International Agency for Research on Cancer

World Health Organization

Scientific Council **SC/62/5**
Sixty-second Session 04/12/2025

Lyon, 11–13 February 2026
Auditorium

SCIENTIFIC FOCUS: LABORATORY-BASED RESEARCH

IARC's laboratory system provides a uniquely integrated and high-quality research environment that strengthens the Agency's role as a global leader in molecular cancer epidemiology. Built on scientific rigor, strong quality assurance procedures, and flexible operational design, this structure enables IARC to generate reliable, innovative, and policy-relevant evidence.

The co-location of all laboratory units in the new IARC building has strengthened internal cohesion and accelerated interdisciplinary collaboration, catalyzing the development of new research initiatives across the Agency's scientific Pillars. This centralized model ensures consistent quality assurance, full traceability, and efficient workflows from biobanking to histopathology to advanced laboratory analyses dedicated for research. Such integration is essential for producing robust data, particularly in the early stages of research and in large international studies.

IARC's laboratories offer technical capabilities that are unique in the global cancer research landscape. These include specialized advanced metabolomics and proteomics platforms, innovative biomarker discovery pipelines, virology and epigenomics assays, and the ability to work reliably with low-volume or low-quality samples common in Low- and Middle-Income Countries (LMIC) settings. These strengths have supported landmark work such as studies on single-dose Human Papilloma Virus (HPV) vaccine efficacy, the development of novel non-invasive biomarkers for early cancer detection or risk prediction and deeper insights into cancer mechanisms and the influence of key risk factors.

Strategic cost-efficiency further strengthens IARC's model: analytical activities are carefully evaluated to determine whether they are best conducted in-house or outsourced, ensuring both resource optimization and support for mission-critical, technically complex work that only IARC can perform.

The laboratory-based research forms an essential foundation for IARC's scientific work, supporting the continuum from discovery to impact within a single, integrated environment, an approach that continues to add significant value to global cancer research. With continued visibility and sustained investment, they are well positioned to further strengthen IARC's scientific leadership, expand its global reach, and fully realize the interdependent vision of the next Medium-Term Strategy (MTS), ultimately enhancing the Agency's capacity to shape the future of cancer prevention worldwide.

[1] Recommendation 5: "*As computational biology needs an increasingly important component of laboratory capacity, IARC should regularly update the SC and the GC on capacity for computational biology in the future*".

Here we present a selection of high-impact IARC laboratory-based research projects

1. **Identification of novel risk factors for hormone-related cancers**

- **Rational and objectives of the project**

Hormone-related cancers, including breast, endometrial, ovary and thyroid cancers pose a significant global health burden, with breast cancer being the most common cancer in women worldwide, accounting for nearly 2.3 million new cases annually. Ovarian cancer, while less common, is a very fatal disease, due to its late detection. In LMICs, over half of breast cancer cases affect women under the age of 50, with a median range of 49–52 years, contrasting with 63 years in High-Income Countries (HICs). While breast cancer five-year survival rates exceed 90% in HICs, they range between 30% and 60% in LMICs. These disparities arise from a variety of factors, including, but not limited to, inadequate access to early diagnosis and treatment, and insufficient healthcare facilities. Collectively, these factors contribute to elevated mortality rates in LMICs. To reduce this burden, it is critical to comprehensively investigate the etiology of breast cancer in LMICs and identify specific, possibly novel, risk factors to effectively prevent breast cancer and lower its mortality.

Recognizing that much remains to be uncovered about the causes of hormone-related cancers, we propose an ambitious portfolio of studies aimed at: 1) identifying novel risk factors and pathways related to breast and ovarian cancers; 2) exploring candidate mechanisms linking risk factors -- whether known or newly discovered -- to the development of these cancers.

To achieve this, within the Nutrition and Metabolism (NME) Branch we take full advantage of cutting edge laboratory techniques (such as proteomics and metabolomics), high quality epidemiological studies within unique datasets worldwide (e.g. European Prospective Investigation into Cancer and Nutrition study (EPIC), South Africa Breast Cancer (SABC)), PRECAMA, EDSMAR, and forefront biobank.

