LUCIA Understanding Lung Cancer related risk factors and their Impact

Horizon Europe Grant Agreement Number: 101096473

Deliverable Number	D6.11
Deliverable Title	Policy brief formulating recommendations based on the research and innovation strand of the 'Understanding' annual cluster meeting-M12
Due date of deliverable	29.02.24
Actual Submission Date	28.02.24
Responsible partner	TECH
Contributors	All partners, projects within 'Understanding' and 'Prevention' clusters
Revision (draft, 1, 2, ...)	1.0
Dissemination Level	Public

Start Date of the project: January 1, 2023
Duration: 48 months

Document information\ Revision History

Description \ Status	Revision date	Authors
1st Draft	07.02.24	Yoav Broza (LUCIA)
2nd Draft	14.02.24	Yoav Broza (LUCIA), Adrián López Canosa (MELCAYA), Marie Nabbe (LUCIA), Clara Frick (LUCIA), Antonio Jesus Diaz Honrubia (LUCIA), Ieronymos Zoidakis (ELMUMY)
3rd Draft	19.02.24	Yoav Broza (LUCIA), Jonathan Wallace (LUCIA), Marie Nabbe (LUCIA), Iván Macía Oliver (LUCIA)
Final	22.02.24	Yoav Broza (LUCIA)

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Acronyms & Abbreviations

Term	Description
AI	Artificial Intelligence
DMP	Data Management Plan
EU	European Union
FAIR	Findable, Accessible, Interoperable, Re-usable
GA	Grant Agreement
GDPR	General Data Protection Regulation
HTA	Health Technology Assessment

Executive summary

This report summarises the Policy brief formulating recommendations based on the research and innovation strand of the 'Understanding' annual cluster meeting-M12. The goal of this deliverable is to provide an annual policy brief with recommendations on R&I on the macro scale, i.e., from the prospective of 'Understanding' (Risk Factors and Determinants) Cluster. This policy brief formulates recommendations to foster collaboration, focusing on data/material management, technological advancements, risk factor analysis, and policy implementation, based on the research and innovation strand of the 'Understanding' annual cluster meeting-M12. This deliverable raises common barriers and potential recommendations as well as practical recommendations for the near future.

1 Introduction to EU Mission on Cancer

The European Union (EU) has put forward the *EU Missions* as a novelty of the *Horizon Europe* research and innovation programme for 2021-2027. Their aim is to bring concrete solutions to some of the greatest challenges of our time, having ambitious goals that will deliver tangible results by 2030. The *EU Mission on Cancer*[1] has the ambitious goal (in combination with *Europe´s Beating Cancer Plan*) of improving the lives of more than 2 million people by 2030 through prevention, cure and, for those affected by cancer (including their families), to live longer and better. The *Cancer Mission* board estimates an improved reduction in the expected mortality rates between 2021 and 2030 with a 20% reduction for females and a 40% reduction for males, rather than the baseline scenario which estimates a reduction of 14% and 30% for females and males, respectively.

The specific objectives of the mission are as follows[2]:

1. *Understanding:* despite huge advancements in the field, much more research is still needed to understand why certain people, gender and age groups are at a higher risk of developing cancer, suffering from side-effects, etc. All these uncertainties limit the design of effective cancer prevention programmes as well as healthcare solutions adapted to each patient. Moreover, cancer research, healthcare providers, patient communities and industries are fragmented in the EU and do not benefit from patient engagement.
2. *Prevention, screening and early detection:* this is the most cost-efficient and long-term cancer control strategy. It is known that 40% of cancers could be prevented, but a more personalised understanding of the disease is needed as well as improvements in the existing prevention programmes and general health literacy among EU citizens.
3. *Diagnosis and treatment:* the time to cancer diagnosis is generally too slow or early diagnostic tests do not exist. The current best practices and standards of care are not

consistently implemented across Europe, which results in unacceptable differences in standards of care and outcomes between Member States or socio-economic backgrounds. In addition, many patients do not have access to the latest personalised treatments across Europe (immunotherapy for instance) or are not empowered to make informed decisions on their treatment.

4. *Quality of life:* there is a clear lack of understanding or sufficient consideration of patient needs. Stigma affects patients and survivors of cancer. It can negatively impact their career and creates challenges in obtaining health insurance and mortgages, generating a substantial burden for patients, their families and countries' health systems.

