Breakthrough Technologies for Health

Purpose, Aims and Vision

The convergence of Life Science Technologies and AI, a transformative opportunity for health care: Molecular technologies, high-resolution imaging, and artificial intelligence (AI) are transforming our ability to understand, diagnose, and treat disease. New approaches can now characterize biological systems across molecular, cellular, tissue, and organ scales, while AI enables integration and interpretation of the resulting multimodal data from healthy individuals and patients. Together, these converging technological revolutions are creating unprecedented opportunities for mechanism-guided precision medicine.

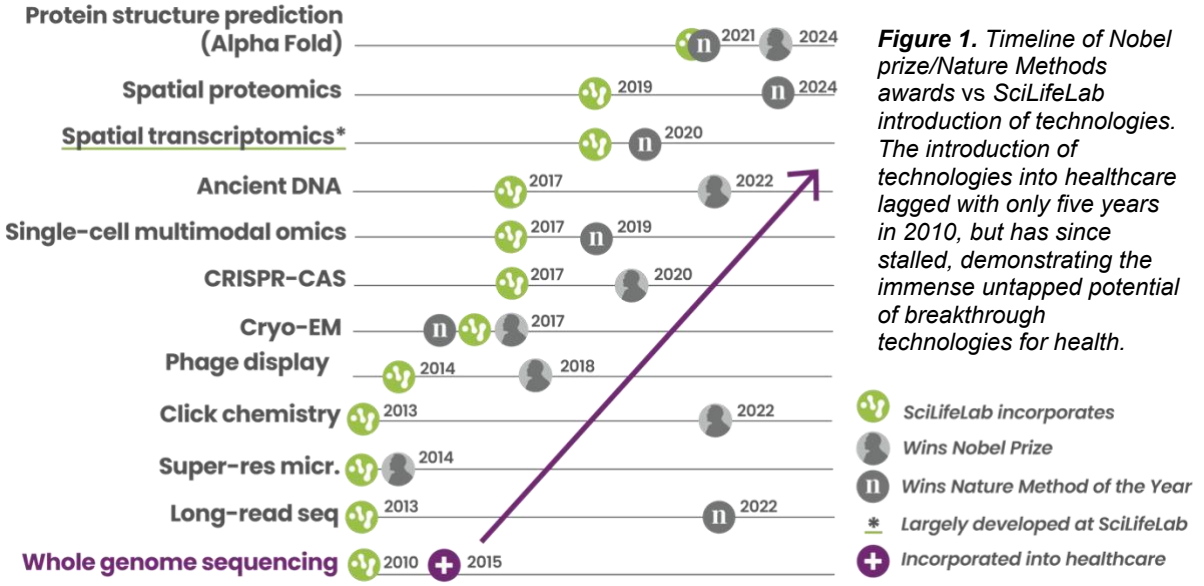


Figure 1. *Timeline of Nobel prize/Nature Methods awards* vs *SciLifeLab introduction of technologies. The introduction of technologies into healthcare lagged with only five years in 2010, but has since stalled, demonstrating the immense untapped potential of breakthrough technologies for health.*

Sweden embraced the life science technology revolution early on through the establishment of SciLifeLab in 2010 as a national research infrastructure for molecular life sciences. Today, SciLifeLab provides access to the most advanced technologies at all major Swedish universities and has transformed the ability of the Swedish life science community to develop and apply breakthrough technologies at the international forefront (Fig. 1), often years ahead of the international competition.

This national strength in life science breakthrough technologies has been further reinforced by the establishment of the MAX IV, which since 2016 has developed a portfolio of beamlines supporting advanced X-ray microscopy and multimodal imaging. Together, SciLifeLab and MAX IV provide a globally unique technological ecosystem for life science research, creating unprecedented opportunities to drive breakthrough discoveries and accelerate their translation into healthcare.

From the beginning, engaging in technology translation to provide transformative solutions for health care and move towards precision medicine has been part of SciLifeLab's mission. Indeed, only five years after the founding SciLifeLab, whole-genome sequencing was introduced into health care practice (Fig. 1), making Sweden an international leader in genomic medicine and demonstrating how strategic investments in research infrastructure can be translated into tangible patient benefit through earlier diagnoses, improved clinical decision-making, and more personalized care.

Yet, in the ten years that followed, Sweden started to lag in translating next generation molecular technologies and the AI revolution to health. Despite the research excellence in life science technologies and the strong clinical research in the medical schools and university hospitals, the separation of academia and health care and the fragmented nature of the health care sector, and the health data in particular, has not allowed Sweden to maintain its international leadership in moving breakthrough technologies to healthcare (Fig. 1).

The bold vision of this excellence cluster is to propel Sweden to an internationally leading position in developing breakthrough technologies for and adopting them in healthcare to move rapidly to precision medicine. The challenge the cluster addresses is therefore not research excellence in breakthrough technology development alone. While disruptive technologies continue to emerge at an accelerating pace, the pathways to validate, implement, commercialize, and scale these innovations for health care are currently fragmented in Sweden. As a result, many promising technologies fail to have societal impact or reach healthcare in a timely manner, and Sweden risks losing its international leadership position despite its strong scientific foundations.

Organization, Team and Feasibility of the *Breakthrough Technologies for Health* Cluster
The excellence cluster "Breakthrough Technologies for Health" will address this challenge by bringing together Sweden's leading organizations in breakthrough technologies and precision medicine: SciLifeLab and MAX IV, hosted by the universities, and the Swedish University Hospital Alliance (SUHA) embedded in the health care regions, (Fig. 2). Through this cluster, these strong partners will establish nationally coordinated platforms that integrates research, healthcare and innovation to dramatically shorten the pathway from scientific discovery to patient benefit.

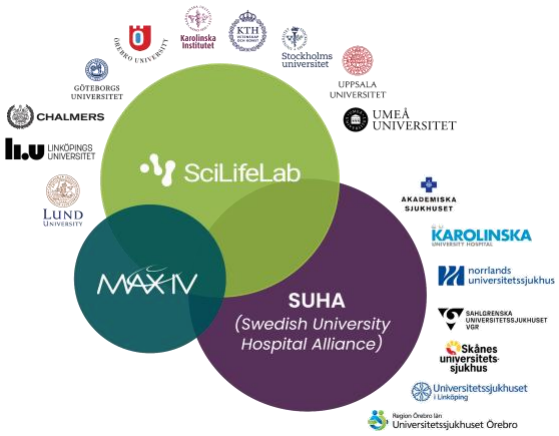


Figure 2. *The excellence cluster 'Breakthrough Technologies for Health' joins* together *SciLifeLab, MAX IV and the medical faculties at the university hospitals with health care through SUHA. The Cluster brings together the excellence from universities with strong regional healthcare to accelerate research, innovation and healthcare implementation.*

The cluster will achieve this through **three strategic objectives**:

1. **Decode disease across biological scales.** Establish a world-leading research environment that integrates synchrotron-based imaging, spatial multiomics, and AI to uncover disease mechanisms from organs to subcellular structures.
2. **Build a SciLifeLab clinical infrastructure platform.** Connect healthcare and technology providers to enable continuous evaluation, validation, and implementation of breakthrough technologies and AI tools for clinical studies, while ensuring data sovereignty and equitable access.
3. **Accelerate translation through a national innovation platform.** Integrate and coordinate technology development, clinical validation, commercialization, and healthcare implementation nationally to bridge the gap from discovery to patient benefit.

Together, these activities will establish a new national model for precision medicine innovation in which breakthrough technologies are developed, validated, implemented, and commercialized in parallel rather than in a complex sequential and fragmented process. By linking world-leading research infrastructures, healthcare systems, industry, investors, and public stakeholders within a single coordinated framework, the cluster will position Sweden as a global leader in precision medicine, health technology innovation, and technology and AI driven healthcare transformation.

State-of-the-Art

Mechanism-guided precision medicine requires decoding human disease to identify disease-driving mechanisms, enable earlier diagnosis, stratify patients, and guide therapeutic interventions. Many diseases currently grouped under a single clinical diagnosis are molecularly heterogeneous, resulting in different disease progression and treatment response. As a consequence, patients frequently receive the wrong treatments and are exposed to avoidable side effects.

Recent advances in advanced imaging, molecular profiling, spatial biology and artificial intelligence have revolutionized our ability to decode disease across biological scales. Today, it is possible to characterize tissues at molecular, cellular, and structural levels while simultaneously integrating clinical and population-level information. This creates exceptional opportunities to move healthcare from reactive and generalized treatment strategies toward predictive, preventive, and individualized medicine.

Sweden is uniquely positioned to take a leading position in this transformation. Through strategic investments into SciLifeLab and MAX IV, the country has established unique and internationally competitive research infrastructures that are technology powerhouses for molecular technologies, advanced imaging, computational biology, and data-driven life science. Importantly, Sweden has already demonstrated leadership in the past with the successful national implementation of genomic medicine into healthcare, through the SciLifeLab Clinical Genomics platform and Genomic Medicine Sweden, providing a strong foundation for the next generation of precision medicine technologies.

Despite these early advances, significant scientific, technological and structural challenges must now be addressed to lead in the next generation breakthrough technologies and AI for health. Most molecular technologies, imaging approaches, and AI methods are currently developed and applied separately, limiting us to realize their potential to decode the molecular complexity of human disease. A major hurdle in pre-clinical and clinical research is therefore the integration of molecular, cellular, tissue, and organ-level information into unified representations of disease.

To address this challenge, the cluster focuses on two transformative research directions. First, recent advances in synchrotron-based phase-contrast X-ray imaging now enable quantitative three-dimensional visualization of intact biological tissues with extraordinary resolution and scale. These technologies bridge the gap between organ-level architecture and single cell molecular information, creating entirely new opportunities for decoding disease mechanism directly in the physiological context of the patient. Second, the emergence of large-scale multimodal AI tools enables integration of imaging, molecular, and clinical data and use them to train predictive and interpretable models of disease. Together, these technologies provide the foundation for a new generation of multiscale AI disease models capable of uncovering disease mechanisms that are inaccessible to current approaches.

However, scientific advances in breakthrough technologies and disease understanding by themselves are necessary but not sufficient to transform healthcare. The major challenge here is now the translation, validation, and implementation of breakthrough technologies in the real-world healthcare system in Sweden, and from there also internationally. To address this challenge, the cluster combines frontier technology development with clinically embedded demonstrator projects and a national innovation and implementation framework with the SciLifeLab Clinical Infrastructure Platform (See the Innovation Plan of this excellence cluster). These unique research and innovation environments will enable development, validation, and adoption of breakthrough technologies by healthcare, enabling continuous interaction between researchers, healthcare providers, industry, and patients (Fig. 3).

