IN FOCUS

MANIFEST: Multiomic Platform for Cancer Immunotherapy

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Summary: Immunotherapy has revolutionized survival outcomes for many patients diagnosed with cancer. However, biomarkers that can reliably distinguish treatment responders from nonresponders, predict potential life-threatening and life-changing drug-induced toxicities, or rationalize treatment choices are still lacking. In response to this unmet clinical need, we introduce Multiomic ANalysis of Immunotherapy Features Evidencing Success and Toxicity, a tumor type–agnostic platform to provide deep profiling of patients receiving immunotherapy that will enable integrative identification of biomarkers and discovery of novel targets using artificial intelligence and machine learning.

INTRODUCTION

Harnessing the immune system to treat cancer has revolutionized survival outcomes for many patients. In particular, over the past decade, immune checkpoint inhibitors have become standard-of-care treatment for many cancer subtypes (1). The next generation of immunotherapies is advancing, with bispecific antibodies and adoptive cell therapy gaining the U.S. FDA approval, promising data emerging from mRNA vaccine trials, and a growing portfolio of cytokines and oncolytic viruses in clinical testing. There is a trend for combining multiple immunotherapy agents or immunotherapy with other cancer therapies, including chemotherapy, targeted therapy, and radiotherapy in clinical trials, and thousands of combinations are in preclinical evaluation (1).

As more tangible treatment options become available in the pursuit of better and personalized medicine for patients with cancer, studying primary and secondary resistance mechanisms to therapies is indispensible for informing new targets and rationalizing treatment combinations. Ongoing fundamental, translational, and clinical research efforts are under way to dissect these in order to further improve response rates and survival outcomes for patients. Despite these advances, to date, only a minority of patients receiving immunotherapy benefit, yet all are exposed to the risk of life-changing and life-threatening toxicities. The added burden of financial toxicity globally is an increasing concern. More rationale use of current and future high-cost interventions is essential, with the pressing need to develop disease- and patient-specific biomarkers to avail treatment options or steer clinical decisions.

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However, almost no biomarkers today can effectively distinguish responders from nonresponders, predict toxicity, or guide treatment choices. Traditional single biomarker approaches often fail to predict efficacy or guide development of next-generation immunotherapies due to the complex tumor microenvironment (TME) and multiple host factors. Whereas large clinically annotated datasets have yielded useful insights (2), lack of standardization between operators limits generalizability. Current datasets mainly focus on bulk profiling of tumor DNA and RNA, lacking spatial TME data or assay readouts that require fresh sampling and time-sensitive processing. Longitudinal data gaps hinder understanding treatment resistance mechanisms and inherent heterogeneity, both across and within patients, and remain a significant hurdle. Furthermore, there is limited integration of omics with routine clinical, histologic, and radiologic data, and patient-reported outcomes and surveillance via wearable technologies are lacking. Deep learning, although increasingly applied to single-modality data, has not been extended to multimodal data to develop reliable predictive signatures. Ultimately, the unmet clinical need of personalizing immunotherapy has profound implications on health resources and economics.

Recently, there have been emerging models of public–private partnerships or consortia, including Europe-wide, pan–United States, or global networks, which have set out initiatives to tackle the biological and clinical unmet needs in the field of immuno-oncology (IO; Supplementary Table S1). For instance, Integrated iMMUnoprofiling of large adaptive CANcer patient cohorts (ref. 3) is a large-scale consortium supported by the European Organization for Research and Treatment of Cancer and European Union, in conjunction with academic and industry partners, to generate molecular and spatial profiling of patients with colorectal, lung, head and neck, breast, and renal cancers treated with standard-of-care immunotherapies; and is a potential rich data repository for biomarker discovery.

In this study, we introduce our United Kingdom–wide consortium and platform, Multiomic ANalysis of Immunotherapy Features Evidencing Success and Toxicity (MANIFEST, www.manifest-io.org.uk), bringing together both academic and industry stakeholders with expertise in cancer immunotherapy, biomarker discovery and development, and clinical trials. MANIFEST leverages existing and novel scalable methodologies to provide deep profiling of each patient receiving immunotherapy and aims to deliver on multimodal data integration and modeling.

