

Topic: Real-world clinical implementation of liquid biopsy

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Topic details

Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages
IMI2 Strategic Research Agenda - Axis of Research	Adoption of innovative clinical trial paradigms
IMI2 Strategic Research Agenda - Health Priority	Cancer

Specific challenges to be addressed by public-private collaborative research

Advancing personalized approaches in cancer therapy, aiding identification and adaptation of treatment strategies for improved outcomes depends on clinical implementation of novel diagnostic technologies. Most precision medicine strategies are based on molecular stratification to select patients. Analysis of circulating nucleic acids in plasma, e.g. circulating tumour DNA (ctDNA) or exosomal RNA species, are options for minimally invasive Liquid Biopsy. While the spatial information and cellular resolution of a tissue biopsy remain highly important for characterization of the primary tumour, Liquid Biopsy can offer an integrated view of a tumour and its metastatic lesions that may better reflect the heterogeneity of the disease. Thereby, therapeutically targetable driver mutations of tumour growth and metastatic progression can be identified and serially assessed in settings where a surgical biopsy represents a risk for the patient or cannot be obtained. Furthermore, Liquid Biopsy could be applied to detect the presence of Minimal Residual Disease (MRD) after surgical resection and guide adjuvant therapy decisions [1][2]. Recently it has been reported that an increase in variant allele frequency (VAF) of potentially resistance-conferring mutations, e.g. in KRAS and EGFR T790M mutations, can precede the diagnosis of relapse according to RECIST v1.1 (Response Evaluation Criteria In Solid Tumours) [3], a phenomenon called molecular relapse. Detection of molecular relapse may open an opportunity to improve early detection of progressive disease providing treatment to patients faster in targeted as well as Immune Checkpoint Inhibitor (ICI) therapy. The frequency of follow-up CT scans may be reduced, and faster therapeutic intervention may prolong overall survival and improve the quality of life of the patients. A Liquid Biopsy-based monitoring of disease may potentially accelerate patient selection and enrolment in clinical trials of targeted therapies. Therefore, real-world implementation of Liquid Biopsy may improve progression-free and/or overall survival in the future as well as enhance therapeutic signal generation for targeted therapies.

In recent years, several ctDNA-based assays for mutation detection, which is the most advanced application for Liquid Biopsy, have entered the clinic and attained partial regulatory approval. In the case of EGFR inhibitors, selection of Non-small cell lung cancer (NSCLC) patients eligible for 2nd and 3rd generation inhibitors can be identified by FDA-approved ctDNA based assays (Roche Cobas[®] EGFR Mutation Test v2, Therascreen EGFR Plasma RGQ PCR Kit). So far, prospective clinical studies have focused on the analytical validity of Liquid Biopsy assays and concordance with invasive tissue biopsy findings to demonstrate non-inferiority of Liquid Biopsies (e.g. Inivata, NCT02906852 and the NILE study, Guardant Health, Inc., NCT03615443). In addition, prospective analysis of serial

Liquid Biopsy ctDNA data after curative resection to monitor disease and to detect recurrence in early stage NSCLC may demonstrate clinical utility of Liquid Biopsy for therapy decision making (e.g. Guardant Health, Inc., NCT03791034).

To that end, implementation of Liquid Biopsy assays in a real-world clinical setting, i.e. detecting and monitoring genetic alterations in prospective multi-centric studies, is needed.

Such an observational study could provide evidence for the clinical utility of Liquid Biopsy in several applications:

- Treatment decisions based on ctDNA content and the presence of clinically relevant genetic alterations in blood, e.g. for targeted therapy approaches
- Early detection of signs of efficacy or failure of a treatment
- Early detection of relapse and shortened time to treatment decisions
- Identification of resistance mediating genetic alterations

The proposal funded by this call should be adaptive in nature and provide important insight into best practice for real-world clinical implementation of Liquid Biopsies in solid tumour indications, thus it may result from a pre-competitively planned clinical study or take advantage of an already ongoing study.

