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A new vision for cancer in European Union. Data, technology and human touch

Position Paper

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A new vision for cancer in the European Union: data, technologies and human touch

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A new vision for cancer in the European Union: data, technologies and human touch

Background: Cancer in the European Union

The World Health Organization defines cancer as "a generic term for a large group of diseases that can affect any part of the body. One defining feature of cancer is the rapid creation of abnormal cells that grow beyond their usual boundaries and which can invade adjoining parts of the body and spread to other organs. Metastases are the major cause of death from cancer". Cancer is usually classified as an aging-associated disease. One third of all new cases were diagnosed in people aged 75 years or older in the EU in 2012 and due to population aging this number is likely to increase. (Jönsson B., Hofmarcher, Lindgren, & Wilking, 2016). But data also shows it affects people of all ages[1].

Although Europe contains only 0.9% of the global population, it accounts for 23.4% of global cancer cases and 20.3% of cancer deaths[2]. According to The European Commission's (EC) science and knowledge service[3]: "There were an estimated 3.91 million new cases of cancer (excluding non-melanoma skin cancer) and 1.93 million deaths from cancer in Europe in 2018. The most common cancer sites were cancers of the female breast (523,000 cases), followed by colorectal (500,000), lung (470,000) and prostate cancer (450,000). These four cancers represent half of the overall burden of cancer in Europe. The most common causes of death from cancer were cancers of the lung (388,000 deaths), colorectal (243,000), breast (138,000) and pancreatic cancer (128,000). In the EU-28, the estimated number of new cases of cancer was approximately 1.6 million in males and 1.4 million in females, with 790,000 men and 620,000 women dying from the disease in the same year".

In the European Union (EU), cancer is the second most common cause of death. The incidence of cancer in the EU is on the rise being directly linked to persistent demographic and lifestyle trends. Cancer claimed the lives of 1.3 million people within Europe (EU-28) in 2015: more than one quarter (25.4%) of the total number of deaths from all causes. Cancer accounted for a higher percentage of deaths in men (28.7%) as compared to women (22.1%), and represents the primary cause of death in an increasing number of European citizens. Four out of ten people will develop cancer in their lifetime[4]. Globally, the probability of developing cancer is 1 in 3 for men and 1 in 5 for woman (Fitzmaurice, 2018).

Across the European Union (EU), there are major differences in access to cancer care and overall survival rates. For instance, 5-year survival rates for cancer range from 40% in Bulgaria to 64% in Sweden. According to the EFPIA, improving these discrepancies would lead to 270,000 more people surviving cancer for more than 5 years[5]. Early diagnosis plays an important role: Around 380,000 lives could be saved in Europe every year if all patients with colorectal cancer were diagnosed in stage 1.[6] However, only an estimated 1 in 10 people over 50 are screened for colorectal cancer. Major discrepancies also exist in the treatment provided following diagnosis: for example, even in western European countries large variations still exist, with up to 30 percent of diagnosed patients in late-stage lung cancer being untreated. (Carrato, et al., 2014) Many more lives could be saved if treatment guidelines would be followed. Depending on the type of cancer, a patient in eastern Europe will have a 30% decreased chance of surviving as compared to someone living in a western European country[7].

Inequalities in access to health care add to the burden of disease. A patient in the Czech Republic waits nearly 10 times longer than a patient in Denmark to get access to a newly approved cancer medicine – 781 days in total. (EFPIA, 2019) In addition, 8 out of 10 EMA-approved medicines are not available in Poland while cancer patients in the UK, Germany, the Netherlands or Austria have access to nearly all newly approved cancer medicines. (EFPIA, 2019)

The analysis published by Jonsson, Hofmarcher, Lindgren & Wilking in 2016,[8] "The cost and burden of cancer in European Union", concluded: "Within the EU Member States, health expenditure related to cancer increased continuously from €35.7 billion in 1995 to €83.2 billion in 2014 and spending on cancer drugs from €7.6 billion in 2005 to €19.1 billion in 2014.[9] Yet the share of total health expenditure devoted to cancer was mostly constant (around 6 per cent). While expenditures on cancer drugs increased in both absolute and relative terms, other expenditures were stable or decreased, despite increases in cancer incidence driven by a growing and ageing population. Reductions in cancer mortality during working age resulted in decreasing production loss due to premature mortality. In terms of total health care expenditure, funds spent on cancer are generally relatively low despite the increasing burden of cancer throughout the EU This is compounded by difficulties to relocate funding within health care systems that are financially challenged and a shift from inpatient to ambulatory care. In fact, income and economic wealth is lower in Central Eastern Europe (CEE) than in other parts of the EU. The Gross Domestic Product (GDP) per capita in Hungary, Poland or Romania is more than 30% lower than the EU average. (Eurostat, 2018) However, one has also to recognize that CEE countries are among the fastest growing economies in the EU. Poland's growth rate in 2018 was twice as high as the EU average. (Eurostat, 2018) Despite this positive development, their spending on health as a share of GDP is much lower compared to richer economies, in some cases half of what the EU average spends. (OECD, 2018)[10] A better prioritization of health and also cancer could contribute to reducing inequalities.

