International Agency for Research on Cancer

World Health Organization

Scientific Council **SC/55/5**
Fifty-fifth Session 17/12/2018

Lyon, 30 January–1 February 2019
Auditorium

PARALLEL SESSIONS

In order to engage as many Scientific Council members as possible in the discussions on cross-cutting research topics, the plenary session has been replaced by parallel sessions, followed by a short plenary session capturing the significant points. The following three topics will be discussed in 2019:

Topic #1: WHO global initiatives on cervical cancer and childhood cancer: defining IARC's contribution

Lead, Freddie Bray (CSU) and Rolando Herrero (EDP) ➔ Auditorium

1. Introduction

In the last year, Dr Tedros Adhanom Ghebreyesus, WHO Director-General, has launched two major Global Initiatives on cancer. In May 2018, a global call to action towards the elimination of cervical cancer was announced[1], building on the renewed political will to make elimination a reality. Calling for all stakeholders to unite behind this common goal, he highlighted the need for cervical cancer services to be embedded in strong health systems and included in approaches to universal health coverage.

In September 2018, WHO announced a new Initiative for childhood cancer[2] with an overarching goal of reaching at least a 60% survival proportion for children with cancer by 2030, thereby saving an additional one million lives globally. The Initiative focuses on the need to scale-up capacities within national health systems to deliver best practice in childhood cancer care.

The following provides a brief overview of the two Initiatives, their current status, and IARC's potential contribution to each; it concludes with specific questions we would like to raise with Scientific Council at the dedicated session with respect to IARC's future role in these Initiatives.

2. Global Elimination of Cervical Cancer Initiative

Cervical cancer is the fourth most common cancer among women globally, with an estimated 570 000 new cases and 311 000 deaths annually, with 90% of deaths occur in low- and middle-income countries (LMICs). Safe and effective vaccines, with a primary target of adolescent girls, are available to prevent Human Papillomavirus (HPV) infection, but introduction has not started in many areas at the greatest need. There is a need for new and less-costly products as well as alternative vaccination schedules to facilitate their introduction. Effective screening and treatment of pre-cancer for women aged 30 years and above can prevent women from developing cervical cancer, but few countries have established programmes achieving appropriate coverage, quality standards and follow-up. The majority of cervical cancer cases in LMICs are diagnosed at late stage and many countries lack adequate diagnostic, treatment or palliative care services, with high variability in survival across the world and poor access to pain relief.

WHO commissioned modelling groups and convened technical and consultative meetings to develop a definition of the elimination of cervical cancer as a public health problem. Indicators and interim targets for the period 2020–2030 are to obtain 90% vaccination of girls, 70% of women screened and treated as needed and a 30% reduction in cervical cancer mortality. The ultimate goal is to achieve the elimination of cervical cancer as a public health problem through continued intervention measures, with the elimination threshold defined as an age-standardized annual incidence rate of 4 per 100 000.

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[1] https://www.who.int/reproductivehealth/call-to-action-elimination-cervical-cancer/en/
[2] https://www.who.int/cancer/childhood-cancer/en/

Ongoing modelling work is demonstrating that elimination of cervical cancer is feasible in this century in all countries with the tools we currently have available, mainly through vaccination, with screening accelerating control of the disease and saving millions of lives in the meantime.

WHO is playing a coordinating role in the elimination effort, including non-state actors to ensure coherence in implementation. Eliminating cervical cancer will yield a high return on investment by reducing the cost and health system burden of treating pre- and invasive cervical cancer and preventing productivity losses. A national surveillance system and population-based cancer registries for reporting incidence, survival and mortality data are critical for monitoring progress towards elimination. A coordinated basic clinical and implementation research agenda can identify new or improved interventions that can lead to a more rapid realization of elimination.

2.1. IARC's potential contribution

Seven working groups (WG) have been established to coordinate actions within the elimination initiative: i) Strategy and action plan; ii) Advocacy and communication; iii) WHO guidelines; iv) Impact modelling, cost and financing; v) Increasing access to interventions (vaccination, screening, treatment and palliative care); vi) Monitoring and surveillance; and vii) Research.

IARC is leading or co-leading three of the WG, as described further below.

