Uppsala HEALTH SUMMIT

Pre-conference report

Care for Cancer

14–15 June 2018
Uppsala Castle, Sweden

#Uppsalahealthsummit

We all know that healthcare today is faced with ever greater challenges. We are faced with both economic and ethical dilemmas, and while advances in research and innovations may open new possibilities for better health and improved care, they do not always reach those who need them.

Uppsala Health Summit is an international arena for frank and challenging dialogue, exploring possibilities and dilemmas associated with advancement in medicine. Uppsala Health Summit stimulates dialogue from various perspectives, such as medical, economic and ethical.

We are an enabler for change, and an arena laying the foundation for long-term relationships and insights that can help you in your work to improve health outcome in your part of the world.

Uppsala Health Summit is arranged in Uppsala, Sweden, by partners with long experience of developing health and healthcare from different perspectives, and who see the potential for improving health and healthcare globally.

The effort is run as a collaboration between Uppsala University, the Swedish University of Agricultural Sciences, Uppsala Region, the City of Uppsala, the Swedish Medical Products Agency, The National Food Administration, The National Veterinary Institute, Uppsala Monitoring Centre, the Swedish Research Council for Health, Working Life and Welfare, and the network World Class Uppsala. This year, we are also proud to have the Swedish Childhood Foundation as a partner to Uppsala Health Summit.

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Preface

In many parts of the world, a cancer diagnosis is still perceived as an immediate and deadly threat. Yet medical advances have led to fantastic new opportunities to treat, and sometimes to cure. For many, however, these opportunities are still not accessible.

The gap between what scientific and medical advances can offer in terms of opportunities to treat, and the actual treatment available to cancer patients throughout the world, is widening. A growing incidence and prevalence of cancer diseases is maintaining, and even increasing, the budget pressure on health systems. We need urgently to investigate what we can do to narrow the gap between medical and real-life possibilities. This is why we are convening Uppsala Health Summit this year on the theme of Care for Cancer.

The development of technologies such as genomics has opened up remarkable possibilities for understanding cancer diseases, creating opportunities for better diagnostics and treatments. This would not have been possible without a simultaneous development of the capacity to collect and analyse large quantities of data. But have we created the infrastructures to enable responsible exploitation of these technologies, so as to implement and make the most of our advances? And have we looked enough into how information technologies can move us closer to a situation of equal access to care?

I expect these to be among the hot topics this year in the discussions at Uppsala Health Summit.

This is our fifth Uppsala Health Summit, founded to bring medical, ethical, economic and other perspectives together to address challenges and dilemmas in implementing our research and innovations. To make better use of research results and innovations for better care and to improve health outcomes, despite limited resources, we need to collaborate across the borders of academia, healthcare, policy-making and industry.

The partners behind this effort have come together because we believe that putting our knowledge to work can produce real change, and that we need different perspectives and experiences to achieve this.

I welcome you to join in this effort and invite you to challenging and rewarding discussions at Uppsala Health Summit 2018.

Anders Malmberg, Professor
Chairman of Uppsala Health Summit Steering Committee
Deputy Vice-Chancellor of Uppsala University

Care for Cancer

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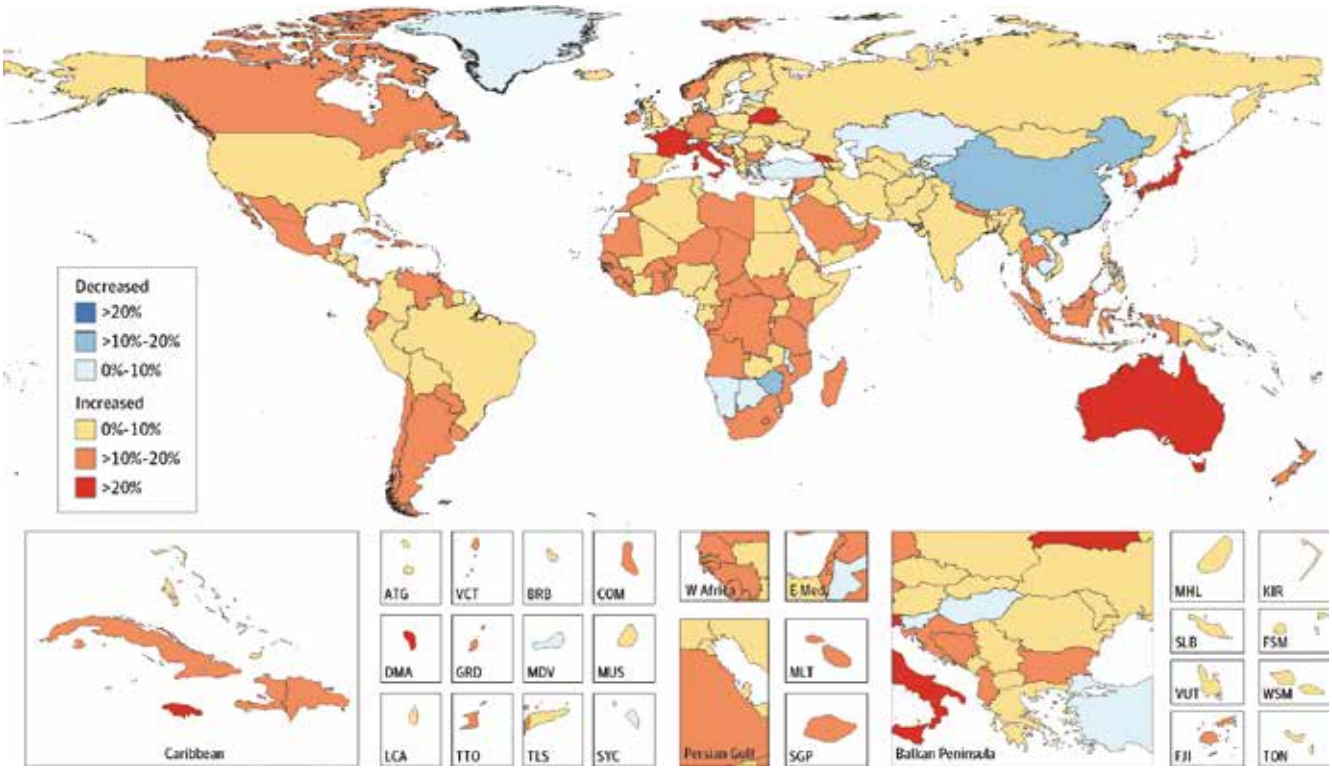

Relative Changes in Age-Standardized Cancer Incidence Rates in Both Sexes for All Cancers in 195 Countries or Territories From 2005 to 2015. Data reflect both sexes for all cancers excluding non-melanoma skin cancer in 195 countries or territories from 2005 to 2015. Source: American Medical Association, in JAMA Oncol. 2017; 3(4):524-548.

A year ago, in May 2017, the World Health Assembly adopted the historic 'Cancer Resolution'. It is an acknowledgement of the fact that although prevention, notably life-style prevention, continues to be important to decrease the incidence of cancer, it is not enough to substantially reduce the burden of the disease.

Development, not only of healthcare systems, but also of education, economies, infrastructures, etc. have all contributed to a general improvement in life expectancy. Cancer is increasingly seen as a disease that we can survive and recover from if society can provide early access to diagnosis and treatments. Compared to previous global policy documents addressing the growing cancer burden, the WHA resolution underlines the need for access to diagnoses and treatments.

A global outlook on cancer epidemiology

Global cancer incidence is steadily increasing and estimated to reach around 23 million new cases in 2030, an increase of 66 % compared to 2012. The rate of increase is larger in low- and middle-income countries mainly due to three factors: a population increase especially in older age groups, a faster decline in mortality from other diseases and an increasing exposure to tobacco in some populations.

A common estimate is that 30 % of cancer deaths could be prevented by lifestyle-related measures: addressing smoking, unhealthy diets and sedentary lifestyles, and by offering vaccination for hepatitis and HPV-infections. There are however still significant gaps in our knowledge about effective strategies to change individual lifestyle habits on a larger scale. Another threat is that we hitherto have seen a pattern where smoking tends to increase under a transition from low to medium income level and only thereafter decline. In that perspective, very large populations are now at risk of being more exposed to smoking.

Cancer mortality is also increasing. The mortality increase is disproportionate between high- and low-income countries, and the risk a cancer will be lethal is much higher in low- and middle-income countries. This is not only due to a higher incidence of cancers with a bad prognosis such as liver and oesophageal cancer in these regions, but also to low access to care. In 2015, less than 30 % of low-income countries reported to the WHO that treatment services were generally available, compared to 90 % in high-income countries. The cancer panorama is also changing in low- and middle-income countries from mainly infectious-related cancers to cancers associated with a westernized lifestyle.

Simultaneously, as a consequence of improved diagnosis and treatment, we experience increasing prevalence of cancer in most countries, except in some poor regions, with an overrepresentation of African countries.

Children – encouraging results, but a slow development

In high-income countries, over 80 % of children with cancer now survive a cancer diagnosis. However, over 80 % of the world's children live in low- or middle-income countries where outcomes are considerably worse. In low-income countries, education of parents in child health and better care pathways could lead to more effective treatment for large paediatric cancer diagnoses where today readily affordable treatments exist.

Despite the promising results from childhood cancer care in rich countries, we still see few resources devoted to research and development for this group. Childhood cancer is a rare disease, representing only 2 percent of all cases and thus the commercial potential for investments in the field is limited. The development of new treatments for children has predominantly to rely on academic research with less financial resources. Another obstacle is that the transition of knowledge from adult cancer to children is far too slow.

Advancements in diagnostics and therapies

An example of the changing biomedical innovation ecosystem is the promising developments in precision medicine. Sequencing technology has opened up for more precise diagnostics, allowing for early detection, even before symptoms appear. Early access to treatment is critical for a positive outcome. The development of rapid gene sequencing, may therefore be one of the technologies that can revolutionize cancer care, also by designing individual therapies to treat individual patients and their individual tumour.

Increasingly, cancers are classified according to which genes are going wrong. Great hopes are placed on the development of immune therapies and cell therapies. The results have also been remarkable for some conditions. In 2017, the FDA for the first time approved a new treatment based on a specific genetic indicator, instead of where in the body the tumour was found, or the tumour type[1]. That same year, the FDA also approved the first two cell therapies, designed to treat advanced lymphomas in adults and acute lymphoblastic leukaemia in children.[2]

But while remarkable advancements have been reported, there is simultaneously a disappointment with many therapies, that have not shown

1 https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm560167.htm

2 https://www.cancer.gov/about-cancer/treatment/research/car-t-cells

more than marginal effects. An evaluation of EMA oncology approvals made during the period 2009–2013, showed that the majority of the cancer drugs approved had led to marginal gains in survival or quality of life.[3]

The informed patient

Another rapidly growing global trend is patients' access to and empowerment by information. Healthcare systems are not yet fully adopted to meet the well-informed patient and family, nor to use the information and knowledge that patients and their kin can contribute with.

The informed patient is not ubiquitous, though. Health literacy and other socioeconomic, as well as cultural, factors influence how patients perceive their role, need and will to have insights and influence the treatment. Does the informed patient have better access to available treatments?

A widening gap

The globally increasing burden of disease imposes large demands on resources for prevention and treatment on already strained health economies. The suggested World Bank *Disease Control Priorities in Developing Countries (DCP3 2016)* essential package of cost-effective and feasible interventions would, if fully implemented, cost 13 % of total public spending on health in low-income countries but would require an even smaller proportion of the budget in high- and middle-income countries.

The increased prevalence of cancer imposes large demands on resources for rehabilitation, management of side-effects, and treatment of recurrences. However, these resources are even more scarce than resources for primary treatment. WHO reported in 2015 that globally only 14 % of all patients needing palliative care got it.

Costs for new therapies have risen to levels that many healthcare providers, even in high-income settings, find prohibitive. It is a seeming paradox that improved survival in cancer leads to new problems, paralleled by the rapid pace of innovations in cancer management, creates a widening gap between what potentially can be done for the individual patient and what is affordable. The increasing gap between possibility and feasibility makes already difficult prioritizations even harder.

A constant flow of new innovations raises questions as to who gets access to the new diagnostic and treatments and at what pace. It has been argued that our infrastructures for making innovations available are not adapted to the new biomedical innovation ecosystem we live in, not even in high-income countries. The value of medical advancements is lost if patients cannot access these therapies.

Differences in access and outcomes after cancer treatment appear on all levels: global, regional and national. There is strong evidence that socioeconomic group and gender strongly influences outcome following a cancer diagnosis.

While on one hand, we see a strong trend of well-informed patients, empowered by information on their diagnosis, and eager to be part of a true dialogue and to participate in decision-making about interventions, large groups still lack fundamental health literacy.

The development of genetic tools, and the surge of data available to support healthcare decision-making, could presumably urge on equal access to the best possible treatment in a given socioeconomic context. But there are many challenges to overcome, as to who shall own and have access to which data; which patient groups or which cancer diagnoses to prioritize in building biobanks and developing biomarkers, just to mention a few.

In the light of patients' growing awareness about the increasing gap between possibilities and affordability, the healthcare system must also be prepared to explain and rationally motivate priorities. Serious healthcare providers who provide evidence-based services should not leave the field open to unreliable actors.

National cancer plans

The WHA resolution urges member states to develop, implement and finance national cancer plans. These have long been strongly endorsed internationally as central to comprehensive cancer control, from primary prevention to palliative care. 87 % of WHO member states reported in 2015 that they had policy, strategy or action plans for cancer, and 68 % reported

[3] Davis, C.; Gurpinar, E.; Pinto, A., BMJ 2017;359:j4530

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that these were operational. However, to achieve an effective management of national cancer issues, the strategy needs to be politically well supported, adequately funded and based on an understanding of current needs and shortfalls, and on reliable estimates of future challenges. One example from high-income settings such as the Scandinavian countries and the UK showing the importance of data, is that reliable data substantiating over-long waiting times for cancer care and socioeconomic differences in outcome after treatment led to strengthening of cancer plans.

Uppsala Health Summit 2018 – Care for Cancer!

When Uppsala Health Summit convenes in 2018, our goal is to launch open and frank dialogues on how we can nurture and take advantage of the latest opportunities created by research and innovation, paving the way for even more patients to benefit from these advances, and for a more equitable access to the best possible diagnosis, treatment and care.

In eight different workshops, we will focus on particular challenges in driving cancer care forward. The workshops will focus on issues that are common to any kind of cancer diagnosis, and conclusions will benefit the general settings for cancer care globally.

It is our belief that the conclusions from Uppsala Health Summit can provide valuable input for the national cancer plans called for in the WHA resolution from 2017 and will inspire further collaborations. It would be a great loss if we close the widening gap between medical possibilities and feasible care plans by slowing down the pace of innovations coming from academia or industry.

References

American Medical Association, *Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015. A Systematic Analysis for the Global Burden of Disease Study*, JAMA Oncol. 2017; 3(4):524-548

Bray F, Jemal A, Gray N, Ferlay J, Foreman D. *Global cancer transitions according to the Human Development Index (2008–2030): a population-based study.* Lancet Oncol 2012; 13: 790–801.

Emmons KM, Colditz GA. *Realizing the potential of cancer prevention – The role of implementation in science.* N Eng J Med 2017;376:986–990.

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. *GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide:* IARC CancerBase No. 11: International Agency for Research on Cancer; 2013.

GBD 2015 Risk Factors Collaborators. *Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study* 2015. Lancet. 2016;388 (10053):1659–1724.

Gelband H, Sankaranarayanan R, Gauvreau CL, Horton S, Anderson BO, Bray F, Cleary J, Dare AJ, Denny L, Gospodarowicz MK, Gupta S, Howard SC, Jaffray DA, Knaul F, Levin C, Rabeneck L, Rajaraman P, Sullivan T, Trimble EL, Jha P. Disease Control Priorities-3 Cancer Author Group. *Costs, affordability, and feasibility of an essential package of cancer control interventions in low-income and middle-income countries: key messages from Disease Control Priorities, 3rd edition.* Lancet 2016;387(10033):2133–2144.

Pritchard-Jones KM, Pieters R, Reaman GH, Hjorth L, Downie P, Calaminus G, Naafs-Wilstra M C, Steliarova-Foucher E. *Sustaining innovation and improvement in the treatment of childhood cancer: lessons from high-income countries.* Lancet Oncol 2013:e95–103.

Torre LA, Siegel RL, Ward EM, Ahmedin J. *Global Cancer Incidence and Mortality Rates and Trends—An Update.* Cancer Epidemiol Biomarkers Prev 2015;25:16–27.

