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# The PRECISE European initiative for cancer-vulnerability mapping and prediction

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PRECISE is a European initiative to move cancer research beyond descriptive atlases toward predictive, mechanistically informed models of tumor vulnerability. By integrating patient cohorts, disease-relevant model systems, perturbation biology, multimodal profiling and artificial intelligence-driven inference, the PRECISE consortium aims to learn generalizable and predictive rules that govern genetic dependencies and synthetic lethality.

Understanding and exploiting cancer vulnerabilities are central challenges in oncology. The inter- and intra-tumoral heterogeneity of cancer creates an enormous multidimensional landscape of genetic, epigenetic, cellular and microenvironmental states, many of which evolve dynamically during disease progression and treatment. Consequently, deriving clinically actionable precision-oncology strategies requires coordinated efforts at scale. Over the past decade, large-scale pharmacological and genetic perturbation screens in diverse cancer models have enabled systematic mapping of cancer dependencies linked to specific molecular contexts. This has created foundational cancer-dependency maps for the functional interpretation of tumor genomes and the identification of therapeutic targets[1,2] (Fig. 1).

However, despite their impact, current dependency maps are largely descriptive: they identify where dependencies occur but offer limited insight into mechanisms, penetrance across contexts, evolution under therapeutic pressure, or predictability in untested settings. As a result, their ability to inform target prioritization, anticipate resistance and guide combination therapies remains incomplete. Complementary approaches, including large-scale molecular atlases of tumors and their microenvironments, provide important context but remain inherently observational[3]. Likewise, predictive computational models remain limited by sparse and biased training data. These limitations reflect a fundamental gap between empirical mapping and predictive understanding.

Cancer vulnerabilities are emergent features of biological systems shaped by tumor niche, tissue lineage, genetic and epigenetics contexts, transcriptional programs, and evolutionary dynamics[4]. As manifestations of molecular circuitry, cancer dependencies are predictable and reflect molecular networks whose system-level properties can be captured through multi-omics profiling. This provides a foundation for learning generalizable rules that govern cancer vulnerability[5] (Box 1). In this setting, predictive models enable extrapolation beyond observed conditions, while mechanistic insight supports interpretability and clinical translation. Having established transformative dependency maps, the field must now pivot toward a predictive, mechanistically grounded science of cancer vulnerability.

PRECISE (Predictive Relationships Explaining Cancer Genetic Interactions and Synthetic Essentiality; http://precise-eu.org/) is a Europe-led initiative established in response to this challenge and to an international call for coordinated efforts to map cancer dependencies[6]. Leveraging advances in multi-omics profiling, artificial intelligence (AI) and machine learning-based modeling, PRECISE shifts the focus from exhaustive cataloguing to predictive, mechanistically grounded modeling of tumor vulnerabilities. PRECISE aims to establish a framework in which cancer dependencies are mechanistically understood and anticipated across contexts.

The PRECISE consortium seeks to progressively expand predictive coverage of the cancer-dependency landscape through iterative lab-in-the-loop prediction–validation cycles, identifying clinically relevant vulnerabilities in untested contexts.

Globally, a substantial proportion of patients (estimated at around 80%) present with tumors that lack clinically actionable genomic alterations under current molecular diagnostic workups[7]. Over the next 5 years, PRECISE aims to demonstrate that predictive models integrating perturbational and multi-omics data can identify vulnerabilities in many of these currently non-actionable cases, provide mechanistic explanations, and quantify confidence in the predictions by leveraging representation learning and generative models to generalize across under-represented contexts.