- **Specific scientific initiatives of ongoing research include the investigation of:**

- Targeted metabolomics analyses on pre-diagnostic samples in a nested case-control study on breast cancer in EPIC. Arginine, asparagine, acylcarnitine C2 and several phosphatidylcholines were identified potentially novel modifiable pathways and biomarkers of breast cancer development;
- Targeted protein analyses to study thyroid physiology in breast and ovarian cancers within EPIC, showed that prediagnostic circulating fT3 and fT4 concentrations were associated with increased breast cancer risk, particularly for HER2-positive tumours, and that high fT4 and low TSH concentrations may be associated with poorer survival from ovarian cancer;
- Untargeted metabolomics analyses to investigate the etiology of triple negative breast cancer within the EPIC cohort. For the first time, a set of metabolites specifically associated with triple negative breast cancer risk, were identified, indicating that metabolic pathways related to tyrosine, uric acid, acylcarnitines, bilirubin, 2-hydroxy-3-methylbutyric acid, caffeine and 2-furoylglycine may help characterize different breast cancer subtypes;

- Untargeted metabolomics to samples from a total cancer cases and population-based controls enrolled in the SABC study. We identified metabolic pathways related to cortisol, kynurenine, and carnitine metabolism may play a role in black African women with breast cancer.

- **Contribution to IARC's priorities (new MTS) and implementation potential**

These projects will contribute to the IARC flagships (EPIC)

- Causes of cancer & omics
- Mechanisms of etiology/carcinogenesis

2. **Using untargeted metabolomics to discover biomarkers of habitual alcohol intake and associations with risk of pancreatic and liver cancers**

- **Rational and objectives of the project**

Self-reported alcohol intake is prone to errors, and it is likely that observed associations between alcohol consumption and cancer risk are compromised. Biomarkers of habitual alcohol use, including light-to-moderate drinking, are largely missing, but would better assess alcohol exposure in epidemiological studies where modest associations may exist. Untargeted metabolomics is a powerful tool for discovering small molecule biomarkers of both endogenous and exogenous origins and was employed in this project to identify novel biomarker candidates of exposure or response to habitual alcohol consumption. The aim was to study the association of the levels of the discovered compounds with risk of pancreatic and liver cancers in the EPIC study and the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC). A further aim was to study the robustness of the dose-response relationships of the discovered candidate biomarkers using metabolomics analysis of blood samples from a crossover alcohol feeding trial (Postmenopausal Women's Alcohol Study).

- **Specific outputs**

- Robust correlations between self-reported habitual alcohol intake and two alcohol-related metabolites. These may serve as objective markers for estimating risk associations and provide mechanistic insight into the health effects of low to moderate alcohol drinking (2-hydroxy-3-methylbutyric acid, ethyl-glucopyranoside).
- Unambiguous evidence of a strong dose-response relationship from the controlled feeding trial.
- Significant associations for 2-hydroxy-3-methylbutyric acid with risk of HCC and pancreatic cancer (EPIC) and with liver cancer (ATBC). Associations were stronger than those for self-reported alcohol intake. Both candidate biomarkers were associated with liver endpoints independent of self-reported alcohol intake, indicating value beyond being correlates of intake.
- Targeted screening of the discovered metabolites possible from other IARC-generated untargeted metabolomics datasets.

- **Contribution to IARC's priorities (new MTS) and implementation potential**

- IARC flagships (EPIC)

• Causes of cancer & omics • Mechanisms of etiology/carcinogenesis

3. **Decoding Epigenomics and Mechanisms of Childhood Cancer: Biomarkers, Exposures, risk factors and Policy Impact.**

- **Rational and objectives of the project**

Childhood cancers represent a major global health burden, with rising incidence and survivors often facing lifelong complications. Their early onset, distinct biology, and generally low mutational burden suggest that **non-mutational processes, especially epigenetic dysregulation,** are key drivers of disease. Moreover, epigenetic mechanisms provide a critical link between *in-utero* and early-life environmental exposures—such as pollutants, contaminants, infections, and diet—and cancer development, potentially linking these exposures to childhood cancer aetiology and mechanisms. Due to the geographical variation in these exposures, this crosstalk may also contribute to explaining the global disparities of incidence in childhood cancers.