World Health Organization; 2016 *Assessing national capacity for the prevention and control of noncommunicable diseases: global survey.*

Workshop

Precision Medicine in Cancer Care

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Precision medicine aims at "matching the proper medical treatment to the right patient". Cancer perfectly exemplifies the modern trend of precision medicine because, even within a single patient's body, tumours may exhibit diverse properties that often complicate efficient treatment. A simple question presented to a cancer patient today: "What is your expectation of your oncology clinic?" is often met with this honest reply: "Take a sample from my tumour (or even better from my blood), test it for the best possible drug and get back to me with that drug as fast as possible"! Simultaneously, a second question is often asked: "May we take all the data we collect from you and share it world-wide, so that treatment of future patients may be improved?" This down-to-earth conversation captures the deeper challenge that precision medicine in cancer faces today. In short, personalized medicine can be summarized in concrete action points: match the right treatment with the right patient, minimize side-effects of compounds and enable the caring community to improve the design of new treatments and drugs.

Workshop aims

Genomic medicine (or tumour classification based on digital image analysis) generates large data-sets containing sensitive information. To provide standardized and optimized decision algorithms in real-time to the treating doctor, genetic profiles are ideally correlated to cancer phenotypes, such as digital tumour images, disease and treatment outcomes and other informative clinical parameters. Generating knowledge networks requires the sharing of data between hospitals, clinicians, academic researchers and industrial partners. Implementation of existing regulations covering legal aspects, security and protection of patient data and ethical standards is a key aspect in the formation and function of such networks.

The workshop aims at:

1. Generating a checklist for a critical minimum of the types of data that should be stored and shared, in order to facilitate their use to tailor the decision toward best treatment in real-time and for future developments.
2. Identifying major legal and ethical obstacles currently limiting data sharing, and then clarifying how these can be overcome in order to implement the necessary changes in national healthcare systems. Precision medicine can then become a part of routine cancer care and stimulate the development of new therapies and diagnostics.

PHOTO CREDITS: © PREAETORIANPHOTO.

Precision medicine: a paradigm shift in how we treat cancer

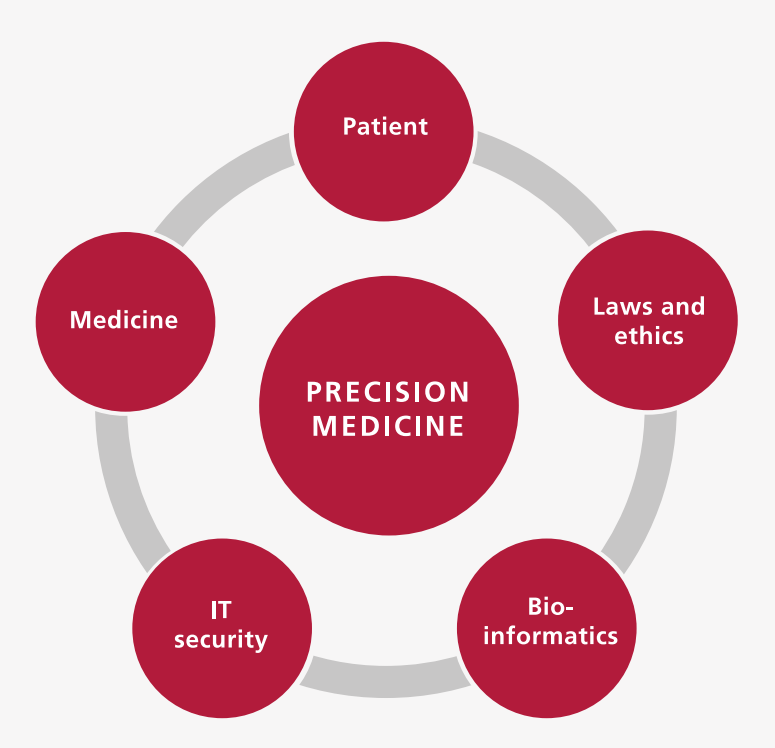
By analysing individual patient susceptibility to cancer development and sensitivity or resistance to therapy, modern genomic sciences rapidly screen the genome of tumours in an individual, identify genetic alterations, and classify this individual using databases and algorithms of cancer type and subtype. The power of modern DNA sequencing is based on high accuracy and rapid delivery of results. The technology is robotized, costs have decreased and the speed of data analysis has picked up. The challenges associated with the need to process large sample numbers at once mean that traditional research laboratories, or oncology clinics, are lagging behind in both infrastructure and IT-capacity.

As new technologies evolve rapidly, their implementation presents challenges that must be dealt with. These include managerial aspects of handling the large amount of data generated, the means by which the information circulates between oncologists and patients and through national/international databases. The shift in clinical practice, needed to support the application of precision medicine, poses ethical and financial problems. Strong computational coupling of all players in the care provision chain is necessary and this requires the implementation of all the relevant technological developments. Effective use of such computational coupling needs to become part of the simple "daily practice" of the modern oncology department.

New competencies needed in healthcare

The interpreter of the precision technology data in the oncology department is ultimately the clinician; who is now asked to collaborate with specialists performing the sophisticated IT-based analyses and yet continue to deliver traditional, simple and concrete diagnostic or consulting services to their patients. In other words, the precision medicine revolution will succeed only when new tools of operation become widespread and routine, and this obviously will involve a new generation of medical professionals who are familiar with both medical and IT language. We may see new workflows where data processing and management require a lot more attention than today, and new structures for the clinical workforce, with bioinformaticians in more prominent roles, bridging the gap between medical professionals and IT experts.

Concrete examples of how today's oncology departments are reorganizing to face the precision medicine evolution can be found in new national initiatives. For example, Genomics England Ltd and Genomic Medicine Sweden are building the infrastructure and communication lines discussed above. Multinational operations, supported by the European Union, coordinate several major oncology departments, with the aim to implement the new models of multicentre identity that facilitate communication, data sharing and effectiveness in patient treatment based on the most up-to-date technological advances.



Precision medicine in cancer demands implementation at a global level via cooperation and open communication between the patient-oncologist unit, the precision research units, the IT security expert panels and the international legal unit. A current challenge in such implementation maximizing efficiency in the overlaps and communication between these principal actors.

A top example is Cancer Core Europe, a consortium of six Comprehensive Cancer Centres[1].

Strategic aspects of infrastructure development

To understand how the biology of an individual affects their medical state, we need reference data with as much detail as possible about the biological variation between humans, and the associated manifestations of cancer. Ideally, we need longitudinal data, with the medical history and observed medical data before and after different treatments, for patients with different genetic setups. The more detail we have in our reference data, the better we will be able to interpret new medical data from an individual and predict optimal treatment. Therefore, *to reach the impact promised by precision medicine, we need to enable the collection and integration of medical and biological data across borders, through the responsible sharing of data between researchers and clinicians*. To drive innovation in diagnostics and therapy, it is also important to enable data sharing with industry. Major pharmaceutical actors are today pro-active in expanding their precision medicine initiatives. While industrial use of the advancements in precision oncology for developing more efficient diagnostics and treatments is a positive thing, uncertainties remain concerning the conditions for access to genomic data.

At the same time, the integrity and privacy rights of the patient have to be safeguarded, and informed consent for data use has to be given or revoked by the patient clearly and unambiguously. Such stringent information handling, and the secure storage, transfer and archiving of patient data all require new IT infrastructures and processes that may be far from what are available today in hospitals around the world. A legal framework of agreements and contracts between organizations, regulating data sharing and management, must be implemented.

Implementing precision medicine in cancer care, meeting the challenges of complex data and strategies for data sharing

The clinical interpretation necessary for cancer care must link the molecular characteristics of an individual patient with data from many other patients, ideally in real-time. Although current clinical practice takes into account only a few actionable genetic markers in reaching clinical decisions, the future challenge is to be able to integrate the correlations between molecular phenotypes and clinical outcomes into decision-making. As more complex analysis inevitably develops, incorporating whole genome/transcriptome information into cancer risk prediction, there will be a growing need for more unbiased processing of large data-sets.

The current practice and immediate future plan is the expansion of large data depositories in super-computer hubs nationally and internationally. Communication and sharing of data between these hubs is of utmost importance. This is easy to state but not so easy to achieve when one considers: a) the perspective of the oncologist needing to access multiple databases; b) the cancer patient wanting to access their own data and protect them legally from unnecessary use or even unanticipated cyber-threats; c) the organized health system wishing to generate informed statistical and policy-driving analyses to inform the general public; and d) the pharmaceutical industry wanting to generate new therapy protocols based on the data.

[1] Cambridge Cancer Centre, the German Cancer Research Centre (DKFZ) and the National Centre for Tumour Diseases (NCT) in Heidelberg, the Val d'Hebron Institute of Oncology in Barcelona, the Karolinska Institute in Stockholm, Gustave Roussy Cancer Campus Grand Paris, and the National Cancer Institute (NKI) in Amsterdam.

When it comes to genomic data, the patient is the legal owner according to established international regulations. The same regulations apply to academic and industrial research units. In Europe, the General Data Protection Regulation (GDPR) gives member countries a unified legal framework and regulates data sharing with non-EU countries. GDPR does not allow data sharing with such countries unless their data protection laws are considered strong enough. For example, the Privacy Shield program registers US organizations deemed to fulfil these data protection criteria set by the EU.

The ongoing centralization of legal authorities and organizations that govern the deposition and sharing of large data-sets needs to coincide with the training of new experts who can work at the interface of law, IT and research, in order for the desired goal of data sharing and internationalized communication to be applied effectively at every oncology department.

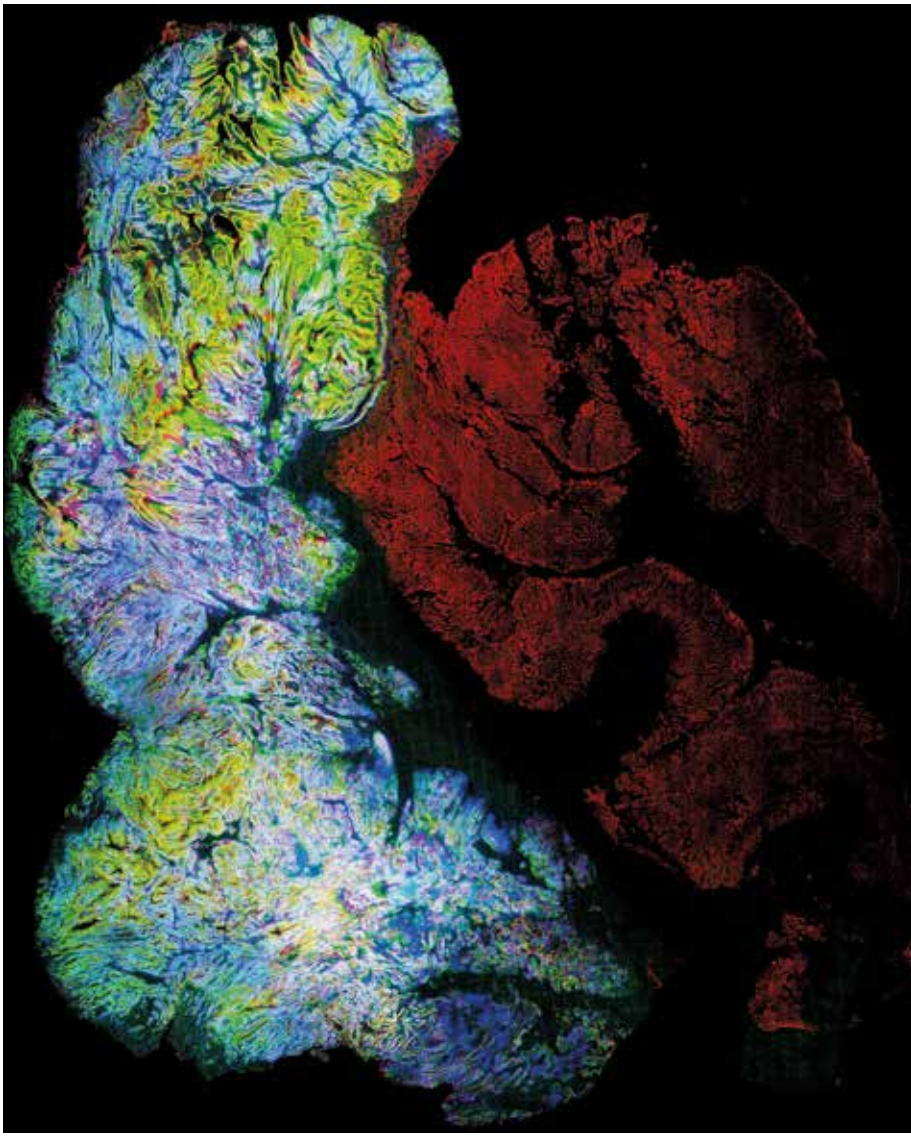
Precision medicine – a technology for all?

Children

The challenge of oncology for children also transcends the technological world: far fewer tumour tissue samples are available which necessitates the use of international biobanks. National approaches, such as Genomics England Ltd and Genomic Medicine Sweden, offer concrete proposals on this front.

Some global dilemmas

- As long as we collect data and tumour tissue from a mainly western/northern population, our knowledge data library will not cover the cancer diseases that are more common in low- and middle-income countries (LMIC).
- Identifying ways of sharing data and collaborating on data analysis is critical for also opening up the opportunities in precision medicine for cancer patients in LMIC, as the establishment of necessary infrastructures will take time to develop in a sustainable way.
- We cannot expect all regions to be ready to take the step into precision medicine before there is a legislative and regulatory infrastructure in place that can provide surveillance and protect patient integrity.



Digital image processing makes it possible to combine markers for protein expression in stomach cancer, and the resulting image information can function as input to an AI system for recognizing pathologies. Data collected by Carla Oliveira et al, IPATMUP/i3S, Portugal, digital image processing by C. Wählby et al, Uppsala University.

This new world in precision oncology aspires to guarantee a much higher security level and a better service level for the patient: the cornerstones of data generation within this field. This workshop intends to map out the opportunities for and obstacles against achieving this on a global scale.

References

Jaffee EM, Dang CV, Agus DB, Alexander BM, Anderson KC, Ashworth A, Barker AD, Bastani R, Bhatia S, Bluestone JA, Brawley O, Butte AJ, Coit DG, Davidson NE, Davis M, DePinho RA, Diasio RB, Draetta G, Frazier AL, Futreal A, Gambhir SS, Ganz PA, Garraway L, Gerson S, Gupta S, Heath J, Hoffman RI, Hudis C, Hughes-Halbert C, Ibrahim R, Jadvar H, Kavanagh B, Kittles R, Le QT, Lippman SM, Mankoff D, Mardis ER, Mayer DK, McMasters K, Meropol NJ, Mitchell B, Naredi P, Ornish D, Pawlik TM, Peppercorn J, Pomper MG, Raghavan D, Ritchie C, Schwarz SW, Sullivan R, Wahl R, Wolchok JD, Wong SL, Yung A. *Future cancer research priorities in the USA: A Lancet Oncology Commission*. Lancet Oncol. 2017;18(11):e653-e706.

Moscow JA, Fojo T, Schilsky RL. *The evidence framework for precision cancer medicine*. Nat Rev Clin Oncol. 2018 Mar; 15(3):183–192.

Korngiebel DM, Thummel KE, Burke W. *Implementing Precision Medicine: The Ethical Challenges*. Trends Pharmacol Sci. 2017; 38(1):8–14.

Workshop

Global Biobanking

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To improve cancer care in low- and middle-income countries (LMICs), it is important that biobanks are embedded throughout the healthcare system, providing fine-grained data and guidance for precision medicine. Currently such data is sparse and much information is lost from LMICs as there is a lack of capacity to aggregate and analyse data in such a way that it can be shared at a national, regional and global level.

Workshop aims

- Develop ideas on how to embed biobanking within the landscape of clinical services and encourage collaboration across disciplines.
- Identify long-term funding opportunities to bring biobanks in LMICs into international collaborations.
- Find mechanisms for strengthening local control over samples and data while encouraging international collaboration.

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By understanding the molecular mechanisms of cancer and why it occurs, we can improve the precision of medical care and deploy more efficient diagnostics, treatments and preventive measures against it. Ten years ago, Time Magazine recognized the potential of biobanks to achieve these objectives and listed them as one of the top 10 ideas changing the world. Since then, significant investments have been made to establish biobanks and improve existing ones, enabling precision medicine to be merged with high-throughput omics technologies. As a result, new tools for healthcare, such as the STHLM3 test which identifies 20 % more aggressive prostate cancers and halves the number of biopsies necessary to diagnose prostate cancer, are making their way into the healthcare system. By providing the infrastructure necessary to handle the samples and time scales necessary for the development of new products and verifying their value in clinical trials, biobanks are an important partner of the industry and the healthcare system.