As an initial objective, PRECISE aims to reduce, by at least 5%, the portion of tumors that remain non-actionable under genomics-only

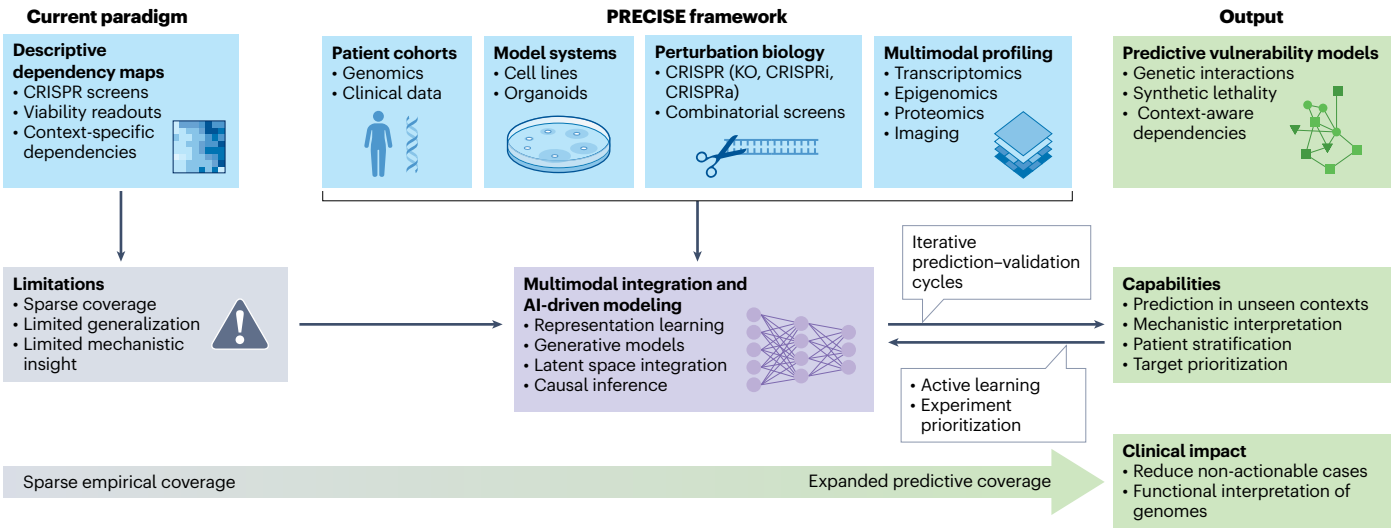


**Fig. 1 | The PRECISE framework.** Existing cancer-dependency maps (left) can identify context-specific genetic vulnerabilities but are largely descriptive and are limited in coverage, mechanistic interpretability and generalization across biological contexts. The PRECISE framework (middle) integrates complementary data sources, including patient cohorts, disease-relevant model systems, perturbation biology and multimodal molecular profiling, within an interoperable computational framework. Multimodal integration and AI-driven modeling approaches, including representation learning, generative models and causal inference, are used to embed heterogeneous data into shared latent representations that capture system-level properties of cancer vulnerabilities: an iterative prediction–validation cycle in which computational models guide the prioritization of perturbations and experiments, and experimental data are used to refine and improve model predictions. The integrated, closed-loop approach (right) enables the construction of predictive cancer-vulnerability models that infer genetic interactions and synthetic-lethal relationships across contexts (including previously untested settings), provide mechanistic interpretations of dependencies, enable patient stratification and prioritize targets. Collectively, this framework enables a transition from sparse empirical coverage to expanded predictive coverage, with the potential to reduce the proportion of tumors that lack actionable vulnerabilities and to provide functionally informed interpretation of cancer genomes. KO, knockout; CRISPRi, CRISPR interference; CRISPRa, CRISPR activation.

approaches, for which no therapeutic hypothesis can be derived from molecular profiling.

Recent genomic analyses and therapeutic target-prioritization efforts indicate that many, potentially most, tumors harbor at least one potentially actionable driver event, which suggests that functionally informed approaches may further expand therapeutic interpretability[2,8].

Here we outline the scientific vision and operational framework of PRECISE to support a transition beyond descriptive dependency maps to a predictive science of cancer vulnerability.

## The scientific framework of PRECISE

Building on recent European Cancer Dependency Map workshops[9,10], PRECISE brings together over 30 experimental and computational research groups across more than 20 research institutes and universities in nine European countries (https://precise-eu.org/members). Participating groups contribute expertise in perturbation biology, disease-relevant models, multimodal profiling and computational biology.

PRECISE is structured around three interconnected components: systematic perturbation across diverse biological contexts; multimodal characterization of perturbational effects; and predictive modeling through iterative learning cycles.