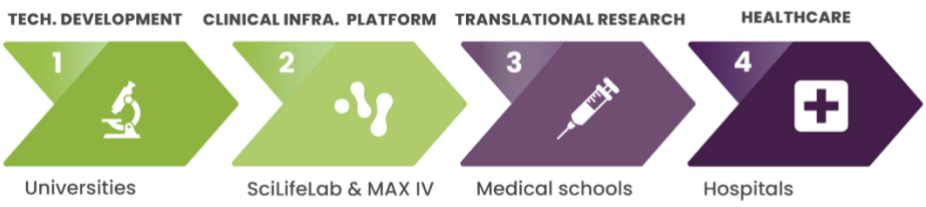


***Figure 3**. The excellence cluster takes a stepwise approach to ensure efficient translation from discovery to clinically implemented and commercially*

By integrating cutting-edge technology development, AI-driven data science, and clinical implementation into a coordinated national framework, the excellence cluster will establish a new paradigm for precision medicine in which scientific discovery, innovation, and healthcare transformation progress hand in hand.

Significance and scientific novelty

The significance of this initiative lies in creating a new paradigm for precision medicine by integrating molecular, cellular, tissue and organ-level information into unified, multimodal representations of human disease. The scientific novelty lies on one hand in the development of revolutionary synchrotron-based X-ray imaging technologies that enable quantitative visualization of intact biological tissues across spatial scales, bridging tissue architecture, cellular organization, and molecular composition within a single framework. On the other hand, the cluster will develop next-generation AI and computational methods that transform complex imaging and molecular datasets into interpretable, predictive, and clinically actionable models of disease. Together, these two major scientific advances in breakthrough technologies will enable decoding of disease that is beyond the reach of current research approaches, and will uncover novel disease mechanisms, biomarkers, and opportunities for new diagnostic and therapeutic approaches, ready to be implemented in healthcare.

The excellence cluster as a whole, including its innovation plan, will enable breakthrough technologies to be developed, validated, implemented, and commercialized in parallel rather than sequentially, fundamentally shortening the pathway from discovery to societal and patient impact. In the short term, the research part of the cluster will deliver novel imaging technologies, AI-enabled analytical workflows and models, and multimodal datasets and decision tools for precision diagnostics and biomarker discovery suitable for clinical use. In the longer term, it has the potential to transform disease prevention, diagnostics, therapeutic development, and clinical decision-making, while positioning Sweden at the forefront of equitable precision medicine and AI-enabled healthcare.

Preliminary and previous results

The excellence cluster members bring highly complementary expertise spanning advanced imaging, artificial intelligence, data science, molecular technologies, clinical research, healthcare implementation and innovation. Together, they represent Sweden's leading universities, research infrastructures, and university hospitals, providing the scientific, clinical, technological, and translational capabilities required to deliver the ambitious vision. Previous results are presented under the different work packages and demonstrator projects below.

Programme description

The research program is organized into interconnected work packages and demonstrator projects (Fig. 4 “VR”), closely integrated with the innovation plan of the cluster (Fig. 4 “Vinnova”). WP1 and 2 focus on the development of breakthrough technologies for health in advanced multiscale imaging and AI-driven computational frameworks for multimodal data integration and analysis, respectively. This fundamental research in new technology and AI is complemented by a starting set of six translational research demonstrator projects A-F, that illustrate how new technologies transform our ability to decode disease mechanism. Empowered by the new clinical research infrastructure for breakthrough technologies and AI in WP3 and 4 of the innovation plan, the demonstrators will drive the establishment of robust workflows to make new technologies and AI ready for molecular characterization of patient material in routine clinical implementation. The demonstrators thus serve as the strong translational bridge linking fundamental research to the healthcare implementation and innovation activities of the cluster, by showing with real-world examples how urgent unmet medical needs are addressed through breakthrough technologies. This strong technology, AI and translational research program is complemented by fundamental social science studies in WP7 and 8 on how the technology and AI driven transformation of the healthcare system will impact Swedens economy and legal and regulatory system.

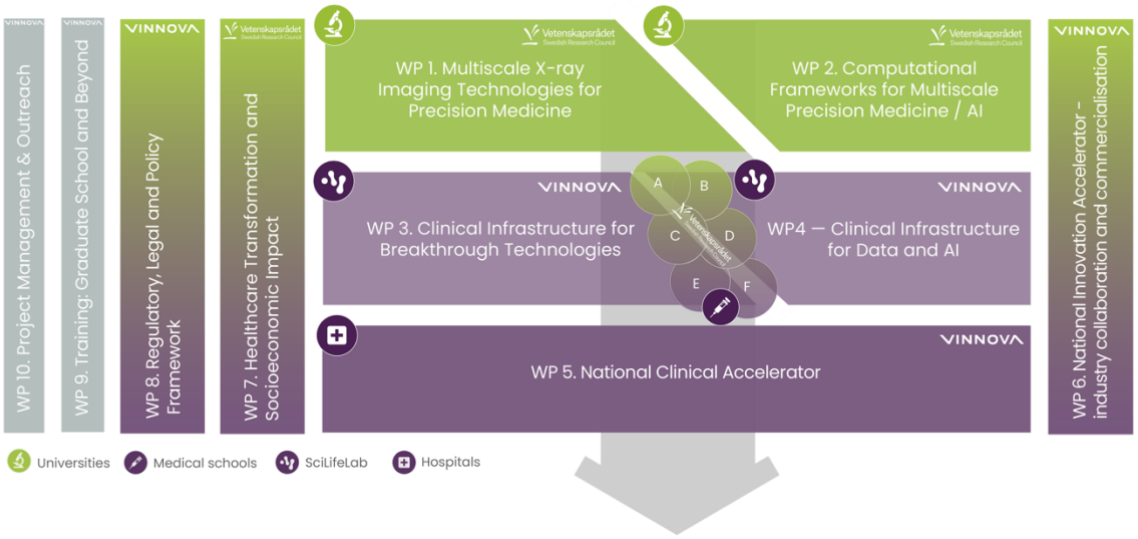


Figure 4. *The Breakthrough Technologies for Health cluster consists of ten interconnected work packages, WP1-WP2 pioneer the technological core, developing multiscale synchrotron imaging and agentic AI for predictive modelling. Implementation is operationalized via WP3/WP4 establishing the SciLifeLab clinical infrastructure platform, clinical acceleration process driven by SUHA, WP5, and WP6's commercialization engine. Strategic sustainability is ensured by WP7 including HTA/legal research, WP8 on regulatory governance-by-design support, and WP9's national graduate school. WP10 provides the governance through a Strategic Steering Board and dual- leadership model (Project Leader/Cluster Manager), supported by an International Advisory Board to ensure global, industrial scaling, project management and communication. With the aim to transform Sweden's scientific excellence into a scalable operating system for precision medicine, the cluster aim to deliver tangible patient benefits and global leadership by 2035.*

WP1. Multiscale X-ray Imaging Technologies for Precision Medicine

This WP, led by Martin Bech and Hanna Isaksson, Lund University (LU), aims to establish a transformative framework for quantitative, multiscale imaging of intact biological tissues using synchrotron-based X-ray methods. The central scientific goal is to overcome fundamental limitations in current biomedical imaging by enabling high-resolution, phase-sensitive visualization of tissue architecture across spatial scales, while preserving the structural context of extended biological specimens. This work bridges the gap between volumetric micro-morphology and cellular-level organization within a single quantitative imaging framework. By advancing phase-contrast X-ray imaging beyond its current capabilities, the work package seeks to evolve state-of-the-art x-ray microscopy into operating protocols while generating fundamentally new insights into biological structure-to-function relationships, with particular emphasis on complex and heterogeneous tissues relevant to a number of diseases, as exemplified in the demonstrator projects.

Task 1. Methodology development: The methodological approach is built on the systematic exploitation of coherence-based synchrotron X-ray imaging, with emphasis on phase-contrast techniques that significantly enhance sensitivity to soft biological materials (Fig 5). Conventional attenuation-based imaging is inherently limited in weakly absorbing tissues, whereas phase-contrast approaches provide access to variations in electron density that

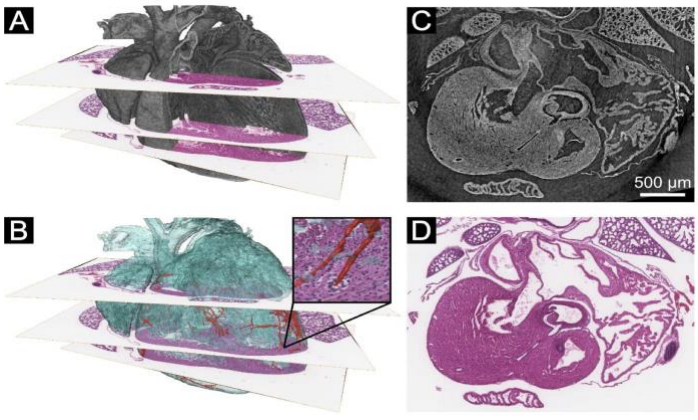


Figure 5. *A-B) Integration of standard H&E staining with X-ray phase-contrast micro-tomography of a mouse heart. C-D) examples of sections through the volume matched between X-ray phase-contrast and histology (18).*

directly relate to biological structure. The fundamental physics of synchrotron-based x-ray imaging at the microscopic length-scale inherently enhances phase-contrast, allowing for much better soft-tissue contrast than is possible with conventional clinical x-ray imaging (1). This work package will further develop and combine multiple complementary phase-sensitive techniques, including propagation-based phase contrast (2), grating-based interferometry (3), and scattering-based methods (4), thereby enabling a rich, multidimensional and multimodal description of biological samples. These imaging approaches will be embedded within a rigorous computational framework that includes advanced phase retrieval algorithms, high-fidelity tomographic reconstruction, and quantitative analysis pipelines. Together, this integrated methodology will ensure that imaging data does not remain descriptive, but becomes quantitative, reproducible, and comparable across studies, which is a key requirement for both biological discovery, quantification of disease-specific features and translational research.