2.1.1. WG3: Guidelines and recommendations

IARC is participating actively in the WG on WHO recommendations/guidelines. The *IARC Handbooks of Cancer Prevention* provide evidence-based evaluations of the effectiveness of different interventions, focusing on primary and secondary prevention. IARC is proposing updated Handbooks for cervical cancer control, which could include the following topics: vaccination against HPV, including alternative schedules and vaccine safety; screening by cytology, visual inspection, HPV testing, emerging screening tools, triage methods, and comparative effectiveness of the different screening algorithms. In addition, the evaluation would take into account special populations, e.g. HIV-positive women. The Handbooks would directly feed into the WHO recommendations associated with the Initiative.

2.1.2. WG6: Surveillance

The main task of the monitoring and surveillance WG is to enhance overall efforts aimed at strengthening data to inform cervical cancer elimination by providing countries with standardized tools and guidelines that can be adopted at country level to collect data, monitor and evaluate cervical cancer programmes and interventions.

Strengthening the ability of countries to collect and report data on cervical cancer and related key indicators will support cervical cancer elimination. A national surveillance system is important to define priorities, assess the effectiveness of existing programmes, and assist with setting future directions and actions to achieve elimination of cervical cancer. As well as ensuring health information systems are integrated to ensure linkage of data from vaccination, screening, cancer and HIV registries, establishing and sustaining population-based cancer registries (PBCR) are a key requirement for reporting incidence and survival to monitor risk exposure and health care coverage, and to evaluate the impact of interventions of national progress towards elimination.

A key concern is the availability of high quality data series on cervical cancer incidence worldwide, particularly in LMICs[3]. More broadly, PBCR are often overlooked at the planning phase of cancer control, and their sustainable development requires their complete integration into national programmes. Technical assistance is available to governments that seek to instigate surveillance plans, through the IARC-led Global Initiative for Cancer Registry Development (GICR, http://gicr.iarc.fr). The GICR was established as a partnership of leading cancer organizations that aims to radically increase the quality, comparability, and use of cancer data in developing countries in informing their cancer policies and cancer research. IARC is co-leading the WG and a critical aim is to ensure PBCR are one of the necessary tools that requires development in monitoring cervical cancer elimination at global and national levels.

2.1.3. WG7: Research

IARC's research over more than 30 years has been essential in the development of the evidence base that has led to the possibility of elimination. IARC leads this WG, and is planning activities in several areas, including the definition of research priorities for the elimination initiative in the different areas (vaccination, screening, treatment of pre-cancer and cancer and palliative care). Further, a consortium of researchers will be established and the Secretariat at IARC will monitor ongoing research and summarize available data for guideline development on implementation priorities, considering trial data, population impact studies, implementation research and health economics. In addition, the group is expected to provide guidance for researchers and donors on crucial data requiring additional research. For example, in the area of vaccination the duration of protection or the need for vaccines with additional valency to cover more HPV types are likely to be included among the priorities. In screening, the role of self-collection and definition of triage methods will be important. Another component is the development of a network of researchers including from LMICs to build capacity and conduct collaborative research.

3. Global Childhood Cancer Initiative

Cancer is a major cause of death in children worldwide, with about 300 000 new cases diagnosed each year among children aged 0–19 years and recorded incidence rates increasing with time. Children with cancer in LMICs are four times more likely to die of the disease than children in high-income countries as their illnesses are not diagnosed, they are often forced to abandon treatment due to high costs, or the health professionals entrusted with their care lack specialized training.

The aim of the Initiative is to increase childhood cancer survival to 60% by 2030, a figure that translates to saving an additional one million lives. This new target represents a doubling of the global cure rate for children with cancer. The aims of the Initiative are two-fold: to increase prioritization of childhood cancer through awareness raising at global and national levels and to expand the capacity of countries to deliver best practice in childhood cancer care. WHO will support governments to assess current capacities in cancer diagnosis and treatment, set and cost priority cancer diagnosis and treatment programmes, and integrate childhood cancer planning into national strategies, health benefits packages and social insurance schemes. The Initiative has support from a host of partners. Among them is St. Jude Children's Research Hospital in the United States, the

[3] Baussano I, Bray F. Modelling cervical cancer elimination. Lancet Public Health. 2018 Oct 1. pii: S2468-2667(18)30189-0. doi: 10.1016/S2468-2667(18)30189-0. [Epub ahead of print]

first WHO Collaborating Centre on childhood cancer, which has committed US$ 15 million to supporting implementation of the Initiative. As with the cervical cancer initiative, Working Groups are being formed, a conceptualizing framework is being developed and there is engagement with multiple stakeholders to designate countries for action.

