

Topic idea submitted to IHI - Reference Number: TI_001311

Are you submitting the idea:

- ☒ in your personal capacity?
☐ on behalf of an organisation?

1 Title of your idea

Please provide a short title that accurately reflects the objective(s) of your idea:

ORACLE-ICI GI: Enabling early prediction of immune-related gastrointestinal toxicity in cancer

immunotherapy

2 Scope

Explain the specific challenges/problems to be addressed by your idea and how these affect relevant stakeholders, taking into account what is already known and/or available in the field:

Immune checkpoint inhibitors (ICIs) have transformed the treatment landscape of multiple cancers, yet their full therapeutic potential is significantly limited by the occurrence of immune-related adverse events (irAEs). Among these, gastrointestinal (GI) toxicities, such as colitis and severe diarrhea, represent one of the most frequent and clinically impactful complications.

A major unresolved challenge is the inability to predict which patients will develop GI irAEs, particularly moderate-to-severe events requiring systemic immunosuppression or treatment discontinuation. Currently, clinical management is largely reactive: toxicity is identified only after symptom onset, often requiring treatment interruption, corticosteroids, or biologics. This not only affects patient quality of life and safety, but can also compromise oncological outcomes by limiting optimal drug exposure.

Despite extensive research, no robust, validated, and clinically actionable predictive biomarkers are currently available. Existing approaches rely predominantly on static measurements (e.g., baseline microbiome composition, circulating cytokines), which have shown limited reproducibility and predictive performance across cohorts. These strategies fail to capture the dynamic and systemic nature of immune activation under ICI therapy.

Emerging evidence indicates that ICI-related toxicity is not a purely local inflammatory event, but rather the result of complex, multi-level interactions involving immune activation, microbiome-derived signals, and host metabolic regulation. In particular, immunometabolic pathways and gut-derived metabolites (e.g., short-chain fatty acids, bile acids, tryptophan metabolites) are increasingly recognized as key modulators of both therapeutic efficacy and toxicity. However, current research remains fragmented, focusing on isolated components rather than integrated system-level dynamics.

This leads to a critical gap: the lack of a framework to identify and model pre-toxicity states, i.e., early, subclinical biological configurations that precede overt GI inflammation. Without the ability to detect these transitional states, clinicians are unable to anticipate toxicity trajectories or stratify patients based on risk.

From a stakeholder perspective, this limitation has significant consequences:

Patients are exposed to unpredictable toxicity, with potential hospitalisation, reduced quality of life, and long-term complications.

Clinicians lack tools to guide personalised monitoring, early intervention, or treatment adaptation.

Pharmaceutical industry faces a major bottleneck in immuno-oncology development, where toxicity limits dosing, combination strategies, and overall treatment efficacy.

Healthcare systems incur increased costs due to adverse event management, hospitalisation, and suboptimal treatment pathways.

Furthermore, current data infrastructures and analytical approaches are insufficient to support integration of multimodal longitudinal data (clinical, immunological, metabolic, microbiome-derived), which is essential to move beyond static biomarker discovery towards predictive, patient-specific modelling.

Taken together, the field lacks:

Dynamic, longitudinal characterization of immunometabolic states under ICI therapy

Integrated frameworks combining multi-omics and clinical data

Predictive tools capable of identifying early risk and guiding clinical decision-making

Addressing these challenges requires a paradigm shift from static biomarker identification to data-driven, system-level modelling of immune-related toxicity, enabling early prediction and personalised management.

Please indicate which IHI specific objective(s) (SO), as described in the IHI Strategic Research and Innovation Agenda (SRIA), your idea addresses:

["SO4: exploit the full potential of digitalisation and data exchange in health care"]

"SO2: integrate fragmented health research and innovation efforts bringing together health industry sectors and other stakeholders, focusing on unmet public health needs, to enable the development of tools, data, platforms, technologies and processes for improved prediction, prevention, interception, diagnosis, treatment and management of diseases, meeting the needs of end-users"]

Please select the keywords that are most relevant to your idea:

["Oncology"]

"Immune system diseases"

"Prediction"

"Treatment"

"Digital health"]

In alignment with the IHI specific objective(s) selected above, specify the objectives of your idea:

In alignment with IHI Specific Objectives SO4 (digitalisation and data integration) and SO2 (integration of fragmented health R&I efforts), ORACLE-ICI GI aims to develop a next-generation, data-driven framework for early prediction and personalised management of immune-related gastrointestinal toxicity in patients receiving immune checkpoint inhibitors.

Objective 1 – Define dynamic immunometabolic states preceding GI toxicity

To identify and characterise early, pre-clinical immunometabolic states associated with the development of gastrointestinal immune-related adverse events (irAEs), through longitudinal integration of multi-omics data (metabolomics, microbiome, immune profiling).