1 Data from https://iarc.fr
2 https://www.who.int/cancer/PRGlobocanFinal.pdf
3 https://ec.europa.eu/jrc/en/publication/cancer-incidence-and-mortality-patterns-europe-estimates-40-countries-and-25-major-cancers-2018
4 https://ec.europa.eu/research/health/index.cfm?pg=area&areaname=cancer
5 https://www.efpia.eu/about-medicines/use-of-medicines/disease-specific-groups/fighting-cancer/
6 Bowel Cancer UK, Belgian Cancer Registry, 2018, "Saving lives, averting costs", Cancer Research UK, 2014; in: Digestive Cancers Europe (to be checked via website)
7 https://www.euronews.com/2018/02/04/cancer-survival-rates-improving-across-europe-
8 https://www.sciencedirect.com/science/article/pii/S0959804916322869
9 https://www.ejcancer.com/article/S0959-8049(16)32286-9/abstract
10 In Belgium, 10 of 100 Euros goes into health care. In HU, PL or RO it is only two third or only half of it.

Between 30-50% of all cancer cases are preventable. Prevention offers the most cost-effective long-term strategy for the control of cancer, according to the World Health Organisation (WHO)[11]. EU and national policies are in place, aiming to raise awareness and reduce exposure to cancer risk factors and to ensure that people are provided with the information and support they need to adopt healthy lifestyles[12]. Despite all these efforts and investments, the number of people diagnosed with cancer increases every year and the rate of avoidable death related to cancer is also high. New prevention and treatment paradigms are urgently required.

Tremendous innovation

Oncology is an area at the forefront of medical research against the background of the decoding of the human genome, unparalleled in other medical areas. The accumulation of information is continuous and often exceeds both the reception capacity of physicians and patients and the ability of the health systems to implement those innovations that bring value to the patient. In oncology, the concepts of disease management sometimes change fundamentally every year, whether we are talking about prevention, screening, precision diagnosis or treatment. For instance, immuno-oncology, a concept that was brought again into the spotlight 6 years ago by the spectacular clinical outcomes regarding malignant melanoma, has already changed the therapeutic paradigm in many types of cancer. There are 2004 immunotherapies in development at the moment, as monotherapy or in combinations, and new fundamental changes of the medical practice are expected in the next few years. On the other hand, in 2018, the first CAR-T cellular therapy was approved for the treatment of some types of hematologic cancers, thus opening up a completely new horizon - 244 cell therapies are being developed at the moment and it is expected that the number of such therapies approved will grow in the next years. In the field of biomarkers and genomics, the evolution is also extremely rapid, and the validation of the biomarkers quickly transforms the way in which a precision diagnosis of cancer is formulated and a precise treatment is prescribed. "Over the last decade, significant advances have been achieved in cancer outcomes, bringing the average 5-year relative survival rate across all cancer types in Europe to 54% for cancers diagnosed between 2000 and 2007 up from 51.5% in 2000-2002. For European patients diagnosed in 2012, over 66,000 more will live for at least 5 years after diagnosis compared to those diagnosed a decade earlier)", according to EFPIA[13]. While sustained improvements in diagnosis and treatment delivery have certainly played their part, so has the availability of a new generation of targeted treatments. The development and availability of new therapies has triggered a major decline in cancer death rates globally[14]. In 1995, only 15 out of 100 lung cancer patients lived longer than 1 year. Today, nearly 70 out of 100 patients are still alive after 12 months. (Schiller, 2018)

Challenges in cancer care in Europe

The number of therapy options available to adult patients has risen significantly; between 1996 and 2016, the number of treatments available to patients with lung cancer increased from four to 19. (IQVIA, 2017) New treatments with fewer side effects have also helped support efficiencies in cancer care, reducing hospital stays and enabling people to receive care at home or in the community. This wave of innovation has generated an unprecedented level of choice and promise, with new treatments – and combinations thereof – continuously advancing treatment paradigms.