Certain regions have emerged as of special interest to the global research community. Iceland, with its carefully kept family records spanning a full millennium, and Finland, with its recent genetic bottleneck followed by rapid population growth, are two such examples where small populations and detailed population records make it possible to understand small but important genetic variations within a relatively homogenous population.

For cancer research and healthcare, LMICs offer many significant areas of interest. Africa, as the ancestral home of our species, offers unique opportunities as its unparalleled genetic variation provides a unique insight into the many variations of cancer and genotype-phenotype connections. LMICs in other regions such as South America also offer important insights as their colonial history provides a mixture of African variation with ancestry from the small population(s) that left Africa some hundred thousand years ago, creating a fascinating mixture of high and low linkage disequilibrium between genes. In addition to genetic factors, LMICs are exposed to distinct environmental and lifestyle factors and have a high burden of infectious diseases that contribute significantly to cancer development.

Strengthening the biobanking capacity of LMICs across the globe is also a matter of national interest in these countries. Improving living standards means that the cancer incidence rate is growing rapidly in LMICs as other, more easily treated, causes of death are prevented.

Improved diagnostics and new cancer treatments significantly improve the quality of life and also provide long-term economic benefits as the average number of productive years increases with increased longevity. Cancer is however an extremely burdensome disease both for the healthcare system and sufferers. Patients remain under care for long periods and require continuous monitoring by doctors to optimize the treatment regime, meaning that also high-income countries are struggling to handle the ever-increasing healthcare costs. In LMICs, where resources are limited, there is great benefit from developing cancer prevention and control programmes. Biobanks play a key role in this research as they provide results and the evidence to develop effective prevention programmes in these settings.

Precision medicine refers to the tailoring of medical treatment to the individual characteristics of each patient by classifying them into subgroups likely to respond favourably to different treatments and is seen as one of the most promising ways to improve cancer treatment. Just as blood typing is a prerequisite for blood transfusions, a similar approach can be taken to optimizing treatment regimens for cancer. Precision medicine is however highly dependent on large-scale biologic databases, powerful omics methods for characterizing patients and computational tools for characterizing disease profiles and the populations suffering from them[1].

Even with a more traditional "blockbuster" approach, it has been realized that many drugs and treatments may require revisions between different populations[2]. With precision medicine, this need for local adaptions becomes even more vital to the development of effective treatments and the establishment of biobanks and research infrastructures for the characterization of populations as well as of their ailments will be necessary to provide modern healthcare in the coming years.

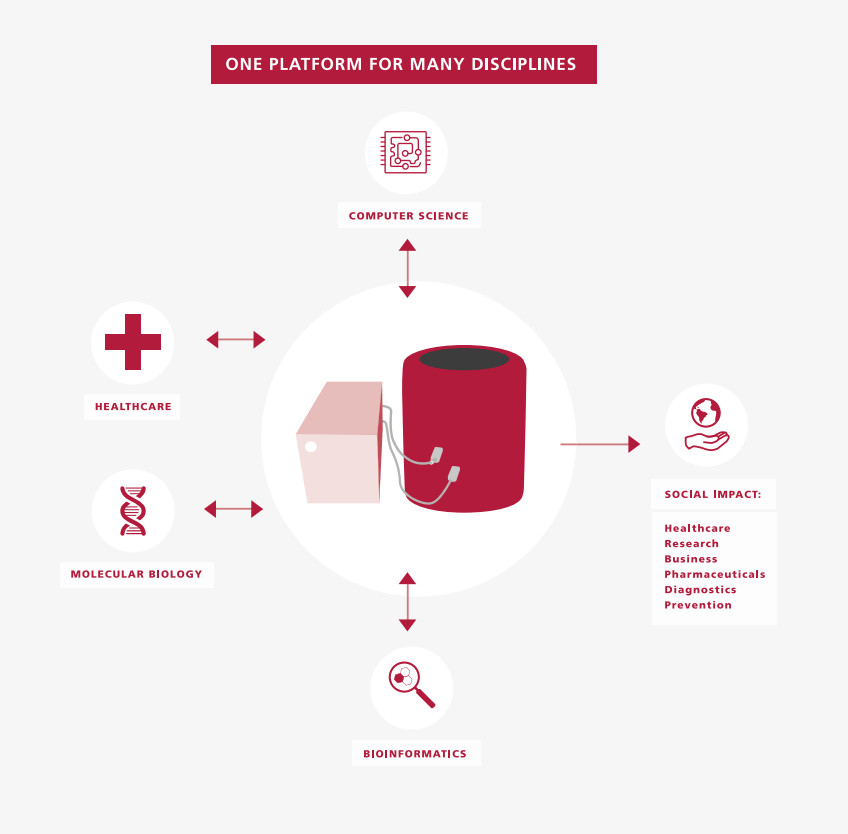

Figure 1. Example of an image illustrating the complex interactions of a biobank.

Building the biobanks we need

Medical and research biobanks are complex operational entities that must be embedded within the healthcare infrastructure and aligned with local research capacity[3]. Healthcare staff must be trained to obtain consent, quickly stabilize samples when they are extracted, process samples and transfer them to a suitable location for long-term storage. From a technical perspective, it is important that biobank operations are supported by a robust and comprehensive data management platform. Medical professionals, molecular biologists, bioinformaticians and computer scientists are all specialists vital to the large-scale research projects enabled by biobanks and must all be able to access study data (Figure 1). For daily operations, it is also important that samples can be tracked throughout the process and that sensitive personal data are tracked, updated and, if necessary, deleted from the system when requested. Establishing such an infrastructure requires a significant upfront investment and there are usually several years

1 Collins and Varmus, 2015.
2 Dandara et al., 2014.
3 Klingström et al., 2016.

between when a project is initiated and when the first impact can be assessed.
In LMICs, there are several factors that prevent governments from committing funding for long-term biomedical research infrastructures. This disadvantage has resulted in an ethically doubtful practice, referred to as "helicopter research", where researchers from high-income countries arrive, collect and leave. As a consequence, there is no consistent quality control over the entire research process and follow-up studies become hard or impossible to carry out as no sustainable infrastructure is created. Another destructive outcome from this practice is the growing reluctance from LMICs to share data and bio-resources. Mandatory consent forms are becoming increasingly restrictive with regards to how samples or data may be transferred or used for multiple purposes. As a result, biomedical research international collaborations can be negatively affected and consequently, new discoveries to improve human health are delayed.

International cooperation, investments and co-funding, are necessary to empower research capacity building in LMICs. Without control over data and the ability to analyse it, increased restrictions for sharing are a natural response as countries struggle to avoid exploitation where valuable data leave the country and generate innovations that are then sold back, at a high price, to the countries that made them possible. Empowering local research institutions allows countries to better assess the benefits, as well as the risks of international collaboration, and thereby limits the need for general restrictions against sharing and collaboration. This increases and enables collaboration while limiting the risk of nationally important research projects being completed outside the country without returning any tangible benefits to the national healthcare system. Longitudinal studies could be carried out in those countries as well as monitoring of sample donors and improvement of quality of the research process. Empowering research capacity building in LMICs will also contribute to building trust and stimulating global biobanking and global research collaboration.

Initiatives such as the Human Heredity and Health in Africa (H3Africa) initiative, Bridging Biobanking and Biomedical Research Across Europe and Africa (B3Africa) and Biobank and Cohort Building Network (BCNet) are therefore important contributions to global research as well as the implementation of national cancer care. The projects provide access to funding and training for healthcare staff and researchers that are necessary for the implementation of National Cancer Control Programmes while also bringing together stakeholders for the development of regulatory frameworks regarding the management of samples and associated data.

Current status of biobanks in LMICs

Biobanking is dominated by the West even if other regions, especially Asia Pacific, are rapidly gaining ground[4]. In South America, many countries have a relatively high number of medical professionals per capita compared to other LMIC regions but lack the biobanks and modern infrastructure to run large-scale biobank-based research projects[5]. In comparison, Africa, despite its genomic significance on a global scale, is severely underdeveloped in respect to healthcare as well as research capacity. Investments in several flagship institutions for biobanking by the H3Africa project and capacity building by BCNet[6] and the Pan African Bioinformatics Network for H3Africa (H3Abionet) are however rapidly expanding the capacity of biobanks and associated research on the continent.

The way forward for biobanking

To advance biobanks in LMICs, it is necessary to combine political initiatives, establish flagship institutions and promote bottom-up initiatives where dedicated researchers and hospital staff are given the opportunity to increase research capacity and engage in translational medicine based on their own initiatives and needs.
The B3Africa project has developed an informatics platform that significantly reduces the technical complexity and costs of establishing a biobank[7].

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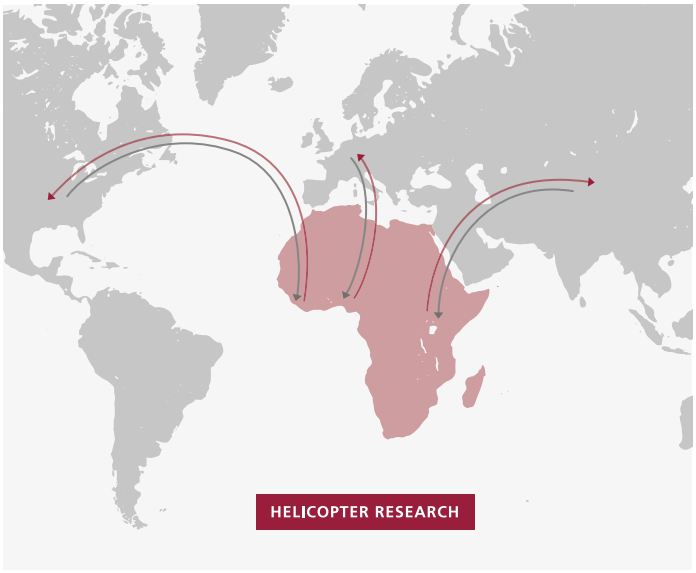
4 Astrin and Betsou, 2016.

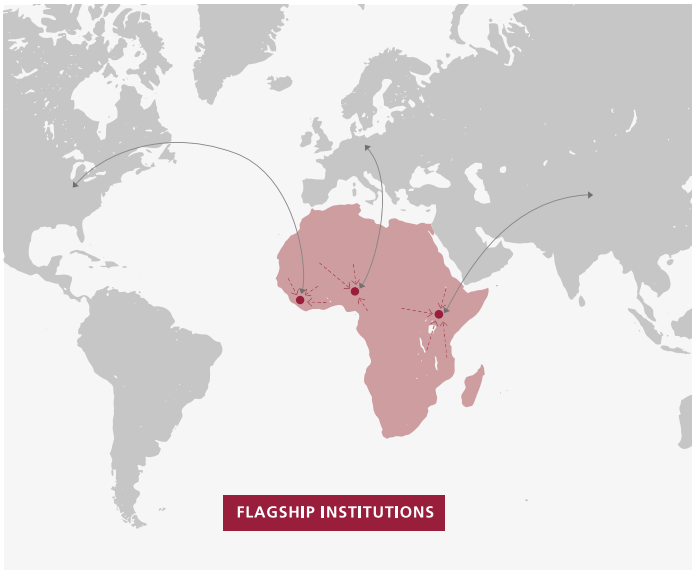
5 Hernández-de-Diego et al., 2017.

6 Mendy M, Caboux E, Sylla BS, Dillner J, Chinquee J, Wild C., 2016.

7 Klingstrom et al., 2016.



Helicopter research: Project-driven funding in combination with weak local research capacity means that collaborations often take the form of sampling with both samples and research results leaving the area.



Flagship institutions: Flagship institutions are established but geographic coverage is poor and the ability to analyse samples and interpret results is still limited. Meaning that local benefits are limited.

Combined with training from BCNet, H3ABionet and the establishment of flagship institutions[8] by the H3Africa project, this means that many of the key components necessary for the establishment of widespread biobank operations are now available in Africa. There is also a growing availability of highly trained researchers committed to the cause of building research infrastructure and distributing funding based on local needs rather than international aid projects[9]. To capitalize on this favourable situation, it is therefore important to get initiatives going that help to capture key talents and justify future investments in the sector. More specifically there is a need of:

- Applied projects that build infrastructure, train staff and can form the basis of future biobanks.
- Sustainable funding that must be available and scaled up as the infrastructure improves.
- Collaborative models between high-income and LMIC countries that must be developed where results and not people are being exploited.
- Cutting-edge technologies transfer to LMICs where relevant studies are carried out to guarantee the same level of participation and benefit from research outcomes.

There is a lack of trust and in many LMICs there is a feeling that valuable samples often leave the country and that results then generated from them are sold back at a high price. As a response, regulatory barriers towards sharing have been built which deprive the world of valuable genetic information and LMICs lose a valuable opportunity to achieve funding for the establishment of national research infrastructures for translational medicine and cancer care.

With increased availability of technical infrastructure and trained professionals, this is an excellent time to build up infrastructures that serve as bridges between continents. There have never been more researchers available to combat cancer across the globe and national governments recognize the importance of international collaboration, even if patience is limited after previous failures. Building projects based on mutual interest is therefore not only feasible but a strategic priority for high-income countries. By strengthening local researchers in LMICs, logistics chains become shorter, cheaper and with advanced local analysis capacity, the cost-benefit ratio of new projects is significantly improved. At the same time, tapping in to the vast genetic resources available in LMICs not only improves their local healthcare but can also help high-income countries to better understand the molecular mechanisms of cancer for the further development of their own national cancer plans and the repositioning of drugs for improved treatments.

8 Douglass, 2014.

9 The Alliance for Accelerating Excellence in Science in Africa (AESA).

Desired situation: Biobanks are embedded throughout the healthcare system providing fine-grained data and guidance for precision medicine. Data are analysed locally but also aggregated and shared at a national, regional and global level.

References

Astrin, J.J., Betsou, F., 2016. *Trends in Biobanking: A Bibliometric Overview*. Biopreservation Biobanking 14, 65–74.

Collins, F.S., Varmus, H., 2015. *A New Initiative on Precision Medicine*. N. Engl. J. Med. 372, 793–795.

Dandara, C., Swart, M., Mpeta, B., Wonkam, A., Masimirembwa, C., 2014. *Cytochrome P450 pharmacogenetics in African populations: implications for public health*. Expert Opin. Drug Metab. Toxicol. 10, 769–785.

Douglass, J.A., 2014. *Profiling the Flagship University Model: An Exploratory Proposal for Changing the Paradigm From Ranking to Relevancy*.

Hernández-de-Diego, R., de Villiers, E.P., Klingström, T., Gourlé, H., Conesa, A., Bongcam-Rudloff, E., 2017. *The eBioKit, a stand-alone educational platform for bioinformatics*. PLOS Comput. Biol. 13, e1005616.

Klingstrom, T., Mendy, M., Meunier, D., Berger, A., Reichel, J., Christoffels, A., Bendou, H., Swanepoel, C., Smit, L., Mckellar-Basset, C., Bongcam-Rudloff, E., Soderberg, J., Merino-Martinez, R., Amatya, S., Kihara, A., Kemp, S., Reihs, R., Muller, H., 2016. *Supporting the development of biobanks in low and medium income countries*. IEEE, pp. 1–10.

Mendy M, Caboux E, Sylla BS, Dillner J, Chinquee J, Wild C; *BCNet survey participants. Infrastructure and facilities for human biobanking in low- and middle-income countries: a situation analysis*. Pathobiology. 2014;81(5–6):252–60.

The Alliance for Accelerating Excellence in Science in Africa (AESA), n.d. *About AESA*. http://aasciences.ac.ke/aesa/aesa/programmes/overview/ (accessed 3.1.18).

Workshop

Clinical Value and Price-setting for New Cancer Drugs

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In the last twenty years, as a consequence of considerable research activity, science has made rapid progress in the field of cancer research. This has resulted in many new approved treatment options along with countless other products which are currently in development.

Some of these new products can provide significant clinical improvements to the available alternative, others perhaps offer only limited additional value. However, the true additional clinical benefits of a new drug can be difficult to judge from early clinical trials and may not be established until after years on the market. This process will require long-term follow-up including patient-reported outcomes.

The cost of new treatments is often substantial and the bodies responsible for payment and reimbursement have to make difficult choices that restrict patients' access to these new drugs. This raises important questions for all stakeholders.