Task 2. Workflow: A central technological component of the work package is the development and deployment of the advanced synchrotron imaging capabilities at MAX IV, with a specific focus on phase-contrast X-ray imaging of intact biological tissues inspired by the pipelines developed in the EMBL lab in Hamburg (5). Access to beamtime and infrastructure will be ensured through the HUB access mechanism, which enables coordinated, long-term, and multi-beamline use of the facility. This model is essential for achieving the ambitious goals of the work package, as it allows the consortium to combine complementary imaging modalities and experimental conditions across several beamlines within a unified research strategy. Within the HUB framework, synchrotron experiments are scheduled through the cluster, and demonstrator projects (as well as other participating research groups) will be coordinated across all stages of the process, from experimental design and planning to beamtime participation, data sharing, and joint analysis. This seamless structure ensures a level of integration and continuity that is not achievable through traditional access modes, enabling rapid iteration of experimental protocols and efficient use of beamtime. The guaranteed allocation of beamtime per cycle further provides the stability required to develop robust methodologies and to generate consistent, large-scale datasets.

Task 3. Technology development: A key innovation in this work package is the development of X-ray optics solutions for beam expansion and beam focusing, specifically tailored for high-coherence undulator beamlines at MAX IV. Current high-resolution synchrotron imaging is typically constrained by a limited field of view, restricting experiments to small sample sizes and thereby limiting the ability to study intact tissues in their full anatomical and structural context. To address this limitation, we will design and implement optical configurations that enable controlled expansion of the X-ray beam while preserving coherence, combined with focusing strategies that maintain sufficient photon flux density at the sample. This will allow imaging of specimens with dimensions up to approximately 20 mm, which is highly relevant for a wide range of biomedical applications. For larger samples, established collaborations with other facilities will be utilized. The development of these optics solutions will involve the use of advanced components such as refractive lenses, multilayer optics, single-crystal Bragg reflectors, and tailored beam-conditioning systems optimized for phase-contrast imaging geometries. By combining large field-of-view imaging with high spatial resolution and phase sensitivity, this work will enable a new class of experiments that bridge the gap between microscopic detail and macroscopic tissue organization.

Multiple initiatives hosted at MAX IV are paving the way for the work proposed in this work package: The beamlines ForMAX and DanMAX are equipped with endstations dedicated to full-field tomography with sub-micrometre resolution, whereas beamlines NanoMAX and SoftiMAX are dedicated to spectral mapping and ptychographic imaging with resolution in the sub-50 nm range. Recent developments for high throughput micro-tomography includes implementation of on-the-fly data reconstruction pipeline at the DanMAX beamline (6) (in collaboration with colleagues at the Advanced Photon Source, APS, USA) and large volume data acquisition using Multilayer Laue Lenses (MLLs (7) and a novel X-ray camera (with optics developed at the Danish Technical University, DTU, Denmark). The most recent initiative for multiscale and multimodal imaging at MAX IV is the development and implementation of beam

expanding optics for undulator beamlines in combination with x-ray phase modulators for quantitative phase-contrast and scatter-based imaging. In a collaboration between MAX IV, Lund University, and Karlsruhe Institute of Technology (KIT, Germany) an asymmetrically cut single crystal is inserted upstream of the sample and detector to modify the field of view obtainable in the x-ray camera (8). With this approach, both beam magnifications and de-magnifications of 10-20-fold can be obtained (9).

The technological developments are closely integrated with multiscale imaging strategies, where large-volume datasets are used to identify regions of interest that can be further investigated at higher resolution (fig 6). This hierarchical approach allows detailed characterization of specific features while retaining the broader structural context, which is essential for understanding complex biological systems and diseases, whether it be micro-structures in lungs (Demonstrator project A), vasculature (Demonstrator project C), or oncology (Demonstrator projects B/D/E/F). These imaging workflows will be complemented by

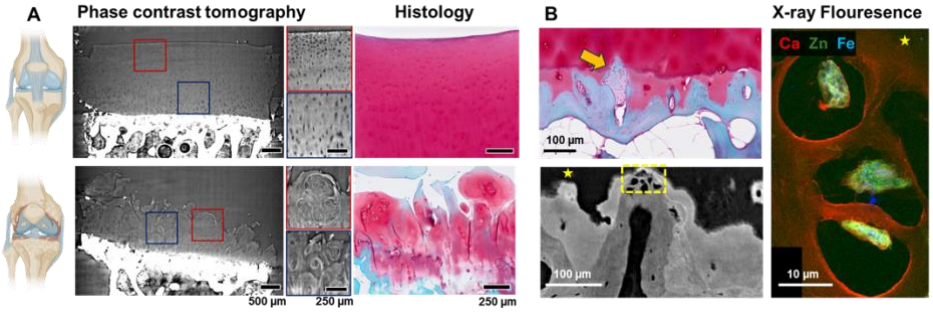


Figure 6. *Multimodal and multiscale synchrotron imaging as A) Virtual histology for phenotyping of osteoarthritis (10), B) linking pain, nerve and vessel ingrowth to cell activity.*

integration of additional modalities through WP2, including optical microscopy, electron microscopy, MRI, as well as spatial transcriptomics and proteomics. As an example, the volumetric imaging of a solid tumor at MAX IV will reveal volumetric micro-morphology, while 2D sections of relevant tumor areas will be analysed with spatial omics methods available at SciLIfeLab to capture tumour characteristics at the molecular level to inform on treatment strategies among a growing portfolio of targeted therapies (exemplified by demonstrator B and D). Another exploratory example of multimodal imaging is the combination of nano X-ray fluorescence with spatial proteomics at single cell level to unravel distribution of platinum-based chemotherapies as a potential resistance mechanism. Through the development of co-registration and data fusion methods, information from these techniques can be combined to produce comprehensive and consistent representations of biological samples across scales. Such multimodal integration is critical for linking imaging observations to biological function and clinical relevance, such as recently presented for disease phenotyping through 3D virtual histology, cell-analysis, tracking blood vessels and nerve-ingrowth (Fig. 6). Thus, to ensure that WP1 delivers not only technical advances but also tangible scientific and translational outcomes, the work package is tightly connected to the demonstrator projects addressing specific biomedical challenges with high scientific, clinical and societal relevance. Applying the developed methods to the concrete biological and clinical questions of the demonstrators will both validate the developed technologies as well as identify and drive further methodological refinements.

This work package is tightly connected to work packages 2 and 4 (data and AI), where WP4 provides the essential computational infrastructure and methodological support for data handling and interpretation. The high-resolution, multidimensional datasets generated through synchrotron imaging present significant challenges in terms of data volume, complexity, and analysis. As an example, one tomographic dataset with <1 micron resolution can easily be > 100 GB in size. WP2 will develop and apply required machine learning and AI approaches for segmentation, feature extraction, and pattern recognition to enable efficient and scalable analysis of the generated large datasets. The imaging data produced in this work package will serve as a key input for training and validating these models, while the outputs from WP2 will enhance the interpretability and scientific value of the imaging results. This close integration ensures that advances in imaging and computation are mutually reinforcing, resulting in a coherent and highly effective research framework.

This work package will deliver both methodological innovation and scientific discovery. Methodologically, it will develop new phase-contrast imaging approaches, advanced optics for large-field high-resolution imaging, and computational pipelines for quantitative image reconstruction and analysis. These tools and protocols will be made broadly available to the research community. Scientifically, the work will generate new insights into tissue architecture, vascular and neural organization, and disease-associated structural changes across biological scales, providing valuable resources for biomarker discovery and mechanistic research.

By combining technology development, advanced infrastructure, and close integration with computational and clinical activities, the WP will establish synchrotron-based X-ray imaging as a key enabling technology for quantitative biomedical research and significantly strengthen the scientific impact of the cluster.

WP2. Computational Frameworks for Multiscale Precision Medicine

The mission of WP2, led by Ida-Maria Sintorn, Ola Spjuth and Carolina Wählby, Uppsala University (UU) is to develop a computational framework for transforming biomedical image (such as synchrotron-based X-ray tissue images from WP1) and correlative molecular data analysis from ad hoc visual assessment and descriptive mapping towards interpretable and predictive modelling. The modelling will be objective, reproducible, mineable and usable across scales and modalities. In turn, this will support precision medicine and innovation, ranging from FAIR and AI-ready data sharing to clinical decision making.

Task 1: Agentic AI for biomedical image data analysis: Fully automatic AI is powerful but not always sufficient in life science and medicine, where expert judgment and annotation remain essential. The objective of this task is to combine machine autonomy with interactive visualization and human expertise, creating a new paradigm for discovery and information mining across large spatial datasets and correlated molecular modalities. Academic and clinical research, as well as industrial innovation will all benefit tremendously from a community-driven effort with compatible data formats and interoperable analysis tools that can be customized for advanced queries or slimmed for highly specific clinical and diagnostic questions. With an agentic AI for biomedical image data analysis, we can revolutionize information use by multi-step visual understanding and action, with broad impact for research and innovation in precision medicine. This will be approached through the establishment of:

1. A Modular Biological Tool Registry: We will develop a set of specialized AI models designed to solve specific, narrow tasks quickly and objectively. Rather than building a singular, complex model of tissue biology, these individual tools will be restricted to atomic tasks, such as extracting localized micro-environmental properties, calculating cell-cell distance matrices, or annotating distinct visual structures (*e.g.*, 2D/3D vascular contours or subcellular transcripts) across modalities.
2. An Autonomous ReAct (Reasoning and Acting) Agent Layer: To transition away from rigid, hardcoded analytical pipelines, we will develop a central agentic orchestrator powered by Large Language Models (LLM). This multi-agent system does not rely on predefined scripts; instead, it uses an iterative Reasoning-Acting-Observation loop to evaluate open-ended human queries (*e.g.*, “Delineate the vascular system in this 3D volume and locate adjacent immune clusters”, building on data from WP4). The agent independently parses the goal, selects the appropriate sequence of specialized tools from the registry, evaluates the confidence of their intermediate outputs, and self-corrects its execution path in real-time. We have substantial experience in building and serving multi-agent systems (11,12) and an infrastructure in place for operalization.
3. An Interoperable, Distributed Data Lake: We will connect the agent with a cloud-optimized data lake built on the OME-Zarr format (13), in close coordination with the clinical data infrastructure set up in WP4. The data lake will host multi-scale, multi-modal imaging (ranging from phase contrast X-ray tomography (WP1) to spatial omics and standard H&E staining *e.g.* from the Demonstrators) alongside historical query caches, segmentation masks, and clinical metadata. The agent interacts with this ecosystem via standardized

Application Programming Interface (API) protocols, allowing it to cross-query independent, distributed datasets to resolve comparative queries without requiring local data downloads, for example, " Which metabolic features correlate with this specific morphology across external cohort?".

