Human-Relevant Non-Animal Methodologies (NAMs)

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

Breast Cancer Models

Reference 1.3 in Full Scope Roadmap

Version 1.0 | June 2026 Edition

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Legal & Scientific Imperative for Universities

Section 2A of the *Animals (Scientific Procedures) Act 1986* imposes a statutory duty on the Secretary of State to ensure compliance with the principles of replacement, reduction, and refinement. The principle of replacement requires that, wherever a scientifically satisfactory method or testing strategy not entailing the use of protected animals is available, it must be used to replace the use of a regulated procedure.

Traditional animal models in breast cancer research (particularly subcutaneous/orthotopic xenografts and PDX models) exhibit significant limitations. These include species-specific differences in mammary gland architecture, stromal composition, hormonal signalling, and 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:

- **Mammary Niche & Stroma Architecture Mismatch:** The human mammary gland architecture and the associated breast cancer microenvironment are unique, featuring human-specific cancer-associated fibroblasts (CAFs), ECM cross-linking patterns, and adipose tissue interactions. 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 progression.

- **Hormonal Signalling & Receptor Discrepancies:** Breast cancer subtypes (e.g., ER+, PR+, HER2+) are heavily dependent on complex hormonal feedback loops. Rodent physiology differs substantially in how these receptors interact with systemic endocrine signals. Consequently, the efficacy of endocrine therapies and hormone-sensitive targeted agents often translates poorly from rodent assays to human clinical practice.

- **Metastatic Tropism & Vascularisation:** Breast cancer metastasis—particularly to the bone, brain, and liver—is a complex, organ-specific process. Rodent models often rely on artificial injection methods that bypass the physiological metastatic cascade. Furthermore, human tumours in rodents develop non-human vascular networks, masking the true distribution, penetration, and efficacy of clinical-stage breast cancer therapeutics.

- **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 patient-derived breast cancer organoids, breast-on-chip platforms, and multi-organ breast–bone metastasis models—is a dual scientific and statutory mandate.

Landmark Regulatory & Scientific Momentum

This section details the transition from traditional animal-based breast 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, hormone receptor signalling, and metastatic behaviour with unprecedented accuracy.
Landmark regulatory & scientific momentum

- **Patient-derived breast cancer organoids:** Increasingly used to model hormone receptor-positive, HER2-positive, and triple-negative breast cancer subtypes, with growing evidence of strong correlation to clinical drug response.

- **Breast cancer-on-chip platforms:** Systems incorporating tumour microenvironment, stromal, and immune components to enable dynamic studies of invasion, metastasis, and therapy resistance under physiologically relevant flow conditions.

- **Multi-organ breast cancer MPS:** Platforms (particularly breast–bone metastasis models) adopted to study the complex mechanisms of bone metastasis, a major clinical challenge in advanced disease.

- **Growing industry & academic interest:** Increased uptake by pharmaceutical companies and academic centres for drug development, biomarker discovery, and personalised treatment strategies, particularly 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 breast cancer research, setting a clear precedent for replacement under Section 2A of the *Animals (Scientific Procedures) Act 1986*.

