International Agency for Research on Cancer

World Health Organization

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Auditorium

PRESENTATION OF CROSS-CUTTING THEMES

Sections have been asked to present three cross-cutting themes where the input of the Scientific Council would be valuable. These topics will be presented as follows:

Sections and Groups

Acronym	Full name of Section/Group	Responsible Officers
CSU	**Section of CANCER SURVEILLANCE**	**Freddie Bray**
EDP	**Section of EARLY DETECTION AND PREVENTION**	**Rolando Herrero**
PRI	Prevention and Implementation Group	Rolando Herrero
SCR	Screening Group	Dr Sankaranarayanan
ENV	**Section of ENVIRONMENT AND RADIATION**	**Joachim Schüz** Deputy: Ausra Kesminiene
GEN	**Section of GENETICS**	**Paul Brennan**
BST	Biostatistics Group	Graham Byrnes
GCS	Genetic Cancer Susceptibility Group	James McKay
GEP	Genetic Epidemiology Group	Paul Brennan
IMO	**Section of IARC MONOGRAPHS**	**Kurt Straif** Deputy: Dana Loomis
INF	**Section of INFECTIONS**	**Dr M. Tommasino**
ICB	Infections and Cancer Biology Group	Dr M. Tommasino
ICE	Infections and Cancer Epidemiology Group	Dr S. Franceschi
MCA	**Section of MECHANISMS OF CARCINOGENESIS**	**Dr Z. Herceg**
EGE	Epigenetics Group	Dr Z. Herceg
MMB	Molecular Mechanisms and Biomarkers Group	Dr J. Zavadil
MPA	**Section of MOLECULAR PATHOLOGY**	**Dr H. Ohgaki**
NME	**Section of NUTRITION AND METABOLISM**	**Dr I. Romieu**
BMA	Biomarkers Group	Dr A. Scalbert
DEX	Dietary Exposure Assessment Group	Dr N. Slimani
NEP	Nutritional Epidemiology Group	Dr I. Romieu

Topic 1: Mobile health (mHealth) technology implementation across IARC
(Dr Iacopo Baussano, Infections and Cancer Epidemiology Group (ICE))

Participating Sections: CSU, ENV, EDP, INF

Mobile Health (mHealth) is the practice of medicine and public health assisted and supported by mobile devices and information and communications technologies (ICT), to collect, transmit, process and analyse information. mHealth is an emerging and rapidly developing field, at a global level, and is playing a key role in transforming the practice of medicine and public health by improving the efficiency of data transfer and their validation. International, regional, and local actors have been increasingly promoting the development and adoption of mHealth technologies for human development. In 2009, the United Nations Foundation published a report entitled “mHealth for Development” to foster the adoption of mobile technology for healthcare in the Developing World. In 2010 the Ministry of Health of Rwanda successfully designed and implemented a mobile phone SMS-based system to track pregnancy and maternal and child outcomes in limited resources settings. The World Health Organization (WHO) and the International Telecommunications Union (ITU) launched in 2012 a joint global mHealth programme on noncommunicable diseases. The “Be He@lthy, Be Mobile” initiative uses mobile phone messaging technology to deliver disease prevention and management information directly to mobile phone users. A first mHealth project on tobacco cessation has been launched in Costa Rica, and one on cervical cancer, encouraging women to get screened and enabling health workers to provide follow-up and scheduling services, is planned in Zambia. Recently, the European Commission has included mHealth in its digital agenda (2016–2020 action plan) and supports mHealth research through “Horizon 2020”, the new EU research and innovation programme (https://ec.europa.eu/digital-agenda/en/mhealth).

Over the past five years, mHealth has been instrumental to IARC research activities on an individual study-by-study basis. In September 2015, a Working Group of IARC mHealth users held a meeting to identify mHealth initiatives conducted within the Agency, to compare aims, methods, operational approaches, and ethical issues across the different initiatives, and to envisage a common ground for mHealth governance within the Agency. During the meeting, it became apparent that, despite the heterogeneity of the mHealth initiatives, the different Groups faced similar challenges and had to take decisions on methods to a) optimize the data storage and retrieval, b) ensure the confidentiality and security of the stored information, c) develop and manage mHealth infrastructures, and d) regulate flows of information for feedback to researchers and health care professionals in the field.