Crucially, this architecture incorporates a formal Human-in-the-Loop escape hatch. When the agent encounters data anomalies, high-uncertainty regions, or low-confidence model readouts, it will halt automated execution and stream the region of interest to the user interface for human validation or steering. The AI-agent will seamlessly incorporate visualization and manual interaction via TissUUmaps (14), enabling experts to natively steer agentic reasoning, correct intermediate actions, and explore massive spatial datasets directly within a zero-download web browser. The agent will incorporate models from the tasks below, benefit all demonstrators, and will be executed in close collaboration with the SciLifeLab BioImage Informatics Unit (part of SciLifeLab's Bioinformatics platform NBIS). An illustration of WP2 is shown in Fig. 7. The agent will be deployed within the Agentic infrastructure being established by SciLifeLab Data Centre, and will comprise multiple LLM back-ends, including both public models as well as frontier open-weights models deployed locally on SciLifeLab infrastructure to sustain working with sensitive data.

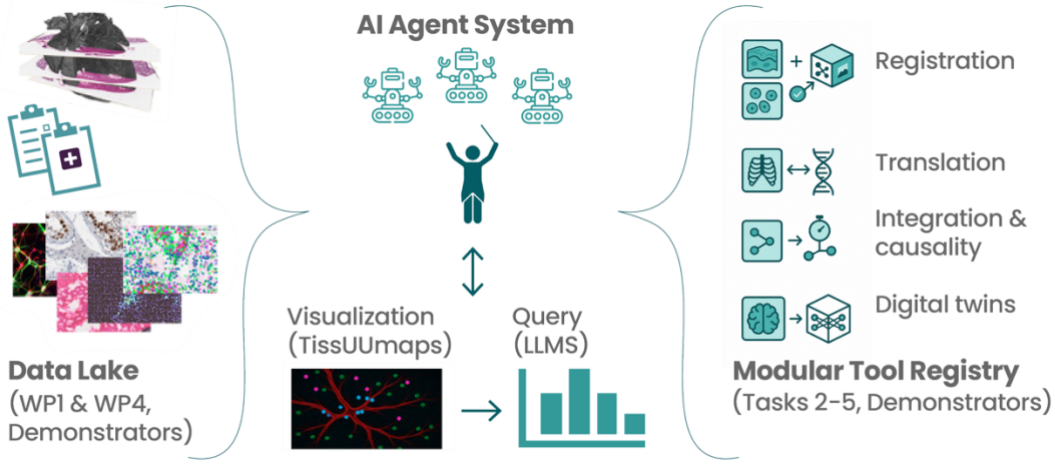


Figure 7. *Overview of the computational framework. A multi-agent system acts on query input from the user, e.g., "Delineate the vascular system in this X-ray Computed Tomography (XCT) volume and locate adjacent immune clusters". It acts and reasons using input from Literature, the distributed Data Lake, the set of developed specialized AI tools. The expert can guide and refine the analysis via interactive visualizations in TissUUmaps.*

Task 2: Multimodal image registration: Combining data across modalities and scales relies on mapping the data to a common coordinate system. Precise and automated digital alignment, or registration, of data requires identification of common 'landmarks', or a shared, dense image representation, applicable to both 2D and 3D. We will approach this by building on our previous work showing that contrastive coding can be used to efficiently learn shared, dense image representations (15). Such AI-generated representations can be learned from comparably small datasets of aligned and shifted image pairs and enable efficient automated alignment of multimodal images where existing registration methods often fail due to a lack of sufficiently similar image structures. Once alignment of the learned image representations has been optimized, the corresponding alignment parameters can be applied to raw data or saved for future reference (as part of the cloud data format OME-Zarr). This approach to image registration has the potential to speed up data alignment across scales by orders of magnitude, enabling efficient downstream analysis and visualization. It serves as a basis for the formation of FAIR AI-ready data. All demonstrators will contribute to, and benefit from, this task.

Task 3: Translation between imaging and molecular data for clinical decision making: Molecular profiling by spatial biology is often restricted to 2D, generating unique representations of *e.g.* gene expression, proteins or specific metabolites, while *e.g.* X-ray tomography offers non-destructive natively 3D imaging providing information on tissue

morphology down to the subcellular level. Once image and molecular data is aligned across modalities (using techniques developed in Task 2), we can extract morphological and molecular image features to translate between modalities (16). By translation, we aim to learn features that correlate across modalities. For example, a specific gene expression profile may for example correlate with specific tissue structures such as the size shape and organization of cells in a sub-structure of an organ. By learning such correlations, we can use generative AI and take advantage of the imaging modalities that are easier and more cost-effective to acquire, to generate semi-artificial representations of other modalities. We will combine data across modalities and validate techniques by sparse real data to, *e.g*., model full 3D organs or neural structures in multiple modalities based on a few tissue samples. Combined modalities can also be used as an alternative to manual annotations, where *e.g*. a vascular biomarker may serve as input for the generative AI to learn and extract the vascular structures from an X-ray tomography image enabling fully automatic 3D analysis. The developments within this task provide a basis for general AI-driven image-based decision support. The first tools will be created in close collaboration with Demonstrator A, quantifying vascular remodelling, and later for connecting molecular data with cardiovascular disease in Demonstrator C. General models will be integrated in the AI agent described in Task 1.

Task 4: Data integration and causality: In contrast to Task 3, we will here investigate AI methods to identify modality-specific information and focus on unique features not shared across imaging techniques. *For example,* disease-relevant heterogeneity observed by one modality, but hidden in another, will provide important clues on disease causality. We will approach this by multi-modal learning, making use of the fact that cause and effect can be described by both a shared latent space (as cause and effect have components invariant to the modality used for observation) and a modality-specific latent space that encodes the difference in feature timing, and thereby causality (17). We will start from data with known disease conditions, contrasting diseased and healthy samples using counterfactual generative models, causal graphs and invariant representation learning that can isolate causal mechanisms from statistical noise. We will further evaluate the encoding of causality intrinsic to tissue samples by exploring underlying molecular mechanisms with biology-informed AI stipulating that changes in gene expression precedes changes in protein expression, and changes in tissue morphology may remain even after a specific gene is no longer expressed. Importantly, this framework allows us to go beyond rare monogenic diseases and approach common and molecularly complex diseases by taking a probabilistic approach to genetic and epigenetic molecular causes, capturing the complex interactions between genes and the environment in disease development and progression. We will initially focus on Demonstrator B, where longitudinal liquid biopsies are combined with spatial omics, and Demonstrator D, combining prostate biopsies with spatial omics and patient records.

Task 5: Dynamic Digital Twins: This task combines imaging and AI as a quantitative bridge between observation and theory. By integrating high-resolution live tissue image data with model construction and refinement, we here aim to establish predictive, interpretable models of tissue behaviour and disease progression. These models can then be used to explore disease pathways and simulate responses to therapeutic interventions in a patient-specific context. Modern imaging techniques constitute rich but sparse information windows to the underlying biological processes. Part of this task is to develop a methodology for creating parametrized models or dynamic digital twins from multimodal data. Biological models will be refined using quantitative data. Biological models will be refined using quantitative data quantitative data. For Demonstrator E this will be e.g. local cell density, velocity fields, interaction & morphological descriptors, derived from live-cell imaging of tissue slices, where multiple cell types are labelled to allow for time resolved tracking of cell behavior (migration, proliferation, interaction) and thus how the local environment influence dynamics and phenotypic transition. For Demonstrator D, large-scale clinical datasets will be used to inform model structure, constrain parameter spaces, and capture variability across disease states, enabling digital twins of tumor development that are grounded in population-level evidence while remaining applicable at the individual level. The sim-to-real gap will be reduced by initializing the biological models with the patient specific data and complementing these with

biophysical constraints, enabling the model to adapt to patient-specific characteristics and treatment responses. A second part of this task is to infer the underlying governing equations directly from live imaging data. AI-driven advances in system identification, including physics- and biology-informed neural networks, provide a powerful framework for discovering or constraining the differential equations that govern observed dynamics.
While imaging data provide only partial and noisy views of the full biological system, combining these approaches with prior biological knowledge and regularization strategies makes it feasible to recover interpretable models that reflect key mechanistic principles.

Demonstrator projects

The demonstrator projects serve as the strong translational research bridge of the cluster, that use new technology and AI to address urgent unmet medical needs where molecular complexity and heterogeneity of many common diseases currently limit diagnostic precision and treatment efficacy. The demonstrators link the fundamental research on new breakthrough technologies and AI in WP1/2 with the translation to health care implementation and innovation activities of the cluster in WP5 and 6. They are empowered by the clinical infrastructures for technology and AI provided by SciLifeLab and MAX IV in WP3/4 in close collaboration with the medical schools and university hospitals.

Our starting set of six demonstrators were selected from over 70 proposals in a national open call for technology-driven translational research addressing unmet clinical needs, that this consortium ran to prepare the excellence cluster. The six projects we initially selected span multiple disease areas and represent different stages of the translational flow, from pioneering technology development and early proof-of-concept studies to clinically validated solutions, standardized assays ready for commercialization and large-scale implementation (Fig. 8). They illustrate the broad transformative potential of technology and AI-drive precision medicine across healthcare and ensure that the cluster captures the full potential of breakthrough technologies to address clinical challenges and the pathway from innovation-to-implementation.

Each demonstrator thus exemplifies a translational research program where Sweden is or can be in a leading position, and spells out the clinical need, the vision to address it by technology and AI innovations, the clinical implementation and national and international impact (Figs. 9A-F). All demonstrators are multi-organisation collaborations, are multi-sited or have a national reach and impact research communities, clinical sites and patients living across Sweden.

While we start the operation of the excellence cluster with the selected six demonstrators, we recognize that they are only spearheading examples of the strong translational research community in Sweden. We will therefore have a rolling funding model during the operation of the excellence cluster that allows new high-potential projects to be onboarded and matured empowered by the cluster's clinical infrastructure. In this way, the cluster will support a continuous flow of new technology and AI innovations that are systematically validated and then spun out into scalable commercial ventures and/or routine healthcare services.