3.1. IARC's potential contribution

Given IARC is the leading institution worldwide in the provision of technical support to PBCR in LMICs and has expertise in childhood cancer surveillance and epidemiology, IARC seeks to collaborate with WHO and St. Jude in a tripartite arrangement that would provide a platform for the evidence-based assessment of status, analysis of needs and development of recommendations for effective childhood cancer control. IARC's contribution, broadly speaking, would be to provide technical support to national colleagues in-country to measure the baseline and trends for the incidence, mortality and survival of childhood cancer. Without this work there will be no way to measure how cancer outcomes evolve following the investment made. Key areas that IARC is seeking to contribute include: i) stakeholder meeting to mobilize all relevant collaborators; ii) country-specific implementation of surveillance, including consultancies and reports on cancer registration status, development and recommendations in targeted countries and their integration into cancer plans; iii) Development of standards for childhood PBCR; iv) adaptation of CanReg5 to registration of childhood cancers; v) joint development of a new edition of the International Classification of Childhood Cancer (ICCC); vi) global benchmarking of childhood cancer incidence and survival to measure the progress resulting from this initiative; vii) online interactive tools to disseminate national estimates; and viii) joint training to support PBCR in childhood cancer surveillance.

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4. Questions or areas of advice to be addressed by the SC members (Topic #1)

a) There has been recognition that these major initiatives from WHO on cancer have a high profile and include IARC scientists. As a research institute:

   i. Where can we make the most significant contribution?

   ii. What are the limits to the scope of IARC's role?

b) Given the multitude of high-profile UN and WHO initiatives on NCDs and cancer control (SDG, GAP, Cancer Resolution) that are underway, how can IARC respond effectively to these in a strategic and coordinated manner?

c) Should the IARC Handbooks expand into the assessment of efficacy of treatment of pre-cancer and cancer?

d) Should IARC further expand research activities on Health economics?

e) To what extent should IARC scientists be involved in advocacy and implementation activities given their research mandate?

Topic #2: Outstanding challenges and opportunities for preventive interventions: the example of weight control and metabolic health

Lead, Marc Gunter (NME) ➔ Princess Takamatsu Hall

1. Background

There are areas where causal risk factors for specific cancers are well established but this knowledge is not necessarily being converted into effective interventions. While IARC is leading a number of intervention studies in the area of HPV and other viral or bacterial causes of specific cancers, the Agency has thus far not led interventions around diet, physical activity or other lifestyle factors. The objective of this theme is to discuss the potential value in developing such interventions for cancer prevention. A possible area to address is weight control and metabolic health. Obesity is now an established risk factor for 13 different cancers and together with type 2 diabetes mellitus (T2DM), it has been estimated that these factors could directly account for at least 15% of cancer cases worldwide with the true proportion possibly much higher. Given the rising prevalence of obesity and T2DM in nearly every region of the world, these conditions could be a growing source of cancer in the coming years.

The established link between obesity and cancers raises important questions regarding translation of this knowledge into effective preventive measures. Clearly, maintenance of a healthy weight is an obvious step to potentially reducing risk of obesity-related cancers. Public health strategies that reduce obesity, promote physical activity and discourage the consumption of high-calorie, obesogenic foods are gradually being implemented in many regions of the world. Although such strategies could, if successful, lead to a reduction in the burden of cancer, the indication from worldwide obesity prevalence data is that the epidemic has not yet peaked and, on the contrary, is still on the rise.