**Systematic perturbation across biological contexts.** Perturbation experiments, coupled with viability and multi-omics readouts, enable causal investigation of genes, pathways and phenotypes. At the core of PRECISE is the generation of perturbational data across diverse model systems (Box 2). Rather than aiming for exhaustive coverage, PRECISE prioritizes informative sampling of genetic and cellular contexts, leveraging combinations of perturbations, genetic backgrounds and cell states that maximize the discovery of functionally relevant interactions.

This encompasses (i) genome-scale and targeted CRISPR-based perturbations, including combinatorial epistasis screens to probe the genetic architecture of cells; (ii) modalities such as CRISPR interference and activation; and (iii) precise genome-editing strategies. These enable systematic exploration of synthetic-lethal and buffering relationships, as well as the assessment of gene dosage-dependent effects relevant to therapeutic targeting (Box 2)). Perturbations are deployed across biologically relevant models, including cancer cell lines, organoids and other patient-derived systems to capture variation in lineage, genetic background and cell state (Fig. 1).

In support of comparability and integration across laboratories, PRECISE promotes the adoption of shared experimental design principles, benchmarked perturbation libraries, harmonized data-processing pipelines, and core sets of reference assays and reporting standards to ensure interoperability and reproducibility across experimental platforms. This framework enables effective integration of data generated across centers while leveraging diverse technologies and expertise across participating groups.

**Multimodal characterization of perturbational responses.** A defining feature of PRECISE is the integration of multiple phenotypic readouts to characterize the consequences of perturbations and enable modeling of genetic interactions across biological contexts (Box 3). Genetic

## BOX 1

# From cancer-dependency maps to a predictive science of cancer vulnerability

Cancer-dependency maps have provided a systematic framework for identifying gene essentiality across diverse cancer models through large-scale perturbational screening, which has led to important discoveries with therapeutic implications, including context-specific vulnerabilities, such as the dependence of microsatellite instable cancers on the Werner syndrome ATP-dependent helicase WRN, and the synthetic lethality between recurrent genomic alterations and inactivation of the phosphorylase MTAP. However, these findings have emerged from resource-intensive empirical investigation of model systems, and their generalization across biological contexts remains limited.

Cancer dependencies are typically defined as context-specific observations based on phenotypic endpoints such as cell viability, with limited ability to explain their mechanistic basis, assess their penetrance across biological contexts or predict their behavior under perturbation or treatment. Moreover, the vast number of possible molecular features and contexts that induce vulnerabilities remains only sparsely explored relative to its combinatorial scale, which constrains inference beyond a limited set of experimentally observed conditions.

Predictive cancer-vulnerability models aim to address those limitations by moving from cataloguing observations to learning generalizable principles that govern genetic dependencies. This requires the integration of perturbational responses with multi-omics measurements to capture system-level properties that arise from the dynamics of interacting molecular processes. In practice, this involves linking genetic and chemical perturbations to their downstream consequences across multiple molecular layers, including transcriptional, epigenetic, proteomic and phenotypic readouts, often at single-cell resolution.

Computationally, these data can be integrated through representation learning and related machine-learning approaches to embed diverse measurements into shared latent spaces that capture interaction structure, pathway activity and context-dependent responses. In this framework, vulnerabilities are treated not as isolated binary outcomes but as structured states that reflect coordinated molecular responses.

This representation enables inference across untested genetic, cellular and treatment contexts by leveraging similarities in underlying system behavior, rather than relying solely on direct empirical observation.

## BOX 2

# Experimental and technological scope of PRECISE

PRECISE integrates a broad range of experimental systems, perturbation strategies and molecular readouts to enable systematic exploration of cancer vulnerabilities across biological contexts.

**Model systems**

Complementary cancer models that span multiple levels of biological complexity will be strategically chosen to capture variation in lineage identity, genetic background, cellular plasticity and interactions with the microenvironment. Such model systems include established cell lines, patient-derived organoids, genetically engineered cellular systems, co-culture and microenvironment-informed platforms, as well as in vivo models such as xenografts and genetically engineered and humanized mouse models.