Europe's cancer care faces a number of challenges, some of the following being highlighted by EFPIA campaign "We won't rest until cancer is nothing to fear"[15]:

- There is a mismatch between the rising burden of disease and a roughly flat spend on cancer care reflective of a sluggish economic recovery and tightening funding constraints
- There are inconsistencies in prioritisation of cancer care on the public policy agenda despite the prevailing disease burden and amplitude of future challenges
- Late diagnosis: Around 380'000 extra lives could be saved in Europe every year if 100% of the patients with colorectal cancer would have been diagnosed in stage 1.[16] Today, a bit more than 1 in 10 people over 50 are screened against colorectal cancer.
- More detailed characterization of tumors and patients earlier in the treatment cycle ('Precision Medicine first'), could increase cure rates, reduce side effects and lower overall heath costs, but is made difficult by differences in the rules for reimbursement of different types off expenditures.
- There is a lack of readiness in healthcare systems to adjust to the rate and type of innovation in cancer treatment (e.g. multi-indication medicines, combinations, personalised medicine)
- Inequalities in access add to the burden of disease, and there are large differences in terms of access to and availability of new cancer treatments across the European Union
- There is a disconnect between regulatory and HTA / pricing & reimbursement procedures and restrictive HTA value assessment frameworks
- There are growing disparities in care delivery and outcomes within and across countries
- Even in Western countries, for example, exist still large variations with up to 30 percent of diagnosed patients in late-stage lung cancer being untreated. (Carrato, et al., 2014) Many more lives could be saved if treatment guidelines would be followed.
- There is a very diverse and fragmented environment for oncology data in Europe.

Capturing the real picture in cancer care

Over the last decade, the understanding of disease biology and care, especially in oncology, has greatly increased. Cancers are increasingly being understood and characterised at a molecular level rather than at a traditional histological level – fifty years ago, blood cancers were categorised into leukaemia and lymphoma; today, 40 unique leukaemia types and 50 unique lymphoma types can be differentiated.

Targeted therapies and immunotherapies use the molecular aberrations of a cancer cell, the cancer environment or cancer-fighting

11 https://www.who.int/cancer/prevention/en/
12 https://www.who.int/cancer/prevention/en/
13 https://www.efpia.eu/about-medicines/use-of-medicines/disease-specific-groups/fighting-cancer/
14 https://www.cdc.gov/media/releases/2015/p0312-cancer-survivors.html
15 https://www.efpia.eu/about-medicines/use-of-medicines/disease-specific-groups/fighting-cancer/
16 Bowel Cancer UK, Belgian Cancer Registry, 2018, "Saving lives, averting costs", Cancer Research UK, 2014; in: Digestive Cancers Europe (to be checked via website)

immune cells. Patients have benefited from these innovations: data show that more people are living longer, better quality lives following cancer diagnosis. New technologies (e.g. CRISPR gene editing, CAR T- cell therapy) will continue to push the frontier and challenge the ways in which cancer is approached. In line with this innovation in oncology, the health data collected on cancer patients, their disease and treatment modalities is evolving rapidly. Randomised controlled trials (RCTs) remain the gold standard for the European Medicines Agency (EMA), health technology assessment (HTA) agencies and payers, but they have several limitations in oncology, as outlined by the "Report on oncology health data in Europe" (Calypso Montouchet, Michael Thomas, James Anderson, Sam Foster 2018)[17]:

- Representativeness – current oncology treatment regimens involve multiple lines of treatment and combination therapies, which cannot be reproduced in a controlled setting at sufficient scale to be statistically meaningful, and trial populations tend to be selected based on their physical wellbeing and thus are younger and healthier than real-world patients
- Timeliness – highly-innovative therapies are increasingly approved through accelerated or adaptive pathways, with limited time to run clinical trials and the need for continuous information post-launch (including, but not limited to, after conditional approval).
- Quality – clinical trials are often conducted for the main indication(s) of a new treatment, such that the data on potential uses of a treatment outside its authorised indications will not be of the same quality as data developed in a RCT programme for those indications, and measures of efficacy may vary from those preferred by regulators (e.g. progression-free survival [PFS] compared to overall survival [OS]).
- Ethics – one-arm trials may represent the only ethically-appropriate approach for patients with rare cancers (in the absence of standard of care or where the hypothesised benefit from the trial drug is superior to the potential comparator), requiring the use of historical controls from registries and other non-RCT sources to fully understand comparative effectiveness.