The above challenges would therefore greatly benefit from the multi-disciplinary consortium of several stakeholders in the cancer oncology precision medicine field:

- **Clinical partners and molecular pathologists** with their knowledge on conducting clinical studies and access to patients and samples;
- **Pharmaceutical companies**, with their knowledge on clinical study design, implementation of biomarkers in clinical studies and requirements for companion diagnostics development.
- **Diagnostic companies**, with well-established technologies in the Liquid Biopsy space;
- **Academic researchers** with their knowledge of molecular disease mechanisms and potential technical improvements to existing methods and protocols;
- **Regulators**, with their knowledge of requirements for the safe implementation of Liquid Biopsy assays in the clinic;
- **Patient advocacy groups**, with their insight into patients' perception of and experience with diagnostic procedures;
- **Health economists and payer organizations**, with their expertise in modelling the impact of diagnostic technologies and their clinical implementation on therapy cost effectiveness

In order to demonstrate the full potential of prospective clinical use of Liquid Biopsy, the suggested proposal will have the highest impact if it involved all aforementioned stakeholders.

Scope

The overall objective of the call topic is to support real-world clinical implementation of Liquid Biopsies in solid tumour indications. The goal is to evaluate whether Liquid Biopsies can become a clinical standard that cost-effectively and safely accelerates clinical trial enrolment, as well as therapy decisions, thereby enabling earlier changes to therapy as compared to RECIST. This would tackle emerging treatment resistance and spare patients from overtreatment and burden of invasively

collected tumour samples. This should contribute to prolonging progression-free survival and potentially overall survival of cancer patients.

A focus should be put on commercially available, globally distributed and analytically validated Liquid Biopsy ctDNA assays in a real-world clinical setting with the aim to complement routine diagnostic procedures to detect genetic alterations and to monitor treatment efficacy and/or MRD.

The consortium is intended to implement a comprehensive prospective Liquid Biopsy protocol in either

- an investigator initiated multi-centric clinical study, in which in addition to standard diagnostic procedures (e.g. tissue biopsy and CT scans) the impact of data derived from Liquid Biopsy can be evaluated.
- and/or an ongoing clinical study or consortium, in which Liquid Biopsy samples can be shared and data can be compared to standard diagnostic procedures (see 'potential synergies with other consortia').

The selected proposal should focus on an advanced and established ctDNA analysis and evaluation workflow. In addition, exploratory analysis of less mature Liquid Biopsy analytes such as cfRNA and/or extracellular vesicles/exosomes may be considered as long as enough material is available. These exploratory markers may have the potential to provide additional clinically actionable information for more difficult to detect alterations like gene fusions.

The selected proposal should focus on one or two solid tumour indications and must include Lung Cancer (NSCLC and SCLC). Additional indications such as breast cancer or prostate cancer may be considered if enough cases and resources are available to prove statistical significance.

Per indication and study, only one assay/gene panel may be selected. Comparative studies between different assays/ gene panels are not within the scope of this call.

Expected key deliverables

Based on these objectives, a number of key deliverables have been identified:

- Real world evidence of standardized clinical use of Liquid Biopsy in cancer patients;
- Liquid Biopsy sampling and handling protocol(s) established at all clinical study sites in alignment with current CEN/TS (European Committee for Standardization / technical specification) and ISO (International Organization for Standardization) standards;
- Decision-relevant Liquid Biopsy-based data for detection and monitoring of response/early detection of relapse and/or detection of MRD from a number of patients large enough to be statistically significant in the questions addressed but, in any case no less than 200 patients per cancer indication. All data (including raw data, patient history and clinical outcome data) needs to be shared with the entire consortium;
- Assessment of differences in therapeutic intervention when decision is based on standard diagnostic procedure vs. Liquid Biopsy;
- Providing data on non-inferiority with molecular profiling data derived from tumour tissue, if available;
- Clinical confirmation of assay parameters, e.g. sensitivity and specificity;
- Assessment of the impact of Liquid Biopsy implementation on patients' quality of life (e.g. more frequent sampling, less invasive);
- Regulatory guidance on using Liquid Biopsy in real-world clinical setting;

- Assessment of economic impact of Liquid Biopsy implementation as potential addition to today's standard procedures when compared to potential benefit for patients and payers.