**Perturbation modalities**

PRECISE employs perturbation modalities that enable systematic investigation of gene function across dosage regimes and facilitate the identification of synthetic-lethal and buffering interactions under clinically relevant conditions. These include genome-scale CRISPR screening and extended to combinatorial perturbations, tunable loss- and gain-of-function approaches (such as CRISPR interference and activation), base and prime editing, epigenome editing, RNA-targeting systems, and chemogenetic perturbations.

**Readouts and measurements**

Perturbational effects are characterized through the use of a range of molecular and cellular phenotypic assays, such as bulk, spatial and single-cell transcriptomics, epigenomic profiling, proteomics, metabolomics, lineage tracing and high-content imaging. Longitudinal sampling is used to study dynamic responses such as cancer cell adaptation and resistance.

**Foundational resources**

PRECISE builds upon existing community resources, including cancer-dependency maps, shared experimental platforms, reference model collections and established data standards, to provide a substrate for hypothesis generation, model training and cross-study integration.

## BOX 3

### Genetic interactions and predictive cancer-vulnerability modeling

Predictive cancer-vulnerability modeling extends traditional dependency atlases by enabling the inference of context-specific genetic dependencies across biological states that have not been directly assayed. By integrating perturbational data with computational models, these frameworks predict the functional consequences of gene perturbations, individually and in combination, across genetic, cellular and environmental contexts.

Central to this approach is the concept of genetic interactions, in which the effect of perturbing one gene depends on the state of others. Synthetic-lethal interactions arise when two perturbations are individually tolerated but jointly lethal, which provides a basis for targeted therapies. In contrast, synthetic-rescue interactions arise when perturbing one gene attenuates the effects of perturbing another and can thereby contribute to drug resistance.

A major challenge in mapping genetic interactions is their combinatorial scale: the number of possible pairwise and higher-order interactions grows exponentially, whereas biologically meaningful interactions are comparatively sparse, rendering exhaustive screening impractical. This is compounded by strong context dependence, with some interaction effects varying across tumor lineages, cellular states, epigenetic configurations and treatment conditions, features that are difficult to resolve through observational patient data alone. Predicting when and where these interactions manifest, therefore, requires integrating perturbational data with rich molecular and phenotypic context.

## BOX 4

### Prediction-first experimental workflows

In prediction-first workflows, computational models actively guide experimental design rather than retrospectively analyzing data. Models are used to prioritize perturbations, model systems and measurements expected to be maximally informative, given current uncertainty.

Experimental assays are then iteratively designed as targeted tests of model predictions, with a focus on resolving ambiguities and validating high-value hypotheses. This creates a closed-loop process in which modeling and experimentation continuously inform one another. Over successive cycles, this approach can improve the efficiency of data generation for the development of predictive models that are generalizable across diverse molecular contexts, including unseen contexts.

By shifting from exhaustive screening to model-guided experimentation, prediction-first workflows enable efficient, scalable exploration of cancer vulnerabilities while maintaining a strong link between predictive performance and mechanistic insight.

dependencies and synthetic-lethal relationships arise from coordinated responses across biological layers, often conditional on genetic background, cellular state, microenvironment or treatment context[11]. PRECISE captures these responses through multimodal measurements, enabling inference and generalization across models and conditions.

While cellular fitness remains a therapeutically relevant phenotypic endpoint, PRECISE will also investigate perturbation effects through the use of high-dimensional readouts. Mapping cellular state determinants across cancers would render cancer cell wiring learnable, analogous to what cancer dependency maps achieved for survival dependencies (Fig. 1). Two complementary approaches, developed by PRECISE groups, enable mapping of how genetic perturbations propagate through the transcriptional and morphological state space: single-cell CRISPR-screens with transcriptomic readouts capture complex molecular responses at single-cell resolution; and optical pooled screens measure subcellular morphological responses through 'generic' optical readouts such as DNA stains, cell painting and label-free brightfield imaging. These readouts provide mechanistic contexts for fitness effects, linking dependencies to biological processes and pathways. Notably, the same high-dimensional state vectors captured by these screens can also be profiled in patient tissue to project learned rules onto clinical material and validate derived predictions.