Considering the scale and the upward trend of the obesity epidemic, the high incidence of many obesity-related cancers might justify more direct interventions than those at the population-level to prevent cancer in those at increased risk. For example, should we target individuals with obesity and T2DM for more directed interventional measures or more regular screening for certain malignancies such as colorectal cancer? Can we go beyond reliance on anthropometric measures such as body mass index and identify specific biological markers or phenotypes that are common in individuals with obesity and that substantially raise the risk of cancer? This information would then enable the development of tailored interventions that target the relevant biological pathways either pharmacologically or through behavioural change. Furthermore, this approach might result in biomarkers that identify individuals at increased risk of cancer who would be eligible for interventions or more frequent screening where possible.

2. Aim of this session

The overall objective of this session is to critically discuss how to best translate etiologic findings into effective interventions for the prevention of cancer using weight control and metabolic health as an example.

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3. Questions or areas of advice to be addressed by the SC members (Topic #2)

1. Should IARC invest into developing large-scale interventions on cancer prevention with a focus on weight control, metabolic health and possibly other lifestyle factors? If so, who would be appropriate partners, which populations should be targeted and where might the resources be obtained for such a study?
2. What is the value of smaller-scale intervention studies that perhaps focus on intermediate endpoints or molecular markers of risk?

Topic #3: Maximizing the impact of IARC: building on the Mutographs platform

Lead, Paul Brennan (GEP) ➔ Sasakawa Halls A&B

1. Background

Large scale cancer genomics initiatives over the last decade have focussed on highly funded comprehensive projects such as the Cancer Genome Atlas (TCGA) and the International Cancer Genome Consortium (ICGC). Together, these projects have resulted in whole genome sequencing of about 5000 cancers, with extensive additional exome sequencing (doi: https://doi.org/10.1101/322859). This data is available to the international cancer research community. The primary justification for these initiatives was to identify genes and gene pathways involved in cancer, and to spur development of cancer therapies. They were largely conducted on cancer samples collected from large cancer centres in Europe and North America, with little collection of risk factor data or clinical outcome data. Since their completion, new initiatives are being developed, including ICGC-ARGO (Accelerating Research in Genomic Oncology) (https://icgcargo.org/). The key rationale for ICGC-ARGO will be to stimulate large scale international efforts in genomic evaluation of cancers, with an aim of 100 000 cancer cases, and advancing the use of genomics in the clinic.

IARC scientists have been members of ICGC and played a key role in the ICGC project on renal cancer (CAGEKID). In particular, IARC coordinated the recruitment of renal cancer patients from five European countries, and the analysis of genomic data (Scelo et al, Nat Comm, 2014). A key outcome from this project was the observation that renal cancer patients from the Balkan region of Europe had a 'mutation signature' in the tumour that was consistent with exposure to aristolochic acid, a known carcinogen that had previously not been linked to renal cancer. This serendipitous finding illustrated the potential for large scale international genomic sequencing studies to elucidate causes of cancer that were not otherwise suspected.

Over 40 different mutation signatures have been identified, with the list expanding as new data accumulates. Some of these mutation signatures have been linked to specific exposures, such as tobacco, UV light, aflatoxin and aristolochic acid, although the majority have not (https://doi.org/10.1101/322859). In-vivo and in-vitro models are also being employed to help link exposures to specific mutation signature profiles. Some of this work is also underway within IARC (doi: 10.1101/gr.220038.116). A catalogue of mutation signatures has been developed by the Sanger Institute (Cambridge, UK) and is hosted on their COSMIC website (https://cancer.sanger.ac.uk/cosmic/signatures).