2 Projects in the *Understanding (risk factors & determinants)* cluster

The LUCIA Project is part of a group of five projects that received funding from the European Commission through the *Horizon Europe* programme (*HORIZON-MISS-2021-CANCER-02-03*) to work on the first objective of the *Mission Cancer* programme, which is aimed at better understanding the impact of risk factors and health determinants on the development and progression of cancer. These projects are:

- **GENIAL:** Understanding gene environment interaction in alcohol-related hepatocellular carcinoma[3]
- **LUCIA**: Understanding lung cancer related risk factors and their impact[4]
- **ELMUMY:** Elucidation of risk factors and health determinants associated with progression of monoclonal gammopathies to multiple myeloma[5]
- **DISCERN:** Discovering the causes of three poorly understood cancers in Europe (renal, pancreatic and colorectal)[6]

- **MELCAYA:** Novel health care strategies for melanoma in children, adolescents and young adults[7]

The main goal of this cluster is therefore to support the mission objective of *Understanding* cancer, create added value, establish a policy feedback loop and increase the impact of the EU funding.

3 Policy brief formulating recommendations

The M12 'Understanding' (Risk Factors and Determinants) annual cluster meeting was organised by the LUCIA project and held in San Sebastian, Spain, on 7 September, 2023. The meeting discussed key areas for scientific collaboration within the cluster that were identified and reported in D6.6. This policy brief formulates recommendations to foster collaboration, focusing on data/material management, technological advancements, risk factor analysis, and policy implementation. based on the research and innovation strand of the 'Understanding' (Risk Factors and Determinants) annual cluster meeting-M12

3.1 Sharing and Agreeing on Common Practices for Data/Material Management:

The cluster produced the common deliverable on the data mangmeant plan (DMP) for the first year (specifically for LUCIA numbered D7.1). Within this deliverable topics as : Accessibility and repository (e.g. UNCAN.eu – also presented and initiated during the annual meeting); Interoperability; Reusability, etc. were included.

The main points for collaboration identified so far between the projects within the cluster are the following:

- Data re-use and generation & relation to the projects' objectives
- FAIR data management
- Data management board, which has been established

Common barriers: One of the problems regarding data is the heterogeneity among data management protocols in different healthcare institutions and across countries.

Recommendation:

- Establish standardised protocols for data/material management and data sharing best practices to ensure transparency, ethical considerations, and adherence to privacy regulations.
- Facilitate the creation of a centralized repository for sharing datasets, promoting seamless collaboration.
- Promote and adopt common nomenclature and establish common data exchange protocols.
- Promote harmonization of GDPR understanding across countries, and stakeholders (e.g. lawyers, data managers, ethical committees…), and the use of one-time consent and/or derogation to allow research without mandatory patient consent.

Practically:

- Organize meetings/workshops to discuss the legal and ethical basis and framework for reusing data and biological samples across institutions, focusing on risk factors and relevant clinical information for future research.
- Create links across different data sources while identifying methodologies and tools for joint exploitation.
- Implementing common data management protocols of progressively mandatory implantation would significantly enhance data quality. Moreover, common data models and software, together with regulations for mandatory data storage, particularly for patients with specific diseases, would ensure data homogenisation, facilitating more consistent data sets and thus knowledge extraction. Additionally, European centralized databases, accessible only with authorization and ensuring

preservation of patient anonymity, to which healthcare institutions must report these data, would provide more complete data sets to perform studies with sufficient sample sizes.

- Editing a clinical guideline related to risk factor information from the project in the cluster.

3.2 Collaborations in Technology, Tools, Knowledge, and Best Practices for Data Exploitation and Computational (AI) Modelling:

Common barriers: There is an issue with data protection and general data access. Whilst new strategies to overcome these barriers include federated learning and generating synthetic data that mimics real data, with a promise to expedite processes. However, much of the technology is yet in development and it is often taken as a complex indirect route to avoid data sharing and data-driven research. Furthermore, federated learning difficult explainability, trustworthiness and validation of models as characteristics of the training data are usually unknown, and synthetic data generation still needs large amounts of real training data and acceptance in some research scenarios and clinical studies.

Efforts still need to be directed towards improving data accessibility and the collection and sharing of data for the benefit of research and the society, as many large projects suffer difficulties in this regard as organization struggle with barriers to data access. Furthermore, it is necessary to involve all relevant sectors, including various professionals, patient groups/organisations, and policymakers.

There is a need to have access to various types of data, encompassing not only information directly related to patients but also registering the actual incidence based on the location where the diagnosis occurs. The reconstruction of events and follow-ups over time and across different places will enhance the detection and understanding of cancer risk factors. This also applies to various habits and lifestyles, where the generation of data, possibly incorporating

high-frequency data collected from a variety of sensors, wearables or apps, could provide valuable insights. Currently, there is a lack of information in this regard, emphasising the necessity for both the generation of relevant datasets and improved data availability.