Objective 2 – Develop an integrated digital predictive framework

To design and validate a digital immunometabolic model (digital twin) that integrates longitudinal clinical and biological data to:
predict the probability of GI irAEs
model time-to-event trajectories
stratify patients according to individual risk

Objective 3 – Enable clinically actionable decision support

To translate predictive outputs into clinically actionable tools supporting:
early patient monitoring
personalised intervention strategies
optimisation of treatment continuity

Objective 4 – Integrate fragmented data into a scalable platform

To establish a harmonised, interoperable platform for integration of multimodal data across centres, enabling:
standardised data collection and sharing
reproducible multi-omics analysis
scalability to other immune-related toxicities

Objective 5 – Generate translational biomarkers and enable future deployment

To identify non-invasive, clinically accessible biomarkers (blood and stool-based) associated with toxicity risk and to define a translational framework supporting:
companion diagnostic development
future clinical validation
industry uptake

3 Expected impacts to be achieved by your idea

Briefly describe the expected impacts to be achieved by your idea, ensuring that they contribute to IHI general and relevant specific objectives, as described in the IHI SRIA:

Impacts are wider long-term effects on society (including the environment), the economy and science, enabled by the outcomes of R&I investments. Impacts generally occur sometime after the end of the project, e.g. successful implementation of digital solutions supporting people-centred care.

IHI general objectives: 1. contribute towards the creation of an EU-wide health research and innovation ecosystem that facilitates translation of scientific knowledge into innovations, notably by launching at least 30 large-scale, cross-sectoral projects, focussing on health innovations; 2. foster the development of safe, effective, people-centred and cost-effective innovations that respond to strategic unmet public health needs, by exhibiting, in at least 5 examples, the feasibility of integrating health care products or services, with demonstrated suitability for uptake by health care systems. The related projects should address the prevention, diagnosis, treatment and/or management of diseases affecting the EU population, including contribution to 'Europe's Beating Cancer Plan'; 3. drive cross-sectoral health innovation for a globally competitive European health industry and contribute to reaching the objectives of the new Industrial Strategy for Europe and the Pharmaceutical Strategy for Europe.

Expected Impact

ORACLE-ICI GI will deliver a transformative framework for the early prediction and personalised management of immune-related gastrointestinal toxicity, directly contributing to IHI general objectives and Specific Objectives SO4 (digitalisation and data integration) and SO2 (integration of fragmented health R&I efforts).

Impact on healthcare systems

By enabling early prediction and risk stratification, ORACLE will reduce:

- hospitalisations and severe adverse events
- use of high-dose immunosuppression
- costs associated with late-stage toxicity management

The development of non-invasive biomarker-based tools (blood and stool) will support scalable implementation across healthcare settings, contributing to more efficient and sustainable care pathways.

Industrial and innovation impact

The project addresses a major bottleneck in immuno-oncology: the unpredictability of treatment-related toxicity. ORACLE will:

- support pharmaceutical companies in improving safety profiles of ICIs
- enable better patient stratification in clinical trials
- facilitate the development of companion diagnostics

The proposed digital immunometabolic framework represents a scalable platform that can be extended to other immune-related adverse events and therapeutic contexts, creating opportunities for future product development and industry uptake.

Scientific and technological impact

ORACLE will advance the field by moving beyond static biomarker discovery towards dynamic, system-level modelling of disease risk. Specifically, it will:

- define novel immunometabolic states associated with toxicity
- establish integrated multi-omics approaches for longitudinal patient profiling
- develop digital twin methodologies applicable to complex immune-mediated conditions

This will contribute to a deeper understanding of the biological mechanisms underlying treatment-related toxicity and open new avenues for precision medicine.

Contribution to IHI objectives

By integrating multimodal data into a digital predictive framework, ORACLE directly contributes to: SO4, by exploiting digitalisation and data exchange to enable predictive, data-driven healthcare solutions

SO2, by integrating fragmented clinical and biological data into a unified platform addressing an unmet public health need

Long-term impact

In the longer term, ORACLE will establish the foundation for:

personalised toxicity risk prediction in immuno-oncology
improved clinical decision-support systems
extension of the framework to other inflammatory and immune-mediated diseases

4 Why should your idea become an IHI call topic?

Explain why collaboration through a cross-sectoral and multidisciplinary public private partnership is needed in particular:

Why does it require collaboration among several industry sectors (e.g. pharma, vaccines, biotech, medical devices, in vitro diagnostics, radiotherapy, medical imaging health ICT)?

Why does it require collaboration between private (industry) and public partners (e.g. academia, healthcare practitioners, patients, regulators)?

Need for a cross-sectoral and public–private partnership

The complexity of immune-related gastrointestinal toxicity in immuno-oncology requires an integrated, cross-sectoral approach that cannot be achieved by any single discipline or stakeholder group alone. ORACLE-ICI GI addresses a multifactorial problem at the intersection of immunology, metabolism, microbiome biology, clinical oncology, and digital health, making a multidisciplinary and public–private partnership essential.

Need for collaboration across industry sectors

The proposed framework combines biological discovery with digital innovation and clinical application, requiring coordinated expertise across multiple industry domains:

Pharmaceutical industry is essential to provide clinical context, access to relevant patient populations, and insight into treatment mechanisms and safety challenges associated with immune checkpoint inhibitors. Industry involvement ensures that the developed predictive framework aligns with drug development needs and can be integrated into clinical trial design and therapeutic strategies.