STUDY DESIGN

MANIFEST is designed as an observational, noninterventional clinical study funded by the UK Office of Life Sciences and the Medical Research Council. The consortium comprises major public hospitals/comprehensive cancer centers (National Health Service), academic institutes, and universities, and is supported by upfront top-up investment from multiple industry partners in noncompetitive partnership.

To demonstrate the utility of the MANIFEST platform, we will deliver exemplar projects, initially focusing on four cancer types (melanoma, renal cell carcinoma, bladder cancer, and triple-negative breast cancer), in which prediction of treatment outcomes and toxicities to both standard-of-care and emerging immunotherapies remains a significant unmet need. Specifically, we have access to preexisting longitudinal samples of >3,000 patients across several reported immune checkpoint inhibitor studies, supported by existing Research Ethics Committee approvals. These retrospective cohorts will stress-test the platform, ensuring assay quality control, harmonization, and performance validation. Outputs from this phase will benchmark multimodal data integration methods and generate the first iteration of multimodal biomarker signatures for evaluation in prospective cohorts.

In parallel, we will utilize existing governance and biobank capabilities at partner National Health Service sites for prospective sample collection (blood, stool, and tissue) and processing. With a tiered approach, we aim to profile patient and tumor samples at a scale of ~3,000 patients with both early- and late-stage disease over 3 years.

APPROACH

As a cancer subtype–agnostic platform, MANIFEST utilizes novel and scalable methodologies, alongside artificial intelligence (AI) and machine learning (ML) approaches, to integrate multimodal data tuned to clinical settings. Our objectives are to deliver predictive biomarkers for immunotherapy response, resistance, and immune-related adverse events (irAE); discover novel therapeutic targets; and establish a preclinical model biobank. Innovations include novel and advanced methods for data production and analysis; a scalable and rapid preclinical modeling platform; centralized and harmonized clinical and multimodal biomarker data; and secure workflows with consideration intellectual property and interoperability with other trusted research environments to maximize learning. Leveraging existing infrastructure and academia–industry partnerships, MANIFEST will harness emerging technologies with a strong theme of cross-collaboration, training, and upskilling across the consortium.

Standard-of-care diagnostic workflows will be implemented for high-volume biomarker discovery (tier 1 participants). In-depth profiling, through tier 2 and 3 participation, will further characterize tumors including discovery-focused techniques, such as high-dimensional peripheral immune profiling, liquid biopsy [cell-free DNA (cfDNA) methylation profiling with deconvolution of cell types, tumor cells, and immune cells), and spatial image-profiling approaches coupled with molecular profiling [whole-exome sequencing, bulk and long-read RNA sequencing (RNA-seq), and T-cell receptor (TCR) and B-cell receptor (BCR) sequencing].

For selected patients, we will expand the utility of representative sequencing (RepSeq; ref. 4), a novel tumor sampling methodology which overcomes a pervasive undersampling bias in solid tumors, and preclinical modeling using patient-derived tumor fragments (PDTF; refs. 5, 6) for drug sensitivity screening. Finally, we will deploy a team of experts in AI and ML to deliver on multimodal data acquisition and integration.