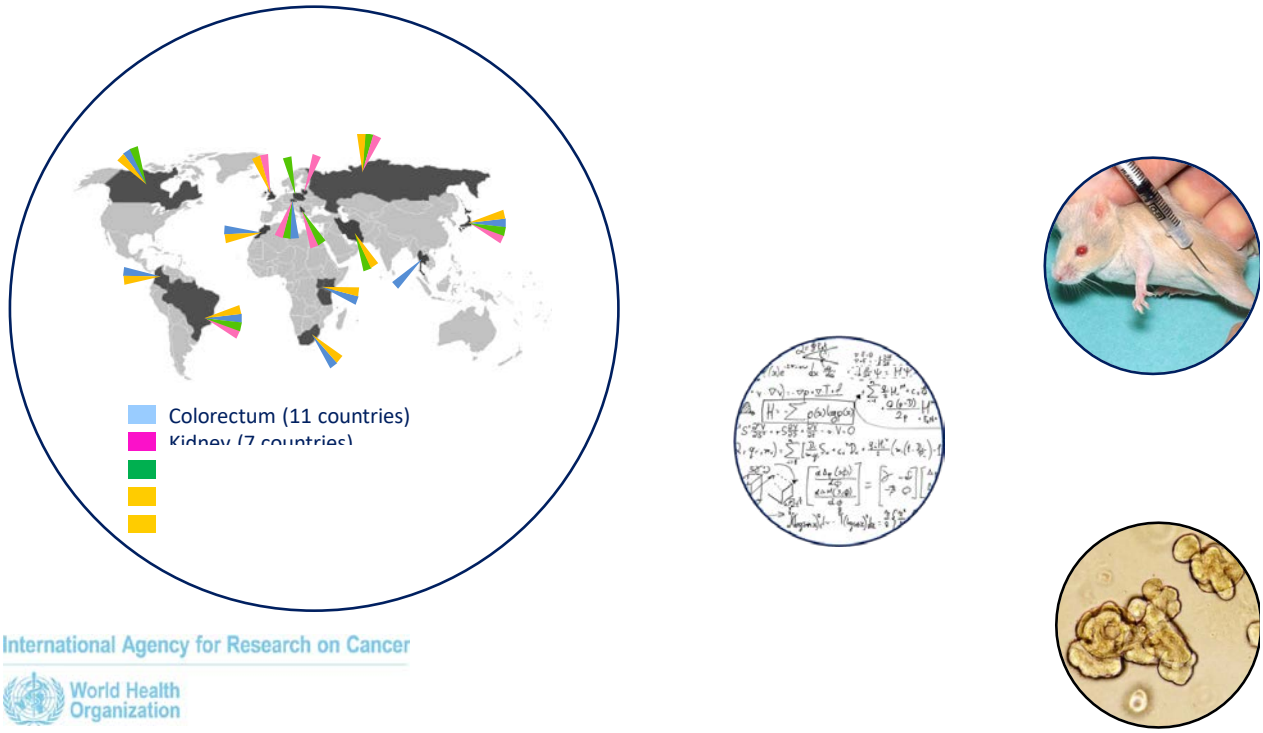
How the Mutographs project developed

The realization that patterns of mutations in tumours could be informative of likely causes of cancer, along with the advent of cost effective next generation sequencing, led to CRUK listing this topic as a potential candidate for the initial Grand Challenge award, with potential research funding of up to GB£ 20 million (https://www.cancerresearchuk.org/funding-for-researchers/how-we-deliver-research/grand-challenge-award). After discussion between IARC scientists and scientists at the Sanger Institute (in particular, Professor Mike Stratton) it was decided to develop a joint application. The resulting project, called Mutographs, proposed whole genome sequencing of 5000 cancer cases,

including five cancer types with important knowledge gaps regarding their underlying etiology, and comprising cases from high and low incidence regions of the world. This recruitment, including cases from 26 partners in 20 countries across five continents, is coordinated by IARC and includes a common protocol comprising extensive risk factor information as well as clinical outcome. The cancer types being studied include oesophageal squamous cancer, oesophageal adenocarcinoma, pancreatic cancer, renal cancer and colorectal cancer.

While this aim of recruiting and sequencing 5000 cancer cases forms the centre-piece of the Mutographs study, other work packages include development of bioinformatic resources for mutation signature analysis, in-vivo and in-vitro analysis of mutation signatures, analysis of mutation profiles in normal tissue, and also detection of mutation signatures in blood DNA as a marker of carcinogen exposure. Based on its scale, geographical coverage and level of funding, this project is one of the most ambitious cancer genomics research projects currently underway. It also illustrates the potential for IARC to stimulate collaborations on a very large scale.

2. The different components of the Mutographs study



The Mutographs project is also expanding, and is undertaking focussed analyses of additional cancers of particular interest. Current projects in the pilot phase include bladder cancer in Iran, and gallbladder cancer in India.