The "Report on oncology health data in Europe" (Calypso Montouchet, Michael Thomas, James Anderson, Sam Foster 2018) also noted: "A growing number of health stakeholders are therefore turning to real-world data (RWD) to supplement RCTs, both in and beyond oncology. Definitions of RWD vary, but a commonly-accepted view in Europe is that RWD constitutes "longitudinal patient level data captured in the routine management of patients that can be repurposed to study the impact of healthcare interventions". This includes:

- electronic health record (EHR) data on patient symptoms, referrals, prescriptions and treatment outcomes (including patient-reported outcomes [PROs]);
- claims data on service usage, insurance and other administrative hospital data;
- omics data (e.g. genomics, proteomic) individuals and associated biomarker data;
- pharmaceutical data such as pharmacovigilance (i.e. medicines safety);
- social media and web data, for example from patient forums;
- data from mobile apps, wearables and sensors;
- additional information from ad hoc sources (e.g. geospatial health data, information on well-being, socio-economic status or behaviour)"

17 https://www.efpia.eu/media/412192/efpia-onco-data-landscape-1-report.pdf

This vast, diverse amount of RWD can be used for numerous purposes (Calypso Montouchet, Michael Thomas, James Anderson, Sam Foster 2018):

Application		Sample benefits
R&D enablement	To support identification of promising compounds, investigation of the genome & smarter clinical trials	The **EHR4CR** initiative enables more precise recruitment, retention & site-selection strategies via better patient-level data
Healthcare context	To understand the context of the disease & patient populations (e.g. population, biomarkers/ genetic characteristics & unmet need)	In Italy, **IBM & the National Cancer Institute of Milan** use genomics to improve the treatment cancers, leading to personalised care & better outcomes
Treatment patterns	To understand real-world usage of anti-cancer treatments, including by patient group, line of therapy & geography	In Hungary, **a national health app** has been used to detect inefficiencies in charging & reimbursement for cancer therapy, leading to pathway adjustment & increased detection
Real-world clinical value	To measure the delivery of cancer interventions' clinical promise in a real-world setting (including outcomes & safety, quality assurance, etc.)	In the US, the FDA granted accelerated access to avelumab based on an open-label, single-arm study supported by RWD in metastatic Merkel cell tumour
Socio-econ value	To measure the value of cancer interventions beyond that provided to patients & health systems (inc. lost employment, absenteeism…)	In Sweden, the societal & humanistic value of new drugs is considered as part of the **health technology assessment** process
Pricing enablement	To provide a mechanism for flexible pricing, based on use, indication and/ or outcomes	In Italy, MEAs established from 2006-2008, mostly for oncology drugs, showed that they helped decrease the time to market by 75% (from 343 to 84 days)
Patient perspective	To offer insight into QoL(inc. PROs), covering aspects of care beyond clinical outcomes	The **PatientsLikeMe epilepsy portal** allows better involvement of patients in clinical trial processes, facilitating research that responds to patient needs

Source: "Report on oncology health data in Europe" (Calypso Montouchet, Michael Thomas, James Anderson, Sam Foster 2018)

Different health decision-makers tend to focus on specific applications: for example, governments and policy-makers typically try to achieve a better understanding of the healthcare context and treatment patterns to improve the quality of care and overall resource allocation. Healthcare professionals (HCPs) consider treatment patterns, the real-world clinical value of drugs and patient outcomes, in order to prescribe the most appropriate treatment for individual patients based on their characteristics and response to the drug. Pharmaceutical, medical device and biotech companies use RWD to inform R&D decisioning and conduct trials more efficiently, and to support discussions with health authorities and fulfil post-approval requirements. (Calypso Montouchet, Michael Thomas, James Anderson, Sam Foster 2018).

Recent years have seen the growing intent in the use of RWD to consider the socio-economic value of economic interventions, enable innovative pricing mechanisms and provide better insight into the patient experience of their disease, treatment and overall wellbeing. These stakeholders are eager to use RWD opportunities to achieve real shared benefits, and this will require increased acceptance of RWD by decision-makers. For all these health stakeholders and society at large, RWD has delivered significant value and will continue doing so as its usage increases. (Calypso Montouchet, Michael Thomas, James Anderson, Sam Foster 2018).
Regulatory agencies are increasingly accepting and even requesting RWD, to document safety or support effectiveness data. With the development of accelerated and adaptive pathways that recognise RWD as critical to measure new treatments' value, the availability and quality of health data developed for this purpose is likely to increase. In addition,

patients are increasingly at the centre of their own care, expanding their reach not only as data generators but also as data consumers. Growing demands for transparency and value realisation from their data are likely to improve accountability in the health data landscape. Beyond mobile health ("mHealth") which is increasingly used across Europe, new technologies such as artificial intelligence, machine learning and blockchain have the potential to revolutionise healthcare data. Although still at a pioneering stage, these show promise in their potential to accelerate data collection, improve quality and foster transparency. However, there are also a number of opposing trends that may limit or delay the use of relevant RWD for oncology (Calypso Montouchet, Michael Thomas, James Anderson, Sam Foster 2018):