To address this, we have launched an integrated programme that maps the **molecular epigenetic landscape of paediatric cancers** across the life course—from prenatal and neonatal stages to diagnosis, remission, and relapse. Our goals are to:

- Identify **precursors of disease initiation**
- Discover **biomarkers for susceptibility, early detection, and progression**
- Define **exposure-specific risk factors** (e.g. mycotoxins, infections, pesticides)
- Uncover **mechanistic pathways** linking early exposures and epigenetic changes to childhood cancer

We focus on major paediatric cancers such as **leukaemia, brain tumours, rhabdomyosarcoma, and endemic Burkitt lymphoma**. Led by IARC scientists and conducted in collaboration with the WHO Global Initiative for Childhood Cancer, and a global network of academic and clinical partners, these efforts will generate robust evidence to inform policy and advance prevention, classification, and care for children worldwide.

Briefly, we implement a multi-tiered research strategy that integrates experimental, molecular, and population-based approaches, with IARC laboratories as the central hub. Our projects leverage large epidemiological and clinical consortia from both HICs and LMICs, with IARC scientists playing a key role in establishing several of these cohorts, especially in LMICs. Using neonatal samples (e.g. blood spots, cord blood) and/or tumour biopsies, we generate high-resolution epigenomic profiles and integrate them—where relevant—with virome/microbiome data (much of it performed at IARC), along with genomic and metabolomic datasets, supported by biomonitoring of *in-utero* exposures.

These efforts are complemented by experimental exposure models—conducted at IARC or with collaborators—paired with epigenomic and transcriptomic analyses to uncover mechanisms, particularly where population data are limited.

- **Specific outputs**

- Scientific discoveries

Identifying Epigenetic Precursors of Childhood Cancers: using prospective birth cohorts and tumour-to-birth backtracking, we profiled the neonatal methylome in B-cell lymphoblastic leukaemia. Consistent hypermethylation of the imprinted gene *VTRNA2-1* at birth—across ancestries and tissues—emerged as the first validated epigenetic biomarker detectable pre-symptomatically, with predictive value for disease progression and survival. Similar analyses are underway for childhood brain tumours.

Studying the synergistic impact of Mycotoxins and EBV in Endemic Burkitt Lymphoma (eBL): In sub-Saharan Africa, we studied the interaction of mycotoxin exposure and EBV infection using blood spot samples from mother–child cohorts in Burkina Faso and The Gambia. Using epigenomic and Luminex platforms at IARC, we found that aflatoxin B1 and ochratoxin A were linked to higher viral infection rates and distinct methylation patterns affecting immune and cancer-related genes. Parallel *in-vitro* models of EBV-driven B-cell immortalisation and new clinically confirmed eBL cohorts (largely established by IARC) with biopsies, blood, and exposure data support mechanistic and biomarker discovery work. This ongoing project will provide much-needed evidence on how contaminated foods may contribute to this EBV-linked cancer—insights that are essential for strengthening prevention efforts in Africa and globally as climate change is expected to increase such exposures globally.

Multi-omic evidence (largely generated at IARC) linking early-life exposures to childhood cancer across diverse settings, we integrate epigenomic, virome/microbiota, transcriptomic, and metabolomic data to uncover how prenatal and early-life exposures contribute to paediatric cancer initiation and progression. Moreover, we identify biomarkers of exposures (such as pesticides, folate, endocrine disruptors, etc.) and risk.

Comparative epigenetic analyses (generated at IARC and in partners institutions) of global cohorts of paediatric leukaemia allowing region-specific comparisons of molecular features and risk factors, advancing understanding of population-specific mechanisms in childhood cancers.

Identifying epigenetic biomarkers of risk of secondary primary tumours by profiling DNA methylome of biospecimens collected from paediatric patients who developed secondary primary tumours.

- Recommendations & Guidelines

Developing evidence-based guidance on environmental and lifestyle exposures linked to childhood cancer, including climate-related risks, and contribute to improved tumour classification through multi- omic integration for the WHO Classification of Tumours.