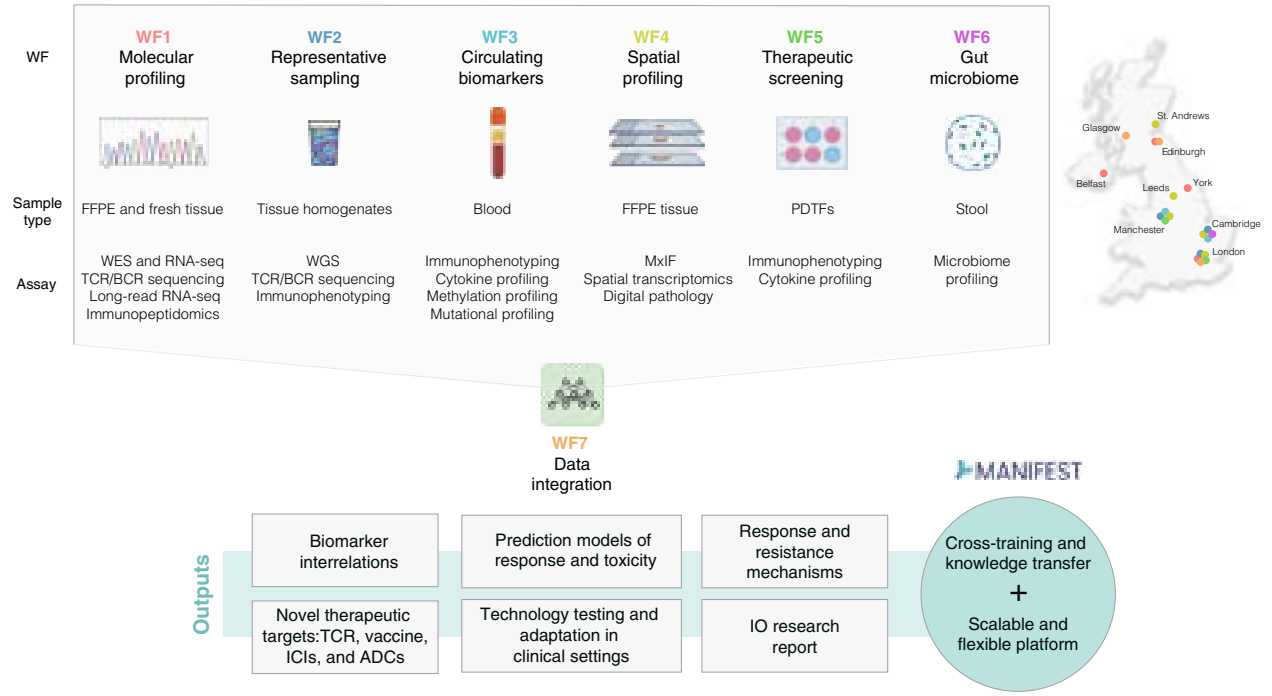

Figure 1. Overview of the MANIFEST platform and respective workflows. ADC, antibody–drug conjugate; FFPE, formalin-fixed paraffin-embedded; ICI, immune checkpoint inhibitor; WES, whole-exome sequencing; WF, work flow; WGS, whole-genome sequencing.

PROJECT WORKFLOWS

Our seven profiling workflows in MANIFEST (Fig. 1) enable comprehensive profiling of fresh and fixed tumor tissue alongside longitudinal blood and stool samples. While supporting scalable biomarker discovery, we aim to integrate nascent technologies to advance biological discovery. The modular nature of these workflows allows for incorporation of novel assays and technologies throughout the platform's lifecycle.

Tumor Molecular Profiling

Immunotherapy biomarkers derived from tumor bulk profiling frequently fail due to pervasive intratumoral heterogeneity and variability in the sequencing modalities and analytical approaches used. Although tumor mutational burden (TMB), PD-L1 protein status, and deficient DNA mismatch repair are FDA-approved, their predictive performance remains context-dependent. Emerging composite biomarkers (e.g., TMB and IFN-γ signature; ref. 7) offer promise but require robust standardization and validation.

MANIFEST will deliver standardized immunogenomic datasets from treatment-naïve samples collected from patients receiving first-line immune checkpoint inhibitor therapy. Formalin-fixed paraffin-embedded samples will be profiled using clinical-grade assays, including whole-exome sequencing and bulk RNA-seq. Established and putative biomarkers such as clonal TMB, neoantigen burden and quality, HLA haplotype, and gene expression profiles will be explored. Composite, spatially stable, immunogenomic biomarkers will be tested for predictive accuracy.

Emerging molecular assays will quantify TCR/BCR metrics, including clone size, expansion, clonality, and diversity, to prioritize antigen-specific clones for cell- and antibody-based therapy development. Discovery-driven approaches, such as long-read RNA-seq and immunopeptidomics, will focus on detecting high-quality neoantigens, refining antigen prediction, and supporting vaccine development.

Representative Tumor Sampling

Intratumor heterogeneity in solid cancers presents a significant challenge for accurate biomarker discovery due to sampling bias caused by distinct subclones in different tumor regions. Multiregional sampling can mitigate this but is limited by cost, labor implications, and challenges for standard-of-care implementation. To address this, MANIFEST uses RepSeq, a novel method that homogenizes surplus surgical tumor tissue to capture comprehensive molecular profiles (4, 8). RepSeq will be applied alongside fixed-FACS, which enriches subpopulations of interest from the homogenate, overcomes low tumor purity, and enables detailed profiling of the TME (4).

