All information regarding future IHI Call topics is indicative and subject to change. Final information about future IHI Calls will be communicated after approval by the IHI Governing Board.

Topic 2: Understanding how infections foster and induce non-communicable diseases

Expected outcomes

The action under this topic must contribute to all of the following outcomes:

1. Accelerated access to interventions:

A better understanding of the potential causal links between infections and non-communicable diseases and their accompanying biomarkers could:

- more precisely define a person's level of risk for long term health complications
- lead to the development of better diagnostic approaches such as early detection and monitoring strategies that will make preventive medicine more effective for the benefit of patients.

2. Development of vaccine strategies:

A better understanding of the potential causal links between infections and chronic diseases could lead to the generation of vaccine strategies with the capacity to prevent the development of one or more chronic diseases over the course of a person's life, significantly reducing the long-term burden of disease.

3. Early intervention strategies:

A clear understanding of the mechanisms of action used by infections to cause chronic diseases could more precisely define which cellular processes, metabolic pathways, enzymatic activities, and gene expression changes should be the focus of early intervention strategies. These strategies could halt or potentially reverse the progression of chronic diseases and would aim to replace many current treatments that only manage symptoms.

4. Improved quality of life:

A better understanding of the potential causal links between infections and chronic diseases, as well as the biomarkers and mechanisms of action involved, could more precisely define development strategies for prophylactic vaccines, early diagnosis, and early intervention therapeutics that could significantly improve the quality of life of individuals by preventing health decline and avoiding escalating healthcare costs.

5. Adoption of innovative approaches:

The establishment of a more systematic collaborative approach to mining existing research cohorts and biobanks to determine potentially causal links between infections and chronic diseases by combining multi-omics, artificial intelligence, and pre-clinical model verification to potentially accelerate the development of prophylactic vaccine, early diagnostic and early intervention strategies.

Scope

Infectious agent (IA) and non-communicable disease (NCD) interplay has driven effective prevention strategies. However, a growing field of research suggests that there are many unexplored connections between IAs and NCDs that could be utilised to develop better diagnostic, preventative, and therapeutic approaches to burdensome diseases. A cohort analysis identified 96 distinct NCDs correlated to IAs [1]. Other cohort analyses identified neurodegenerative diseases, defined as the progressive loss of neurons

resulting in loss of motor function or cognition, with links to viral infection [2], including Alzheimer's disease, amyotrophic lateral sclerosis, dementia, vascular dementia, Parkinson's disease and multiple sclerosis. IA links to cardio-metabolic NCDs such as HSV (Herpes simplex viruses) and coronary artery disease [3], CMV (cytomegalovirus), EBV (Epstein-Barr virus), VZV (varicella-zoster virus), influenza and parvovirus B19 have been shown to induce cardiomyopathies [4], and *H. pylori* infections may drive myocardial infarction [5].

While cancer, autoimmune, neurological, and cardiometabolic NCDs all have significant links to IAs, the scope of this topic is focused on neurodegenerative and cardiometabolic diseases, which carry significant disease burdens, potentially caused by direct, immune-mediated, or microbiota-gut-brain-axis damage/dysregulation, and lack early intervention strategies. Via the action funded under this topic, Europe's research community could potentially find more infection-based approaches for diagnosing, preventing, and treating NCDs.

The action funded under this topic aims to identify potential causal links and biomarkers leading to mechanism of action (MoA) studies. The literature [6][7][8] demonstrates research cohorts' utility in exploring the interplay between IAs and NCDs, increasing the likelihood of success. For instance, causative links were determined for oncolytic viruses, EBV [9] and human papillomavirus (HPV) [10], using Hill's causation criteria. The action funded under this topic should:

- develop methodologies to demonstrate non-carcinogenic IA to NCD causal relationships;
- consolidate data in one repository of IA/NCD causal relationships, biomarkers, and MoAs.

Applicants are expected to define a strategy to assess non-carcinogenic infection-associated NCD causative links and related biomarkers, incorporating a modelling perspective alongside AI-assisted data mining, appropriate statistical methodologies, and prioritisation approaches for the exploration of mechanisms of action (MoA). Applicants should also detail their methodological approach and data collection procedures, providing preliminary data to show potential for success and strategies for mitigating main methodological risks and limitations.