Current challenges with oncology health data in Europe

Data – requiring broader, deeper & interoperable datasets	• Most current data sources do not collect all the relevant information that is useful in oncology (e.g. biomarkers, ECOG scores, surrogate endpoints, etc.) • Much of the data used to manage cancer is unstructured and coded in different languages • Data quality varies across datasets, due in part to insufficient quality control mechanisms
Structure – needing a stable, open and supportive environment for data	• Few cancer plans and country policies explicitly target health data • Member states have the ability to legislate locally for health, genetic and biometric data • Funding for health data tends to be short-term and come with individual interests • Linkage is key to enrich decision-making but remains limited for legal, societal and technical reasons
Process – progressively scaling up to world-class, transparent processes	• Access requirements differ widely across datasets • Patient consent is not optimised and can both delay and limit the availability of data • The timeliness of data availability and access is a significant problem • Significant resources must be expanded to protect patient data and privacy
Technology – enabling solutions that were previously difficult	• The lack of interoperability between systems limits the ability to link different sources of health data • Software and platforms are rarely user-friendly, limiting the ability to collect enough data • Existing technologies may be outdated or likely to become so given new processing requirements
People – building skills & mindsets for involvement & sharing	• There is a lack of awareness and misconceptions undermine the full potential of health data • Patient concerns around their privacy remain strong • Healthcare providers remain concerned about the use and sharing of their patients' data • There is a lack of qualified individuals to undertake the increasingly complex task of collecting data • Vested interests and stakeholders' own agendas hinder collaboration in private and public settings

Source: "Report on oncology health data in Europe" (Calypso Montouchet, Michael Thomas, James Anderson, Sam Foster 2018)

Unlocking the mysteries of cancer: genomics (and other -omics techniques), AI/mechanistic models, machine learning

Cancer is driven by genetic (and epigenetic) modifications in the genome DNA. A new era in science has emerged in the last decade with the field of study of genomics and other -omics techniques, whit the aim to try to better understand health through integrating broad information on the genome and other molecular parameters with data on environmental factors such as nutrition, physical fitness and disease. Genomics has already transformed prevention, diagnosis, treatment and management of different types of cancer. Using genomics, clinicians are now able to perform far more accurately assessments of each individual's personal risk of breast, ovarian or prostate cancer, reducing the need for other medical procedures that could be harmful and costly. Using the genomic information for cancer prevention allows a move away from a reactive approach to long-term management plans that combine targeted screening and different preventive interventions.

Every tumor is different, tumors are often heterogeneous: cells of the same tumor can be different as well

Tumors form in individuals with different genomes, in cell types with different epigenomes, through random processes, usually with additional differences arising during tumor growth. It is therefore not surprising that every tumour (and even cells within the same tumor) can react differently to the therapy. Compounded by pharmacogenomic, microbiome and immune system differences between patients, likely to affect the results of drug and immunotherapy, cancer is, in its essence, a deeply personal disease, severely limiting what can be achieved by standard therapies or biomarker driven stratification. No tumour has ever identically occurred, and even cells of the same tumor might very well differ in their response to a specific therapy. On its deepest level, every individual tumor on every individual patient is therefore an (exceedingly) rare disease, represented by exactly one case. Precision medicine, the stratification of patients based on a deep molecular analysis of tumour and patient, has clearly helped to improve therapy for many patients, replacing blunt instruments like chemotherapy approaches, which typically aim to kill all dividing cells in the body, by targeted drugs often targeting molecules (e.g. fusion proteins driving tumor development) without counterparts in normal cells of the body, increasing specificity and reducing side effects. Even in this situation, the response of tumour cells will potentially depend on other changes in the tumor (e.g. remaining drivers in the same pathway downstream of the first one and/or in other pathways, tumor repressors etc, tumor heterogeneity) and host factors (pharmacogenomics, microbiome, immune system). In view of this enormous (and irreducable) complexity it seems clear that stratification approaches ignoring most or all of this complexity are, at best, crutches on the way to a true personalisation of therapy selection, based on the full (relevant) complexity of the real situation in every individual patient. If the tools we have available at the moment can not handle the real complexity of the tumour/patient situation, we have to develop new ones, and not let the limitations of current tools shape our view.

The deep molecular analysis of tumor and patient: precision medicine

The enormous progress in both deep molecular analysis techniques (genome, epigenome, transcriptome, proteome, single cell analysis approaches, spatially resolved -omics techniques etc) and availability of cost effective computing power have brought us to an inflection point: we can now (cost effectively) learn more about the biology of an individual

disease in an individual patient than we knew about all of human biology a few decades ago, knowledge, which can be used to predict, to some extent, the response of tumor and patient to specific drugs. This is not simply a question of genomics. Analysis of the tumor transcriptome often provides key information. Genes that are not expressed are not functional in a biologic sense even if there are no mutations in the genes. Recessive oncogenes can therefore be as easily eliminated by epigenetic processes (e.g. promoter methylation) as by mutation. Spatially resolved proteomics can provide key information on the tumor micro-environment. Deep analysis of the status of the immune system of the individual patient will ultimately give us additional insights for targeting immunotherapy etc.