Main focus areas

Our goal is a more balanced understanding of the true clinical value and fair price-setting of new cancer drugs. We aim to initiate discussions about:

- the appreciation of a lifecycle perspective to achieve a more comprehensive, dynamic, balanced, sustainable, and knowledge-based foundation for the continuous evaluation of the true clinical value (benefits-risks) and as a base for prioritization, health-economy evaluations, and price-setting at a certain time-point post marketing.
- the potential implications of a lifecycle perspective for the formal decisions and communication ("information package") of marketing approvals by the authorities as well as the potential implications for other stakeholders.
- sustainable models for price-setting which reward continuous monitoring and gathering of knowledge.

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Cancer – a major threat to population health worldwide

Globally, cancer is the second leading cause of death, being responsible for nearly one in every six deaths[1, 2]. Late-stage presentation and inaccessible diagnosis and treatment are common. In 2015, only one in three low-income countries reported having diagnostic and treatment services generally available in the public sector[3]. The economic impact of cancer is significant and is increasing. Its total annual economic cost worldwide in 2010 was estimated at US$ 2.5 trillion including costs for diagnosis and treatment and productivity lost due to the consequences of the disease[4].

The trend towards more tumour-specific drugs

Progress in molecular medicine has led to greater understanding of how cancer evolves, how cancer cells are characterized by, for example, defects in DNA repair mechanisms or with respect to cellular signal transduction pathways (hormonal, growth factors, immunological). Accumulating understanding of cancer pathophysiology has also led to new approaches to the design of new cancer drugs and the development of such drugs is moving faster than ever. A large proportion of drug development today is allocated to cancer drugs. Among US biotech companies, half focus on cancer and in 2015 more than 800 new cancer agents were said to be in development[5]. The trend is that new cancer drugs are often designed for very tumour-specific characteristics (e.g. immunological, genetic, etc.) leading to limited indications aimed at smaller patient subpopulations within a certain cancer form. In some cancer forms, where standard treatment is ineffective, the great demands for new options give some of these drugs higher priority ("fast track") by the authorities in the regulatory process.

How can new improved therapeutic options become available to all those who would benefit?

The development of newer and potentially more effective cancer drugs has for some cancer forms improved the therapeutic options. However, these drugs are not even available in high-income countries for all who might benefit from them because of high prices and limited healthcare resources. These circumstances put increasing demands on healthcare systems to prioritize between the available treatments and indications in order to get maximum benefit for their limited resources.

1 Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C et al.

2 International Agency for Research on Cancer, IARC.

3 World Health Organisation, *Cancer, Fact sheet*, 2017.

4 International Agency for Research on Cancer, IARC.

5 Jönsson, B., Persson, U., Wilking, N.

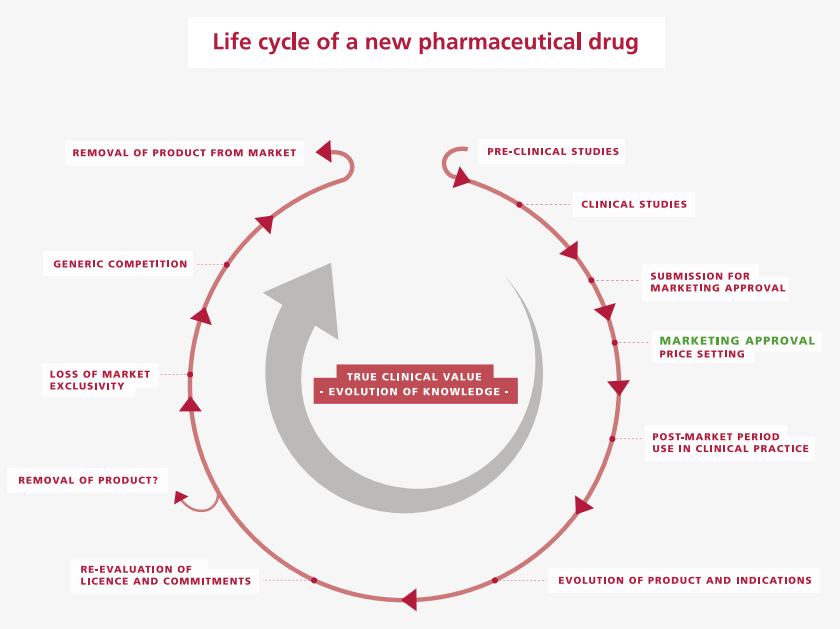

Fig. 1.

The regulation of health products, e.g. cancer drugs, is a critical component of every country's public health system and ensures that high-quality, safe, and effective products reach those who need them most as fast as possible. However, regulatory systems can differ between regions of the same country, both in terms of the models applied and their capacity to assess and monitor drugs. The models to allocate priority to certain cancer drugs/treatments but not others also differ between healthcare systems all over the world and are more or less developed globally[6]. Thus, enabling platforms for collaboration and harmonization of these processes and transferring knowledge between regulatory authorities in different countries would be one of several actions which could challenge these differences.

Adopting a lifecycle perspective towards new cancer drugs

Drug development is a difficult and time-consuming process often taking up to 10 to 15 years and combining both great potential with significant risk. The investment required for individual drug development is high and only a fraction of the compounds in preclinical testing ever make it to clinical trials and approval for patient use. When marketing approval for a drug is given by the authorities, the decision, based on the product documentation, is made from a balanced consideration of the benefits and risks. However, the true magnitude of the effect of a new drug is often uncertain at the time of marketing approval. One reason is that the clinical documentation in the application for marketing approval is sometimes based on studies with rather small numbers of patients, and often with a short-time follow-up (so-called phase-2 studies). Although there are outcomes in the registration files that give the authorities useful predictions of potential benefits of a new drug, many data are still associated with a high degree of uncertainty. Another reason is that the preconditions for using a drug in routine clinical practice differ to those in a clinical trial. Many perspectives, e.g. patient selection, age, stage of the disease, concomitant diseases, etc., may change when a new drug takes the step from clinical trial into clinical routine. These factors have quite an important influence on the outcome of both effects and side-effects of a drug. Thus, the clinical value of a new drug is uncertain and not fully determined at the time of approval, not at least with respect to long-term data on effect, side-effects and especially as a basis for health-economic considerations. The knowledge of the clinical value of a drug evolves continuously during its lifecycle (Fig. 1). Thus, there is still much to do in order to develop a process of continuous collection of knowledge for the understanding of the true, short- and long-term clinical value of new cancer drugs. This is important from many perspectives, from the patient's view (e.g. improved measurements and collections of life quality data) as well as from the view of society (e.g. firmer ground for health-economic evaluation compared to already existing treatments and for price-setting and negotiations).

Thus, when the level of knowledge of a drug at a certain time during its lifecycle is known, then the willingness to pay (the buyer's perspective) for the product can be based on much firmer grounds.

Fair price-setting for all stakeholders

New possibilities to cure, or at least delay, cancer have been presented frequently during the last decade and often take the form of new pharmaceutical drugs or a new combination of drugs. The pharmaceutical industry claims that the high price-setting of many new drugs is motivated by high development costs. However, if new medicines and health products are to be used to optimal effect, they must be available at affordable prices. The price paid for new

6 World Health Organisation, *Towards Access 2030*, 2017.

products (as well as existing ones) must be fair to all – affordable in different countries yet sufficient to ensure a sustainable industry to produce them. Establishing fair and transparent pricing models valid during the lifecycle of a drug is thus an urgent priority. New drugs, including cancer drugs, get their marketing approval at a time point where the effect and safety documentation is limited and partly uncertain, especially with respect to long-term results. It is therefore important to find fair pricing models, taking a lifecycle perspective into account, to share the financial risks between stakeholders (producers and vendors; buyers and payers).

Determining the true clinical value. Can new options be created that enable continuous collection of evidence after marketing approval?

This workshop will involve the participants in suggesting feasible strategies for allocating priority to certain drugs/treatments and establishing models for monitoring healthcare outcomes of new cancer drugs. This will be done in the context of an imaginary country (e.g. an OECD-country) with established authorities.

According to which principles should stakeholders (producers and vendors; buyers and payers) in healthcare make new, promising cancer drugs available and affordable for those patients where the effect is optimal?

What options are there to include a lifecycle perspective for all stakeholders to accumulate knowledge of a drug post marketing and not only focus on marketing approval per se, and what will it take?

What are the prerequisites for sustainable models for price-setting and financial risk-sharing between stakeholders (producers and vendors; buyers and payers)? The more we know about a drug's benefits and risks (clinical value), the more precisely we can find acceptable models for price-setting and willingness to pay at certain time-points of knowledge post marketing approval. Is it possible to allocate priority to certain cancer drugs/treatments but not to other cancer drugs?

How should new cancer drugs be monitored with respect to real-life data after their introduction into healthcare routines? It is complicated for practical reasons and often impossible from an ethical perspective to perform traditional randomized controlled trials (RCTs) of a certain drug post marketing approval. But then, what are the alternative strategies for obtaining data for the true clinical value based on scientific methodology? Can data from, for example, a quality register or computerized medical records help us to assess the true clinical value of new drugs? Is the essence of what a market access decision covers well understood by patients and healthcare? Or is there a risk of misinterpretation or misunderstanding? Is inclusion and consideration respectively, of data from patients' experienced value of the therapy and the life quality it provided, compulsory in the background documentation for the determination of the clinical value of specific new cancer drugs? How should we consider the perspectives of children and older people respectively in order to achieve information on, for example, the influence of age-specific factors of life quality, tolerance and safety of a specific new cancer drug?

When a new, potentially effective cancer drug appears in clinical routines, some years from now, how shall we manage a controlled introduction for access, use and follow-up in order to assess the true clinical value of the drug? How acceptable are such measures to different stakeholders such as regulators and ministries of health, medical practitioners, consumers, and pharmaceutical industries?

There is obviously a demand for international and stakeholder interactive activities to meet the challenges of all aspects of cancer disease therapies in the future. Do we have the platforms, national and international, for these types of interactive discussions between different stakeholders?

References

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. *GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide:* IARC CancerBase No. 11: International Agency for Research on Cancer; 2013.

International Agency for Research on Cancer, Stewart, B.W. and Wild, C.P. (editors) *World Cancer Report 2014*.

Jönsson, B., Persson, U., Wilking, N., *Innovative treatments for cancer in Europe-value, cost, and access*. IHE Report. 2016:2, 2016.

World Health Organisation, *Cancer, Fact sheet*, Feb. 2017.

World Health Organisation, *Towards Access 2030: WHO Essential Medicines and Health Products Strategic Framework 2016–2030, (WHO/EMP/2017.01),* 2017.

Workshop

Long Term Care for Cancer Survivors

– Striving for the Best Quality of Life Possible

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The number of long-term cancer survivors is steadily increasing primarily in high-income countries, with the arrival and increased use of successful treatments. A similar increase is projected globally in low- and middle-income countries alongside the steady improvements and developments taking place in healthcare systems, where increasing attention is given to non-communicable diseases.

Survival rates increased rapidly in the 1970s and 80s, due to improvements such as novel intensive treatment regimens, better supportive care, and adequate risk-group-adapted treatment and clinical organization.

Earlier, just being alive was previously an adequate source of contentment for both cancer survivors and the healthcare professionals who had treated them. However, with the development of more successful treatment methods, increasing numbers of survivors, and with this "new normal" where more patient groups are expected to be cured, this attitude is increasingly being replaced by the understanding that mere disease cure is not enough. Ex-cancer patients expect and demand the opportunity to live as full and rich a life as possible. Cumbersome long-term or late side-effects, such as secondary tumours, infertility, cardiac and neuropsychiatric toxicity limit their ability to do so. These issues are now rightly receiving more attention.

Desired outcomes from the workshop

- Guidance regarding the creation of national cancer plans globally to include systems for long-term follow-up of cancer, building on existing experiences and guidelines for young cancer survivors
- Guidance on development of sustainable post-cancer knowledge centres or systems whether virtual or real, adaptable to local context; defining reasonable minimum elements required for their establishment

Taking into consideration:

- limited resources in most settings; guidance on prioritization,
- good patient engagement practices,
- the need for effective detection of both known and hitherto unknown late side-effects of treatment to allow improved treatment and potentially prevention,
- variable health literacy among patients: not every patient can be expected to be their own strong and responsible advocate.

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A paradigm shift in our perception of cancer could be imminent

With rapid development of targeted drugs and other modern treatment modalities on the horizon, a true paradigm shift in the perception of cancer diseases appears to be within reach. If new drugs continue to deliver improved levels of disease-free survival, we may in the future be able to compare development in the cancer field as a whole with the HIV epidemic before and after the arrival of antiretrovirals, or with renal failure before and after the emergence of dialysis and renal transplants. Zero or low long-term survival rates could be replaced by a situation where most cancer patients survive and live long and healthy lives. Managing and minimizing the long-term side-effects of treatments, again when mere survival is not enough to satisfy us, is becoming an important focus for the future.

How do we globally move towards this goal of post-cancer life being as healthy and fulfilling as possible? What best practice can we all learn from and what are the most important issues to tackle?

Detection—Treatment—Life
The uneasy transition from oncology to other levels of healthcare for the ex-patient

A young male patient has completed his gruelling treatment for cancer. He is cured. He has started to adjust following an excruciatingly overwhelming period of his life where every day has been meticulously controlled according to some carefully crafted plan. The staff at the oncology unit have been his and his family's close allies for months or years. The oncology follow-up is over and he is waved off to live the rest of his life. After initial adjustments, he starts believing in a normal future. A bright future lies ahead. Everything is over. Or is it?

Our patient may have received some information from his oncologist on the need for future handling of remaining post-treatment side-effects or on the potential risk for new cancers. He may have joined an online support groups of more or less informed co-patients.

The gap is enormous between immediate handling of the disease which the oncologist with other specialized staff are well equipped to do, and what comes after this period.

Gaps in the knowledge of the non-oncologist

When a health problem arises later in a patient's life, he may, depending on its nature, not necessarily seek the aid of his oncologist, as he may not suspect a connection with previous treatment. The non-oncology part of the healthcare system, e.g. primary healthcare professionals, will probably lack essential knowledge and insight into the possibility of a causal relationship with previous cancer treatment. This may lead to unnecessary delays in correct diagnosis and treatment or even a lack of adequate treatment.

The patient's doctor, a general practitioner (GP), may or may not have been handed information on the treatment from the treating oncologist, a treatment she may only be vaguely familiar with. There may be some suggestions for future need for further long-term follow-up, whether or not available. She may have had no training of common or rare drug-induced long-term health problems and since she would only rarely meet such patients, it would be difficult for her to discern iatrogenic from idiopathic health problems, which may require very different treatments to be successfully handled.

In essence, primary and secondary care professionals usually lack experience in delivering effective aftercare to cancer patients. In the best-case scenario, non-oncology healthcare professionals may have had some training on diagnosing and managing cancer patients early in their careers, but as knowledge evolves over time and, as skills and knowledge not constantly practised will obviously wane, the management of these patients may not be optimal even with otherwise skilled non-oncologists.

One must also realize that not all patients and settings are equipped to manage larger parts of their own care to an extent that is sometimes optimistically projected. Different solutions for different situations must be considered.

Whose responsibility is it to identify survivors' health issues as potentially late effects of a previously treated cancer? Presumably not the patients themselves, so should their GPs take the responsibility? How can knowledge be disseminated throughout healthcare systems? How can we reach survivors, not yet included in follow-up programs, to give them access to new methods for prevention and treatment of long-term negative health effects of cancer treatment? How can information on growing needs be integrated in healthcare systems, what kind of training would be desired and how can patients themselves be more actively engaged in the improvements in this area?

In some settings, creating paramedical oncologic positions for specially trained auxiliary staff could be discussed to cater for some patient needs, both regarding early and late aftercare, and act as a filter and contact point for more qualified oncology staff.

Some long-term negative effects have a high relative risk and may hence be known to science and hopefully also clinically. On the other hand, rarer and/or less severe effects may go undetected by patients and the healthcare system but nonetheless affect the survivor's quality of life. Effective methods to detect such problems need to be further developed in relation to long term follow-up of survivors.

The key role of patient organizations

In diagnoses with a higher incidence and higher levels of survivorship, patient organizations are more and more actively pressing for engaging patients in the development of all parts of care, e.g. in the increased integration of care between specialists in oncology care and primary healthcare. Patient groups may also be successful in detecting and handling (new) side-effects of their treatments, for example via discussion fora or other means. Regarding rarer cancer diagnoses, with their respective treatments, such patient movements are less powerful to successfully engage in change. The degree of patient empowerment and engagement is influenced by factors such as the size of the overall population in a country, language or cultural barriers and the level of overall health literacy. Patient move-

ments and support organizations have so far been most prominent in North America, and European ones are gradually gaining in importance and visibility.