Recommendations:

3.2.1 Information and Knowledge Models:

Develop a framework for standardised information and knowledge models, fostering interoperability, consistently representing cases and outcomes, and facilitating cross-disciplinary collaborations that should be complemented with reference implementations for future developments.

There is a need for systemic assessment of explainability and interpretability of risk models used in the screening and early detection of cancer. To enhance uptake and trust of such models among healthcare professionals and patients, interpretability needs to be prioritised when developing innovative AI-based models.

Practically, this will result in composing a white paper on AI-powered technologies to educate the public about exactly what AI is, and its role and impact within the broader scope of the technologies implemented in the cluster projects.

Public and semantic databases would help researchers to model and extract new knowledge from the existing data. This aligns with European common databases, which could be complemented by semantic graphs. Additionally, developing new methodologies that aim to extend the common graph could be elaborated so that specific knowledge from other projects can be easily added and reused in the future.

Finally, creating an online repository and a regulation requiring institutions who train AI models related to the aforementioned databases to push them into that repository would ensure transparency and provide a clear knowledge of the current state of the work. These

measures would enable any new European-funded project related to risk factor discovery to include these data sources as mandatory components among the data to be used in the project.

3.2.2 Methodologies, Technologies, and Tools for Data Integration, Feature Extraction, and Classification:

Encourage collaborative projects to advance methodologies, technologies, and tools for efficient data integration, feature extraction, and classification. Foster the development of open-source tools and platforms.

Searching information, patterns, and relevant data related to biological and environmental factors, and finding connections between them, is expected to yield a comprehensive and central knowledge base. This, in turn, is anticipated to generate new predictions and formulate hypotheses.

There is a need for more frequent rigorous testing and increased external validation of risk prediction models. To help ensure that the models are not only accurate within the study population but also generalizable across diverse populations and healthcare settings, projects could strive to conduct thorough validation using independent datasets as well as prospective validation at multiple sites.

Initiatives should be explored to access databases of collaborators in other countries in order to facilitate the development of AI tools across the cluster to leverage the cluster work.

3.2.3 Development of New Statistical and/or Computational (AI) Models for Personalized Prediction of Risk:

Support joint initiatives within the cluster for creating innovative statistical and computational models, emphasising personalised risk prediction. Establish a platform for sharing model architectures and methodologies. The first step could be to organise regular

meetings among the AI teams from each project to facilitate sharing and cross-comparison of approaches based on collected data.

3.2.4 New Technologies and Tools for Data Analytics, Hypothesis Generation, and Discovery:

Facilitate interdisciplinary collaboration to develop cutting-edge technologies and tools for data analytics, hypothesis generation, and discovery. Encourage joint research projects and promote knowledge sharing.

To assist in evaluating the effectiveness and ethical implications of innovative technologies, develop a common framework to guide the life cycle assessment of innovations and provide guidelines on how to transfer/adopt results in EU healthcare systems under the new health technology assessment (HTA) Regulation.

Continuous improvement of the proposed frameworks based on emerging technologies is needed.

3.3 Sharing and Cross-Comparison of Risk Factors and Molecular Features:

All projects share a focus related to analysing omics information to understand disease onset. Many projects also have an interest in characterising the molecular features and biological pathways driving a change from healthy or precancerous lesions to cancer. Common barriers relate to the lack of adequate infrastructure for data analysis across projects (centralised vs federated, etc.) and limited computational capacity.

Recommendation: Establish a collaborative platform for researchers to share and cross-compare data on risk factors and molecular features. Initially it could be achieved by organising regular meetings between relevant project representatives in charge of this topic, in order to share and perform a cross-comparison of the results on identified gene mutations, environmental factors and molecular characteristics, with the aim of finding cross-cancer

features, genetic risk factors and therapeutic targets. This will enhance our understanding of cancer heterogeneity and improve risk assessment models.

Addressing differential probabilities of risk factors adds value to the cluster projects. This could be achieved by a joint comparison and common publication.

Highlight common background questions (mechanisms, molecules) between cancers studied within the cluster, and define pan-cancer features in a common biological context.