- As part of the first objective of proposed activities, applicants should work toward generating robust evidence toward proof of causality rather than only strengthening the known associations of IAs and NCDs. Applicants should take advantage of the available research cohorts, biobanks, and exposome data, including microbiota-gut-brain-axis samples from large general population studies, neurodegenerative disease cohorts, or cardiovascular disease cohorts. Association strength, consistency, and specificity should be indicated by similarity of measurement across different cohorts. Insurance data could be used to analyse temporality where infection occurs prior to medically attended disease. Cohorts from patients that have received transplants or immunosuppressive treatments with longitudinal data could demonstrate temporality and biological gradient effects from opportunistic infections, the strength of the immune response to IAs to demonstrate elements of causality driven by immune-mediated damage. Selection of research cohorts should prioritise data sets with populations from diverse ethnicities, socio-economic statuses, and balanced for gender. Applicants should develop/use pre-clinical models for causal link plausibility verification. Applicants are expected to follow and comply with all relevant ethical and data privacy standards for research. Applicants are also expected to conduct their consortium work with full transparency, clearly communicating data provenance, model interpretability, traceability, and limitations, especially when using AI modelling and decision-making.
- The second objective is identifying novel biomarkers, ideally to classify associated IAs, to better stratify individuals (children, adults, the elderly) who are at risk of developing NCDs post infection. This could be done using immune or metabolic markers, host and microbiome metabolomics, sequencing, etc. This pillar can utilise the same cohorts, biobanks, and exposome data used for pillar 1 if sufficient, but should supplement with additional cohorts where needed. To ensure outcomes within the 5-year timeframe of the project, the launch of new prospective

cohorts is out of scope but limited recruitment to fill specific data gaps in existing cohorts could be considered.

- The third objective is to define the MoA that IAs use to drive NCD development. MoA identification would require tissue samples from pillars 1 & 2, as well as pre-clinical or *in silico* experimentation according to the targeted conditions or diseases.

No product development is expected from this action in the proposed timeline.

Applicants are expected to consider the potential regulatory impact of the results and, as relevant, develop a regulatory strategy and interaction plan for generating appropriate evidence as well as engaging with regulators in a timely manner. Additionally, applicants should anticipate engaging regional healthcare systems and authorities to prepare for clinical implementation and outcome acceptance when necessary.

Applicants should include in their proposal a strategy to ensure sustainability of the outputs of the project beyond the funding period.

The funded project should explore synergies with the funded project from IHI Call 11 Topic 'Towards precision medicine: platform for transdiagnostic stratification of brain dysfunction' (once the funded projects are awarded) to increase impact. Applicants are also expected to consider synergies with other relevant global, European and national initiatives including projects generated from Cluster Health topic "Relationship between infections and non-communicable diseases (HORIZON-HLTH-2023-DISEASE-03-07).

Expected impacts

The action under this topic is expected to achieve the following impacts:

- accelerate the EU's access to more cost-effective interventions for the most burdensome diseases;
- decrease the risk of developing serious diseases later in life by defining specific prevention strategies;
- contribute to halting the progression of chronic diseases by using biomarkers in early interventions;
- improve the quality of life for healthy individuals and patients by preventing further health decline, avoiding escalating care costs, and properly stratifying individuals and patients earlier in the diagnostic pathway;
- accelerate the adoption of innovative approaches to diagnostic, preventative, and therapeutic strategies, strengthening the EU positioning as an innovator in healthcare.

The action will also support the EU political priority to boost European competitiveness and contribute to a number of European policies/initiatives, which include the European Commission's European Health Data Space Regulation (EHDS)[1] and the EU Artificial Intelligence Act[2].

Why the expected outcomes can only be achieved by an IHI JU action

Elucidating the potentially complex relationships between infectious agents and non-communicable diseases can take decades using traditional research structures. In order to accelerate the understanding of how infectious agents drive non-communicable diseases, a multi-disciplinary approach is necessary to bring together multi-omics data, AI modelling, and existing cohort resources. This will shorten the timelines required to design appropriate studies and analyse longitudinal samples, making translational outcomes for the work feasible in the timeframe of a project. As many of these disease areas do not

[1] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=OJ:L_202500327
[2] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32024R1689

traditionally overlap with infectious disease research, the understanding of the interplay between infection and chronic disease also requires a dedicated partnership between academic researchers with expertise in microbiology, multi-omics approaches and NCDs and private companies currently pursuing preventative and therapeutic options for the selected disease areas. This new collaborative partnership could be an extremely fruitful way to develop preventative and therapeutic interventions over the long-term.

The greatest advantage of the IHI model is that it increases the access of all players in the ecosystem to existing research cohorts, biobanks, and exposome datasets, including the microbiome. Such datasets, whether privately held by industry players or largely publicly available, may need to be compared directly to effectively extract biomarkers, pathways activated and novel pathogen information. Additionally, biomarker identification in at-risk populations may lead to the development of diagnostic strategies for early intervention. The unravelling of the MoAs will inform on the right clinical endpoint diagnostics in time for clinical development of new prophylactic/therapeutic strategies.