Current mHealth activities at IARC are implemented to support cancer registration and field studies in low- and middle-income countries. The Section of Cancer Surveillance (CSU) at IARC has developed CanReg5, an open sourced desktop application, to allow population based cancer registries to collect, store, check and analyse data at an individual record level. Currently many registries record new cases on paper in the field before manually entering them into the CanReg5 database. Leveraging mHealth in this context would allow users to limit work duplication, and provide some real-time quality control in the field, thus improving overall data quality as well as time efficiency. A proof of concept has been developed using open-sourced tools for software development. This has been designed in such a way that users run a small CanReg5 database on their mobile device for data collection. Data is

automatically uploaded from the mobile device to a secure server if a connection exists; otherwise new cases are held on the device for later upload.

Similarly, mHealth software and applications have been developed, in-house or outsourced, to support field studies conducted by the Sections of Infections (INF), Environment and Radiation (ENV), Early Detection and Prevention (EDP) and Laboratory Services and Biobank Group (LSB/DIR). Field studies include cross-sectional surveys and follow-up studies conducted in Bhutan, Rwanda, survival studies conducted in five sub-Saharan African countries (South Africa, Namibia, Nigeria, Uganda and Zambia), clinical trials conducted in India, and an international Pathology Review Panel. Mobile devices used in these studies include a wide range of portable handsets from simple phones with text messaging capabilities, to *phablets* (i.e. smartphones or tablets) and laptops with a camera, internet access, and Wi-Fi capabilities. The mHealth systems have been devised to support data collection and participants' management at the enrolment, screening, and follow-up visits. Also mHealth systems support study logistics, standardize the collection and retrieval of data for Biobanks, and facilitate tracking of enrolled participants in highly mobile populations.

Study data are collected either through face-to-face interviews or self-imputed by participants; clinical and laboratory data are also collected through the mHealth system. In some cases the follow-up protocols are embedded in the mHealth system, which serve as a study management tool by prompting the follow-up visits. Study participants are contacted for the follow-up either through local health workers, directly or through next-of-kin mobile phone numbers.

Although mHealth is meant to limit work duplication and improve data collection, the concurrent use of paper records is maintained in some settings as an option to overcome possible technical failures of the local ICT infrastructure and to ensure a flexible integration with the existing local clinical registries. However, the African Breast Cancer Disparities in Outcomes (ABC-DO) study, was supported with specific funding for the development of a tailored mHealth application, which is used throughout the entire study, with the only paper retained locally by the study being the signed consent form. In this setting, the small proportion of women that do not have a phone are given a basic one, thus follow-up can be achieved at great distances from the original diagnostic centre.

The IARC Working Group on mHealth identified a set of advantages and disadvantages to be considered for future planning, as the field and scope of mHealth is likely to expand in the next few years. The real-time collection on mobile devices of data from different sources and their rapid transfer to data-managers/analysts ensures a time-efficient quality control of the information and a closer interaction with the field. It is, however, still unclear to what extent digitalization of the data can become exclusive, as in some settings paper records still play a crucial role in data collection and storage and cannot be easily overcome because ICT infrastructures are still unreliable or limited. Also, the mHealth approach needs specific resources and technical support from trained local personnel. Technical skills are also needed to ensure the encryption and confidentiality of the data.

Questions or areas of advice to be addressed by the Scientific Council

1. What ethical and security issues should be taken into account in developing mHealth approaches at IARC?
2. To what extent should IARC develop mHealth facilities and skills in-house? Or would it be preferable to outsource mHealth systems?
3. To what extent is it safe and sensible to collect data only in an electronic format? Do we still need data collection on paper?
4. To what extent should IARC be engaged in developing mHealth approaches transferable to low- and middle-income settings in which cancer control and prevention is actually implemented?