Core Specialised Breast Cancer Models & Enabling Platforms

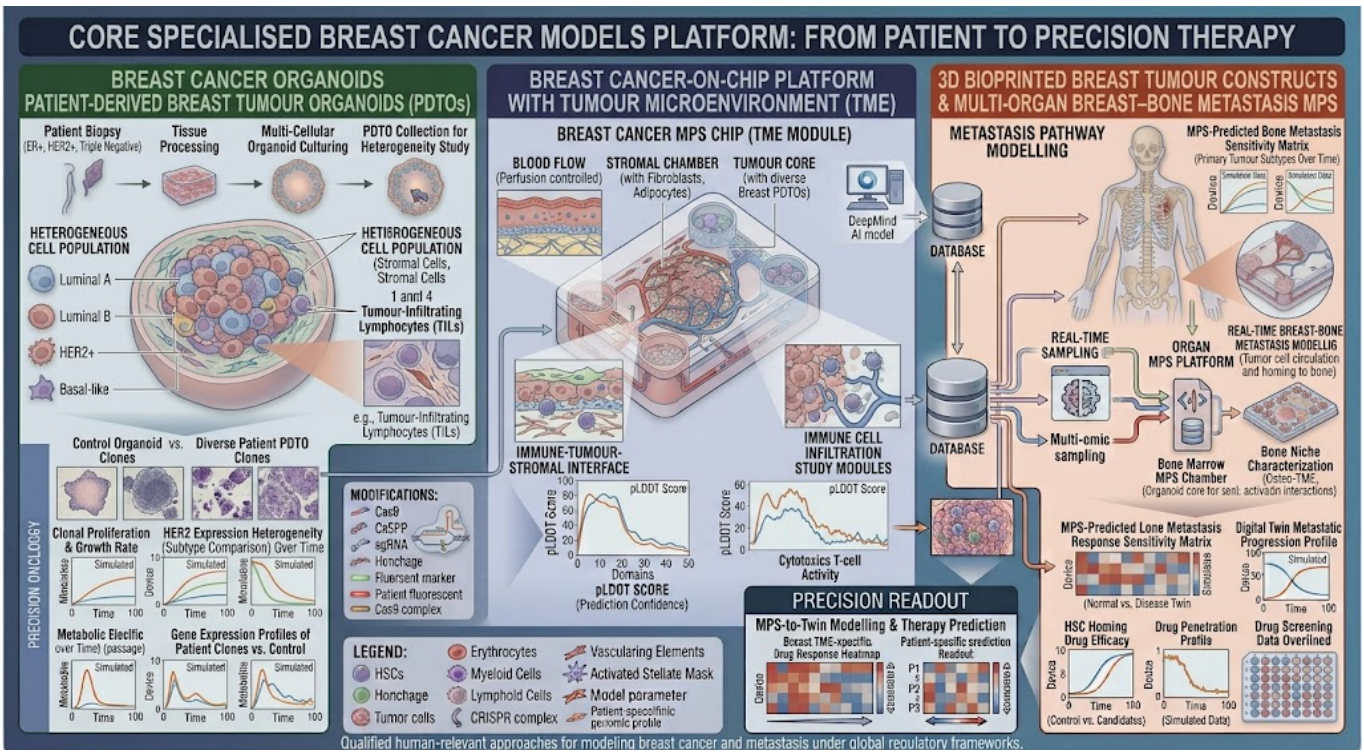

Figure 1: Core Specialised Breast Cancer Models
Breast cancer organoids / patient-derived breast tumour organoids with heterogeneous cell populations (left), breast cancer-on-chip with tumour microenvironment including stroma and immune components (center), and 3D bioprinted breast tumour constructs plus multi-organ breast–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 Breast Cancer Models

Platform / Mod	Description	Key Applications	Benefits for 3Rs
Breast Cancer Organoids	3D structures from patient tissues replicating tumour architecture.	Hormone receptor & dru sensitivity profiling.	Preserves patient-specific tumour heterogeneity.
Breast-on-Chip	Microfluidic systems integrating stroma & immune components.	Dynamic studies of invasion & metastasis.	Replaces invasive orthotop animal models.
Multi-Organ Metastasis MP	Interconnected chips (e.g., breast bone).	Investigating bone/brain metastatic niches.	Bypasses high-severity metastatic induction.
3D Bioprinted Constructs	Precisely engineered tissue with vascular channels.	High-throughput therapeutic testing.	High experimental control reproducibility.
iPSC-Derived Models	Patient-derived iPSCs tailored to specific mutations.	Mechanistic studies of therapy resistance.	Enables mutation-specific, human-centric research.

Cross-Cutting & Enabling Platforms for Breast Cancer Research

These platforms complement the core breast cancer models and are widely applicable across cancer research, regardless of the specific tissue model."