Electronic medical records accessible to both healthcare providers within a system and patients exist in some countries and make the sharing of information easier. These are still not commonplace, however, which renders information-sharing more challenging. Systems also vary between countries and regions due to data protection policies, practical organization and development levels of healthcare, where different institutions' software tools may not "communicate" with each other, creating barriers to improvement of patient care.

Resources and constraints

Time and resource constraints are present in healthcare in most countries. How can we, despite this, achieve high quality in the long-term care of cancer patients? Primary healthcare, if at all available, is often under strict time and economic pressure, how does this kind of care fit in and be supported to help manage after-care?

Risk-adapted care is important in order to use limited resources in a responsible way. To accomplish this, cooperation between patients, specialists from oncology with knowledge of possible risks from cancer treatments and organ specialists is essential. We need to form multidisciplinary teams around these patients.

Often in these situations, one can argue that the additional effort to provide comprehensive assessment and management as well as care coordination for patients with complex needs may result in further strain at the primary care level, even if these efforts may generate savings overall for the healthcare system or the society as a whole.

Moving forward to achieving sustainable, long-term aftercare with the ultimate goal of caring for former cancer patients living a good-quality life will require joint, forward-looking efforts by healthcare policymakers, medical professionals, patients (assumingly predominately through advocacy organizations), and other stakeholders.

Gathering the experiences from childhood cancers

Childhood cancer is the field where long-term aftercare efforts have developed the furthest and hence may serve as best practice for subgroups of cancers in adults with improving survival rates. The follow-up organization of childhood cancer survivors began in the United Kingdom (UK), where recommendations for long-term-follow up were published in 1995. The UK National Health Service (NHS), in the beginning of the 2000, established an organization for long-term follow-up of childhood cancer survivors.

In North America, the first follow-up recommendations were published a few years later and have thereafter continuously been upgraded by the Children's Oncology Group (COG). In Sweden, recommendations for long-term follow-up of childhood cancer survivors were developed in 2007 but were mainly known by paediatric oncologists. This resulted in reasonably good follow-up until the age of 18, when the patients were supposed to be incorporated into adult care. However, many complications develop later in adult life and are of many different types which could involve almost any medical specialist area. Long-term follow-up for childhood cancer survivors in adult care was at that point only existing in three of the six healthcare regions.

The Swedish Strategic Cancer Plan was published in 2009. It included five main goals, of which one was to increase the survival time and to improve the quality of life of cancer survivors. This presented a natural opportunity to write Swedish national guidelines on long-term follow up for childhood cancer survivors. It included a cycle of referral to national societies of specialities and presumed user organizations. This has increased the awareness of this patient group in Swedish healthcare. Long-term follow-up clinics for adult survivors of childhood cancer are now in operation in five out of seven university hospitals in Sweden.

Examples from Sweden include: A "survivorship passport", which includes a treatment summary and recommendations for follow-up, developed during the 1990s. In 2012, a new part of the Swedish childhood cancer registry was

launched, which included treatment summary data and the possibility to register recommendations for follow-up. The doctor responsible for the patient can give the patient and other caregivers a pdf-version of a personal survivorship passport from the registry.

The SIOP[1] Strategic Plan was published in 2015 by the European Network for Cancer Research in Children and Adolescents (ENCCA), a network of excellence that was run from 2011 to 2015 under the EU 7th Framework Programme for Research and Innovation. In a subsequent Horizon 2020 project, there are seven objectives including: to improve the quality of survivorship; to address the consequences of cancer treatment such as long-term side-effects; to better understand the genetic background/risk of an individual; and to improve the quality of life of childhood cancer survivors.

PanCare is a pan-European multidisciplinary network of health professionals, survivors of paediatric cancer and their families. Its goal is to reduce the frequency, severity and impact of late-treatment side-effects, with the aim of ensuring that every survivor of childhood cancer receives the best possible long-term care. The number of childhood cancer survivors is currently estimated to be more than 300 000 in Europe, a figure that is expected to rise to around 750 000 in 2030.

The Childhood Cancer Survivor Study, or CCSS, is a component of the Long-Term Follow-Up Study, which began in 1994 and is a collaborative, multi-institutional US study. The CCSS is coordinated through St. Jude Children's Research Hospital in Memphis, Tennessee. The study includes more than 35 000 childhood cancer survivors diagnosed between 1970 and 1999, and over 5 000 siblings of survivors who serve as the comparison group for the study.

The International Late Effects of Childhood Cancer Guideline Harmonization Group, IGHG, is a worldwide endeavour initiated by several national guideline groups and the Cochrane Childhood Cancer Group in partnership with the PanCareSurFup Consortium to collaborate in guideline development. The goal is to establish a common vision and integrated strategy for the surveillance of chronic health problems and subsequent cancers in childhood, adolescent, and young adult cancer survivors. So far, harmonized guidelines have been published in four different areas, and work is ongoing for many more.

[1] The International Society of Paediatric Oncology.

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Workshop

Towards Useful Cancer Biomarkers to Improve Care for Cancer

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Early discovery followed by efficient surgical resection of a local tumour translates into high long-term survival for people with cancer. Furthermore, the effectiveness of cancer care would greatly increase if there were simple tests that determine if a tumour will recur or respond to a specific treatment. Blood biomarkers for early detection, as well as prediction of drug response or disease recurrence, have therefore been intense areas of research for the past decades. However, progress has been limited as evidenced by the low rate of regulatory approval of such tests.

In this workshop, we will discuss measures to enhance and accelerate biomarker discovery and validation processes to improve effective transition into clinical use. A breakthrough in this field would be of great interest to many actors: oncologists, researchers, regulators, funders, the pharmaceutical industry, etc. A greater range of proven biomarkers for all types of cancer, if quickly and robustly discovered, validated and put to clinical use, will transform the lives of millions of patients by greatly improving cancer detection, treatment selection and knowledge in prognosis decisive for follow-up and decisions on adjuvant treatment. Much more effective 'discovery to application' processes would make better use of scarce funds, precious clinical samples, focus regulatory attention, target scientific effort, enhance academic-industry linkages, and hasten product to market business cycles.

Questions to be addressed in the workshop

- Which forms of cancer are most in need of diagnostic biomarkers versus prognostic versus predictive biomarkers?
- How should we improve the design of academic and industrial biomarker discovery programmes to better address the criteria for regulatory approval?
- How can we most effectively build a sound, best-practice platform for biomarker development?
- What are the benefits of comparative oncology for accelerated biomarker discovery and application?
- How can comparative models (non-rodent mammals) enhance biomarker discovery and validation?

What is a biomarker and how is its performance assessed?

A *biomarker* is a characteristic in the body or bodily products that can be measured objectively. Tumour biomarkers can be *diagnostic*, *prognostic and/or predictive*.

Diagnostic markers

Population screening programmes are to discover early stage tumours in seemingly healthy individuals. Furthermore, better tumour markers can help to identify cases with unspecific symptoms that may be tumour-related, this will enable more advanced diagnostics to be focused on a lower number of cases. As there would then be a greater chance of making a correct cancer diagnosis, this would be of great ethical and economic value.

Effective early discovery programmes currently only exist for cancers of the breast, cervix, and colon but rely on labour-intense procedures. Academic and corporate biomarker discovery efforts have therefore sought effective *diagnostic biomarkers* based on blood sampling. Despite major investment from public and private research funding bodies, measurable success in terms of such biomarkers for early discovery regulatory approved by the Food and Drug Administration, FDA, in the US remains scant.

Prognostic markers

Prognostic markers are helpful for deciding if, and when, cancer treatment should be started, considering the marker reported risk of tumour progression or recurrence. If tumour markers could help in prognosticating a treatment outcome at an early stage of treatment planning, the probable result would again be positive effects in terms of both quality of life and health economy. Finally, if a marker proves to have the capacity to detect microscopic disease before relapse is clinically evident, rescue therapy might be commenced earlier and, at least in theory, have a better chance of success. Today there are very few useful tumour markers that meet these criteria.

Predictive markers

Predictive markers report whether a proposed treatment will be beneficial or not for the specific patient. For example, activating mutations in Ras genes confer resistance to epidermal growth factor receptor (EGFR) antagonist treatment in colorectal cancer. Many tyrosine kinases contribute to tumour formation when mutated, and a large class of drugs has been developed to inhibit them. Thus, assessment of the tyrosine kinase status may predict the efficacy of inhibitors. Examples of such mutated tyrosine kinases are *Bcr-Abl* in chronic myelogenous leukaemia and *c-kit* in human and canine mastocytosis. Promising advances in liquid biopsy technologies based on detection of mutated tumour DNA in blood and other bodily fluids have recently been made in this area.

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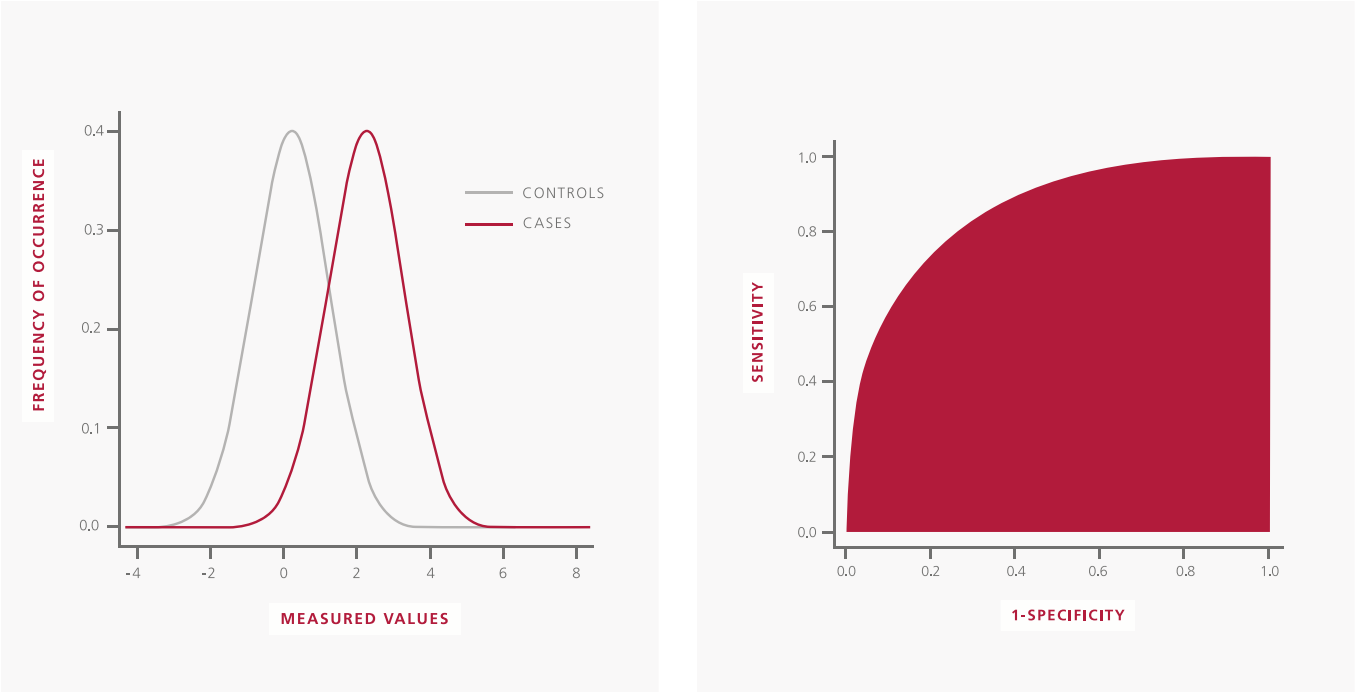

Figure 1. Illustration of ROC-curve (right) obtained from biomarker measurements (left) of sets of controls (grey line, left) and cases (red line, left). Various choices of cutoffs yield numerous sensitivity and specificity pairs, and by plotting all those pairs in a ROC plot, a continuous ROC-curve (right) is obtained. The higher the ROC-curve, the better the biomarker, and a numeric measure of the overall highness of the ROC-curve is AUC, the area under the curve (red area, right).

How is the performance of a biomarker measured?

Ultimately, the performance criterion of a biomarker test is its accuracy: to what extent are subjects with the condition diagnosed positively and subjects with condition absent diagnosed negatively. The percentage of subjects with condition present that are diagnosed positively is referred to as *sensitivity*, and the percentage of subjects with condition absent that are diagnosed negatively is referred to as *specificity*.[1] The *sensitivity and specificity pair* is the primary measure of diagnostic accuracy[2]. Typically, biomarker-based diagnostic tests produce a positive/negative test result by comparing the biomarker measurement to a *cutoff value*. The choice of cutoff value will highly influence the sensitivity and specificity pair, and by altering the cutoff, many distinct pairs of sensitivity and specificity are obtained. A *Receiver Operating Characteristic (ROC)* plot is obtained by plotting all sensitivity and specificity pairs[3]. When the cutoff can be continuously altered, the ROC-points form a *ROC-curve*. A convenient way of expressing the performance of a biomarker in a single number is to compute the *Area Under the ROC-Curve (AUC)*.[4] The AUC-value can be interpreted as the average sensitivity over the range of specificities. For example, the diagnostic prostate cancer biomarker *Beckman-Coulter PHI* (BC-phi) has AUC-value 0.71[5]. From a statistics point of view, an ROC-analysis has several desirable properties: it is not affected by normalizations of the measurement data, and the probability distribution of the measurement data has no influence on the ROC-points per se, yielding an intrinsic robustness. As ROC-analysis also addresses the core issue of sensitivity and specificity, it is justified as the method of choice of regulatory authorities.

Why have past and current discovery efforts failed to produce clinically useful blood biomarkers?

There are literally hundreds of research papers discussing the reasons for failure in cancer biomarker discovery. Some well-known shortcom-

1 CLSI EP12-A (2002), p. 9.

2 U.S Food and Drug Administration, 2007, p. 7.

3 CLSI GP10-A (1995, reaffirmed May 2001), p. 9.

4 CLSI GP10-A, p. 10.

5 U.S Food and Drug Administration, 2012, p. 27.

ings include too small cohorts being used for biomarker discovery and validation, cases and controls being drawn from different populations, variations induced by pre-analytical sample handling, and too little emphasis on statistical aspects of study design[6]. However, the literature describing how such studies should be designed to maximize the likelihood of success is scant. The field appears to lack a common approach, as studies are regularly underpowered, a wide variety of statistical approaches are applied to the datasets, and the statistical methods used in the discovery part of the vast majority of biomarker discovery studies do not concern the core biomarker properties sensitivity and specificity[7], but rather differences between means of groups. Since the purpose of the biomarker development effort is success in a prospective clinical study, the null-hypothesis of the statistical hypothesis testing during biomarker development must be chosen so that the biomarker is assessed as effective for its intended use. For example, the standard for effectiveness applied in the approval of the improved PSA test BC-phi[8] was *superiority* relative to an existing biomarker-based diagnostic test. Based on these known issues and observing sound statistical principles, would it be desirable to develop a consensus framework for biomarker discovery and early validation to improve the likelihood of successful translation into clinical practice?

How can the regulatory requirements guide biomarker discovery?

Regulatory (e.g. FDA) approval of a biomarker-based diagnostic test is based on three top-level criteria: effectiveness, safety, and benefit-risk. *Effectiveness* is evaluated through the sensitivity and specificity pair as determined through a pivotal clinical study, juxtaposed with the sensitivity and specificity pairs of existing diagnostic tests. *Safety* is determined through an analysis of the consequences of erroneous test results under the specified intended use and principles of operation of the diagnostic test, as well as analysis of laboratory test results of interference (effects of potential interfering substances), precision and reproducibility (consistency under different lots, runs and users), robustness (tests under potential failure modes), guard banding (accepted ranges for each reagent and process step), specimen stability (transport and storage over a five-year period), intermediate product stability (storage conditions for extracted intermediate products/sera), reagent stability (test-kit shelf life), and any other notion that the regulator deems is useful for the assessment of the safety of the biomarker-based diagnostic test. *Benefit-risk* is evaluated through an analysis of the benefits of accurate test results under the specified intended use, versus the risks of the biomarker-based diagnostic test. An approval order may include post-approval requirements and restrictions.

How can the bench to bedside translation of biomarkers be accelerated?

The clinical trials required for clinical validation and FDA approval of a cancer biomarker may require 10 years or more to conclude, depending on tumour type and the type of biomarker. Given the significant financial risks involved with the clinical validation of new biomarkers, combined with the limited gain from sales of a diagnostic as compared to drugs, is there a need for governments and funders to absorb some of the risk? Early phase risk reduction could be in the form of collecting and providing the retrospective samples required for the early validation and clinical assessment. The collection efforts need to be ongoing in several independent populations, sample patients with cancer at diagnosis and longitudinally, and be linked to population based studies where samples before cancer diagnosis are available[9]. Late phase support could target screening centres to enable prospective evaluation of new tests.