- Capacity & Dissemination

Securing major grants, publishing high-impact research, and engaging in broad scientific communication, including media and conferences. Efforts include training early-career researchers

through the IARC Learning Programme; establishing cohorts and biobanks in underrepresented regions; technology transfer where possible and sharing findings via joint initiatives with the World Health Organization (WHO) and childhood cancer organizations.

- **Contribution to IARC Priorities (MTS) and Implementation Potential**

Our project advances IARC's mission by enabling prevention and early intervention, generating actionable data for policy, and identifying risk biomarkers for childhood cancer. We contribute to IARC flagships (e.g. *IARC Monographs*, WHO Tumour Classification, World Code Against Cancer), strengthen research on cancer mechanisms globally, promote equity-driven prevention in LMICs, and foster cross-disciplinary international collaboration.

4. **Urine Biomarkers for the early detection and monitoring of bladder cancer**

- **Rational and objectives of the project**

Bladder cancer is a growing global health concern due to its increasing incidence and high recurrence rates, highlighting the urgent need for improved, non-invasive diagnostic and monitoring tools. The general objective of the project is to develop and validate non-invasive biomarkers, particularly urinary TERT promoter mutations (uTERTpm) and others, for the early detection, monitoring, and recurrence prediction of bladder cancer. By coordinating a large consortium of international case-control and cohort studies, including high-risk groups and LMICs, the program aims to assess the clinical performance of these biomarkers compared to existing methods like urine cytology and cystoscopy.

- **Specific outputs**

- <u>Capacity Building, Innovation, and Patent Development</u>

Our group has pioneered the development and optimization of sensitive urine-based assays for detecting TERT promoter mutations (uTERTpm) demonstrating excellent diagnostic accuracy in multiple case-control and prospective cohort studies. A patent for the uTERTpm urine-based assays is planned for filing, marking a key step toward clinical application.

- <u>Biomarker Comparison and Health Technology Assessment</u>

Through the EU-funded UbioBca study, we are conducting multicentric biomarker comparisons (including uTERTpm) across diverse populations with collection of > 1500 urine samples (Canada, France, Germany). The study evaluates four key biomarkers for bladder cancer detection and recurrence monitoring. Our uTERTpm data will inform a predictive model for tumour recurrence and support an early Health Technology Assessment (HTA), analyzing cost-effectiveness and quality-of-life outcomes associated with biomarker-guided surveillance. These insights will guide decisions on the adoption of urine-based tools in clinical settings.

- Robust Clinical Validation for Early Detection in Asymptomatic Populations

While we showed that uTERTpm can detect bladder cancer years before clinical diagnosis, we aim at validating its performance in five large prospective cohort studies. This will generate robust evidence on its ability to detect pre-clinical bladder cancer, with direct implications for population-level screening and early intervention strategies—particularly in high-risk, asymptomatic individuals.

- Equity in Innovation: Application in LMICs and High-Exposure Populations

The program extends its impact to LMICs, evaluating uTERTpm and newly IARC developed mutation panels in populations with high environmental or occupational risk (Bangladesh, Malawi, Morocco and Tanzania). This supports global health equity by ensuring access to validated, affordable, and context-appropriate screening methods.

- Evidence-Based Policy Guidance

We developed an IARC Evidence Summary Brief with clinicians and patients to inform health stakeholders, supported by editorial publications and collaborations with the European Association of Urology and the World Bladder Cancer Patient Coalition. Ongoing engagement with clinicians, policymakers and patient advocates helps translate biomarker evidence into policy recommendations and future guidelines for bladder cancer screening and surveillance.

- New Frontiers in Biomarker Science

Complementary research explores novel biological mechanisms of bladder cancer progression, including sex chromosome loss in urothelial and immune cells and the role of pathogens, using liquid biopsy assays developed at IARC. This work could lead to future biomarkers and deeper insights into disease biology.

- **Contribution to IARC's priorities (new MTS) and implementation potential**

These projects represent pivotal steps towards translating research-based evidence into clinical practice, potentially revolutionizing the detection and clinical management of bladder cancer worldwide, including in LMICs. It will contribute to shaping public health policy and strategic guidance on bladder cancer prevention and clinical management.