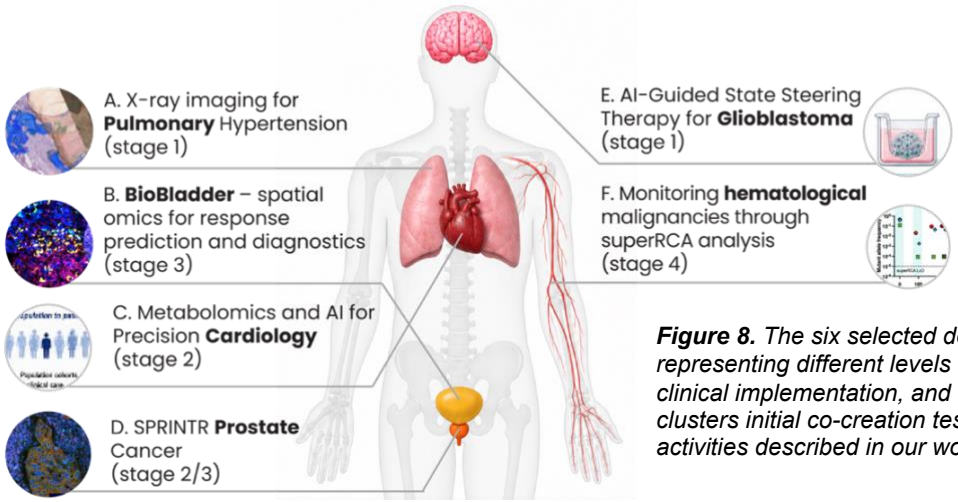
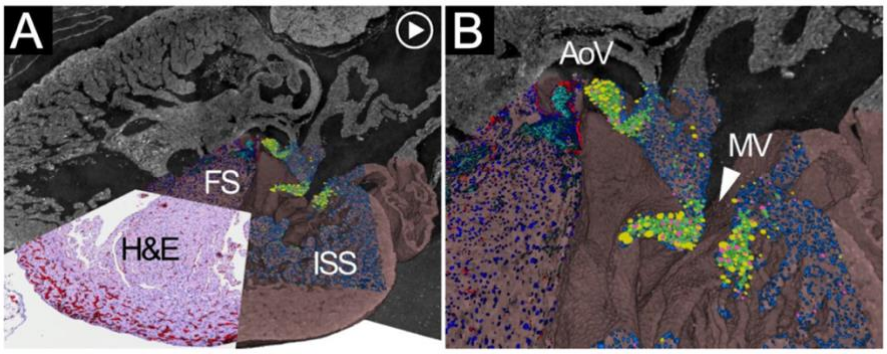


Figure 8. *The six selected demonstrator projects representing different levels of maturation toward clinical implementation, and that will function as the clusters initial co-creation testbeds to refine the activities described in our work packages.*

Demonstrator A: Synchrotron-based 3D imaging combined with spatial transcriptomics to cure pulmonary hypertension



Clinical and Scientific Challenge: Pulmonary hypertension is lethal, as current treatments relieve symptoms and improve prognosis at best. For most patients, the last resort remains lung transplantation. The underlying cause can be hereditary or idiopathic, and the condition may also develop secondary to congenital heart disease or lung disease. One of the most severe forms is pulmonary veno-occlusive disease (PVOD), which commonly presents in children and young adults.

General Goal and Vision: To effectively cure all forms of pulmonary hypertension, the pulmonary vasculature must be restored to reducey vascular resistance and pressure. For this, improved understanding of both structural and functional consequences of pathological lung vasculature remodeling in the lung is essential. Due to the complexity of lung vascular network, this can only be achieved by 3D and multiscale visualization approaches.

Together with radiation physicists at MAX IV, this is now being developed by Karin Tran-Lundmark using synchrotron-based phase contrast micro-CT of lung tissue from patients with different types of pulmonary hypertension. It has already proven to be very useful for deciphering micro-anatomical remodeling features. By combining this with high resolution molecular characterization, the aim of the current project is to reveal underlying pathophysiological mechanisms in a 3D context, with the long-term goal to identify therapeutic targets for different subtypes of pulmonary hypertension to enable personalized care.

Scientific and Technological Innovation: In a preliminary study focused on mouse cardiac development, successful integration of Xenium spatial transcriptomics with synchrotron-based imaging was demonstrated. Thus, images from Xenium (5000 transcripts/mRNAs) were fully integrated with the CT volumes, and the same tissue section was subsequently used for immunofluorescence and traditional histology (hematoxylin-eosin) (18).

The same approach will now be used to analyze mechanistic differences between hereditary and sporadic PVOD. The Tran-Lundmark group has recently published 3D-imaging of lung tissue from two pediatric PVOD patients, one without a known genetic mutation and one who is homozygous for a mutation known to cause PVOD (19). Both children were lung transplanted at the age of 8 with similar clinical symptoms, making the comparison ideal. RNAScope was successfully used, and promising additional tests of RNA quality have now been performed on the tissue in collaboration with Dr Tiklova from SciLifeLab.

Data Integration and AI: Based on contributions from WP2, AI-informed analyses of micro-CT 3D volumes will be applied to reveal and grade vascular remodeling and to extrapolate information from 2D data at different levels.

Clinical Translation and Implementation: Dr Tran-Lundmark is a cardiologist at the Pediatric Heart Center, Skåne University Hospital, and treats children with severe heart failure, pulmonary hypertension, or following heart transplantation, and thus has access to clinical data and tissue samples, and expertise enabling translation of findings.

Expected Outcomes and Impact: Key therapeutic targets will be identified for the development of novel pulmonary hypertension therapies to be tested in clinical trials.

Figure 9A: *Demonstrator A is led by Karin Tran-Lundmark, Lund University and Skåne University Hospital, where contrast micro-CT visualizations are performed with technology experts at MAX IV, and spatial characterization of the lungs from these patienst is done together with Katarina Tiklova, SciLifeLab, together with WP3/WP4 of the innovation part of the cluster.*

Demonstrator B: BioBladder, the national observational platform for all stages of urothelial cancer

Clinical and Scientific Challenge: Urothelial cancer (UC) represents a major global health burden, with over 600,000 new cases and over 220,000 deaths annually. Despite advances in immune-checkpoint inhibitors (ICIs), targeted therapies (antibody–drug conjugates (ADCs), FGFR inhibitors), and combination regimens, response rates vary and relapse is common, with poor long-term survival in advanced disease. Marked variability in treatment response highlights the urgent need for robust prognostic and predictive biomarkers to support individualized treatment strategies.

General Goal and Vision: BioBladder is a national observational platform that systematically collects patient samples and real-world clinical data across all stages of urothelial cancer, creating a unique resource for biomarker discovery, and studies of tumor evolution and treatment resistance. The project aims to develop and implement the next generation of histopathology and liquid biopsy assays that enable patient stratification, prediction of treatment response and real-time monitoring of minimal residual disease, thereby supporting personalized treatment and earlier clinical intervention.

Scientific and Technological Innovation: To allow for analyses of PD1-PDL1 interactions between immune- and tumor cells in intact tissue sections, we have recently developed an integrated assay using in situ Proximity Ligation Assay (isPLA) and multiplexed-immunofluorescence (mIF, cellular phenotyping). Using this approach, all responders could be separated from the non-responders (20), and a patent covering the spatial biomarkers is filed (STABN/P97852SE). The mIF stainings of the ADC protein targets Nectin-4, HER2 and Trop-2 were optimized along with RNA profiling and immune cell markers (21) and a combined mIF–DNA FISH protocol developed, to address the relevance of copy number variations in ADC target genes for treatment efficacy.

Data Integration and AI: The project generates high-content image data suitable for development of AI-driven analysis that will leverage deep learning models for image feature extraction,

multimodal data fusion, and pattern recognition across imaging, omics, and clinical datasets. Development of spatial-aware machine learning models that can integrate protein expression, gene amplification status, and protein interaction signals to generate predictive biomarkers of treatment response will be developed as part of WP2.

Clinical Translation and Implementation: The systematic cohort design of BioBladder enabled rapid initiation of several biomarker-discovery studies with focus on ICI and ADC therapies. Here, the importance of comprehensive ADC target profiling for refined individualized treatment strategies was underscored, as ADC target expression patterns were highly heterogeneous both intratumorally and between patients. Additional prospective biomarker- and interventional studies are now underway, where mIF and conventional omics-approaches such as genomics (ctDNA) and transcriptomics are integrated.

Expected Outcomes and Impact: New insights into mechanisms of response and resistance to ADC and ICI therapies and identify clinically actionable biomarkers with relevance across multiple solid tumors. These findings will support development of validated diagnostic tools for patient stratification and treatment selection, improving outcomes while reducing unnecessary therapies. Through multimodal diagnostics, AI-supported decision tools, and new IP, BioBladder has strong potential for commercialization and industry partnership.

Figure 9B: *Demonstrator B is led by Charlotte Stadler, KTH, and Anders Ullén, Karolinska Institute and Karolinska University Hospital, uniting clinical oncology excellence with cutting-edge technological development at SciLifeLab. The team encompasses a broadly interdisciplinary national network of oncologists, urologists and pathologists working side-by-side with experts in multi-omics, translational research and data service, and will mature the work of WP3/WP4.*

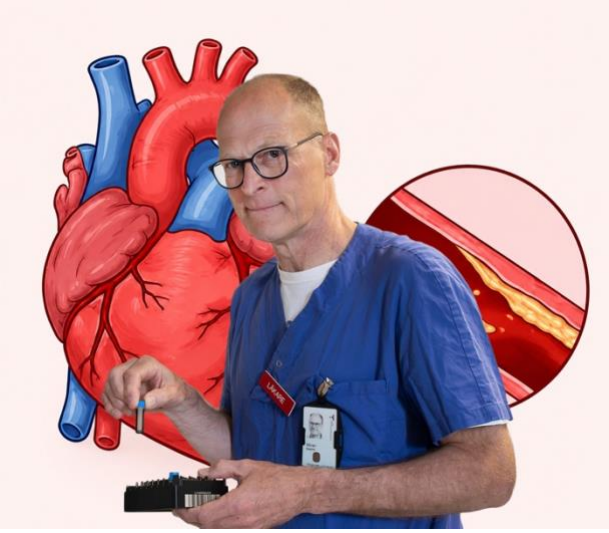
Demonstrator C: Multimodal data integration for precision cardiology

Clinical and Scientific Challenge:
Cardiovascular disease (CVD) remains the leading global cause of death despite major advances in prevention and treatment. Current diagnostics and risk prediction models are largely population-based and insufficiently capture the biological heterogeneity underlying disease development and treatment response. As a result, many high-risk individuals are diagnosed too late and receive suboptimal interventions. Existing healthcare workflows cannot effectively integrate molecular, imaging, and longitudinal health data into actionable clinical decision support.