How can veterinary science and comparative oncology help biomarker development?

The domestic dog has become increasingly useful as a comparatively spontaneous cancer model to study genetic and environmental risk factors as well as easing the transition between rodent and human clinical trials for cancer drug development[10, 11]. The many similarities between various cancer types affecting humans and dogs and the spontaneous development of these cancers in immune competent canine individuals living in a shared environment with us suggest a common

6 Pavlou MP, Diamandis EP, Blasutig IM.

7 Baker S.G.

8 U.S. Food and Drug Administration, 2012.

9 Baker, S.G., 2009.

10 Paoloni M, Khanna C, 2008.

11 Gordon I, et al., 2009.

aetiology. The shorter lifespan of dogs and the shorter time to relapse after cancer treatment allows data regarding efficacy, short and long-term toxicity and side-effects of novel cancer drugs to be generated in years rather than decades as in human clinical trials.

However, certain limitations need to be overcome to make full use of the dog model. Slightly different classification systems for common cancers limits translation of data and clinical outcome from dog to human. The canine genome and annotation, especially of immune gene families, could be improved to allow a more careful and correct comparison with the human genome. Tumours such as mammary neoplasia (breast cancer), malignant lymphoma (Non Hodgkin Lymphoma) and osteosarcoma do all deserve attention and are found to be similar in tumour morphology, biology and response to treatment where improved models would benefit human studies.

Treatment of metastatic tumours in dogs is generally not successful today and disease prevention and early diagnostics will significantly reduce animal suffering, improve animal welfare and reduce costs for pet owners. For biomarker research, many analyses will be done on already collected tissue and blood for routine diagnostics in the clinical setting and thus reduce discomfort for living animals.

The potential benefits in using dog spontaneous tumor models in biomarker research are many;

- Trying out new diagnostic techniques and refine methodology before using in human oncology where availability of samples many times are a hurdle for technique testing.
- Rodent models will yield less material and are not performed in spontaneous tumour models and translation into human clinical setting has not always been successful, both in therapeutic studies as well as in biomarker research.
- Informing on how comorbidities may reduce sensitivity specificity of one or several biomarkers in marker panels are of interest to know early, as comparison between tumour samples and blood donors seldom reflects how the markers are used in the clinical setting and early promising results usually are significantly revised, when used in more mixed patient populations. Again, benefiting from the greater sample pool often available in the dog models will spare unessecary or non-strategic use of limited patient material in humans.
- Many technical/diagnostic platforms used in medical research are already validated in dogs and with the knowledge of the dog genome and proteome, validation efforts still needed are many times easy and cost effective.

Together with studying spontaneous tumours instead of induced tumours in experimental animals, this is well in line with the Replace/Refine/Reduce (3R) principles. Although, biomarkers in tumour tissue have mostly been investigated in dogs, recent promising findings on serum thymidine kinase 1 (TK1) either alone or in combination with CRP and also circulating micro RNAs have been suggested as potential biomarkers for canine neoplastic disease. With the necessary tools and resources acquired/supported, the domestic dog is now a fully-fledged model that is ideally suited to biomarker research and to informing human oncology in a parallel comparative approach.

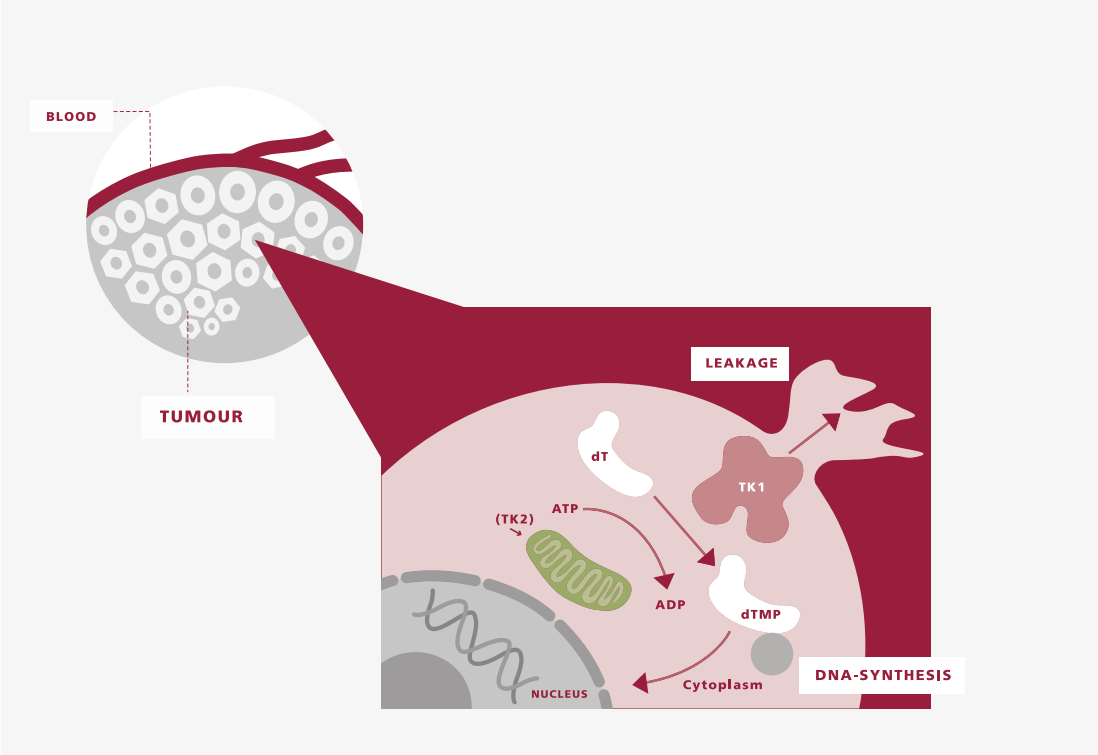

Figure 2. Example on how a protein (Thymidine Kinase 1 – cell cycle regulating protein) from an over-expression in a tumour can leak out in circulation and be measured in a blood sample.

References

Baker SG., *The central role of receiver operating characteristic (ROC) curves in evaluating tests for the early detection of cancer*, J Natl Cancer Inst. 2003 Apr 2;95(7):511–5.

Baker SG., *Improving the Biomarker Pipeline to Develop and Evaluate Cancer Screening Tests*, J Natl Cancer Inst. 2009 Aug 19; 101(16): 1116–1119.

Clinical Laboratory Standards Institute, CLSI, GP10 A Ed. 1 (1995/R2001), *Assessment Of The Clinical Accuracy Of Laboratory Tests Using Receiver Operating Characteristic (roc) Plots*, 2001.

Clinical Laboratory Standards Institute, CLSI, EP12-A, *User Protocol For Evaluation Of Qualitative Test Performance*, 2002.

Gordon I, Paoloni M, Mazcko C, Khanna C, *The Comparative Oncology Trials Consortium: using spontaneously occurring cancers in dogs to inform the cancer drug development pathway*, PLoS Med. 2009 Oct;6(10):e1000161.

Karlsson E.K, Lindblad-Toh, K., *Leader of the pack: gene mapping in dogs and other model organisms*, Nature Reviews Genetics volume 9, pages 713–725 (2008).

Paoloni M, Khanna C., *Translation of new cancer treatments from pet dogs to humans*, Nat Rev Cancer. 2008 Feb;8(2):147–56.

Pavlou MP, Diamandis EP, Blasutig IM., *The long journey of cancer biomarkers from the bench to the clinic.*, Clin Chem. 2013 Jan;59(1):147–57.

U.S. Food and Drug Administration, *Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests*, 2007.

U.S. Food and Drug Administration, *Pre-Market Approval of Access Hybryitech P2PSA on the Access Immunoassay Systems, Summary of Safety and Effectiveness*, 2012.

Workshop

Using Data for Better Cancer Treatments

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In high-income settings, many types of cancer are nowadays curable, or treatable in a way that they can be considered as a chronic rather than a fatal disease. Nevertheless, the number of patients being diagnosed with cancer every year is increasing and survival and effective treatment is dependent on early detection as well as on continuous monitoring. This highlights the importance of collecting and analyzing large amounts of data in an effective manner.

At the same time, there are already large amounts of health-related data that are readily accessible to healthcare professionals today, e.g. electronic health records, biobanks, and knowledge banks. Cancer patients, however, do not necessarily have access to this kind of information despite their growing interest. Furthermore, patients often compile information themselves, e.g. regarding nausea, pain, medication etc. These "medical logbooks" are currently not used on a regular basis, e.g. discussed during a visit or used to continuously monitor progress.

The workshop will address these issues and is aimed at creating a common understanding of how the future might be, using a vision seminar process approach.

Main focus areas for the workshop

- Joint analysis of critical incidents related to the diagnosis and treatment of cancer. The critical incidents will be related to all stakeholders involved in the process. What are the enablers, barriers, and learning opportunities?
- To create visions of how diagnosis and treatment of cancer can be informed by more effective and integrated use of existing data by different stakeholders.

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Introduction

Cancer care has come a long way and treatments are constantly improving. Some cancer conditions are today considered as chronic and not necessarily fatal. The number of people diagnosed with cancer globally is, however, constantly increasing, particularly in low- and middle countries. For economic and logistical reasons, many advances in cancer diagnostics and treatment are not yet accessible in these countries, resulting in a high number of fatalities. Equal access to healthcare is still a long way off. Demographic differences, especially when it comes to diagnosis and outcome, can be seen between children and adults. Cancer in children is often not discovered early enough. Moreover, cancer treatment is facing the same issues as healthcare at large, including more elderly patients, gender differences, more patients with multiple chronic conditions and a major lack of personnel and considerable differences globally in access to care. eHealth has emerged as one possible solution to some of these problems, and increased access to and use of healthcare data is often mentioned as one way forward. Such things have the potential to improve quality, make treatment more efficient, and expand capacity.

There are three main data user groups in cancer care. *Healthcare professionals,* who need to see data related to their patients, such as blood tests, radiology results, and notes from previous meetings with doctors. *Patients,* who want to see not only their own data but also aggregated data from other patients (available, for example, on platforms such as www.patientslikeme.com). And *researchers,* who both generate and use extensive amounts of data coming from biobanks and quality registries, or clinical notes. There are other kinds of users, such as statisticians, managers, drug industry representatives, and politicians, but these seldom interact with the data on a daily basis and their needs are not addressed in the workshop.

New technology, new opportunities

New technologies are not only rapidly changing society, but also opening up for new possibilities in healthcare. Various data sources have been available for some time now, and it is likely that both the number of sources and the amount of data will increase even more. Digitalization in healthcare is on top of the agenda all over the world, though implementation capacity varies greatly. Eventually all patient data will be digital and enable analysis that can advance not only research and treatment, but also cancer prevention.

High-performance computing opens new door for analysis

New technologies also bring new opportunities to engage in innovative research, for example making use of large quantities of data to identify patterns in specific types of cancer. Previously, this was not possible as the data were either not available, or high-performance computing was not sufficiently advanced. Advancements in distributed computing aim to increase processing power, for example by making use of idle computers and even smartphones. The technology knows no limits!

The ever-increasing data points have also given rise to artificial intelligence solutions, like cognitive computing in diagnostics[1]. This technology accesses vast amounts of data sources and finds patterns that can be vital for cancer diagnostics. This is one example of how artificial intelligence has moved into the medical domain, powered by existing data.

Technology and medical developments also go hand in hand. For example, due to the decrease in cost, genetic sequencing has become more popular. This is particularly interesting for oncology in terms of precision medicine, such as identifying personalized treatment options for the patient. Technology can help medical professionals find appropriate evidence-based treatment options, explore clinical trial opportunities, and recruit participants for research studies much more easily.

Today, genetic testing is even available as a consumer product. Furthermore, the widespread use of advanced devices, such as smartphones and wearables, allow users to collect a vast amount of data about their own health and wellbeing. This is not only relevant to current patients, but to everyone who might become one. In some incidents, data from fitness trackers have proven useful in preventing or detecting heart attacks, for instance. These data could also be used to measure the continuous health effects of ongoing cancer treatments.

Barriers to overcome

Although there seems to be no limit to the opportunities, there are many barriers to overcome regarding the successful use of technologies in healthcare. Sadly, between 50 and 70 per cent of information and communication technologies (ICT) development projects fail to reach their goals. In addition, healthcare professionals and patients often struggle with the systems implemented in their own organization. Although automation, big data, smart technologies, and distributed computing offer great possibilities for healthcare, they need to be incorporated in an ecology of computer systems and people that is already quite complex and becoming more so all the time. The barriers to the successful implementation of eHealth initiatives can be categorized in many different ways. Furthermore, they are interrelated, overlapping, and situated on different levels in society and organizations.

The barriers to eHealth are often organizational

Many would argue that the challenge for successful eHealth implementation is not related to technical but rather organizational and infrastructural aspects. *Organizational barriers* include managing organizational change and development so that technology is efficiently incorporated into work. Changes may be required in structures, business processes, and culture. This can be very challenging, especially in low- and middle-income countries that are still establishing a basic working infrastructure. *Infrastructural barriers can* include access to electricity and internet as well as to high tech IT solutions.

ICT must be integrated not isolated

A barrier related to ICT is *usability*. Far too many systems are not effectively integrated into everyday work practices, and score badly when it comes to effectiveness, efficiency, and satisfaction. The use of data needs to become part of a work environment that supports the professional development of healthcare personnel while providing useful support in their work.

[1] Chen, Y., Elenee Argentinis, J.D., and Weber, G.

Technical and ethical aspects of interoperability
Another problem is related to system *interoperability*, i.e. programs are not compatible with one another and thus there is no information exchange. This makes it more difficult to link up databases to find new patterns and gather data from different systems to discover correlations. Problems with interoperability result in data redundancy as the same information is documented in several systems, inefficient work, and lack of information from other areas or countries. The establishment of interoperability is challenging, as the system architecture has to allow for efficient exchange of information between systems with different levels of confidentiality, some of which is collected by patients (e.g. through self-monitoring or wearables), while at the same time preventing unauthorized access. In other words: Storing sensitive information in the same place can be seen as an invitation for hackers. Therefore, standards and architectures have to be developed that ensure efficient and trustworthy exchange of information.

Moreover, eHealth innovations often run into *legal and ethical* challenges. Laws and regulations need to be adjusted to accommodate new initiatives, while also addressing integrity and privacy issues. Health data used in research are usually anonymized, however, anonymization is extremely difficult when it comes to big data or data used in genetics research.

Under-representation of certain cancer types in existing data banks
Inequality between high-income and low- and middle-income countries is still prevalent as regards access to data and advanced treatment methods. Large amounts of data are gathered through, for example, patient communities and in biobanks and genetic banks in most European countries and in the United States. Since the infrastructure and knowledge necessary to gather and make use of these quantities of data are not yet in place in low- and middle-income countries, cancer types which are most frequent in these countries are under-represented in the available repositories. This is problematic for both healthcare professionals and researchers. This inequality, as well as eliminating the digital divide, needs to be addressed when discussing how to utilize existing data in diagnostics and treatment. Another ethical dilemma relates to artificial intelligence solutions. Although they provide great opportunities, it is still open to question how much the conclusions drawn by a machine can be trusted.

A watershed in the doctor-patient relationship thanks to new technology
The introduction of new technologies also has an effect on relationships within healthcare. Patients today are more involved (see, e.g. Chen, Y., Elenee Argentinis, J.D., and Weber, G), want to access their medical data, and also contribute, for example, by sharing data from self-monitoring. Although this provides many opportunities to increase the quality of care, it also has consequences. These have to be accounted for by technical and organizational infrastructures, laws, and medical education, as roles and responsibilities in the relationship between patients and healthcare professionals are changing.

Using Critical Incidents and visions of the future

This workshop will focus on practical issues, challenges, and opportunities related to using existing data for the diagnosis and treatment of cancer. In the first phase of the workshop, real-life **Critical Incidents** will be presented from the perspectives of doctors, nurses, patients and researchers, respectively, and used to inspire discussions on how existing data are being used today, and what the problems and opportunities are.

The second phase of the workshop will begin with a keynote on **visions of the future**, and what visions are good for in relation to societal change. Different visions from the stakeholders' perspectives will then be developed by the participants. These will include scenarios and descriptions related to how various types of existing data can be used for the diagnosis and treatment of cancer.

References

Chen, Y., Elenee Argentinis, J.D., and Weber, G. (2016). *IBM Watson: How Cognitive Computing Can Be Applied to Big Data Challenges in Life Sciences Research*. Clinical Therapeutics (38: 4), pp. 688–701.