MANIFEST will apply RepSeq coupled with molecular profiling assays across 200 tumors to identify clonal and persistent neoantigens, assess mechanisms of immune escape, and associate their relationship to immunotherapy response. In parallel, the platform will evaluate the utility of a representative TCR and BCR repertoire as a biomarker of immunotherapy response and therapeutic discovery, applying emerging TCR assays to representative homogenates. Additionally, tumor molecular features will be integrated with TME characterization using fixed-FACS to quantify tumor-infiltrating lymphocytes, PD-L1 expression, and ratio of immune cell subsets.

Circulating Biomarkers

Circulating biomarkers provide dynamic insights into disease burden, treatment response, tumor profiles, and irAEs. Peripheral immune biomarkers, cytokines, and cfDNA approaches have shown promise in predicting immunotherapy outcomes but require robust standardization and validation.

To address this, MANIFEST will use high-resolution spectral cytometry to characterize peripheral blood mononuclear cell subsets to develop peripheral immune response signatures which underpin immunotherapy response and development of irAEs. Recognizing the growing trend for cross-modality treatments, MANIFEST will leverage longitudinal samples from observational cohorts to explore the impact of non-IO therapies on immune profiles. Cytokine profiling will complement these efforts, starting with a discovery panel that will be refined for prospective use.

Additionally, cfDNA approaches will be deployed to assess minimal residual disease, monitor response to therapy, and characterize immune profiles. Tumor-informed assays will be utilized in collaboration with commercial partners, alongside global DNA methylation profiling assays, including emerging deconvolution techniques to analyze cfDNA from circulating immune cells (9).

In Situ Profiling

Advances in spatial profiling and ML offer opportunities to explore the TME in the context of immunotherapy. Understanding the spatial distribution of TME components is critical for developing therapeutic strategies, yet spatial biology tools remain underutilized due to high costs, specialized expertise requirements, and a lack of standardized approaches for data collection and image analysis. Whereas multiplex immunofluorescence (MxIF) and IHC have primarily served as discovery tools, protocols previously developed by the MANIFEST consortium demonstrate their potential for quantitative validation nearing clinical applicability (10).

MANIFEST will deploy several low-plex MxIF panels for high-throughput, reproducible tissue profiling. Tissue microarrays representing multiple tumor regions and longitudinal samples, where available, will facilitate cost-effective and scalable analyses. Standardized protocols aligned with expert consensus statements will facilitate assay onboarding and regulatory validation for clinical use. High-plex MxIF (>40 markers) and spatial transcriptomics will complement these efforts in subsets of patients with exceptional response, integrating protein and RNA data and to quantify key targets such as chemokines to drive discovery.

Through high-throughput computational pathology pipelines, MANIFEST aims to identify morphologic and topographic features from diagnostic hematoxylin and eosin digital whole-slide images that associate with immunotherapy response. Where matched molecular data are available, these morphologic correlates will be interrogated further to develop computational pathology biomarkers, representing a cost-effective and scalable approach. Additionally, virtual staining techniques will be deployed using matched whole-slide image and MxIF data, providing scalable insights across thousands of samples.

PDTFs

Preclinical models are essential for generating functional insights from observational data, but reproducibility and scalability remain significant challenges in immunotherapy research. PDTFs are fresh surgically resected tumor material, cut into 1 to 2 mm diameter and subsequently cryopreserved, that retain the native architecture and immune microenvironment (5, 6). Notably, PDTFs can faithfully predict clinical responses to various immunotherapy agents in donor patents, providing a rapid (<48 hours), versatile, and accurate model with which to evaluate the response to treatment, including novel assets and combination strategies, of tumor-infiltrating immune cells (6). PDTFs also potentially hold promise to discover biomarkers of response and resistance to standard-of-care immunotherapies, particularly in assessing the benefits of adjuvant therapy.