General Goal and Vision: Our vision is that Sweden will become a world-leading testbed for precision cardiology, integrating AI, breakthrough technologies, and nationwide health data infrastructures to transform cardiovascular prevention and care. By combining multimodal data with interpretable AI, the project will shift healthcare from reactive treatment of symptomatic disease to proactive, mechanism-guided precision prevention and intervention for personalized risk prediction, earlier diagnosis and targeted treatment strategies.

Scientific and Technological Innovation: Multi-modal and multi-omics data from the SCAPIS study, including long-read sequencing, single-cell and spatial single cell omics, high resolution 3D synchrotron X-ray tomography, AI-driven image analyses and multimodal foundation models will be integrated into a unified precision medicine framework. Unlike current fragmented solutions, the project combines longitudinal real-world data with interpretable AI models, including digital twins, capable of learning disease trajectories and supporting clinical decisions.

Data Integration and AI: A multimodal AI platform integrating registries, biobanks, imaging, omics and electronic health records (EHRs) will be developed into secure, privacy-preserving analytical pipelines (WP4). In a breakthrough initiative, the use of EHR data from the Västra



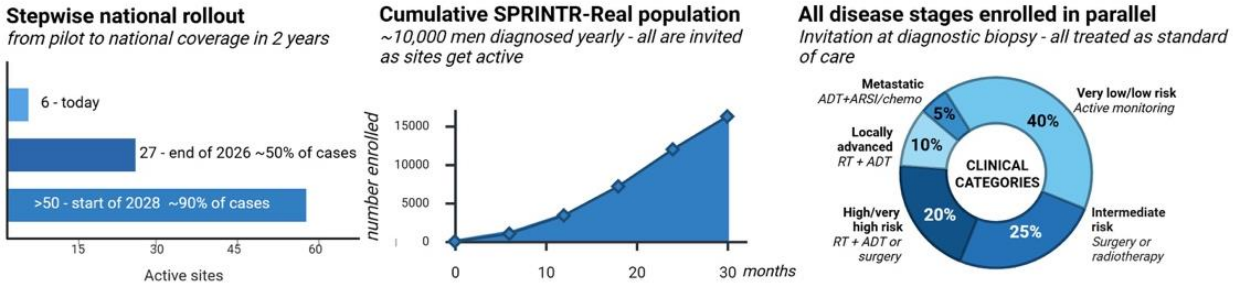
Götaland Region will be established and prepared for next-generation on-premise foundation models trained on healthcare data, anticipating future legislation enabling broader secondary use and facilitated secure extraction and utilisation of EHR data for research, AI development, and clinical trial recruitment. We will actively drive the establishment of robust frameworks for EHR Extraction and 2ndary use in compliance with GDPR and the European Health Data Space

Clinical Translation and Implementation: Biomarkers and AI models will be validated in SCAPIS and BiKE cohorts, and integrated nto healthcare workflows through trial-in-care pipelines and multi-centre implementation studies, WP5. Technologies will be co-developed with healthcare, MedTech companies, and pharma partners, to address lack of interpretability, limited generalisability, and regulatory complexity.

Expected Outcomes and Impact: In addition to identification of new biomarkers, clinically validated AI decision-support systems, improved risk prediction, and precision-guided treatment strategies will be developed, with the long-term impact of reduced morbidity and mortality and establishing Sweden as an international leader in precision cardiology innovation.

Figure 9C: *Demonstrator C is led by Göran Bergström, University of Gothenburg and Sahlgrenska University Hospital, and builds on extensive national collaborations across healthcare, registries, biobanks and SciLifeLab. The demonstrator serves as an integrated use case for WP2–WP6, showcasing multimodal data integration, foundation models and AI-driven clinical decision support for precision cardiovascular medicine.*

Demonstrator D: SPRINTR: A National Precision Medicine Ecosystem for Prostate Cancer



Clinical and Scientific Challenge: Prostate cancer affects ~10,000 Swedish men annually. Treatment decisions are based on clinical risk categories with limited precision, causing both overtreatment and undertreatment at scale. Molecular profiling has not been integrated into routine diagnostics, and candidate biomarkers are typically evaluated in isolated settings, preventing head-to-head comparison and validation.

General Goal and Vision: SPRINTR, a national, clinically embedded precision medicine ecosystem (22), will accelerate the transformation of prostate cancer care toward mechanism-guided, individually tailored treatment, serving as a transferable model for other cancer forms (23).

Scientific and Technological Innovation: Scientific innovation rests on integrating prospective clinical infrastructure with cutting-edge molecular platforms. The SPRINTR observational backbone, generating a study-ready population cohort, is active at all Swedish university hospitals and 20 other sites, covering ~50% of newly diagnosed patients in 2026 with ≥90% coverage expected by 2028. A novel standardized pathology workflow prospectively captures biopsy tissue, enabling DNA panel- and RNA sequencing, proteomics, IHC and digital pathology across all disease stages. Blood and urine are biobanked nationally, and longitudinal data, including imaging, treatment trajectories, patient-reported outcomes and national register data, are continuously updated. Selected patient subgroups undergo deep molecular characterization resolving tumour heterogeneity, resistance mechanisms and microenvironmental interactions.

Data Integration and AI: Data integration and AI are structural features, not additions. SPRINTR's consent framework explicitly permits reuse of all multimodal data for AI development and validation. Data from harmonized prospective workflows provide a robust environment for

training the molecular AI models being developed within the cluster (WP2), with direct applications in digital pathology, spatial omics and longitudinal disease modelling. The longer-term ambition is digital twin development across disease stages, with maturation timelines of 2–15 years depending on stage, uniquely realizable within a prospective cohort of this scale and duration. Local and federated architectures, built to national interoperability standards, position the dataset as a regulatory-grade environment for health-technology innovation (WP4).

Clinical Translation and Implementation: Clinical translation is built in from the outset. Participants prospectively consent to selected re-invitation into future studies based on their molecular or clinical profile, creating a continuously expanding study-ready population accessible nationwide, directly addressing inequitable trial access and substantially lowering recruitment burden. Three trials will launch within the platform in 2027: two biomarker-stratified platform trials addressing low-risk and high-risk localized disease respectively, and one cluster-randomized study evaluating a novel medical device. SPRINTR will use a molecular tumour board portal supporting both biomarker-driven study recruitment and treatment stratification.

Expected Outcomes and Impact: The 10-year impact rests on biomarker development and validation under uniform real-world conditions, with quality-of-life and health-economic evidence collected in parallel, generating the evidence base needed for clinical and reimbursement decisions. The SPRINTR model for prospective validation of innovations is being extended into SPRINTR-Pancreas and SPRINTR-Glioma built on the same generic concept and infrastructure.

Figure 9D: *SPRINTR is led by Andreas Josefsson, Umeå University, Karin Welén, Gothenburg University, Lukas Orre and Janne Lehtiö, Clinical Proteomics SciLifeLab, and Carolina Wählby, Uppsala University.*

Demonstrator E: AI-Guided State Steering Therapy for Glioblastoma

Clinical and Scientific Challenge: Glioblastoma (GBM) causes ~350 deaths per yr in Sweden, and a disease burden comparable to breast cancer and leukemia. Five-year survival remains <5% (24). Recurrence is driven by therapy-resistant invasive cells at the tumor edge, which possess distinct epigenetic states and therapeutic vulnerabilities (25), highlighting the need for new strategies targeting tumor invasion and relapse.

General Goal and Vision: To develop a precision medicine approach for GBM, longitudinal patient sampling, ex vivo characterization of living tumor tissue, and AI-driven models predicting tumor evolution and treatment response will be integrated. Building on unique resources; a large, well-characterized glioblastoma biobank (26), validated anti-invasive targets, and emerging digital twin models (27,28), the project will generate patient atlases, drug-response maps, and predictive stratification tools. Long-term goals are to establish clinical decision-support systems that guide personalized treatment based on diagnostic biopsies extendable to other cancers.

Scientific and Technological Innovation: We have established clinical pipelines for collecting living, patient-matched tumor core and edge samples at diagnosis and relapse (29), enabling analysis of the epigenetic states and vulnerabilities of invading cells. These samples are profiled using single-cell multi-omics and functional assays, including CRISPR-based cell labeling, large-scale chemical and genetic perturbation screening, and the GlioTrace live imaging platform in intact human brain tissue (28). The infrastructure is fully operational and supported by prospective patient inclusion, building on a unique biobank, large-scale screening datasets, and the identification of an HDAC2-dependent pathway driving glioblastoma invasion (28).

Data Integration and AI To augment data analysis, we will combine two AI-driven strategies. First, our prototype system. OmegaCell integrates genome-scale CRISPR, pharmacological, and transcriptomic data to predict responses across ~115,000 publicly profiled agents per patient, tractable where physical screening is not, stratifying patients by response type (cytotoxic,

state-selective lethality, or epigenetic reprogramming) (30). Second, digital twins extend omegaCell from static response to sequential treatment trajectories, calibrated by GlioTrace observations via Approximate Bayesian Computation; an explainability layer (language model over a biomedical knowledge graph, 12) translates predictions into ranked mechanistic pathway hypotheses, addressing the recognised barrier to pharma adoption of AI-guided CNS drug discovery.

Clinical Translation and Implementation: The pipeline has been proven operational in 11 patients (29). OmegaCell returns ranked hypotheses within 10 days of biopsy RNA; at relapse, the workflow repeats and the digital twin updates. Predictions are validated in a preclinical prediction–perturbation–validation loop before advancing toward a molecular tumour board prototype evaluated with WP7; SOX Therapeutics (patented SOX2/9 ASOs) and Key2Brain (ANXA1 ASOs) provide therapeutic tools directly coupled to state transitions the model predicts and the twins steer.

Expected Outcomes and Impact: The project will generate the first longitudinal atlas of living GBM samples and a patient–drug–response atlas, providing an open resource for research and therapy development. Clinically, it will deliver predictive stratification tools and digital twin models (developed jointly with WP2) to support personalized treatment decisions and future molecular tumor board applications. The innovation outcomes include prioritized therapeutic targets for industrial partners, an explainable AI framework for CNS drug discovery, and a platform that can be extended to other state-driven cancers.