Topic 2: Key IARC activities that link surveillance, prevention, screening and implementation science in the context of health in the UN post-2015 development agenda (Dr Isabelle Soerjomataram, Section of Cancer Surveillance (CSU))

Participating Sections/Groups: CSU, EDP, INF, ENV, NME, IMO, MCA, GEN, ETR

IARC has a mandate to reduce the burden of cancer worldwide by conducting high quality, multi-disciplinary and multi-collaborative research. The nine scientific Sections at IARC provide an integrated approach to cancer research that focuses on surveillance, prevention and early detection for national, regional and global cancer control planning. The Agency provides the evidence base for cancer control action that supports WHO in implementing the noncommunicable disease (NCD) Global Action Plan, and Member States in monitoring progress of the 25 indicators and targets agreed at the 66th World Health Assembly[1], as part of the Global Monitoring Framework.

More recently the UN Division for Sustainable Development has developed Sustainable Development Goals (SDGs)[2] as an integral part of the UN development agenda beyond 2015. The SDGs consist of 17 goals, of which one specifically on health (Goal 3), each comprising a number of specific targets. It is instructive to examine how IARC is directly supporting specific targets. As can be seen in Table 1, the various targets for which the different IARC Sections contribute mainly relate to Goal 3: 'to ensure healthy lives and promote well-being for all at all ages', although the Agency's role is indirectly linked to achieving other goals.

As the definitive source for global cancer statistics, CSU provides quantification of the cancer burden, a key component in setting national targets and assessing progress to reduce premature mortality from cancer (Targets 3.2 and 3.4). In the future, longer-term projections will be made of trends in cancer burden to enable assessment of the progress towards achievement of the SDG targets. Within the same theme, DEX/NME is coordinating a global action to improve dietary surveillance hence assisting research and decision-making to assess the role of dietary factors on the burden of cancer. To further assist decision-makers in setting priorities in cancer control, CSU is coordinating a few IARC-wide projects to estimate the population attributable fractions (PAF) for major risk factors as well as for specific geographic regions (Targets 3.3, 3.5, 3.9 and 3.10). At the global level, INF and CSU have now developed the methodology to assess the PAF of cancer related to infection and obesity. To provide a comprehensive view on the role of obesity, collaborative work between NME and CSU is ongoing to integrate the role of metabolic risk factors and also anthropometry. Building on this, preparation is under way to estimate PAF related to tobacco (including smokeless tobacco: CSU, IMO, ENV, GEN) and alcohol (CSU, NME, GEN, IMO). The co-development of comprehensive attributable fraction estimates in France with the National Cancer Institute (INCa) is in direct support to implementation of the third National Cancer Plan project and will provide PAFs for most known risk factors in France; a similar plan with WHO EMRO is in progress to provide PAF for the main risk factors in the Eastern Mediterranean region.

[1] http://apps.who.int/gb/ebwha/pdf_files/WHA66/A66_8-en.pdf
[2] http://www.un.org/ga/search/view_doc.asp?symbol=A/RES/70/1&Lang=E

Table 1. Overview of goals/targets of the SDGs and the activities across IARC's Sections that support their attainment

	CSU	EDP	INF	ENV	NME	IMO	MCA	GEN
Goal (3) Ensure Health for all								
3.2. End preventable deaths of children	X			X		X	X	X
3.3. Combat hepatitis & other communicable diseases		X	X					X
3.4. Reduce mortality from NCD through prevention	X	X	X	X	X	X	X	X
3.5. Strengthen the prevention of harmful use of alcohol	X				X	X		X
3.9. Reduce deaths and illnesses from hazardous chemicals	X			X		X		
3.10. Strengthen the implementation of the WHO Framework Convention for Tobacco Control	X	X				X		
3.11. Support the research of vaccines	X	X	X					
3.12. Increase development, training and retention of health workforce	X	X	X	X	X	X	X	X
3.13. Strengthen the capacity in low- and middle-income countries (LMICs)	X	X	X	X	X	X	X	X
Other SDGs Goals								
8.7. Promote safe working environment				X		X		
12.4. Minimize adverse effect of chemicals on health				X		X		
16.6, .7 & .8 Develop accountable institution, participation of LMICs in global governance	X					X		
17.3, .6 & .9 Mobilize funding to LMICs, enhance international collaboration, access to science, and capacity building	X	X	X	X	X	X	X	X