3.4 Cross-Comparison and Integration of Risk Stratification/Early Diagnosis Tools:

Introducing new technologies to study risk factors in projects is challenging. The fact that it involves clinical studies with tools that are not yet CE marked (at the research stage) raises hurdles for achieving the ethical approval. Moreover, there is no one specific regulation and as such each country involved in the study has its own regulations and demand. As an example, within the current cluster, MELCAYA and LUCIA have initiated collaboration on non-invasive tools, specifically skin measurement. In this collaboration, common information was gathered and shared between the projects and specifically between the representatives dealing with ethical information and approvals as well as sharing technological information. This aided the submission of ethical approval across both projects.

Recommendation:

1. Facilitate collaborative efforts to cross-compare and integrate risk stratification and early diagnosis tools. Develop frameworks for standardized assessment and validation of these tools to enhance their clinical applicability.
2. To aid in the process of ethical approvals across different countries for different technology/clinical supported studies, produce a common outline format for the European Commission that can support submission to EU ethical agencies. This format will be part of the initial Grant Agreement (GA) for each project and as such could aid and speed up this process particularly when a number of countries are involved.

3.5 Sharing of Best Practices on Implementation of Healthcare Policies:

Effective policy implementation is crucial for ensuring the delivery of high-quality services, improving patient outcomes, and optimizing resource utilization. However, the complexity of healthcare systems, coupled with diverse socioeconomic and cultural contexts, presents challenges in translating policies into actionable strategies.

Possible common barriers for sharing best practices include:

- Language can make the transmission of knowledge and best practices more difficult. Patients and healthcare professionals do not always speak English, and even when they do, they may not be fluent. Some terms may also not exist across languages and projects do not necessarily have a translator among partners so there may be biases on this point.
- A lack of consensus on the optimal risk prediction model and uncertainties surrounding their robustness means strategies to pre-select participants for screening have not yet been implemented in many EU countries.
- One of the aims in the cluster projects is to share best practices in target population management. Therefore, the database should collect data to validate the implementation of best practices and ensure the accuracy and relevance of all data. In some cases, within the Understanding cluster, the aim is to design and implement public health strategies for rare or ultra-rare diseases (as in the MELCAYA project). Policy design and implementation for ultra-rare disease is a novel area, in many cases still under investigation, and thus not typically addressed in the classical policy development approach.
    - How to gather comprehensive data/information to build policy and ethical approaches is difficult.

- How to prioritize the design and implementation of policies for rare and ultra-rare disease over other diseases (including other types of cancers) is still a pending subject. Therefore, it is very difficult to identify any emerging initiatives in the studied countries.
- How to translate findings from our research into practical health policies and strategies that can be implemented across diverse EU markets and how to address medium and long-term societal impacts.
- Harmonisation of policies across different EU countries to ensure equitable policies implementation.
- To design healthcare strategies that truly understand the patient's journey and address their needs. Since the prevalence, in some cancer diseases, is very small, pathways may be heterogeneous among patients.
- Assessing the effectiveness and ethical implications of innovative technologies for those projects developing new technologies. Since technologies being developed for understanding, early diagnosis and prevention are very novel and different from traditional health technologies used in healthcare systems, this poses challenges in capturing the criteria/elements to assess their effectiveness as well as how to capture their ethical implications.

Recommendation: Create a knowledge-sharing platform for healthcare policymakers to exchange best practices in cancer prevention, diagnosis, and treatment. Encourage collaborative projects aimed at implementing evidence-based policies for better patient outcomes.

Practically this wil be achieved through organising dedicated meetings during the final year of the projects, when most results should be available, to consolidate clinical guidelines for cancer prevention. The aim is to then present these findings to key EU stakeholders for discussions on their implementability across different EU healthcare systems.

In the final stages of the projects, once technology assessment tools have been evaluated/developed, organise a meeting (or dedicated slot in the annual meeting) to present the findings to other projects and discuss how to use these for the evaluation of the technologies developed within their respective projects.

4 Conclusions

Advancing cancer research and innovation requires collective efforts, strategic investments, and sustained collaboration. By implementing the recommendations outlined in this policy brief, we can accelerate progress towards a comprehensive understanding of cancer and the development of effective strategies for prevention, early detection, and treatment.

In this report, we have presented the main barriers and relevant recommendations based on the information gathered during the first year of the ”Understanding (risk factors & determinants)“ cluster projects. These findings could serve as the basis for future directives in the cluster work and mission.

5 References

[1] EU Mission on Cancer webpage

[2] European Commission, *European Mission on Cancer Implementation Plan*, September 2021.

[3] GENIAL factsheet in CORDIS webpage

[4] LUCIA factsheet in CORDIS webpage

[5] ELMUMY factsheet in CORDIS webpage

[6] DISCERN factsheet in CORDIS webpage

[7] MELCAYA factsheet in CORDIS webpage