Grünloh, C., Hallewell Haslwanter, J.D., Kane, B., Lee, E., Lind, T., Moll, J., Rexhepi, H., and Scandurra, I. (2017). *Using Critical Incidents in Workshops to Inform eHealth Design*. In: proceedings of the 16th IFIP TC 13 International Conference on Human-Computer Interaction, INTERACT 2017 (Mumbai, India, September 2017). pp. 364–373.

Riggare, S., and Unruh, K.T. (2015). *Patients organise and train doctors to provide better care*. BMJ (351). H6318.

Workshop

Implementing Physical Exercise in Cancer Care

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Physical exercise in the context of cancer treatment is a question of global importance given the rising cancer incidence and growing number of cancer survivors[1]. As well as preventing the development of cancer, physical exercise also relieves the toxicity of cancer treatment and diminishes the negative, long-term consequences of both the disease and the treatment. In addition, observational studies in several diagnostic groups suggest that exercise is associated with a lower risk of cancer recurrence and improved survival. Thus, the implementation of clinical guidelines to support and encourage physical exercise during and after cancer treatment cannot be overestimated and will be beneficial for individuals, the healthcare sector and society as a whole.

Desired outcomes of the workshop
The workshop aims to target implementation barriers and incentives for promotion and organization of physical exercise among cancer survivors during and after treatment both **within and outside the healthcare system**. Discussions will be on societal, organizational and individual levels, e.g. cultural aspects, legislation, financial incentives, subsidized costs, priorities, knowledge and skills.

Of particular interest will be the identification of implementation barriers and the devising of strategies to overcome these.

- for **policy and decision makers in clinical cancer care** to facilitate promotion of physical exercise among cancer survivors during and after treatment.
- to **change clinical cancer care** so that healthcare staff consistently promote physical exercise among survivors during and after treatment.
- to involve actors and arenas **outside healthcare** in organizing cancer survivors' physical exercise during and after treatment.
- on an individual level, to inspire motivation among **cancer survivors** to initiate and maintain physical exercise during and after treatment.

[1] Here the term "cancer survivors" includes not only persons who are undergoing cancer treatment but also those who have completed it.

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The modern patient – a partner in care

Traditionally, healthcare has applied a paternalistic approach, regarding the patient primarily as a target for medical interventions and thus mainly focusing on diagnostics and treatment of the cancer. However, during the past two decades, the necessity of including the patient as a partner in care has been debated increasingly. Nowadays, patients are seen as having their own competence and therefore able to take an active part in treatment and rehabilitation. They are no longer simply a victim of the disease. Nevertheless, there are still major differences within and between countries regarding the development of person-centred care. Building a strong partnership between patient and professional requires a series of activities that enable a cancer survivor to implement and sustain behaviours to manage the illness, including support from actors both within and outside the healthcare sector.

Long-term consequences of treatment

Cancer treatment often causes events that affect patients' wellbeing negatively and make it more difficult for them to work and manage daily activities. Cardiovascular disease is one of the most worrying complications of cancer therapies that may occur not only soon after treatment but also many years after treatment completion. Risks need to be assessed so that the prescribed exercise programme can be adjusted to individual needs.

Attitudes towards exercise for patients are changing

In the past, patients were commonly advised to rest and refrain from physical exercise during cancer treatment. Nowadays, many (but far from all) physicians and nurses in cancer care inform patients about the benefits of physical exercise, but the prescription of individualized exercise programmes and support to implement exercise in daily life are usually not part of clinical care. Thus, there is a widespread lack of evidence-based interventions to promote physical exercise during treatment in clinical cancer care. This is confirmed in scientific studies revealing that many people decrease their physical activity when they are diagnosed with cancer, a result recognized by professionals.

Also among children struck by cancer, a decrease in physical activity has been noted both during and after completion of treatment. This is alarming given that a majority of childhood cancer survivors develop late complications

from treatment that could be prevented, at least to some extent, by a healthy lifestyle including regular physical exercise.

The scientific evidence of benefits of physical exercise during and after cancer treatment
The first randomized controlled trials (RCTs) investigating the effects of physical exercise during cancer treatment were conducted in the late 1980s and early 1990s. During the past two decades, the number of RCTs in this field has increased rapidly. The most common diagnostic groups included are women with breast cancer and men with prostate cancer but several other groups have also been investigated, including patients with a curable and an incurable disease. Trials have been conducted globally but with a prominent overemphasis on high-income countries.

Results from RCTs and systematic reviews show that physical exercise during and after cancer treatment has beneficial effects on muscle mass and strength, cardiorespiratory fitness, cancer-related fatigue, emotional status and other aspects of quality of life. Also, supervised exercise seems to be more efficient than unsupervised. However, there is still a need for additional research. Questions to be asked include the optimal duration of the exercise programme, frequency, intensity, type and time.

Few adverse events from exercise have been reported, the most frequently reported being common musculoskeletal disorders related to physical exercise, hypertension and dizziness. In addition, single serious complications including cardiac events have been reported. To conclude, physical exercise during and after cancer treatment is regarded as feasible and safe and there is strong scientific evidence suggesting it improves physical status and quality of life.

The effects of physical exercise for children undergoing cancer treatment have not been investigated to the same extent as for adults but there is preliminary evidence suggesting that an individualized physical exercise programme during treatment is feasible, safe and potentially beneficial.

Creating individual exercise guidelines for adults
Evidence-based clinical guidelines regarding exercise for adults with cancer have been developed in some countries but is not clear to what extent these have been implemented in routine cancer care. Existing guidelines suggest that people who are undergoing treatment can be prescribed exercise programmes in a similar way to healthy individuals. Thus, cancer survivors should be advised to engage in 150 minutes of weekly moderate-intensity aerobic exercise and resistance training at least two times per week. Those who are unable to exercise due to their health status should be as physically active as their conditions allow and inactivity should be avoided. Thus, the exercise programme needs to be adapted to the individual survivor based on their health status, treatment and disease trajectory. A medical assessment is needed to ensure the safety of exercise.

Challenges to physical exercise promotion
The consensus in international recommendations is a good starting point, but there are obvious challenges to performing and maintaining physical exercise during cancer treatment. Disease and treatment may affect physical, psychological and social aspects of health, potentially decreasing the chances of maintaining recommended levels of physical exercise. People accustomed to a sedentary lifestyle are likely to face even greater barriers.

The role of information
Health professionals have an important task to provide information and give advice to patients concerning disease, treatment and symptom management. When it comes to physical exercise, they should give a clear and consistent message to patients: given individual adaptations, it is safe and beneficial in terms of health and quality of life. As credible sources in this context, their capacity to impact patients' health should be used strategically. Can professionals change their clinical practice and provide both general and individualized advice based on patients' conditions and preferences as a routine? Whatever the case, information alone will not be sufficient to actually change patient behaviour.

Changing behaviour
To actually understand and possibly influence exercise habits, it is necessary to explore the person's motivation, incentives, expectations, limitations and resources as well as contextual factors such as culture, family, physical environment and exercise history.

Motivation is closely linked to incentives and seems to be a mixture of importance, beliefs in own capability, and readiness to take action. Different cultural contexts influence attitudes to exercise – is it viewed as something beneficial or something to be avoided? The following three questions can be useful: How important is it to you to perform a specific type of exercise? How confident are you about doing it? How ready are you to do it? Rating answers on a 0–10 scale provides information about that the likelihood of a person actually performing a specific behaviour. Other important incentives refer to joy and rewards: rewarding activities boost autonomous motivation and facilitate exercise.

There are several effective behaviour change techniques in the field of exercise. Self-monitoring, which is about registering behaviour and outcomes, e.g. by using exercise diaries or pedometers, can be effective. Individual goal-setting and planning are also useful, as long as they are relevant and realistic.

How can this knowledge be used to implement physical exercise among cancer survivors? Drawing on research and clinical experiences, we know that supervised exercise is better than simply home-based activity and a group setting is better than an individual one (with reservations for individual preferences). How can health professionals learn to use powerful behaviour change techniques and prompt cancer survivors to seek social support for their exercise? Is it possible for cancer care to inform and initiate physical exercise, explore patients' history and preferences, and then guide them towards a committed pathway to other exercise options outside the hospital? Such changes would need some changes in clinical practice, which may take considerable time and effort.

Changing clinical practice

Successful implementation of physical exercise in cancer care, namely individualized recommendations of suitable exercise options, is dependent on a number of factors. To start with, how are the suggestions perceived by health professionals? If they are clear-cut and seen as beneficial, they are more likely to be implemented. Another prerequisite is that the professionals have adequate knowledge and skills to give advice and guidance. If not, what can be done to improve the situation? The relationship between health professionals and patients is important and varies between countries and cultures. The readiness for change among cancer survivors is also important – do they have the necessary knowledge and attitude? And is exercise highly valued or not? The professional interaction context has to be considered: colleagues who are hesitant about changing clinical routines may hinder the implementation process. Moreover, are there resources in terms of information, incentives, time, and feedback? System barriers in terms of leadership, workload or feelings of tension about change have to be addressed, as well as any political and legal issues likely to hinder implementation. The local climate and the provision of a secure environment are important when it comes to outdoor exercise, and women may face specific challenges in some countries and cultures. All of these domains may need to be addressed.

Physical exercise promotes health but organizing it needs resources and funding. How can we develop cooperation between actors to facilitate the process, and how can we identify ways to exercise that are cheap and feasible in different cultural contexts? Workshop discussions during Uppsala Health Summit will help to identify ideas for change and collaboration to move forward in a way that will ensure health benefits and quality of life among cancer survivors.

References

Bourke L, et al. *Interventions for promoting habitual exercise in people living with and beyond cancer.* Cochrane Database of Systematic Reviews. 2013.

Flottorp S ,et al. *A checklist for identifying determinants of practice: a systematic review and synthesis of frameworks and taxonomies of factors that prevent or enable improvements in healthcare professional practice.* Implementation Science. 2013; 8:35.

Samdal GB, et al. *Effective behavior change techniques for physical activity and healthy eating in overweight and obese adults: systematic review and meta-regression analyses.* International Journal of Behavioral Nutrition and Physical Activity. 2017; 14:42.

Segal R, et al. *Exercise for people with cancer: A clinical practice guideline.* Curr Oncol. 2017; 24(1), 40–46.

Sweeger MG, et al. *Which exercise prescriptions improve quality of life and physical function in patients with cancer during and following treatment? A systematic review and meta-analysis of randomised controlled trials.* Br J Sports Med. 2017.

Workshop

Drug Repositioning

– An Underused Strategy for Cancer Drug Development and Access to Next-line Cancer Treatment?

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This workshop will focus on a less conventional way to develop new cancer drugs, i.e. 'drug repositioning': the use of a drug already approved for another indication. In the light of several successful examples of this strategy, along with the often-modest benefit from and low cost-effectiveness of new cancer drugs, drug repositioning is seemingly a promising approach that could, in theory, provide new cancer drugs more rapidly and at considerably lower costs for the development phase. Randomized clinical trials based on national registers are one approach that have proved to be successful and could be developed. In addition, drugs that are candidates for repositioning into cancer drugs could be offered as 'last-line' treatments to patients with disease progression while on established treatment.

However, both drug development based on repositioning and individual patient use of drug repositioning candidates outside of clinical trials within routine healthcare run into problems from scientific, economic, ethical and healthcare resources points of view. This workshop will address these issues from the perspectives of the different parties mainly involved: patients, healthcare staff, medical authorities and pharmaceutical companies.

Workshop key issues to be addressed

- Assess the overall potential and limitations of 'drug repositioning' for development of new cancer drugs and in 'innovative practice'.
- Discuss if there are ways to make cancer clinical trials less complicated, resource-demanding and expensive with the overall aim to allow for more patients to participate in drug development based on the principle of drug repositioning and, thus, to more rapidly move cancer drug development forward. Furthermore, are there ways to make cancer drug development based on drug repositioning more attractive for pharmaceutical companies?
- Elaborate on ways to use 'innovative practice' based on drug repositioning and within a scientific context to the potential benefit of the individual patient and as a starting point for more definitive clinical trials and preclinical research.
- Consider the ethical, scientific and healthcare issues of drug repositioning and 'innovative practice'.

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New drugs, high costs, unclear benefit

Despite considerable progress in basic cancer biology knowledge in recent years, the development of new, more efficient cancer drugs has, with some exceptions, not been very succesful[1, 2]. Thus, newly introduced drugs, mostly categorized as 'targeted', for the most common solid cancer types have typically provided little benefit and meant nothing more than adverse effects and very high costs[3]. This situation increases the need to look into complementary drug development strategies, e.g. drug repositioning, exploiting the possible use of substances on the market that, if properly investigated, can propose additional treatment options.

The cancer patient's 'last-line' dilemma

For cancer drug treatment in advanced disease settings, the evidence cumulated through randomized trials in the major cancer diagnoses typically results in the recommended use of a limited number, up to a handful but often fewer, 'lines' of treatment that can be used in sequence, with the use of a 'next-line' treatment following on from the previous one. After the last line of recommended treatment, or its cessation for other reasons, e.g. intolerance, the performance status of many cancer patients does not allow for consideration of new treatments directed towards the disease itself and the best option from a quality-of-life perspective is to provide symptom-guided palliative care.

When palliative care is not the only option

However, more than a few patients still have a good performance status following guidelines directed by the last-line treatment and are not in need of advanced palliative care. For very understandable reasons, these patients and their relatives frequently ask for additional treatment attempts.

If the treatment centre has an active clinical trial in which the patient could participate, this may be an alternative to providing the patient with yet another 'line' of treatment hopefully for a treatment benefit while at the same time contributing to the accumulation of new knowledge that might benefit future cancer patients.

But when no clinical trial protocol is available or the patient status does not fit with an active protocol, the patient could be said to be in 'no man's land': too fit for advanced palliative care but with no cancer treatment options left.

1 Davis C., Naci H., Gurpinar E., et al, 2017.

2 Prisad V., 2017.

3 Workman P., Guilio F., Schellens J., et al., 2017.

Many patients and relatives accept this situation while others turn to alternative, unscientific treatments or try to find clinical trials at other hospitals, in their own country or abroad, with the hope of travelling there and participating. Often these strategies are felt to be very unsatisfying, both from the point of view of the patient and relatives and from that of the physician in charge of the patient. In addition, for many these alternatives are beyond reach.

Drugs approved for other medical conditions offer new possibilities

A physician would still be allowed to prescribe an 'old' drug to an individual patient, provided there is sufficient scientific evidence behind such a decision. Such a procedure could be beneficial for the individual patient. But to drive the development of healthcare forward, benefitting the global cancer community, a clinical trial procedure would be needed.

For the sake of patient safety, a clinical trial has to be preceded by numerous safety studies. Even if the drug substance is already on the market, such pre-clinical studies may need to be performed in order to evaluate potential risks and benefits related to the specific disease in question. The actual clinical trial will typically need a large number of patients, recruited, treated and monitored according to a standardized protocol.

An additional challenge for setting up clinical trials is, of course, that the number of patients suitable to be included will most surely be very small if data and patients cannot be gathered from a very large community of healthcare centres.

Considering the complexity of clinical trials, why not just continue with individual patient-based prescriptions of old drugs?

A more structured approach to evaluating the effects of old drugs for new indications can provide knowledge on how to treat cancer that, if successful, can benefit a much larger patient group. If unsuccessful, the results should also be shared with the research community.

A structured evaluation for repositioning of drugs would also be necessary for most healthcare systems to include the treatment in standardized care plans.

From an ethical point of view, leaving patients in the no-man's land between approved treatments and palliative care, or risking 'losing' them to unscientific programmes, is, of course, most unsatisfactory.

Finally, considering the increasing pressure on healthcare budgets, repositioning of old drugs may be a cost-efficient contribution to the selection of cancer treatments.

Even if much new knowledge and data needs to be gathered when repositioning an approved drug, an advantage is that basic knowledge and investigations are already there and, that the drugs are immediately available for testing in patients for the new indication[4].

The starting point for a drug repositioning project is mostly findings in preclinical research using various cancer models but can also be based on epidemiological data or serendipitous findings of unexpected anti-cancer effects in patients starting drug treatment for a concomitant disease. Going through published data thus provides a great number of reasonably well-founded ideas for the repositioning of available drugs for use in cancer.

The quest for an alternative to conventional clinical trials

The process for starting and performing clinical trials has been criticized for becoming not only over-regulated, but also slow and very expensive. This makes cost-effectiveness so low that the use of some of the approved drugs is prohibited in many healthcare systems. The complexity of the process limits the performance of pivotal, game-changing clinical trials to those initiated or supported by major pharmaceutical companies.