With respect to supporting the combat against infectious disease (Target 3.3) and research on vaccines (Target 3.11), IARC is engaged on the evaluation of effectiveness of vaccines against some infectious agents (HBV – GHIS/DIR, HPV – EDP and INF) and eradication or control of others (*Helicobacter pylori* – EDP, appropriate use of antiretroviral treatment – INF). Moreover, the prevention of cancer in HIV-infected people is also being evaluated in Europe and sub-Saharan Africa (INF). The work on infections involves working closely with national immunization programmes and local governments (e.g. Gambia Hepatitis Intervention Study and Guanacaste HPV vaccines). The Agency has also embarked on the area of implementation science (EDP/PRI, INF), where it considers the role of health systems in the delivery of vaccination programmes, eradication of infectious agents and screening/early detection programmes. Currently plans are being drafted to extend this work to identify factors affecting successful implementation and scale-up of primary prevention programmes on tobacco control or reduction of alcohol consumption.

High quality cancer registry data is the cornerstone of quantification of the burden of cancer. The Global Initiative for Cancer Registry Development (GICR, CSU) draws an ambitious plan to address the current shortcomings in quality and coverage of cancer registration in LMICs through its multi-partner collaborative project. Six IARC Regional Hubs are operational, acting as resource centres to provide technical and scientific support, training and advocacy to registries in countries in defined regions (Targets 3.12 & 3.13). In collaboration across IARC Sections, the Education and Training Group (ETR) further supports this action through its wide-ranging courses and Fellowships programme. IARC also supports prevention through improved communication of the risk factors to the lay public, through press releases and Q&A on important results of the IARC Monographs and Handbooks of Cancer Prevention, and more

recently through the publication of the 4th edition of the European Code Against Cancer (ECAC, ENV, INF, EDP, IMO, NME). This European initiative informs people about actions that they or their families can take with the aim to reduce their risk of cancer.

Finally looking beyond the targets set-up within the health goals, IARC also supports other UN SDG goals in particular strengthening the means of implementation and revitalizing the global partnership for sustainable development (Goal 17). The Director's Office is responsible for developing and maintaining strategic partnerships to achieve common goals and ensure both that IARC's priorities are informed by knowledge of these partners and that its findings are disseminated in return. In this context the Agency's participation in the UN Inter-Agency Task Force is important, with a particular focus on cervical cancer and a tripartite cooperation on cancer control with the International Atomic Energy Agency's Programme Action for Cancer Therapy (IAEA-PACT) and WHO.

Questions or areas of advice to be addressed by the Scientific Council

1. What are the main priorities for the Agency's research programme in support of public health policy development in:
   i) Providing the evidence base for supporting cancer control planning in WHO Member States (low-, middle- and high-income) as part of their response to the high-level SDG?
   ii) How should IARC go about this task given the broad scope of opportunities presented through increased liaison with WHO and other UN agencies and non-governmental organizations?
2. Many aspects within the SDGs encompass other health conditions beyond the scope of IARC's research agenda. How does the Scientific Council suggest IARC should address this issue? Are there benefits in involving other agencies to perform a comprehensive assessment for example on one target looking at impacts on several health conditions including cancer?

Topic 3: Evaluation of biomarkers for cancer screening and early detection (Dr Raul Murillo, Prevention and Implementation Group (PRI))

Participating Sections/Groups: EDP, NME/BMA, INF, MCA, GEN/GEP, GEN/GCS, DIR/LSB

Detection of malignant neoplasms at early stages determines to a large extent the success of cancer treatment. Major achievements in knowledge of cancer biology and biomarker development are observed; however, only a few markers specific to early detection or screening have become incorporated into clinical practice. Given the availability of low-tech platforms and lower operator dependence, early diagnosis and screening biomarkers are more amenable to successful implementation in lower-resourced settings compared with imaging technologies and observer dependent tests; however, developing diagnostic markers, and particularly screening markers, could be highly resource-demanding and challenging.