From stratified medicine to a true personalisation of therapy choice.

In all other areas where we face complex problems, we have succeeded in minimizing risks, costs and time by a simple principle. It is much less dangerous and expensive to make mistakes, which are unavoidable, whenever we have to make decision in difficult situations, on computer models rather than in reality. Similarly, if we can construct computer models of the tumour and those aspects of the patient relevant to predict response to the therapy or therapies under consideration, we should be able to test all possible therapies and select the one with maximal effect and minimal side effects on the individual, a true personalisation of therapy choice.

Where do we get the models?

The models we need have two main aspects: the basic structure, defined pretty well by decades of cancer and related research (estimated to cost of the order of a trillion dollars since the beginning of the 'War on Cancer' declared by Richard Nixon in 1971), and the quantitative parameters required to numerically solve the very large systems of differential equations specified by the models. These parameters are, however, largely unknown, possibly the main remaining stumbling block on the way to a much better prediction of the response of a specific patient to a specific drug, a key step towards a true personalisation of the therapy with targeted drugs in oncology. Based on model simulations (H. Lehrach, pers. comm.) we do now have suggestive evidence, that this problem, maybe last major remaining bottleneck to a true personalization of therapy choice in oncology, might be solvable, given sufficient resources to generate the necessary experimental data and to provide the required computing power to analyse them.

AI, machine learning

Depending on the definition of AI used, mechanistic models, the tool universally successful in solving similar problems up to now, is part of AI (i.e. "the study of how to make computers do things at which, at the moment, people are better" (Rich and Knight, 1991)). Many current forms of AI are, however, currently limited to identifying correlations, not causality (The Book of Why: The New Science of Cause and Effect, Judea Pearl), severely limiting their application on making accurate predictions in situations with large, complex data sets, an area in which mechanistic models excel (e.g. weather forecasts). They are however many useful application areas in which they are likely to perform very well (e.g. classification of pathology slides). Classical AI techniques might also have an important role as complement to mechanistic models, for generating hybrid models that integrate mechanistic and AI components, and may become generally more applicable, when new, causality aware, explainable AI systems become available. In our view, in the current situation, classical AI and machine learning are useful tools in specific areas, but far from a panacea able to personalise therapy choice simply based on large amounts of diverse historical data.

The future of cancer prevention and treatment - the DigiTwins approach

The DigiTwins (www.digitwins.org) initiative is building on convergent technological and scientific developments to offer a future vision of sustainable cancer management (and health care in general), rooted in a data and model driven approach. Predictive mechanistic models and purpose built computational approaches, including AI, to guide medical decisions will be developed to provide the most effective therapy or prevention recommendation for individuals. Instead of testing the preventative, well-being or therapeutic measure on the real individual, all possible options will first be tested on a personal digital twin, to identify the best option for him/her. These digital twins are set to play a key role in disease prevention and the personalization of treatment in the future. For prevention purposes, digital twins could be used to identify individuals who are more predisposed to the onset of cancer, helping to make lifestyle choices and pin-point the early onset of disease. For facilitating therapy choices, the models can be used to predict the effect and side effects of a range of drugs (both singly and in combination) on the individual tumour and patient. As the models develop, they will be able to incorporate all the factors that impact the effect and side effects of a given treatment, from the host immune system to the impact on healthy cell types. The predictions of these models will be as good as existing scientific results defining the model structure and available data defining the model parameters allow. As they are applied, both structure and parameters will improve, providing increasingly accurate predictions. Combined with increasing knowledge on modelling other relevant components of the body of the patient (pharmacogenetics, microbiome, effects on normal cell types, immune system), we can expect, over decades, increasingly accurate predictions of the effects of therapy and prevention on every individual.
These models ('Digital twins') will not only form a valuable and integral part of sustainable health care systems, but they will promote the development of a learning health care system, in which the modelling tools developed to personalise care and prevention will open new avenues for research, forming a crucial feedback look from 'bench to bedside' and back.

Empowering the patient

Patients are increasingly at the centre of their own care, expanding their reach not only as data generators but also as data consumers.