In addition, multimodal phenotypes can characterize early and intermediate perturbation responses, adaptive evolutionary trajectories, and transcriptional and epigenetic cell states, as well as compensatory mechanisms that may precede or modulate effects on cell fitness[12]. These measurements link molecular changes to cellular fitness and therapeutic sensitivity.

**Predictive modeling and iterative learning.** The third component of PRECISE focuses on computational models capable of learning generalizable relationships that govern cancer dependencies. These models integrate perturbational data across contexts to infer the structure of the underlying genetic interaction networks and how they are modulated by molecular traits and context. Approaches include statistical modeling, machine learning and emerging AI foundation models trained on large-scale multimodal datasets, including clinical cohorts (Fig. 1).

Cancer vulnerabilities are dynamic properties shaped by tumor evolution, cellular plasticity and therapeutic pressure[13]. PRECISE therefore incorporates longitudinal and context-resolved data, including pre- and post-treatment samples, disease-progression models and time-resolved perturbational profiling, to capture how dependencies emerge or disappear over time. These data model non-genetic adaptation and transient states that influence therapeutic responses. As a result, predictive models are designed not only to infer vulnerabilities across biological contexts but also to assess their temporal stability, anticipating trajectories of adaptive escape.

A central principle of the framework is the use of iterative predict-test-refine cycles (Box 4). AI models prioritize the most informative perturbations for experimental testing, learning through successive iterations, and thereby increase the value of data generation. This iterative strategy progressively maps the interaction landscape,

## BOX 5

# AI and multimodal learning for predictive cancer-vulnerability modeling

Recent advances in machine learning, representation learning and large-scale multimodal data integration have created an opportunity for transitioning cancer-dependency research from descriptive mapping to predictive and mechanistically informed modeling. PRECISE is explicitly designed to leverage this 'AI moment' by placing advanced computational approaches at the core of its framework.

At the heart of PRECISE is the integration of heterogeneous perturbational and molecular datasets across genetic, transcriptional, epigenetic, proteomic and phenotypic layers. This framework adopts representation learning strategies that embed diverse data modalities into shared latent spaces. Approaches such as autoencoders and transformers allow the extraction of low-dimensional representations that capture the underlying data structures. These latent representations enable comparison across model systems, batch correction and alignment of in vitro and patient-derived data, as well as generalization across biological contexts.

Building on those representations, PRECISE will develop predictive models that infer the effects of genetic and chemical perturbations that are conditional on cellular context, such as lineage, epigenetic state, and treatment history. These include supervised and semi-supervised learning approaches trained on large-scale perturbational datasets, as well as graph-based models that incorporate prior knowledge of molecular interactions[15]. A central component of this effort is the development and application of foundation models designed to learn generalizable rules that govern cellular responses to perturbation, which will enable the prediction of vulnerabilities in untested systems, including patient-derived samples. Beyond predictive performance, these approaches also provide a basis for mechanistic insight. By analyzing latent representations, feature attributions and learned interaction structures, models can reveal pathway-level dependencies, compensatory mechanisms and network constraints that underlie observed vulnerabilities.

International efforts to develop 'virtual cell' models aim to simulate cellular behavior by integrating large-scale molecular data into unified computational systems. While these approaches share methodological foundations with PRECISE, including the use of multimodal data and foundation models, their primary objective is to simulate cellular processes, often with a focus on transcriptional programs. PRECISE addresses a complementary challenge in clinical application: extracting predictive, mechanistically interpretable rules of vulnerability across the full spectrum of human malignancy to guide treatment. Thus, these efforts are synergistic, with potential for cross-fertilization in data, modeling strategies and biological insights.

transforming sparse observations into increasingly predictable cancer vulnerabilities. Initially, substantial value will derive from training models on large-scale multimodal datasets that span hundreds of disease-relevant models, thousands of perturbational conditions and diverse patient cohorts. As predictive performance improves, data generation will progressively shift toward smaller, targeted datasets designed to refine model generalizability across contexts.

Collectively, an interoperable, federated framework links perturbation, multimodal profiling and predictive modeling in a self-reinforcing cycle, transforming static dependency maps into dynamic, mechanistically informed and context-aware predictions of cancer vulnerability.