IARC has a long tradition on biomarker development research and currently most of the research groups are working in different stages of the pathway for this purpose (Figure 1). Discovery of biomarkers for exposure and cancer risk is an area with intensive activity, robust models, and extensive internal and external collaborations in place. The exposome-wide association approach acknowledges the mediator role of the internal chemical environment between external exposures and cells. Accordingly, the relationship between endogenous signalling molecules and exogenous chemicals with mutations, gene expression, protein status, and metabolites is investigated using high-tech omics (metabolomic, genomic, epigenomic) and bioinformatics tools.

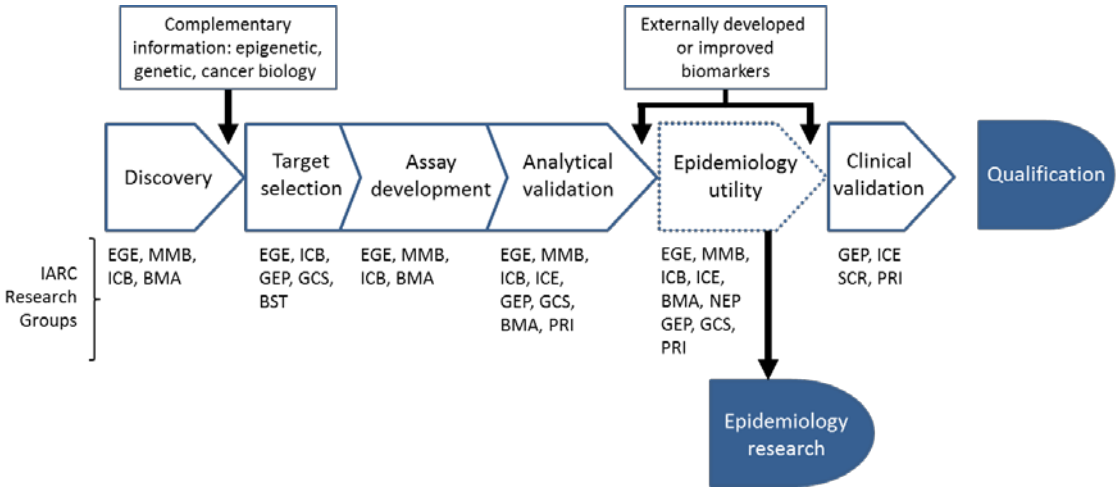

Figure 1. Pathway for biomarker development at IARC

At the same time, multi-faceted research programmes on epigenetic mechanisms of carcinogenesis and identification and validation of epigenetic-based biomarkers of exposure and cancer risk have enabled the testing of new etiological hypotheses. Studies in the field aimed at identifying epigenetic signatures associated with environmental exposures with potential to serve as biomarkers of exposure and cancer risk in specific cancers and surrogate tissues. In addition, the work on genetic mutation profiling by tumour sequencing, the study of genomic early markers (circulating tumour DNA and microRNA), and the development of diagnostic assays for cancer-associated infections have also allowed the identification of potential markers for exposure and risk assessment.

Thus, a broad range of biomarkers including nucleic acids, proteins, metabolites, and cytogenetic parameters, have been identified, classified and validated in epidemiological studies by different IARC research Groups. Furthermore, a comprehensive approach for biospecimen collection has been tested including cell pellets, blood, urine, saliva, and faecal samples for different markers. Components of diet, air pollution, water contamination, smoking, and infections among other risk factors have been characterized and successfully included in epidemiologic research to help reduce the uncertainty of observational measures (questionnaires) and the potential influence of confounders. The preliminary evaluation as to the validity of a putative biomarker as well as the application in subsequent epidemiologic research relies on large case-control and cohort studies with increasing availability of biobanks linked to databases with exposure and long-term follow-up data on health outcomes. These methodologies and tools have proven to be important in enabling multidisciplinary studies on cancer etiology.

Research at IARC on diagnostic and early detection markers has been less intensive; however, some work is already in place. The identification of human papillomavirus (HPV) persistent infection as a necessary cause for cervical cancer opened new opportunities for screening, now extended to other HPV-related tumours. Circulating antibodies to HPV 16 E6 have shown good performance for detecting associated oropharynx tumours in case-control studies[3] and novel markers for the expression of oncoproteins E6/E7 in cervical cells (in partnership with external collaborators) are currently under evaluation in a cross-sectional diagnostic trial aimed at recruiting 50 000 women and in a pilot study with self-collected samples in 2500 women. Likewise, innovative assays to detect specific HPV genotypes in urine samples have proven good analytical validity[4] and they have been successfully evaluated in the context of public health surveillance for HPV vaccination programmes in Colombia, Bhutan, and Rwanda.