Clinical trials for new substances are mostly sponsored by a commercial pharma company, with the financial and administrative resources available to conduct the pivotal clinical trial.

[4] Pantziarka P., 2017.

However, when it comes to a possible repositioning of already available drugs, there are rarely such actors to support and drive a clinical study.

The pharmaceutical industry has however little interest in supporting and financing such clinical trials. Among the obstacles are, e.g. the risk that the trial reveals new adverse effects or simply because the patent is about to, or has, expired. Thus, most cancer drug repositioning candidates will never move beyond the status of being promising based on preclinical and in some cases also very preliminary clinical findings.

A strategy for drug repositioning?

Thus, given the relatively modest progress in cancer drug development based on completely new molecular entities and the complexity of this process, as described above, there is an increasing interest in this much simpler repositioning strategy that, at least, could be considered as a potentially fruitful approach which is complementary to the traditional one.

National registries offer opportunities for a new approach

Pioneering work has been done by Uppsala Clinical Research Centre on the concept of building prospective randomized trials based on the Swedish national clinical registries, using the existing hospital networks and the registry infrastructure for patient identification, trial enrolment, randomization and follow-up. These registry-based randomised clinical trials (R-RCT) are now well developed as a type of pragmatic trial and a number of studies have been successfully concluded and changed international guidelines.

The new R-RCT concept provides the means for a faster and more cost-effective process for bringing approved drugs into use for new indications and at the same time limiting the cost and some of the burden for the investigators. The trial concept has been developed in the cardiovascular field but is moving on to other areas of medicine. Oncology is a field with a considerable need for more extensive evaluation of pharmaceutical agents in large representative patient cohorts.

However, some challenges and hurdles remain, regulative as well as practical. A guideline document has been written explaining how to design and run such trials and there is a belief that they have the potential to revolutionize the way future prospective trials are conducted. It is possible to design studies for building evidence for drug repositioning of already approved drugs for new indications. In this way we can avoid having to go through the costly and time-consuming work of building trial platforms, extensive safety testing and repeated patient visits and instead focus on the efficacy of the new indication.

Healthcare as an arena for research and development

Closely related to the problem of selecting drugs for repositioning into evidenced-based options by means of the generation of data from clinical trials, is how to deal with patients in 'no man's land'. How can we help when clinical trial protocols are not available but there are published scientific data, preclinical, clinical or epidemiological, that one or more established drug in use for other purposes could have beneficial effects for the cancer type in question? If such a drug is inexpensive and known to be well tolerated, it is tempting to let the patient try it in what could be denoted 'innovative practice'. Such treatment of an individual or even a few patients would be in agreement with the Declaration of Helsinki, provided that patient-informed consent is obtained and that the information so generated is documented and, as applicable, made publicly available and then made the focus for research.

However, this would potentially be in conflict with the basic principle that healthcare should always be based on scientific evidence and/or extensive experience and mere preclinical data will probably be considered insufficient for this in most healthcare systems. There is, of course, also a risk that individual physicians set the level of scientific evidence for individual 'repositioning treatment' too low, putting the patient at risk and undermining the confidence in healthcare. In addition, this kind of treatment very soon comes close to research and would then run into conflict with the principle of committee and authority approval to safeguard ethics and scientific quality.

There is an obvious bridge from healthcare to science here if the experience and outcome of treatment of individual patients based on a scientifically based 'repurposing' rational are made public as 'N of 1 or few' studies. Such case studies could then form a basis for the selection of treatments which are worthwhile to investigate more thoroughly in adequately powered and controlled clinical trials.

Overall, this sensitive grey zone between healthcare, science and unacceptable use of unjustified beliefs seems relevant to discuss with the aim of finding ways forward to benefit individual patients while simultaneously satisfying scientific and ethical principles.

References

Cohen D. *Cancer drugs: high price, uncertain value*. Br Med J 359:4543, 2017.

Davis C., Naci H., Gurpinar E., et al. *Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by the European Medicines Agency: retrospecitve cohort study of drug approvals 2009–13*. Br Med J 359:1–11, 2017.

James S., Rao S.V., Granger C.B., *Registry-based randomized clinical trials – a new clinical trial paradigm*, Nature Reviews Cardiology 12:312–316, 2015.

Pantziarka P. *Scientific advice – is drug repurposing missing a trick?* Nature Rev Clin Oncol 14:455–456, 2017.

Prisad V. *Do cancer drugs improve survival or quality of life?* Br Med J 359:4528, 2017.

Workman P., Guilio F., Schellens J., et al. *How much longer will we put up with 100.000 dollar cancer drugs?* Cell 9:579–583, 2017.

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AstraZeneca

Astra Zeneca is investing heavily in all aspects of precision medicine, from identifying new drug targets through genome sequencing, to the development of biomarkers for diagnostics and combinatorial treatments. In this interview, *Senior Vice President and Head for Global Medicine Developments, Oncology, Dr. Klaus Edvardsen*, outlines the opportunities and challenges associated with the advancement around implementing medical advancements, such as targeted therapies.

"We are in the beginning of a new era in medicine which provides enormous opportunities. Science is at the heart of everything we do, but it will be of no use to society if can´t deliver new medicines to patients. The new therapies are very costly, therefore we have to also be involved in delivery and in working out mechanisms for pricing that will work for different healthcare systems. But it is all in the beginning, we need to have a differentiated way of looking at it. As we develop an oncology medicine, we often develop it for different indications, the effect size may differ in various indications. Therefore, there has to be a mechanism in discussions with payers that the price will also be related to the effect size, which is a direct translation of the value it offers.

The pharmaceutical industry plays an important role in helping build the evidence-base needed for healthcare planners to make priorities and assign value to targeted therapies and biomarkers. This is necessary to know what treatments are efficacious and to avoid spending resources on giving medicine to patients that will not benefit. Fundamentally, we as an industry have an accountability to make sure that we deliver that value from a scientific perspective.

We do this through trials where biomarkers define patient populations to a large extent. As an example, Astra Zeneca and the investigators we are collaborating with are currently involved in more than 500 active oncology trials that enrolled almost 90,000 patients to date.

A concrete example, which really highlights the success we can have when we aim for something very specific is Astra Zeneca's molecule which is targeting a specific mutation driving a number of cancers, especially non-small lung cancer. The Phase 3 AURA3 trial results show a median progression free survival of 10.1 months for patients on this new therapy versus only 4.4 months for patients using the second-line treatment of platinum-based chemotherapy."

An important part of precision medicine is the uncovering of the genetic drivers which creates unprecedented opportunities for drug discovery. Can you tell us about Astra Zeneca's involvement here and the challenges to overcome before genome sequencing becomes an integrated part of general healthcare?

"Our AstraZeneca MedImmune Genomics Initiative is a partnership which was launched in 2016 together with the UK Biobank, the FinnGen consortium, Wellcome Trust Sanger Institute, University of Cambridge, UK, Columbia University, US, and several other partners with the bold ambition to analyze up to two million genomes by 2026. It will lead to new insights into the biology of disease and create a foundation from which we can create new medicines. It goes for all therapeutic areas, not just cancer, but cardiovascular and metabolic diseases as well. It will allow us to stratify our clinical trials and lead to an understanding why some patients respond to treatments when others don´t. It really is a crucial aspect of precision medicine. But it is not something the pharmaceutical companies can lift alone.

As an example, the MedImmune Genomics initiative, will be sequencing 500,000 genomic samples donated by patients from Astra Zeneca´s own clinical trials that we have collected over a 15 year period, so we have a huge amount of material internally. To make something out of it in the long-term, we are completely dependent on partnerships with the outside world; the academic research and hospitals where the patients are. For the next step, and for genome sequencing to really be an integrated part of healthcare, we also need to get the healthcare financiers and the regulatory agencies into play. Each healthcare system will need to see the value of investing in the infrastructure that is needed to use the technology, including the biomarkers and diagnostic

testing to find the right patients, otherwise it will be like finding a needle in a haystack. The pharma industry can help in building the evidence-base that all healthcare planners need for any investment.

So we have a big task ahead of us of developing pricing mechanisms and regulatory processes around precision medicine to make it available for all the patient groups it holds promises for."

With genetic testing and biomarkers comes the opportunity to use combinatorial treatments. What are the obstacles associated with taking these treatments from the lab to the patient?

"If you really want to make sure that you tailor treatments, you have to have a very broad approach and partnerships, because it will unlikely be one single company that has all of the compounds that can target all of the genetic abnormalities that drives one phenotype. Imagine that as a doctor, I have a complete understanding of the genetic make-up of what drives a specific phenotype in the patient in front of me. The best treatment would be to perhaps combine compound X from Astra Zeneca with compound Y from another company. But how do you conduct clinical trials around these possibilities? We don't yet have a good mechanism for how to handle these opportunities because that is not how drug development is traditionally done.

I think one important aspect of combinatorial treatments is to look at the diagnostic part. The use of circulating tumour DNA Biomarkers, liquid biopsies, might be what enables the use of the combination therapies. Improving and facilitating the process of biomarkers is an integrated part of our strategy, which has to go hand in hand with the development of medicine. You need to find the patient in the real world setting that would benefit from your medicine, so it is complex and we are not quite there yet, but it is an ambition."

Despite the complexities and challenges that we need to overcome, are you hopeful that in a not too distant future we will be able to bridge the advancement in technology with the growing cancer patient population globally?

Dr. Klaus Edvardsen, Senior Vice President and Head for Global Medicine Developments, Oncology, AstraZeneca.

"I am extremely hopeful. To take the example of lung cancer, not that many years back, we didn't even have the wildest belief that we could cure non-small cell lung cancer patients or transforming them into long term survivors. Over the past years there has been a tremendous development in targeted therapies that are really substantially benefitting patients that we never thought we could manage before, so I am very hopeful.

I believe that we are just in the beginning of all of this and the more we get involved in genomics and the more we understand about the drivers of disease, the better we can tailor treatments. It is an extremely exciting moment. I am not denying the obstacles; there are obviously many things that needs to go hand in hand to be successful here, but I fundamentally believe that we all work for the same goal and we are making progress every day towards curing cancer."

Novartis

The importance of patient power is being recognised across healthcare, including the pharmaceutical industry. In this interview, Judith Love, General Manager for Novartis Oncology Nordics, explains what a patient focus means for development of cancer care. She also discusses how to provide safe patient access to Car-T cell treatments and what the company is doing to increase access to cancer treatment in regions where resources are scarce.

"There are two aspects to patient involvement, internally how we operate as an organization, and externally how we enable a better experience for patients and their families through working to make healthcare more accessible. I think the pharmaceutical industry in general can go a long way in improving the perception people have of us as an industry, in some ways we need to re-write our contract with society. At Novartis, we have a commitment to become more patient focused across the organization; it is part of our vision of re-imagining medicine. That means we need to make it real and alive in our everyday actions.

We have a new Novartis commitment to patients and to caregivers so that we can make a bigger impact on patients at the end. This commitment was co-created with patients' input so that we focused on what was important to them. We worked with 40 patient organizations, representing over 200 million patients, so it is a good start.

From an outside societal perspective, we need to find ways to address the gap between available infrastructure and the technological advances that enable better screening, diagnosis and treatment. This will allow treating patients with the right drug at the right time. The technology is moving faster than the regulations and policies and in my view, from the pharmaceutical perspective, the gap just keeps growing. There is a massive disconnect between the two. We got to shorten that timeline."

In August 2017, the U.S. FDA approved the first Car-T cell treatment to treat children and young adults suffering from acute lymphoblastic leukaemia (ALL). The treatment is not yet approved in Europe, and healthcare is aware that though the treatment may save lives, it is not an easy treatment to give, nor to receive. How is Novartis collaborating with healthcare to develop safe patient access?

"Car-T cell treatment is a real breakthrough; it is trail blazing and requires that we work together with the healthcare system. It is not a drug; instead, it is a completely novel therapeutic process that enables the patient's own T-cells to be re-engineered via a unique manufacturing process to be reinfused into the patient.

We started collaborating with University of Pennsylvania in 2012. Thanks to that collaboration, we now have a very good understanding of what it takes to successfully launch, manufacture and establish a network of certified treatment centres that are able to actually carry out this therapeutic procedure in a way that is safe for the patient. We need a rigorous approval system to ensure that we have the right medical centres to treat these patients. We also need to develop novel pricing and access schemes that are outcome- and value-based.

Novartis has never walked down this path before – nor has the healthcare system, so this is our opportunity to sit together and find ways to bring this exciting treatment to the patient. What is required at a hospital level, from pricing and from policy? It is a unique opportunity to work together, but of course that is also where many of the challenges lie. Imagine if we get this right, and what it could mean for other novel therapies."

The majority of new cancer cases are projected to occur in low-and middle-income countries the next twenty years. Can you tell us something how you can contribute to developing care in these regions?

"Novartis collaborates with the Max Foundation on a broad initiative that is very patient focused in that we are working with an NGO for the treatment and support at no cost for the individual patient. We do this with the explicit goal of assisting people living with Chronic

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Judith Love, General Manager, Oncology Nordics.

Myeloid Leukaemia and to ensure that they receive hands-on support, not just providing the drug like many other projects would do. This is more of a closed loop that entails four key steps which includes donating the medicine, funding the Max Foundation which then delivers the medicine to the health centres where physicians provide the medicine. The last step is the Max Foundation providing continued psycho-social support and education through their local advocacy organization.

We plan to invest more than 29 million into this collaboration and provide 315 million doses of medicines over the next four years. We have 34 000 patients currently in the programme in 70 countries across 4 continents, that involves 1 400 trained physicians and 450 treatment centres. So, it is more than a donation, it's more of a sustainable footprint that enables the system to be educated at the same time"

What are your expectations for Uppsala Health Summit?

"I hope that there will be a lot of really constructive dialogue on the issues that count. It is about understanding each of our perspectives and working together with a shared view to transform cancer. We only need to do it on a small scale to begin with, just pick small projects to collaborate together on, give it a go and then see how we can work together and scale it further. We all need to have the courage to try to work together on mutual challenges!"

Care for Cancer

Uppsala Castle, Sweden

Wednesday 13 June

17:30 **Reception at the Skandion Clinic, Scandinavia's proton therapy centre, including a guided tour.**

Thursday 14 June

09:00 **Official opening**

09:15 **A Visionary Outlook**

Dr. Susan Galbraith, Head of Oncology, iMed, Innovative Medicines, AstraZeneca

Professor Max Parkin, Nuffield Dept. of Population Health, Oxford University

Professor Klas Kärre, Chairman of the Swedish Cancer Society's research committee

10:30 **Coffee break, with delegate match-making**

11:15 **Workshops in parallel**

A. Precision Medicine in Cancer Care

B. Biobanking for Global Cancer Care

C. Clinical Value and Price Setting for New Cancer Drugs

D. Long Term Care for Cancer survivors

12:45 **Lunch**

13:45 **Workshops continue**

15:15 **Coffee break, with delegate match-making**

16:00 **Patients as a driving force to develop care**

Gregory C. Simon J.D., President, Biden Cancer Initiative

Ingela Franck Lissbrant, MD, PhD, Sahlgrenska University Hospital and Swedish National Prostate Cancer Registry

Marie Ennis O'Connor, Patient Empowerment Foundation and Health Care Social Media.

Kelechi Eguzo, MD, MPH, Nigerian Christian Hospital; Chairman Marjorie Bash Foundation, Nigeria

17:10 **Reports from workshops**

19:00 **Dinner**

Friday 15 June

08:45 **Welcome back**

09:00 **Access to treatments and diagnostics**

Dr. Mariângela Simão, WHO, Assistant Director General

Professor Arnie Purushotham, King's College London and Tata Trust, Mumbai

Thomas B. Cueni, Director General, International Federation of Pharmaceutical Manufacturers & Associations (IFPMA)

10:00 **Coffee break, with delegate match-making**

10:45 **Workshops in parallel:**

E. Towards Useful Biomarkers for Cancer Care

F. Using Data for Better Cancer Treatments

G. Implementing Physical Exercise in Cancer Care

H. Cancer Drug Repositioning

12:15 **Lunch**

13:15 **Workshops continue**

14:45 **Coffee break**

15:15 **The threats against public health: Governance vs behavioural changes to stop smoking**

Professor Mike Kelly, Institute of Public Health, University of Cambridge

Dr. Vinayak Mohan Prasad, Programme Manager, WHO Tobacco Free Initiative

Professor emerita Barbro Westerholm, Member of Swedish Parliament

16:25 **Reports from workshops**

16:55 **Conclusions and take-home messages**

A summarising dialogue with Programme Committee Chair **Professor Lars Holmberg** and delegates

Governance

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