In the context of recent developments in public health genomics the patients – or better citizen – has even more important implications. Prognostic testing which discovers a disease that cannot be mitigated or cured – for example in Alzheimer's disease – might in some cases do more harm than good for the individual and their relatives. While some authors focus on the many challenges of genetic testing for the individual, others see the potential since they put "the citizen, and no longer the researcher or the physician, in the driver's seat". (Brand & Brand, 2011) Health literacy, i.e. the ability or skill to make the right decisions concerning one's own health, becomes increasingly important. (Kickbusch & Maag, 2008) Health literacy has always been a two-partite concept: Future developments in health do not only require "health literate" citizens or patients but equally "health literate systems" which ensure navigation support and are readable for community members, consumers, and patients from all walks of life. (WHO , 2013)

Some cases are very clear, e.g. Angelina Jolie: She was unfortunate to have inherited one faulty version of the BRCA1 gene, harboring the kinds of changes that she reported would give her an 87% chance of developing breast cancer in her lifetime – as well as a 50% chance for ovarian cancer. She decided to be proactive and to have a preventive double mastectomy[18]. Such "dispositions", discovered by chance or on purpose, overshadow the present and may create additional burden. New technologies contribute to the "disenchantment" and limit as Maio notes the privilege of innocence, i.e. the "right not to know", the latter being sometimes an important factor of quality of life[19]. In light of these new options health literacy becomes a critical skill.

In May 2018, the General Data Protection Regulation (GDPR) came into effect, with the aim of harmonising data privacy laws, of protecting and of empowering EU citizens. Patient consent remains at the core of data collection, but it is not optimised and can both delay and limit the availability of data. Only 13 of the 28 EU countries have specific rules regulating patients' consent for EHRs, while frameworks and best practice tend to remain local[20].

Consent processes differ widely, are often unclear for patients and can be quite complex: consent forms for research can range from three to 30 pages, with an average readability suitable for a college graduate.
Opt-in consent management solutions, user-friendly videos and other tools could be used to facilitate the consent process, allowing patients to have a better view of the data they offer and how this is used for different applications.
The GDPR sets out to delineate stronger and clearer conditions for consent, but if not done properly, this could also increase the amount of information that patients are required to consider, understand and agree to.
Beyond ethics and consent, significant resources must be expanded to protect patient data and privacy. Patient data can be de-identified, but this is not infallible; full anonymisation may be necessary but can be challenging, requiring multi-stage de-identification with clear governance and controls approved by relevant authorities.
Patient concerns around their privacy remain strong, particularly given recent scandals and data breaches. Only 38% of EU patients believe that healthcare providers offer effective data security, and many fear that their data could be used for profiling by insurers. As a result, numerous efforts to collect patient data meet continued opposition or have failed.
Processes are already complex and burdensome, and likely to become so given the understandable GDPR push for transparency and better use of health data. Better planning and systematic efforts to put patients at the centre of data collection and use in a user-friendly way, most likely using new technologies, represent the best options to simplify this environment.
Lack of awareness and misconceptions undermine the full potential of health data: even in healthcare, many individuals cannot readily point to the benefits of health data. For this reason the awareness campaigns on data donations could increase the trust of the patients/citizens and their willing to share the data.
It is, however, worth keeping in mind that the situation behind much of the data protection and ethics discussion in oncology might be about to change. While, in statistical/stratificationbased medicine data generated on the individual were predominantly benefitting others (future patients, researchers, pharma companies), in truly personalized medicine the patient him/herself is by far the main beneficiary. It benefits the patient to ensure that the therapeutic decision is based on a maximum of personal information and that the information might be made available to others, potentially generating new therapy relevant insights. Especially in life threatening diseases like cancer, it might therefore be very much in the interest of the patient to opt for very open consent mechanisms, e.g. the "open consent" approach developed by George Church in the "Personal Genome Project" (PGP).

A new vision
EU Cancer Plan based on data, technologies and human touch

Our goal is to promote a visionary EU Plan on Cancer based on human touch, data, technology and modelling approach that empowers citizens.
Various initiatives including the EU Master Plan to Fight Against Cancer and the German Decade against Cancer could provide a strong framework for this vision. (Weber, 2018)
At the centre of our vision is the citizen/patient and the need for a true personalised approach for prevention, early detection, diagnosis and treatment of cancer. Every citizen/patient is unique and deserves the best possible healthcare but this is not always possible due

18 Jolie A. My Medical Choice. New York Times. 2013 May 14

19 Maio G. Chancen und Grenzen der personalisierten Medizin – eine ethische Betrachtung. GGW – Das Wissenschaftsforum Gesundh und Gesellschaft [Internet]. 2012;Heft 1 (Ja. Available from: https://www.igm.uni-freiburg.de/Mitarbeiter/maio/chancen-und-grenzen-der-personalisierten-medizin.pdf/view

20 https://www.efpia.eu/media/412192/efpia-onco-data-landscape-1-report.pdf

to heterogeneity of the disease (every cancer is unique) and the heterogeneity of the health systems.