MANIFEST will scale-up PDTF biobanking to systematically evaluate immune responses to immune checkpoint inhibitors and other therapeutic approaches. The platform will facilitate the testing of rational combinations and emerging compounds through in-depth profiling, including high-dimensional cytometry, MxIF, cytokine/chemokine profiling, and TCR and BCR sequencing. With real-time clinical readouts in prospective cohorts, the potential of PDTFs as *ex vivo* avatars that contain the natural tumor immune cell infiltrate will be explored to predict the benefits of adjuvant therapy. Their utility as noninterventional biomarkers, with the potential for integration into clinical trials, will be assessed.

Gut Microbiome

The gut microbiome has been linked to immunotherapy response and irAEs, but the identification of consistent microbiome-based biomarkers across different patient groups and immunotherapies remains challenging (11). This limitation arises partly due to incomplete reference genome databases and an overreliance on species- and genus-level classifications, despite the strain-specific nature of bacterial functions. Microbiome biomarkers can be used to inform the development of orally delivered live biotherapeutic products (definited consortia of bacteria) that stimulate immune responses to enhance immune checkpoint inhibitor efficacy. In collaboration with commercial partners, the MANIFEST platform will evaluate validated microbiome signatures for their applicability across exemplar tumor types and IO agents. Prospective cohorts will enable the integration of microbiome data with clinical and multiomics datasets to derive predictive signatures of immunotherapy response, resistance, and irAEs.

Analysis and Deep Learning

Immunotherapy biomarker development has traditionally focused on single data types, failing to capture the complexity of antitumor immunity. Multimodal predictors of immunotherapy response and irAEs offer greater potential for understanding resistance mechanisms and identifying new therapeutic targets. However, progress in multimodal data integration has been hindered by lack of orthogonal datasets, limiting opportunities for benchmarking methods. Data generated through abovementioned MANIFEST workflows

will be curated and analyzed centrally within a trusted research environment, supported by high-performance computing infrastructure and commercial partnerships for cloud and governance solutions. Leveraging standardized, large-scale, high-quality datasets, the platform will systematically explore the complementarity and interplay between data modalities.

Unimodal models will first be developed to predict immunotherapy response and irAEs, followed by their integration into scalable, modular multimodal models using late fusion techniques (12). These models will combine data from diverse sources, whilst addressing missing data and variability. AI safety, explainability, and robustness will remain central, using techniques such as knowledge distillation, uncertainty quantification, and *post hoc* analysis to build confidence in model predictions. MANIFEST will look to deliver unimodal and multimodal models for immunotherapy response and irAE prediction, with explainability tools to identify biomarkers and enhance clinical interpretability. Additionally, mathematical models will simulate tumor–immune interactions, predicting the impact of spatial TME architecture on immunotherapy response and enabling virtual trials of immunotherapy strategies.

FUTURE OUTLOOK

MANIFEST offers a comprehensive precision medicine solution to the current challenges in immunotherapy and facilitates biomarker discovery, aiding in predicting treatment outcomes and toxicities for standard-of-care and emerging interventions. Our standardized approach across multiple cancer types ensures broad applicability and facilitates reverse translation, with potential for technology transfer.

We envision that MANIFEST will deliver on a rich complex data repository to facilitate further discovery and translational research through streamlined data access. Clinical and sample-level data will be pseudonymized, and multimodal datasets will be centralized within a trusted research environment, with robust firewalls for data partitioning. Metadata tagging ensures seamless integration of multiomics datasets, enabling both patient-specific analysis and cohort-level discovery of novel biomarkers to inform immunotherapeutic strategies. Data generated can also potentially become a reference set for evaluating heterogeneity of emerging biomarkers and targets. An ultimate goal is to ultimately provide a tool for researchers and clinicians to advance discoveries, similar to the impact of consortia like The Cancer Genome Atlas and others in the field of cancer research.

In the expansion phase, we will continue utilizing satellite projects to stress-test the platform and contribute to the master database, thereby growing our assets. Additionally, we aim to expand the platform's utility as a companion diagnostic tool, delivering meaningful translational insights to both academic and commercial partners. Long-term sustainability will be achieved through a large data and assay ecosystem to support investigator-led studies via our clinical networks and through private sector collaborations. Our pledge is based on a virtuous cycle whereby those utilizing the platform commit to their data being used for iterative learning.

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Note

Supplementary data for this article are available at Cancer Discovery Online (http://cancerdiscovery.aacrjournals.org/).

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