Expected impact

In their proposal, applicants should describe how the outputs of the proposed work would contribute to the following impacts and include baseline, targets and metrics to measure impact:

- Demonstrate suitability of Liquid Biopsy in clinical practice;
- Establish reliable and economically feasible Liquid Biopsy protocols in a routine clinical environment;
- Establish a network of clinical sites with necessary infrastructure and training to include serial Liquid Biopsy sampling and handling;
- Establish Liquid Biopsy markers to monitor disease progression, detect recurrence early and inform treatment choices, thereby increasing treatment success for patients, benchmarked to other treatment informing criteria (e.g. RECIST);
- Support reimbursement by public health care providers for Liquid Biopsy testing;
- Support establishment of regulatory processes for Liquid Biopsy in Europe.
- In their proposals, applicants should outline how to leverage the public private partnership model to maximise impact on innovation, research & development; regulatory, clinical and healthcare practices, as relevant. This could include a strategy for engagement with patients, healthcare professional associations, healthcare providers, regulators, HTA agencies, payers etc, where relevant.

In addition, applicants should describe how the proposal will impact on the competitiveness and growth of companies including SMEs;

In their proposals, applicants should outline the following:

- The management of data including use of H2020 data standards.¹
- How to address dissemination, exploitation and sustainability of the results. This may involve engaging with suitable biological and medical sciences Research Infrastructures.²
- The communication of the project activities to relevant target audiences.

Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures²) in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

Industry consortium

The industry consortium plan to contribute the following expertise and assets:

¹ Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm

² <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

- Support with established Liquid Biopsy technologies and process clinical samples using these technologies (sample collection, stabilization, extraction, biomarker detection, analysis and interpretation);
- Implementation of CEN/TS and ISO Standards;
- Support with ctDNA testing and analysis and raw data processing;
- Expertise in clinical study design and biomarker operations know-how;
- Support in regulatory and health economic aspects;
- Support in Programme and Project management (all WP).

Indicative duration of the action

The indicative duration of the action is 60 months.

This duration is indicative only. At stage 2, the consortium selected at stage 1 and the predefined industry consortium may jointly agree on a different duration when submitting the stage 2 proposal.

Expertise and resources expected from applicants at stage 1

The stage 1 applicant consortium is expected, in the submitted short proposal, to address all the objectives and key deliverables of the topic, considering the expected contribution from the industry consortium which will join at stage 2 to form the full consortium.

The stage 1 submitted short proposals should include suggestions for creating a full proposal architecture which could be in line with the suggested architecture described below, though this architecture is only a suggestion.

This may require mobilising, as appropriate, the following expertise:

- Clinicians and molecular pathologists with expertise in the field and having access to clinical samples (longitudinal blood sample collection and processing and handling expertise), agreed-upon patient data (histology, treatment history, corresponding tumour molecular profiling at baseline) and RECIST assessment (CT and CT/PET scans)
- Academic research groups with a track record in the analysis of molecular profiling data in cancer and data base set-up with a understanding of what it takes to establish Liquid Biopsies as new method in clinical practise in oncology (network of clinicians, molecular pathologists, health insurers).
- Established clinical service laboratories with marketed Liquid Biopsy assays with appropriate certification
- SMEs to contribute with fit-for-purpose marketed Liquid Biopsy assays (use in clinical studies demonstrated and results published in peer-reviewed journals), or other relevant innovative service or technology solutions would be of high value for the proposal.
- Additional required expertise includes statistics and bioinformatics, regulatory and health economy.
- Patient-advocacy organizations helping to work on QoL aspects would be appreciated (either as beneficiaries or through involvement in consultations)

The size of the consortium should be proportionate to the objectives of the topic while ensuring its manageability.

It may also require mobilising, as appropriate, the following resources:

- Proven access to clinical samples and agreed-upon patient data.
- Patient Informed Consent (PIC) of participating institutions which cover third party use, data storage and sample exchange across national borders and GDPR conformity.

The early involvement of regulatory authorities and health insurance providers in the proposed activities, either as official partners or as permanent members of the Advisory Board might be extremely beneficial for achieving the expected objectives.

Considerations for the outline of project work plan

In their stage 1 proposals applicants should

- Give due visibility on data management; dissemination, exploitation and sustainability; and communication activities. This should include the allocation of sufficient resources for these tasks which will be further developed in stage 2 proposal.
- Consider including a strategy for ensuring the translation of the projects results to drug development, regulatory/ Health Technology Assessment (HTA) settings (e.g. through scientific advice/ qualification advice /opinion, etc.), clinical and healthcare practices and/or decision-making processes.