In a different field, several markers (externally developed) for gastric cancer precursors are under evaluation in a nested study within the intervention arm of a clinical trial aimed at determining the efficacy of H. pylori eradication. Gastric cancer antibodies, gastrin, pepsinogen, and volatile markers are analysed, and blood, faeces, and gastric biopsies collected for future research. In addition, an assay developed in-house to test H. pylori in saliva and the oral microbiome is under analytical validation.

These examples illustrate IARC's capacity to integrate all dimensions of biomarker research; however, we face several challenges to consolidate the research in this field. Possible approaches in the search of biomarkers for screening and early detection include investigation of differential molecular characteristics of indolent and aggressive tumours (breast, thyroid, prostate), markers of cancer precursors (stomach, colon/rectum, cervix), and exploration of early markers for preclinical disease without restriction by cancer site. In all cases, tumour tissue and other specimens properly collected from patients with early disease are essential in preclinical studies but are not widely available; the progress in biorepository management and the consolidation of international networks by the IARC Biobank are an opportunity to enhance

[3] Kreimer AR, Johansson M, Waterboer T, et al. Evaluation of human papillomavirus antibodies and risk of subsequent head and neck cancer. J Clin Oncol. 2013 Jul 20;31(21):2708-15.
[4] Vorsters A, Micalessi I, Bilcke J, Ieven M, Bogers J, Van Damme P. Detection of human papillomavirus DNA in urine. A review of the literature. Eur J Clin Microbiol Infect Dis. 2012 May;31(5):627-40.

biospecimen collections in variety and quality of samples specifically aimed at developing the type of markers under discussion.

Regarding study designs, a broad range would be necessary for clinical validation. Case-control studies are useful in initial exploratory phases; however, they overestimate accuracy of diagnostic tests, lack heterogeneity of patients, and may suffer inadequate protocols for specimen collection. Longitudinal observational studies have limitations to harmonize biospecimen collection with lead time of the disease, and may be subject to chance and bias. Cross-sectional diagnostic studies are more suitable for clinical validation but they do not provide major information on the integration of screening and treatment and the final efficacy on disease control. Moreover, biomarker validation in cross-sectional diagnostic studies and clinical trials (the gold standard) requires greater specificity in study design according to the targeted cancer and the proposed biospecimen. Clinical studies have also ethical implications for disease management, and early markers under research may face major challenges for implementing feasible, accurate, and cost-effective protocols for confirmatory diagnosis and follow-up of positive-screened patients without clinical signs of disease, a situation that varies according to the context of use (screening, diagnosis, prognosis, etc.) and the intended diagnosis (pre-cancer, cancer).

An additional issue is the need for integration with qualification processes in regulatory agencies. In contrast to markers for epidemiologic research which are essentially subject to scientific judgment, any marker for clinical practice should undergo approval by the corresponding governmental agencies. The objective of the qualification process is to verify that the marker fits the clinical application proposed and it frequently implies an iterative exchange of data between developers and regulatory agencies that could require additional experiments or modifications of assays and prototypes. Given this situation, qualification is proposed before clinical validation in some pipelines for development of diagnostic biomarkers. WHO implemented a pre-qualification process useful to biomarker developers and manufacturers but its final objective is to decide on eligibility for inclusion in the UN procurement tenders, which indicates the need for an advanced stage in the development process prior to submission.

Questions or areas of advice to be addressed by the Scientific Council

1. How can IARC best use the limited resources to increase research activities on biomarker development for cancer screening and early detection?
2. Should IARC seek opportunities to help clinically validate biomarkers developed outside the Agency (including in the private sector) that are amenable to cancer screening and early diagnosis in low- and middle-income countries?
3. How can IARC meet the needs for high-throughput, large-scale studies for biomarkers developed in-house?
4. What different models of in-house biomarker development through to qualification are open to IARC, recognizing the constraints faced as a part of the UN family?