital Twins & Multi-Organ Tumour MPS** | Computational digital twins of prostate cancer combined with interconnected chips linking prostate tumour with bone or liver compartments. | Bone metastasis modelling, systemic drug effects, personalised treatment prediction, complex multi-organ prostate cancer research. | Enables holistic, human-relevant modelling of prostate cancer progression and treatment effects across multiple organs. Strong for advanced translational research. |

## Strategy • Skills & Capacity

### Regulatory Software & Strategy Frameworks

- **Regulatory acceptance of NAMs**—referred to as "fit-for-purpose qualification"—is not a one-size-fits-all process. Researchers should utilise the following frameworks to ensure their computational strategies align with the Animals (Scientific Procedures) Act 1986 and industry best practices:
- **Context of Use (COU) Documentation:** Before deploying computational models, clearly define the specific scientific question the model is intended to address. This is critical for demonstrating that the NAM is reliable and suitable for its intended regulatory purpose.
- **Technical Characterisation**: Maintain comprehensive Standard Operating Procedures (SOPs) and study plans for both the biological NAM and any software used to analyse its output. This transparency is vital for successful project licence applications.
- **Early Regulatory Engagement**: Leverage institutional or external regulatory support software to track "fit-for-purpose" milestones. Early engagement with the Home Office/ASRU is strongly encouraged to test the acceptability of a computational or NAM-based approach before full project submission.
- **Weight-of-Evidence (WoE) Frameworks**: Use integrated digital dashboards to aggregate data from both in vitro (NAM) and in silico (computational) sources. Building a strong "weight-of-evidence" argument is the most effective way to strengthen Replacement justifications when moving away from traditional animal models.

### Skills • Training and Capacity Building

Successful adoption of high-maturity Non-Animal Methodologies (NAMs) requires a strategic shift in workforce development. To ensure the long-term success of the platforms outlined in this series, universities should prioritise the following training initiatives to build institutional capacity:

- **Integrated Prostate Cancer & Data Science:** Training programmes should bridge the gap between bench-top laboratory biology and computational analysis. Researchers require dual proficiency in 3D cell culture techniques (such as organoids and microphysiological systems) and the digital pipelines used to interpret complex imaging and high-throughput drug-response data.
- **Regulatory Competency:** Staff should receive formal training on "Fit-for-Purpose" qualification and the specific regulatory expectations of the Home Office/Animals in Science Regulation Unit (ASRU). This includes understanding how to document evidence for the 3Rs—Replacement, Reduction, and Refinement—within formal project licence applications to ensure they meet legal standards.
- **Technological Literacy:** Skills in CRISPR-based functional genomics, advanced microscopy, and high-throughput screening are increasingly critical for modern precision oncology research. Universities should facilitate internal workshops or establish external partnerships to provide PhD students and postdoctoral fellows with hands-on experience in these specialised tools.
- **Ethics & Translation:** Education should focus on the scientific imperative of human-relevant research, emphasising why NAMs—rather than traditional rodent models—provide more predictive insights for clinical outcomes in **prostate cancer therapy**. This fosters a culture of excellence and ethical research design that is fully aligned with modern international oncology standards

### Table 3: Skills • training, and capacity building

| Capability Domain | Focus Area | Impact on 3Rs/Replacement |
|---|---|---|
| **Technical** | 3D organoid & chip engineering | Replaces PDX/xenograft models |
| **Bioinformatics** | AR-pathway & drug-response analysis | Bypasses animal-based tumour measurements |
| **Regulatory** | Fit-for-purpose qualification | Facilitates faster ASRU approvals |
| **Computational** | Metastatic cascade modelling | Eliminates invasive animal efficacy studies |

**Strategic Note:** This section demonstrates that your department is investing in the human expertise required to operate these platforms safely and effectively, which is a key component of a robust

## Clinical Translation Case Studies

### Case Study 1: Prostate Cancer Organoids in Precision Oncology and Drug Development

Patient-derived prostate cancer organoids are being used in academic medical centres and pharmaceutical programmes to model both hormone-sensitive and castration-resistant prostate cancer. These models have shown strong correlation with clinical response to androgen receptor-targeted therapies and have been used to identify novel resistance mechanisms, supporting more informed clinical development decisions.

### Case Study 2: Prostate Cancer-on-Chip Platforms for Androgen Signalling and Resistance Research

Prostate cancer-on-chip systems with dynamic microenvironment are being adopted to study mechanisms of androgen receptor signalling and therapy resistance. These platforms have identified clinically relevant resistance pathways that were not accurately modelled in conventional xenograft studies, improving translational predictions for next-generation androgen receptor inhibitors.

### Case Study 3: Multi-Organ Prostate–Bone Metastasis MPS in Drug Development

Pharmaceutical companies are increasingly using interconnected prostate–bone MPS platforms to study bone metastasis, which is a major cause of morbidity and mortality in advanced prostate cancer. These systems have enabled more accurate modelling of the bone metastatic niche and testing of bone-targeted and metastasis-preventing therapies, supporting better-informed clinical development.

# Executive Summary & Compliance Dashboard

## Executive Summary

Traditional rodent models of prostate cancer often fail to capture the complex, AR-driven dynamics and site-specific metastatic behaviour of human tumours. This roadmap transitions research toward human-relevant NAMs. By adopting these high-fidelity systems, the institution enhances scientific reproducibility, reduces dependency on unreliable cross-species extrapolation, and fulfills the ASPA 1986 mandate.

## Compliance Dashboard

| Focus Area | Primary Animal Model | NAM Replacement Technology | ASPA 1986 Status |
|---|---|---|---|
| Prostate Cancer | PDX / Xenograft Models | Organoids & Prostate-on-Chip | High |

## Maturity Matrix

**Phase 1 (Exploratory):** Audit animal use in prostate cancer efficacy and metastasis studies.

**Phase 2 (Pilot):** Integrate prostate cancer organoids into drug screening protocols.

**Phase 3 (Integration):** Implement prostate-on-chip and multi-organ prostate-bone MPS.

**Phase 4 (Standardisation):** Replace 100% of high-severity metastatic induction protocols.

## Final Compliance Statement

All proposed models satisfy the Section 2A statutory duty of ASPA 1986. By adopting these methodologies, the institution positions itself at the forefront of the global transition toward human-centric, cruelty-free medical science.

### Integration Context: Roadmap Conclusion

The modules detailed in this roadmap—from fundamental oncology (1.1) and haematology (1.2) to breast cancer (1.3) and prostate cancer (1.4) models—demonstrate that replacement is not a siloed scientific exercise but an integrated institutional strategy. By mapping these specialised NAMs into a unified framework, the institution moves toward a standardised, human-centric research paradigm. This systemic integration is the essential prerequisite for fulfilling the ASPA 1986 statutory duty, ensuring all research is scientifically accurate, ethically aligned, and regulatory compliant.