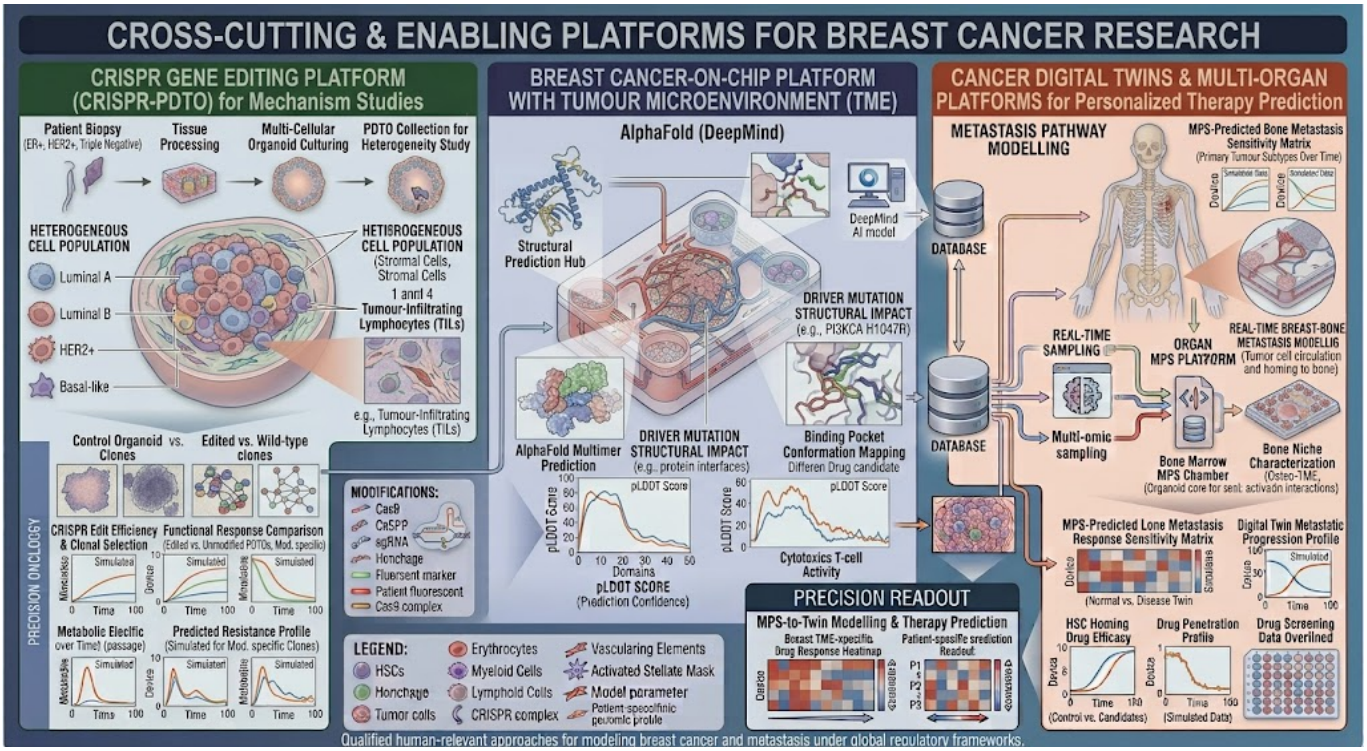

Figure 2: Cross-Cutting & Enabling Platforms for Breast Cancer Research
CRISPR gene editing in tumour organoids for cancer mechanism studies (left), AlphaFold (DeepMind) predicting structures of cancer-related proteins (centre), and cancer digital twins or multi-organ tumour

Table 2: Cross Cutting & Enabling Platforms in Breast Cancer Models

Platform / Model	Description	Key Applications	Benefits for Universities & 3Rs
CRISPR-Based Functional Genomics in Breast Cancer Organoids	Gene editing applied in breast cancer organoids and PDOs to model oncogenic drivers, study resistance mechanisms, or validate therapeutic targets.	Mechanistic studies of breast cancer drivers (e.g. BRCA, HER2, PIK3CA), synthetic lethality screening, endocrine resistance research, target validation.	Directly addresses animal model limitations in genetic modelling. Powerful for mechanistic breast cancer and precision oncology research.
AlphaFold & Structural Biology for Breast Cancer Targets	Use of AlphaFold and related tools to predict structures of breast cancer-related proteins (e.g. BRCA1/2, HER2, oestrogen receptor, PI3K) for drug design and mutation impact analysis.	Structure-based drug design for breast 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 breast cancer workflows.
Breast Cancer Digital Twins & Multi-Organ Tumour MPS	Computational digital twins of breast cancer combined with interconnected chips linking breast tumour with bone, brain, or liver compartments.	Metastasis modelling, systemic drug effects, personalised treatment prediction, complex multi-organ breast cancer research.	Enables holistic, human-relevant modelling of breast 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 Oncology & 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 breast 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	Multi-omic & 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 institutional roadmap.

Clinical Translation Case Studies

Case Study 1: Breast Cancer Organoids in Precision Oncology Clinical Trials

Patient-derived breast cancer organoids are being used in several academic medical centres and pharmaceutical programmes to guide treatment selection for patients with advanced or treatment-resistant breast cancer. In published studies, organoid drug sensitivity profiles showed strong correlation with clinical outcomes, particularly for endocrine therapies and targeted agents in hormone receptor-positive and HER2-positive disease.

Case Study 2: Breast Cancer-on-Chip Platforms for Metastasis and Drug Resistance Research

Breast cancer-on-chip systems with dynamic microenvironments are being adopted by research consortia to study mechanisms of invasion, intravasation, and therapy resistance. These platforms have identified clinically relevant resistance mechanisms and drug penetration issues that were not accurately modelled in conventional xenograft studies, improving translational predictions.

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

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

Executive Summary & Compliance Dashboard

Executive Summary

Traditional rodent models of breast cancer often fail to capture the complex, hormone-driven dynamics and site-specific metastatic behaviour of human tumours. This roadmap transitions research toward human-relevant NAMs, including patient-derived organoids and breast-on-chip platforms. 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
Breast Cancer	PDX / Xenograft Models	Organoids & Breast-on-Chip	High

Maturity Matrix:

Phase 1 (Exploratory): Audit animal use in breast cancer efficacy, hormone-signalling, and metastatic studies.

Phase 2 (Pilot): Integrate patient-derived breast cancer organoids into hormone receptor and drug sensitivity protocols.

Phase 3 (Integration): Implement breast-on-chip systems and multi-organ breast–bone metastasis microphysiological systems (MPS).

Phase 4 (Standardisation): Replace 100% of orthotopic and metastatic induction animal protocols with validated, human-relevant NAMs.

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)—demonstrate that replacement is an integrated institutional strategy. This systemic integration is the essential prerequisite for fulfilling the ASPA 1986 statutory duty.