3. Other large sequencing efforts currently underway

The IARC biorepository also includes a large collection of cases with extensive collection of tumour and normal tissue, clinical and demographic information and also risk factor information. These series have been recruited over a number of years, and for certain cancers number in the thousands. They are increasingly being made available for similar large sequencing efforts including:

Never-smoking lung cancer

The US NCI has initiated a large tumour sequencing programme with the specific aim of identifying mutation signatures and underlying causes of cancer. Their initial project is called 'Sherlock', and aims to conduct whole genome sequencing, transcriptomic analysis and epigenetic analysis of up to 2000 cases of lung cancer among never smokers. Approximately 250 of these cases will come from the IARC biorepository based on the lung cancer cases recruited by the Genetic Epidemiology Group (GEP) over the last 10 years.

Head and neck cancers

The IARC biorepository will also contribute about half of all cases to an initiative to conduct whole exome sequencing on up to 2000 cases of head and neck cancer from five countries in Europe, as well as North America (both US and Canada) and Latin America (Brazil, Argentina and Colombia). These studies are led by GEP and funded by the US NIH (NIDCR) and the European Commission H2020 programme.

Breast cancer in populations in epidemiological transition

IARC has also built a large biorepository of breast cancer cases with currently around 1000 cases recruited through three studies led by the Section of Nutrition and Metabolism (NME); (i) an ongoing multicentric case-control study in Latin America (Mexico, Costa Rica, Chile, Colombia, and Brazil) that focuses on premenopausal women (PRECAMA); (ii) a case-control study of breast cancer in Black women from Soweto, South Africa; and (iii) an ongoing case-control study of breast cancer in Fes and Rabat, Morocco. Recruitment protocols have been standardized for questionnaire data and clinicopathological annotations of the tumours.

Colorectal cancer samples from the EPIC study

NME is also collecting tumour blocks from participants to the EPIC prospective cohort study. The advantage of this large, international effort is that questionnaire and measured biomarkers are pre-diagnostic.

Lung neuroendocrine tumours

IARC's particular role in facilitating international collaboration allows meaningful numbers of rare tumours to be assembled for comprehensive genomic analysis. For example, IARC has coordinated the world's largest collection of rare lung neuroendocrine neoplasms. Supported by NIH, the French INCa and La Ligue Nationale contre le Cancer, and the Dutch Cancer Society, this collection from 22 centres across 10 countries includes fresh frozen material from 462 patients, with detailed clinical and epidemiological annotations, which is undergoing genomic, transcriptomic and epigenomic analysis.

4. Aim of this session

IARC does not possess laboratory facilities that allow for large scale cancer genome sequencing efforts, and has focussed instead on developing a medium scale genomics facility. However, when coupled with large external genomic facilities, past experience shows that we can lead large cancer genomics studies.

Areas of strength for IARC scientists include the following:

1. An important focus on cancer prevention and cancer causation, whereas the predominant focus of most cancer genomics studies up to now has been on cancer biology and clinical outcome.
2. Extensive experience in field work for recruitment of diverse types of cancer including validated protocols for recruitment, biosample collection, pathology evaluation, clinical follow-up etc.
3. A network of collaborators spanning all major regions of the world, with successful experience of having conducted population based research with these collaborators.
4. Extensive experience in the conduct and analysis of multi-disciplinary genomic-based studies including dealing with genomic, genetic, pathological and epidemiological data once it is generated.

The aim of this session will be, taking the experience of the last 10 years into account, how can we maximize the impact of IARC, in particular with respect to genomic studies related to cancer prevention and cancer survival.

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5. Questions or areas of advice to be addressed by the SC members (Topic #3)

1. Strategic investment in large scale recruitment of cancer cases, using common protocols for biosample collection, pathology evaluation and clinical outcome, has resulted in extensive use of these cases in subsequent studies. Should this activity be expanded, and if so, how?