Biotechnology sector contributes advanced platforms for high-throughput multi-omics profiling (e.g. metabolomics, microbiome analysis, immune phenotyping), enabling the generation of high-quality, standardised datasets required for robust biomarker discovery.

In vitro diagnostics (IVD) sector is critical for translating biomarker signatures into clinically actionable assays. Their involvement ensures that identified markers can be developed into scalable, regulatory-compliant diagnostic tools suitable for routine clinical use.

Health ICT and digital technology sector provides the expertise needed to develop and implement the digital immunometabolic twin, including data integration, machine learning, and predictive modelling. This component is central to transforming fragmented data into actionable insights.

The convergence of these sectors enables the transition from data generation to clinically usable tools, which cannot be achieved within a single industrial domain.

Need for collaboration between public and private partners

A strong public–private partnership is essential to bridge the gap between discovery, validation, and real-world implementation:

Academic partners bring deep expertise in mechanistic biology, immunometabolism, microbiome research, and data analysis, driving innovation and ensuring scientific robustness.

Clinical centres and healthcare practitioners are indispensable for patient recruitment, longitudinal data collection, and clinical interpretation of results. Their involvement ensures that the developed models address real clinical needs and are feasible within healthcare workflows.

Industry partners ensure scalability, standardisation, and future deployment, supporting the transformation of research outputs into products, such as companion diagnostics or clinical decision-support tools.

Patients and patient organisations contribute to defining meaningful clinical outcomes, acceptability of monitoring strategies, and real-world relevance of the proposed solutions.

Regulatory stakeholders (where relevant) are key to aligning biomarker development and digital tools with regulatory requirements, facilitating future translation into approved diagnostic or decision-support systems.

Added value of the partnership

The integration of these actors creates a unique ecosystem where:
mechanistic insights are directly linked to clinical data
digital tools are developed with real-world applicability in mind
biomarker discovery is aligned with regulatory and industrial pathways
This ensures that ORACLE moves beyond isolated research efforts towards a coherent, scalable, and impactful solution, fully aligned with IHI objectives of accelerating innovation and improving patient outcomes.

Why is the contribution of industry needed to achieve the expected impacts?

***Contribution of industry:** Large companies that are members of the IHI industry partners (i.e. COCIR, EFPIA, EuropaBio, MedTech Europe, Vaccines Europe) contribute to the programme, primarily through 'in-kind' contributions (e.g. their researchers' time, laboratories, data, compounds). At least 45% of each project's total costs have to be in-kind contribution.*

Why the contribution of industry is essential to achieve the expected impacts
The expected impacts of ORACLE-ICI GI—namely the development of clinically actionable predictive tools, improved management of immune-related toxicity, and scalable implementation of data-driven approaches—cannot be achieved without strong and active involvement of industry partners.

1. Translation from discovery to deployable solutions

While academic partners can identify immunometabolic signatures and develop predictive models, industry is essential to transform these outputs into robust, standardised, and scalable products.
In particular:

In vitro diagnostics (IVD) partners are required to convert biomarker signatures into clinically validated, reproducible assays suitable for routine use.

Pharmaceutical partners ensure that predictive tools are aligned with therapeutic strategies and can be integrated into clinical development pipelines and treatment optimisation.

Without this contribution, results would remain at the level of exploratory biomarkers, limiting their real-world impact.

2. Integration into drug development and clinical trials

A major expected impact of ORACLE is to improve the safe and effective use of immune checkpoint inhibitors. This requires:

access to clinically relevant patient populations

alignment with ongoing and future clinical trials

understanding of dosing, combination therapies, and safety constraints

These elements are uniquely accessible through pharmaceutical industry partners, who play a critical role in ensuring that predictive models are usable in real drug development and regulatory contexts.

3. Development of scalable digital and data-driven solutions

The implementation of a digital immunometabolic twin requires:

advanced data infrastructure

interoperable systems

machine learning pipelines deployable in clinical environments

Health ICT and digital industry partners are essential to ensure that models are:

scalable beyond individual research settings

compliant with data standards and regulatory requirements

transferable across healthcare systems

Without industry involvement, digital tools would remain proof-of-concept rather than actionable solutions.

4. Regulatory alignment and market uptake

To achieve long-term impact, outputs such as predictive biomarkers and decision-support tools must:

meet regulatory standards

be integrated into clinical workflows

demonstrate value for healthcare systems

Industry partners bring critical expertise in:
regulatory strategy
quality assurance and standardisation
pathways for commercialisation and adoption

This ensures that project outcomes can move from research to real-world implementation.

5. Maximising impact across stakeholders

The involvement of industry is also essential to ensure that the project delivers value across all relevant stakeholders:

for patients, by enabling safer and more personalised treatment

for clinicians, by providing actionable decision-support tools

for pharmaceutical companies, by improving treatment optimisation and reducing toxicity-related limitations

for healthcare systems, by reducing costs associated with severe adverse events

Industry participation is therefore not only complementary but indispensable to achieve the full impact of ORACLE-ICI GI. It enables the transition from discovery to implementation, ensuring that scientific insights are translated into clinically usable, scalable, and sustainable solutions in line with IHI objectives.