Figure 9E: *Demonstrator E is led by Sven Nelander, Uppsala University, together with Lene Uhrbom, Rebecka Jörnsten and collaborators in AI, systems biology and therapeutic development, and serves as an integrated use case for WP1–WP6, combining breakthrough technologies, chemical and genetic perturbation screening, digital twins and AI-guided disease modelling to accelerate the development of next-generation precision therapies.*

Demonstrator F: Early detection cancer through ultra-sensitive superRCA

Clinical and Scientific Challenge: Early detection of cancer relapse through highly sensitive molecular methods can guide treatment decisions and improve survival. Monitoring measurable residual disease (MRD) is therefore increasingly used to assess treatment response and relapse risk in patients with leukemias and solid tumors. In acute myeloid leukemia (AML), standard MRD monitoring relies on flow cytometry and molecular assays targeting recurrent mutations or fusion transcripts. However, many patients lack standardized molecular markers, and current methods may not fully capture patient-specific residual disease.

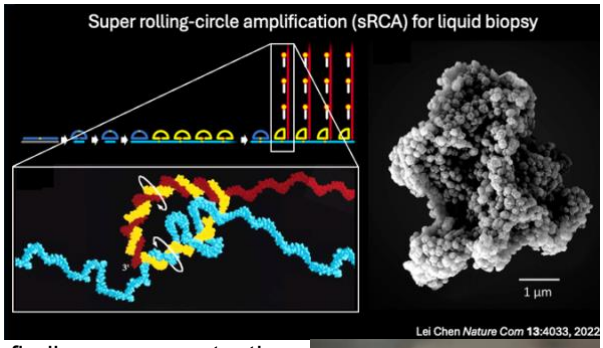
General Goal and Vision: To improve precision diagnostics and outcomes for patients with AML by demonstrating the value of highly sensitive longitudinal mutation monitoring. Using a clinically implementable technology, the project aims to support treatment selection, monitor therapy response, and advance patient-centered care.

Scientific and Technological Innovation: The project will take advantage of the superRCA technology, first established at Uppsala University (31) and further developed at the local spin-out company Rarity Bioscience to provide commercial and scalable solutions. The technology has leading sensitivity for rare mutant DNA in blood, where read out uses standard flow cytometers available in clinical diagnostic laboratories.

To move the technology towards solid tumor applications, it will be further developed to *e.g.* improve sensitivity and throughput. Importantly, a set of internal standards for absolute mutation counts will be established using synthetic "3rd alleles" to give the highest degree of diagnostic certainty. The feasibility of combining reaction steps and means to monitor larger sets of mutations in parallel will be explored.

Data Integration and AI: Generated data will be combined with clinical information, to set intervention criteria using data modeling.

Clinical Translation and Implementation: The superRCA technology has previously been evaluated retrospectively in AML and benchmarked for IDH1/2 mutation detection (31). Recent studies in myelodysplastic syndrome indicate that superRCA can detect molecular residual disease earlier than digital PCR and may enable monitoring from peripheral blood, reducing the need for bone marrow biopsies. These



findings support the prospective evaluation of superRCA as a personalized MRD monitoring strategy in AML in a multicenter longitudinal study, where up to three patient-specific mutations will be targeted. In an initial observational cohort (n=40), results will not influence clinical management but will be used to assess feasibility, performance, clinical utility, lead time to relapse, and implementation costs. If predefined criteria are met, a second cohort (n=40) will evaluate the use of superRCA results to trigger additional confirmatory testing, while treatment decisions remain based on standard-of-care methods.

The potential application of superRCA for MRD monitoring in other hematological malignancies, including acute lymphoblastic leukemia and lymphoma, will also be explored.

Expected Outcomes and Impact: Expected Outcomes and Impact: Genetics-based ultrasensitive, rapid, and cost-effective MRD screening for hematological malignancies has the potential to improve patient outcomes, reduce healthcare burden, and provide new insights into disease progression. This project will evaluate its clinical utility and prepare for broader implementation in routine care. Longer term, the approach will be extended to other malignancies as a broadly applicable method for tumor monitoring, while the integrated datasets generated will serve as a valuable resource for future multimodal studies.

The innovation component focuses on further simplifying the assay, enabling absolute mutation quantification, facilitating minimally invasive sampling (e.g., finger-prick blood collection), and increasing sensitivity through the parallel detection of larger mutation panels.

Figure 9F: *Demonstrator F is led by Ulf Landegren, Uppsala University, and Malin Melin, SciLifeLab and Uppsala University. Building on the ultra-sensitive superRCA technology and its clinical translation, the demonstrator serves as an integrated use case for WP1–WP6, advancing precision diagnostics from technology development and validation to healthcare implementation, commercialization and industrial adoption.*

WP7. Healthcare Transformation and Socioeconomic Impact

Breakthrough technology and AI-driven precision medicine have the potential to transform healthcare by enabling more accurate diagnosis, earlier interventions and personalized treatments through the integration of advanced molecular and imaging technologies, real-world data, and predictive analytics. As demonstrated by the demonstrator projects, these innovations will improve outcomes in major disease areas. Beyond their clinical impact, they will also generate significant societal value by reducing the burden of disease, improving healthcare efficacy and increasing productivity through healthier populations.

However, realizing these benefits requires more than technological and scientific advances. To achieve sustainable implementation at scale, innovations must be clinically valuable, cost-effective, legally robust, ethically acceptable, and compatible with healthcare systems and regulatory frameworks. This work package addresses these critical challenges by developing the health-economic, legal and regulatory foundations required for the successful adoption of breakthrough technologies in healthcare. By generating evidence on value, affordability, governance, and implementation, the work package will help ensure that precision medicine innovations can be translated into equitable, sustainable, and widely accessible healthcare solutions.

WP7.1 Health Economics: Lars-Åke Levin, LiU

The aging population and increasing high burden of chronic disease make successful implementation of precision medicine particularly relevant in Sweden, given the value of even modest health gains through reduced sick leave and longer working lives. Broad implementation of precision medicine will also improve allocative efficiency to better match treatments to patients most likely to benefit, thereby reducing ineffective care (32,33), which is especially relevant for the next-generation of molecularly targeted therapeutics. However, in a tax-funded system with fixed budgets, adoption of new technologies entails opportunity costs, making it essential to assess health gains in relation to displaced care (34). This is also consistent with Swedish priority setting, which is guided by the ethical platform for priority setting in healthcare, including the cost-effectiveness principle, whereby costs are considered in relation to health effects in decisions on the allocation of healthcare resources.

Sweden provides a strong setting for studying the broader societal and economic implications of precision medicine, given its extensive health data infrastructure, national registers, and established life sciences environment. These features support analysis not only of health effects, but also of its relevance for research, innovation, and implementation within healthcare (35). At the same time, precision medicine poses substantial challenges related to high upfront costs, data integration, and regional variation in access and use, as highlighted in European analyses (36,37). Together, these considerations underscore the need to assess the technologies of precision medicine from a longer-term perspective that captures health outcomes, resource use, and implementation challenges within the Swedish healthcare system.

A central challenge in health technology assessment (HTA) concerns when to evaluate a technology, as captured by Buxton's law: *"it is always too early to evaluate a technology—until suddenly it is too late"* (38). Early in the innovation process, evidence on clinical effectiveness and cost-effectiveness is often sparse, creating substantial decision uncertainty. Once technologies enter routine practice, however, they may be difficult to reassess or withdraw, even when later evidence raises concerns about their value. This dilemma is well recognised in the health economics literature (39,40) and is particularly acute in rapidly evolving fields such as precision medicine. Current HTA frameworks are not well equipped either for decision-making under early-stage uncertainty or for the re-evaluation of technologies later in the innovation lifecycle. Conventional economic evaluation typically relies on mature evidence, whereas decisions on emerging technologies must often be made using limited and uncertain data. This creates a clear need for methodological approaches that address uncertainty across stages of innovation. Early economic modelling and value-of-information (VOI) analysis can help quantify uncertainty, prioritise evidence generation, and support decision-making over time.

Beyond methodological challenges in evaluation, an additional research need concerns how innovators understand the pathway from technological development to clinical translation, implementation, market access, and scale-up. Within the cluster demonstrators, limited awareness of evidence requirements, market conditions, and implementation timelines may constrain the development, and uptake of new technologies.

The aim of WP7.1 is therefore to advance methods in health economic evaluation and HTA across the innovation lifecycle, from early-stage technology development to mature use and health care implementation. In addition, and in collaboration with WP6, the implementation pathway perspectives of the demonstrator projects will be investigated to generate empirical knowledge on how innovations can be better prepared, from an early stage, for assessment, evidence generation, and eventual implementation within healthcare systems.

To achieve this aim, WP7.1 has six objectives, namely, to:

1. Develop methods for early-stage health economic and HTA assessment of breakthrough technologies under limited evidence;
2. Improve the assessment and management of decision uncertainty, including value-of-information (VOI) approaches;
3. Identify evidence gaps and provide efficient strategies for evidence generation;
4. Develop approaches for the evaluation, re-evaluation, and disinvestment of mature technologies in clinical practice;
5. Establish an integrated framework for health economic evaluation across the innovation lifecycle; and
6. Generate empirical knowledge, through qualitative interviews, on how innovators understand clinical translation, market access, and implementation.

WP7.1 will thereby make use of the unique opportunity of the strong demonstrator cases in different technology and disease areas, to address the six objectives across the innovation lifecycle in a general and national fashion for precision medicine. For Objectives 1 and 2, alternative PICO (Population, Intervention, Comparison, Outcome) specifications will be developed and assessed using decision-analytic models, including health state-transition models, to estimate health outcomes, cost-effectiveness, and decision uncertainty for early-stage technologies. Sensitivity analysis and value-of-information methods will be used to characterise uncertainty, identify evidence gaps, and inform efficient evidence-generation strategies (Objective 3). As evidence matures, the models will be refined using registry-based data on health outcomes and costs, enabling the evaluation, re-evaluation, and potential disinvestment of technologies in clinical practice, including in relation to emerging comparators (Objective 4). For Objective 5, findings from early-stage and mature evaluations will be synthesised into an integrated framework for health economic evaluation across the innovation lifecycle. For Objective 6, qualitative semi-structured interviews will be conducted with innovators involved in the demonstrators and analysed thematically using an abductive approach. Repeated interviews will provide empirical insight into how understanding of these processes develops over time.