Pre-identified industry consortium

The pre-identified industry consortium that will contribute to this cross-sectoral IHI JU project is composed of the following medical technology industry beneficiaries (‘constituent or affiliated entities of private members’):

- Gates Ventures LLC
- Sanofi (Lead)

In addition, the following philanthropic organisation will participate in the IHI JU action:

- Novo Nordisk Foundation

In the spirit of partnership, and to reflect on how IHI JU two-stage call topics are built upon identified scientific priorities agreed together with a number of proposing industry beneficiaries (i.e. beneficiaries who are constituent or affiliated entities of a private member of IHI JU), it is envisaged that IHI JU proposals and actions may allocate a leading role within the consortium to an industry beneficiary. Within an applicant consortium discussing the full proposal to be submitted for stage 2, it is expected that one of the industry beneficiaries may become the project leader. Therefore, to facilitate the formation of the final consortium, all beneficiaries, affiliated entities, and associated partners are encouraged to discuss the weighting of responsibilities and priorities regarding such leadership roles. Until the role is formalised by execution of the Grant Agreement, one of the proposing industry beneficiaries shall, as project leader, facilitate an efficient drafting and negotiation of project content and required agreements.

Indicative budget

- The maximum financial contribution from the IHI JU is up to EUR 7 127000.
- The indicative in-kind and financial contributions from industry beneficiaries is EUR 8 167 000.
- The indicative in-kind and financial contributions from the philanthropic organisation is EUR 1 020 000.

Due to the global nature of the participating industry partners, it is anticipated that some elements of the contributions will be in-kind contributions to operational activities (IKOP) from those countries that are neither part of the EU nor associated to the Horizon Europe programme.

The allocation of the EUR 1 000 000 financial contribution (FC) from industry beneficiaries will be decided by the full consortium at the second stage when preparing the full proposal.

The allocation of the EUR 1 000 000 financial contribution (FC) from the philanthropic organisation will be decided by the full consortium at the second stage when preparing the full proposal.

The indicative in-kind contribution from industry beneficiaries may include in-kind contributions to additional activities (IKAA).

Indicative duration of the action

The indicative duration of the action is 60 months.

This duration is indicative only. At the second stage, the consortium selected at the first stage and the predefined industry consortium may jointly agree on a different duration when submitting the full proposal.

Contribution of the pre-identified industry consortium

The pre-identified industry consortium expects to contribute to the IHI JU project by providing the following expertise and assets:

1) Expertise and Assets:
    - **Expertise and access to cohorts and patients' data in Disease Areas of Interest**:
        - Neurodegenerative diseases (e.g., Parkinson's disease, Alzheimer's disease); especially access to the European Platform for Neurodegenerative Diseases (EPND) data hub
        - Cardiometabolic/cardiovascular diseases.
    - **Pillars of Interest**:
        - Infectious agent target discovery expertise and methodology;
        - Tools and methodology for biomarker identification (infectious agents & health conditions);
        - Mechanisms of action.
    - **Resources**:
        - Data and cohort access;
        - Biomarker identification (multi-omics);
        - Immune profiling;
        - Microbiome expertise;
        - *In silico* modelling, preclinical investigations *in vitro* and *in vivo*;
        - Federated analyses;
        - Internal expertise, wet lab work;
        - Advanced multi-omics including immuno-proteomics, spatial proteomics, plasma proteomics, bioinformatics;
        - Expertise in analytics;
        - Initiatives focusing on the better use of health data and cohorts;
        - Knowledge transfer and early detection initiatives;
        - Artificial intelligence and machine learnings.
2) General Contributions:
    - **Data and cohort Access**: Access to large cohorts and biobanks for data mining and biomarker identification;

- **Biomarker identification**: Expertise in multi-omics, immune profiling, and advanced proteomics, including artificial intelligence/bioinformatics;
- **Therapeutic expertise**: Small molecule drug discovery, vaccines, and therapeutic interventions;
- **Knowledge transfer**: Initiatives focusing on health data usage, early detection, and disease associations.

These contributions aim to leverage existing resources and expertise to advance the project's goals in understanding and addressing the interplay between infectious agents and NCDs.

Applicant consortium

The first stage applicant consortium is expected, in the short proposal, to address the scope and deliver on all the expected outcomes of the topic, taking into account the expected contribution from the pre-identified industry consortium and contributing partner(s).

This may require mobilising the following expertise and/or resources:

Academic institutions can provide complementary expertise in neurodegenerative and cardiometabolic/cardiovascular diseases, as well as access to innovative assets and methodologies such as the following list of suggested, non-exhaustive capabilities:

Expertise:

1. **Infectious diseases:**
   - Microbiology expertise in virology, bacteriology or parasitology;
   - Preclinical model of infection to determine causality, pathogenesis and mechanisms of action;
   - Omics expertise: sequencing, spatial transcriptomics, proteomics to identify the infectious agents;
   - Immunology to study serostatus, immune profiling, cytokines and single cell ribonucleic acid (RNA) sequencing to understand the pathogenesis and mechanisms of action.
2. **Neurodegenerative diseases, cardiometabolic/cardiovascular**:
   - Cellular and molecular biology to understand molecular mechanisms;
   - Expertise in neuroscience, cardiometabolism to understand pathogenesis, especially the microbiota-gut-brain axis for neurodegenerative diseases;
   - Innovative preclinical models including organ-on-chip and/or organoid to understand mechanisms and pathogenesis;
   - Multi-omics expertise such as sequencing, epigenetics, transcriptomics, proteomics, lipidomics, metabolomics to identify biomarkers and expertise to understand pathogenesis and mechanisms of action.
3. **Bioinformatics and biostatistics**:
   - Expertise in data analysis, integration and modelling;
   - Original data mining techniques;
   - Statistical methodologies for data interpretation.
4. **Biomarker discovery**:
   - Expertise in identifying and validating biomarkers;
   - Expertise in designing, monitoring and diagnostics assay.

Assets:

1. **Large patient cohorts**:
   - Access to cohorts, databases, and patients;

- Access to samples, databases, and cohorts available from relevant public-private European partnership platforms in neurodegenerative and cardiometabolic diseases.

2. **Enhanced Consortium Capabilities**:
   - Improved understanding and addressing of neurodegenerative and cardiometabolic/cardiovascular diseases;
   - Access to digital twins for understanding how infections could increase risk for NCDs post infection.

At the second stage, the consortium selected at the first stage and the predefined industry consortium will form the full consortium. The full consortium will develop the full proposal in partnership, including the overall structure of the work plan and the work packages, based upon the short proposal selected at the first stage.

Dissemination and exploitation obligations

The specific obligations described in the conditions of the calls and call management rules under 'Specific conditions on availability, accessibility and affordability' do not apply.

Eligibility for funding

The specific conditions whereby applicants may receive funding in Call 11 will be published together with the Call 11 topic text.

References

[1] Lape, Michael et al. "After the Infection: A Survey of Pathogens and Non-communicable Human Disease." medRxiv : the preprint server for health sciences 2023.09.14.23295428. 30 Dec. 2024, doi:10.1101/2023.09.14.23295428. Preprint.

[2] Levine, Kristin S et al. "Virus exposure and neurodegenerative disease risk across national biobanks." Neuron vol. 111.7 (2023): 1086-1093.e2. doi:10.1016/j.neuron.2022.12.029.

[3] Roivainen, M et al. "Infections, inflammation, and the risk of coronary heart disease." Circulation vol. 101,3 (2000): 252-7. doi:10.1161/01.cir.101.3.252.

[4] Martens, Colton R, and Federica Accornero. "Viruses in the Heart: Direct and Indirect Routes to Myocarditis and Heart Failure." Viruses vol. 13,10 1924. 24 Sep. 2021, doi:10.3390/v13101924.

[5] Zito, Francesco, et al. "Helicobacter pylori infection and the risk of myocardial infarction: Role of fibrinogen and its genetic control." Thrombosis and Haemostasis, vol. 82, no. 07, 1999, pp. 14–18, https://doi.org/10.1055/s-0037-1614622.

[6] Lape, Michael et al. "After the Infection: A Survey of Pathogens and Non-communicable Human Disease." medRxiv : the preprint server for health sciences 2023.09.14.23295428. 30 Dec. 2024, doi:10.1101/2023.09.14.23295428. Preprint.

[7] Levine, Kristin S et al. "Virus exposure and neurodegenerative disease risk across national biobanks." Neuron vol. 111.7 (2023): 1086-1093.e2. doi:10.1016/j.neuron.2022.12.029.

[8] Miklossy, Judith. "Alzheimer's disease - a neurospirochetosis. Analysis of the evidence following Koch's and Hill's criteria." Journal of neuroinflammation vol. 8 90. 4 Aug. 2011, doi:10.1186/1742-2094-8-90.

[9] Sugden, Bill. "Epstein-Barr virus: the path from association to causality for a ubiquitous human pathogen." PLoS biology vol. 12,9 e1001939. 2 Sep. 2014, doi:10.1371/journal.pbio.1001939.

[10] Bosch, F X et al. "The causal relation between human papillomavirus and cervical cancer." Journal of clinical pathology vol. 55,4 (2002): 244-65. doi:10.1136/jcp.55.4.244.

Glossary

Acronym	Meaning
CMV	CytoMegaloVirus
EBV	Eibstein Barr Virus
EMA	European Medicines Agency
FC	Financial contribution
IHI JU	Innovative Health Initiative Joint Undertaking
HSV	Herpes Simple Viruses
IA	Infectious agent
IKKA	in-kind contributions to additional activities
MoA	Mechanism of action
NCD	non-communicable disease
VZV	Varicella Zoster Virus
IKAA	in-kind contributions to additional activities
IKOP	in-kind contributions to operational activities