Suggested architecture

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry participation including their contributions and expertise.

The architecture outlined below is a suggestion. Different innovative project designs are welcome, if properly justified.

The consortium is expected to have a strategy for the translation of the relevant project outputs into regulatory practices, clinical and healthcare practices. A plan for interactions with Regulatory Agencies/health technology assessment bodies with relevant milestones, resources allocated should be proposed to ensure their advice on real-world implementation of Liquid Biopsies for cancer patients.

The proposed activities should focus on implementation of (a) Liquid Biopsy protocol(s) that is based on (a) marketed assay(s) with published analytical performance data. This could include but is not limited to NGS- or digital PCR-based approaches for ctDNA detection, monitoring and MRD. In addition, exploratory evaluation of new assay formats, e.g. circulating RNAs, or extracellular vesicle/exosome analysis could be considered, particularly when allowing orthogonal assay validation, if sample requirements can be accommodated. The applicant consortium is asked to plan for a centralized analysis of the samples in an appropriately qualified laboratory for quality assurance and comparability.

If synergies with existing and ongoing studies and consortia are used, work packages (WP) may be affected, in particular WP2 and 3.

Work package 1 - project management and communication

Dissemination of project results (e.g. press releases, website, meetings, interaction with stakeholder groups and other research initiatives in the field worldwide) and organization of the consortium administration including legal and ethical issues.

Work package 2 - study planning

Study protocol, ethics approval, set-up logistics, training and implementing SOPs. (Alternative: use of existing studies). Definition of primary and secondary outcome measures as well as analyses to be performed.

A rationale for the number of patients should be provided based on expected effect sizes and corresponding statistical calculations. Feasibility of timely recruitment of the required number of patients should be provided. In addition, the requirements for sample volume and handling that is needed for the suggested Liquid Biopsy approach must be considered and realistically accessible in the study population.

Regulatory implications using Liquid Biopsies should be addressed. Quality of Life (QoL) assessment should be considered.

Responsible for study implementation, logistics and training.

Work package 3 - study management

Clinical and bio sample operations: Recruitment and tracking of a sufficiently large patient cohort (dependent on therapeutic challenge to be addressed) and collection/tracking/shipment and storage of bio samples.

Work package 4 - sample analysis

- Shipment of bio samples to analytical laboratories for centralized testing (central lab); quality assurance, sample accession and reconciliation and data generation and reporting of results.
- Molecular analytics and improvement of analytical protocols as needed.
- Orthogonal testing of identified mutations by independent assay, e.g. by PCR.
- Molecular profiling of tumour tissue, if applicable.

Work package 5 - data management

Statistical analysis (including QC) and bioinformatics is suggested to be performed in a centralized manner in order to avoid bias.

Work package 6 - health economic analysis

The proposal should include cost-effectiveness analysis and cost-utility analysis of Liquid Biopsies in the EU and H2020 Associated countries, if applicable. Develop reimbursement strategy and work with health insurers.

Additional considerations to be taken into account at the stage 2 full proposal

At stage 2, the consortium selected at stage 1 and the predefined industry consortium jointly submit the full proposal developed in partnership. The full proposal is based upon the selected short proposal at stage 1.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the

roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

Data Management

In their stage 2 proposal, applicants should give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.³

Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and the exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project⁴, and updated during the project lifetime and could include identification of:

- Different types of exploitable results
- Potential end-users of the results
- Results that may need sustainability and proposed sustainability roadmap solutions

Enough resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures (RIs).⁵

References

- [1] Abbosh C, Birkbak NJ and Swantin C. Early stage NSCLC – challenges to implementing ctDNA-based screening and MRD detection. *Nat Rev Clin Oncol*. 2018;15(9):577-586. <https://doi.org/10.1038/s41571-018-0058-3>
- [2] Chae YK, Oh MS. Detection of minimal residual disease using ctDNA in lung cancer: Current evidence and future directions. *J Thorac Oncol*. 2019;14(1):16-24. <https://doi.org/10.1016/j.jtho.2018.09.022>
- [3] Eisenhauer EA, Therasse P, Bogaerts J...Verweij J. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *EJC* 2009; 25:228-247. <https://doi.org/10.1016/j.ejca.2008.10.026>

³ Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm

⁴ As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply

⁵ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>