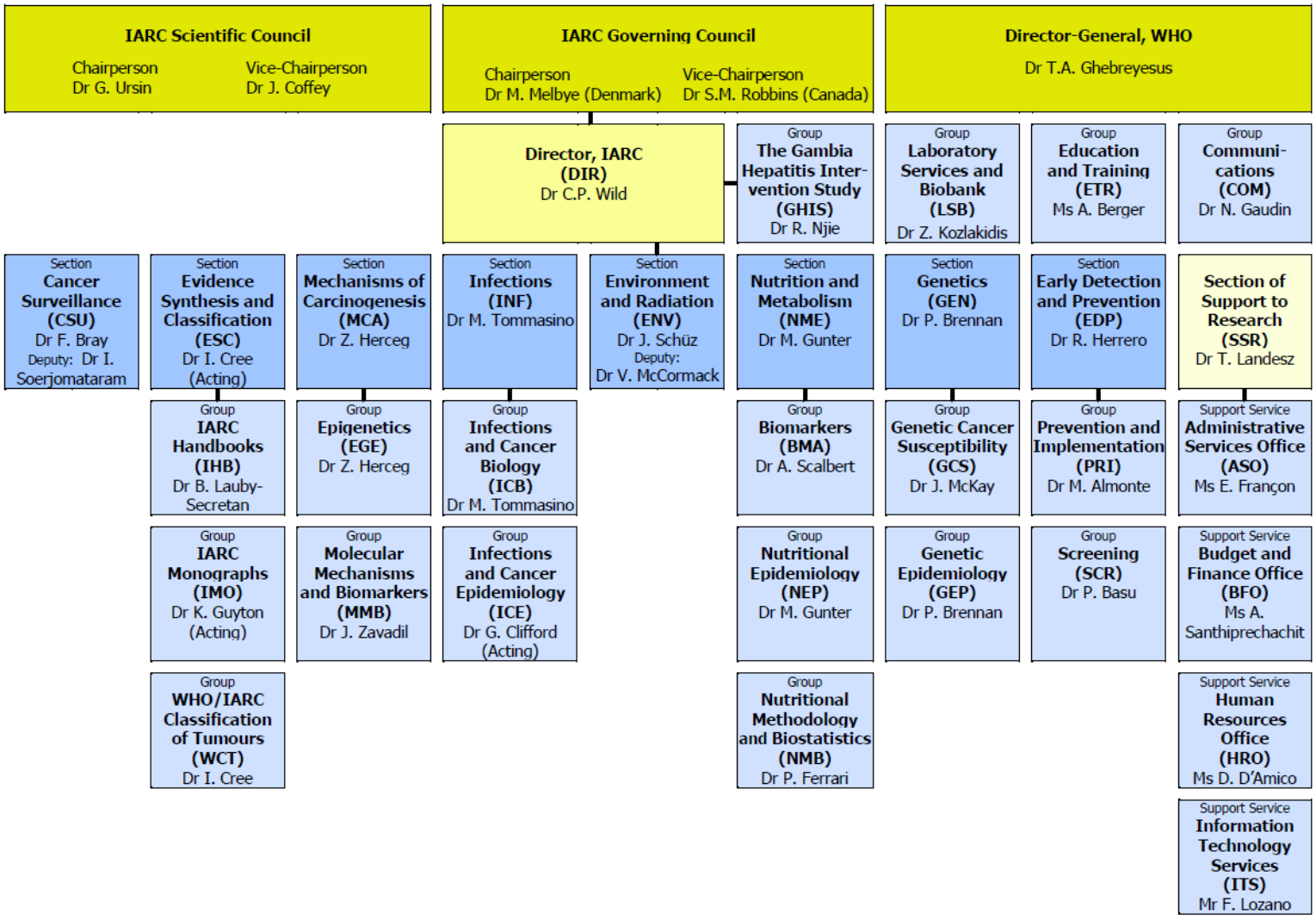
2. Are there priority cancers, with important international differences in incidence that are not explained, or important trends, that should be prioritized? Should large recruitment efforts be undertaken in order to stimulate future large genomics studies similar to Mutographs?

3. Does the experience of the Mutographs project suggest ideas for other large scale projects on a similar scale? Should future studies give similar priority for other omics technologies, e.g. transcriptomics and epigenetics?

IARC Organizational chart (see below and here)

International Agency for Research on Cancer
World Health Organization

1 December 2018



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