Taken together, WP7.1 will advance methods for health economic evaluation and HTA across the innovation lifecycle, strengthen approaches to uncertainty assessment, evidence generation, re-evaluation, and disinvestment, and generate empirical knowledge on how innovators understand clinical translation, market access, and implementation. By integrating these strands, the work package will provide a stronger scientific and practical basis for decision-relevant evaluation and implementation of emerging health technologies in Swedish healthcare and thereby support better informed priority-setting decisions. WP7.1 will work closely with WP5 on clinical implementation to ensure that health economic evaluation, evidence generation, and implementation strategies are aligned early in the translational pathway, thereby facilitating scalable, sustainable, and clinically relevant adoption of precision medicine technologies within regional healthcare systems.

WP7.2 Resolving Legal Gaps between Sector-Specific Public Regulation and Private Law: Björn Lundqvist, Stockholm University (SU) and Santa Slokenberga, UU

The legal arm of WP7 focus on the structural misalignments between sector-specific EU public-law regulation — the IVDR, MDR, AI Act and forthcoming Biotech Act — and the private-law arrangements (contracts, IP licences, financing instruments) governing the development and commercialisation of AI-driven precision medicine, addressing legal uncertainties and challenges, and providing solutions. It aims to supply the legal architecture on which WP4–WP6 and WP8 depend to make their technological and clinical ambitions legally viable. The work is organised around two horizontal themes — (I) sector-specific public law and (II) private and civil law, including competition law and intellectual property — paired in five vertical projects (A–E), as outlined in table 1. The objective is to identify legal gaps and misalignments and to develop actionable legal solutions to support bringing on the market and putting into use in healthcare AI-driven precision medicine.

AI-driven precision-medicine outputs, including AI-enabled IVDs, companion diagnostics, structural-biology pharmaceuticals, digital therapeutics and data-driven treatment platforms, are simultaneously subject to public-law regimes and private-law frameworks that were not designed for them, creating legal uncertainty that deters investment, delays patient access and enables regulatory arbitrage; WP5 identifies this as the primary system-level barrier to Sweden's precision-medicine ambitions. MAX IV exemplifies the challenge: its structural-biology outputs feed each category along a distinct regulatory and commercial trajectory. The Draghi Report (2024) (41) and the EU's Omnibus deregulation package, along with MDR/IVDR revisions, sharpen the urgency.

A red thread throughout is the focus on collaborations and an aim is to ensure that healthcare institutions that during the translational period take part in the precision-medicine development can use the resulting innovations at affordable and reasonable cost. Importantly, each Theme I project is analytically aligned with its Theme II counterpart, and the five pairs run as sequential phases across the cluster's lifetime:

Phase	Theme I Sector-Specific Public Law	Theme II Private & Civil Law (Competition & IP)	Key deliverables (Arts.)
Yrs 1–2 Entry & capital formation	TI-A Regulatory Classification: classifying AI-enabled IVDs, companion diagnostics and digital therapeutics at the MDR/ IVDR/AI Act interface; a framework able to accommodate continuously-learning AI diagnostics.	TII-A Financing Framework: early-stage R&D finance, SAFEs, convertible instruments, blended public–private finance, adapted to university and spin-out settings; seeds the de lege ferenda basis for the Research Data Royalty Certificate (RDRC).	Classification framework; map of precision-medicine financing; RDRC concept and lex lata obstacles. (4)
Yrs 3–4 Development & scale-up	TI-B Manufacturing & Scale-Up: obligations on the research-to-commercial manufacturing transition (incl. structurally derived drug targets); GMP compliance tools for research facilities (MAX IV) entering the pipeline.	TII-B R&D Collaboration, Co-Development & Standardisation: model co-development and patent/ data-pooling structures, while providing a structural standardisation policy benefitting competitiveness; AI Act/IVDR harmonised standardisation.	Model co-development agreements; AI Act/ IVDR dual harmonised-standards solution; GMP toolkit. (3)
Yrs 5–6 Data & evidence	TI-C Real-World Data & Secondary Use: structuring the EHDS, GDPR and AI Act to enable precision-medicine research and AI training while protecting individual rights; data-sharing models for federated architectures of WP4.	TII-C Data Governance & RDRC Architecture: governance and value-allocation of health-data ecosystems; develops the RDRC, allocating value compatible with public-interest healthcare while preserving innovation incentives .	Complete RDRC legal architecture; federated data-governance models; mid-term conference. (3)
Yrs 7–10 Deploy-ment, account-tability & market access	TI-D/E Individual Protection, Accountability & Liability: revised informed-consent frameworks and clinician professional-liability guidance; liability allocation across the multi-actor chain under the revised PLD, the AI Act and Swedish tort law.	TII-D/E Patent Protection, Innovation Markets, Pricing & Reimbursement: patents, SPCs, data exclusivity and thicket risks; pricing and reimbursement of AI-driven precision medicine as a continuously-updatable clinical service.	IP reform proposals; pricing/reimbursement frameworks; liability framework; final anthology + practitioner database. (5+)

Table 1. *Project outline: Years 6–10 consolidate and extend the foundational work of years 1–5 into reform proposals and practical instruments, culminating in an edited volume. Successive postdoctoral and PhD appointments are matched to project expertise; Frantzeska Papadopoulou (PI WP8) supervises PhD Project under D/E under Theme II (years 7–10), integrating WP8, with the two PIs providing methodological continuity throughout.*

Three breakthrough innovations anchor the work: the **Research Data Royalty Certificate (RDRC)**: the first conceptual framework for innovation-rent tokenisation for health research data, building on Lianos, Minssen, Rikap & Santos Rutschman (2026) (42); the **dual AI Act/IVDR harmonised-standards solution**, a problem of immediate practical urgency; and the first offering of an analysis of the precision medicine translational pipeline as a legally integrated ecosystem aiming to provide a **precision medicine translational legal roadmap**. Cross-theme alignment is structural: classification shapes financing (A), manufacturing shapes co-development (B), secondary-use permission defines private data arrangements (C), and access conditions shape IP strategy, pricing and liability (D/E).

Distinctive contributions across the projects include the following: The first systematic legal analysis of precision medicine financing across the translational chain and ecosystem wide. This ranges from EIC/VR/Vinnova grant conditions through SAFEs and convertibles to blended finance, with a contained *de lege ferenda* analysis of tokenising health data and research outputs and includes the coordinated EHDS/GDPR/MiCA reforms to establish what a viable RDRC regime would require. The treatment of standardisation in TII-B and TII-C, not merely as compliance but as a strategic force shaping the competitive structure of the AI-IVD market, including merger control and acquisition of nascent innovators, is new to precision medicine. Moreover, it is also the first investigation of whether patent-thicket dynamics, including *de facto* thickets arising from research infrastructure, risk emerging in AI-diagnostic standardisation.

Scholarly and societal contribution: This the first effort to treat the precision medicine translational pipeline as a legally integrated system, resolving gaps that has not previously been addressed. Its societal aim is to let Sweden and the EU realise the cluster's ambitions while protecting patients and securing public return on research investment: the RDRC has the potential to return value to public research contributors; outcome-based reimbursement keeps AI-driven diagnostics within public-healthcare budgets; and the reforms protect innovation incentives without the exclusivity structures that have made comparable technologies inaccessible elsewhere. Throughout, healthcare institutions that co-invest in and contribute to precision-medicine development should be able to use the resulting innovations at an affordable and reasonable cost.

Data analysis and statistics

The Research Plan generates complex, high-volume, multi-modal data as described in WP1 and demonstrators, while WP2 is focused on developing technologies for data analysis. A dedicated database will be established for X-ray imaging (WP1), including anonymised sample identification numbers in order to track sample orientation, scan parameters (X-ray energy, resolution, exposure time etc), reconstruction parameters (phase retrieval, filters, etc), and other sample history (preparation protocol, storage conditions, handling dates, etc). Data collected from the same samples using other imaging modalities will be associated with the same identification numbers and associated experimental parameters, and together they make up the basis for the data lake described in WP2. This will ensure that information flow relevant to a sample is efficient throughout the lifetime of the project and bridges methodologies across work packages and demonstrators as well as future projects handled in the scope of the excellence cluster. In parallel, we will establish a federated digital infrastructure to bridge between data and real-time clinical decision-making, as described in WP4. Statistical analyses will be an integrated part of the data analysis in WP2, and include mixed-effects models, Bayesian machine-learning approaches, uncertainty quantification, and false-discovery-rate controls adapted to each data type and clinical question. All AI models will be evaluated using strict separation of training and validation data, prospective holdout experiments, and external validation cohorts.

Equipment and need for research infrastructure

In addition to the two national research infrastructures MAX IV and SciLifeLab (represented by the applicants), the proposal will engage the national e-infrastructure for high-performance computing — primarily NAISS (the National Academic Infrastructure for Supercomputing in Sweden) and the Berzelius AI supercomputer at NSC Linköping for training and validation of the large molecular AI models in WP2, and relies on the participating university hospitals to provide clinical equipment for biopsy collection, standard pathology, MRI/CT imaging and the regulatory-grade laboratory environments. All major equipment is in place; the Research Plan does not require new large-scale instrumentation purchases.

International and national collaboration

The Cluster brings together Sweden's major life science universities through the work packages, demonstrator projects, and the national infrastructures SciLifeLab and MAX IV. Clinical integration is ensured through the Swedish University Hospital Alliance (SUHA), which

connects all seven university hospitals and healthcare regions into a coordinated national research and implementation framework.

The cluster is embedded in strong international networks through initiatives such as ELIXIR, EUCAIM, and TEF-Health, while the demonstrator projects engage leading academic, clinical, and research partners across Europe and North America. Industrial collaboration includes partnerships with leading life-science and technology companies, including Olink, 10x Genomics, Thermo Fisher, AstraZeneca, Navinci Diagnostics, and Rarity Bioscience, providing direct links to technology development, validation, and commercialization.

Breakthrough Technologies for Health, vision beyond 2035

Our long-term vision is to transform healthcare from a system that reacts to symptomatic disease into one that predicts, prevents, and precisely treats disease based on its underlying molecular mechanisms. By integrating breakthrough molecular technologies, multiscale imaging, artificial intelligence, clinical infrastructures, healthcare implementation and innovation within a single national framework, the cluster will establish the foundations for mechanism-driven precision medicine empowered by a constant flow of new breakthrough technologies and AI solutions. Beyond advancing scientific discovery, it will create a sustainable model for translating breakthrough technologies into patient benefit, positioning Sweden as a global leader in technology and AI empowered precision medicine provided by equitable healthcare.

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