### Leveraging Europe's strengths

Europe hosts a world-leading and uniquely complementary ecosystem of experimental and computational capabilities, yet these strengths remain fragmented across institutions and funding structures. Realizing their full potential requires coordinated pan-European efforts to transform this distributed excellence into a unified, predictive science of cancer vulnerability.

A major strength lies in the availability of advanced, patient-relevant model systems, including organoids, patient-derived cultures and genetically engineered models that capture tumor heterogeneity, lineage identity and dynamic cell-state transitions. In parallel, laboratories in Europe have developed considerable expertise in perturbation technologies, including genome-scale and combinatorial CRISPR screening, as well as genome-engineering approaches. These are complemented by extensive multimodal profiling capabilities that span single-cell and spatial transcriptomics, epigenomics, proteomics, imaging and metabolomics, which enable perturbational effects to be characterized across multiple molecular and phenotypic layers. Collectively, this expertise provides a strong foundation for predictive cancer functional genomics.

Europe also hosts a rapidly expanding computational ecosystem and data infrastructure[14], with strengths in machine learning, statistical modeling and causal inference, including emerging foundation models capable of integrating heterogeneous, high-dimensional datasets (Box 5). PRECISE will champion open and equitable access to these resources. In addition, extensive clinical and translational infrastructures — often embedded within large, integrated healthcare systems — provide access to genomic initiatives, longitudinal cohorts and biobanks and provide critical links between experimental systems and patient-derived data. Together, these structures enable the projection and validation of predicted vulnerabilities in clinically relevant contexts and the identification of patient subgroups in which specific dependencies manifest, thereby anchoring predictive models in clinical application.

Despite these strengths, the full potential of this ecosystem remains underexploited, owing to fragmentation across platforms, model systems and data modalities. PRECISE addresses this challenge through a federated framework in which data and experimental systems remain locally governed but globally interoperable. This is enabled by shared experimental design principles, harmonized data standards and integrated analytical pipelines.

The PRECISE web portal (https://precise-eu.org) represents an entry point to the consortium and will become a gateway to distributed FAIR (findable, accessible, interoperable and reusable) data resources to support findable, standardized access and the integration of datasets and tools across participating laboratories. Within PRECISE, data generation is coordinated to prioritize informative perturbations and aligned multimodal readouts, to ensure that datasets are complementary and suitable for downstream modeling. This will include capturing a diversity of populations on the basis of ancestral diversity, geography and gender. Moreover, PRECISE establishes a coherent data flow that links experimental design, data acquisition and predictive modeling within an iterative learning framework.

PRECISE is currently a structured, growing consortium built around a shared scientific vision and coordinated research priorities. The consortium operates through regular interactions, including annual workshops that rotate across participating institutes, an ongoing seminar series, a biannual conference open to the wider scientific community[9,10], and active cross-institutional coordination, with institutional grant offices working jointly to support collaborative funding applications. Together, these activities provide an organizational foundation for aligning experimental and computational efforts, developing common methodological standards and advancing joint projects.

PRECISE thus combines the flexibility of a federated infrastructure with the consistency and accessibility required for large-scale data integration and community use. Cross-disciplinary coordination, including joint scientific activities and shared resources, further supports collaborative development. Although it is currently organized as a European initiative, PRECISE is consciously designed for global extension: its federated model provides a scalable framework for fostering international partnerships, enabling interoperable data sharing and building capacity across the global cancer research community.

## Concluding remarks

PRECISE aims to transform cancer-dependency mapping into a predictive and mechanistically grounded framework for cancer-vulnerability inference. By integrating diverse perturbation modalities, multimodal molecular profiling and advanced computational modeling, the PRECISE consortium seeks to uncover generalizable rules that govern genetic dependencies, synthetic lethality and adaptive responses across biological contexts. Bridging Europe's expertise within a federated, interoperable framework, PRECISE will progressively expand predictive coverage of the cancer-vulnerability landscape. In doing so, it complements genomic precision oncology by providing functional insight, advancing therapeutic target prioritization, anticipating resistance mechanisms and guiding rational, context-specific therapeutic strategies.

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