New technologies, as described above, require new skills which are closely linked to the concept of health literacy as recognised in the Council Conclusions of the Luxembourg EU Presidency. New technologies allow a prognosis of risk that was unthinkable a few years ago and lead to new levels of health- and health policy related decision-making for the individual but also health systems which directly touch on the concept of health literacy. (Roediger, Immonen-Charalambous, Kujawa, & Sorensen, Nothing about me without me: why an EU health literacy strategy embracing the role of citizens and patients is needed, 2019)

Personalised, digital health approaches are the single most effective means to revolutionise healthcare, as they amplify the potential of value-based medicine and reduce healthcare costs, while providing better and safer treatment, prevention and well-being options on an individual basis.

A vision for every citizen and every cancer patient

Digital twins, accurate data-driven computer models based on the key biological processes that keep us healthy or lead to disease, are essential for predictive personalised medicine approaches in cancer. Using these models, better therapies, preventive or lifestyle measures can be identified, without exposing individuals to unnecessary risk and the healthcare system to unnecessary costs. Individual predictive models of patients and citizens will however not only provide powerful tools to select the optimal therapy prevention measure or measures to enhance the well-being of healthy individuals. They can also be used to explore the effects of potential changes in healthcare policies and reimbursement strategies on the local, national, European and ultimately world wide level (diseases travel quickly in todays highly interconnected world). Such Digital twin models could, however, also be used to improve a major limitation we are facing: it is still much too expensive and takes much too long to develop the new drugs we will need in the future to help increasingly small groups of patients. Models of individual patients as well as any experimental models used in preclinical research in drug development, could, in principle, significantly decrease risks, cost and time needed to develop new drugs. This could be conducted using low cost (possibly quite large) in-silico clinical trials on virtual patient populations to identify whether a drug candidate is likely to address the medical needs of a group of patient not adequately covered, prior to entering preclinical development. Resulting savings on all these levels can be redistributed, reinforcing the positive effects on health maintenance and well-being: Europe's citizens will live healthier for longer.
At the same time, these new opportunities have also some ethical implications, which require the "buy-in" of its "users". Health literacy may be a catalyst as it ensures that health policies are not developed "on behalf of" but "with" and "through" people who are in turn able to participate more fully and exert a higher degree of control over their health and wellbeing.

A vision at the health system level

For health systems, we have to be able to make the transition from the current model (the scientific foundation of healthcare systems from EU Member States dates back one century) to learning health systems capable of continuous improvement in the way that care is delivered.

A healthcare system integrating continuous improvement will only work based on the ability to track what is happening in the health system, and also be able to analyze it. For the moment, even if we had "a perfect dataset on cancer" we will not be able to take all the advantages due to the fragmentation and the way health systems are organised and conducted. At the core of the learning healthcare systems is the opportunity to collect and analyze at individual level (citizen/patient) real world data and systematic, large-scale and routine use of outcomes measurement - this could enable the transition to outcomes-based system but also to new regulatory and reimbursement pathways. Last but not least, such "learning health systems" only work if they also become "health literate systems" which ensure navigation support and are readable for community members, consumers.

Implementation of the vision

Political support is crucial for the implementation of an EU cancer plan. Cancer was one of the key topics on the recent EU Elections Campaign[21] and we expect the commitment to be translated into action with the new Commission and new European Parliament in office. The European Commission should play in the future a key role in coordination, implementation, development and evaluation of the digitally-enabled EU Cancer Plan.

Despite the fact that health is a national competency of Member States and this contributes to the fragmentation, the EU has already developed some tools that can be used to reinforce the battle against cancer based on data and the new technologies.
The Commission has proposed to establish the European Innovation Council (EIC) as one of the key novelties of the new EU programme for Research and Innovation, Horizon Europe[22] (2021-2027). The EIC will be a one-stop shop to bring the most promising ideas from lab to real world application and support the most innovative start-ups and companies in scaling up their ideas. Cancer is one of the potential 6 Missions proposed by the European Commission for Horizon Europe[23].

At Member States level, political will is also very important for the implementation of the vision. Voluntary cooperation of Member States driven by European Commission should be reinforced on the following initiatives, as a background for a common action on cancer at EU level:

- E-health Network
- European Network of Cancer Registries
- Million European Genome Analysis Project
- Declaration of cooperation on Artificial Intelligence
- European Network for Health Technology Assessment
- International Consortium for Personalised Medicine

21 https://manfredweber.eu/a-european-master-plan-to-join-our-forces-in-the-fight-against-cancer/
22 https://ec.europa.eu/info/designing-next-research-and-innovation-framework-programme/what-shapes-next-framework-programme_en
23 http://ec.europa.eu/transparency/regexpert/index.cfm?do=calls.calls_for_app