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**“European Groundshot—addressing Europe’s cancer research challenges:
a *Lancet Oncology* Commission”**

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Summary

Cancer research is a critical pillar for countries to deliver more affordable, higher quality and more equitable cancer care; patients treated in research-active hospitals have better outcomes than those who are not. Yet cancer in Europe is at a crossroads. Already a leading cause of premature death pre-pandemic, the disastrous impact of COVID-19 on early diagnosis and treatment is likely to set back cancer outcomes in Europe by almost a decade. Recognising the pivotal importance of research not just to mitigate the pandemic today, but to build better European cancer services and systems for patients tomorrow, the *Lancet Oncology European Groundshot Commission on Cancer Research* brings together a wide spectrum of experts, with detailed new intelligence of cancer research activity across Europe from the last 12 years. We have deployed this knowledge to help inform Europe's Beating Cancer Plan, the EU Cancer Mission and set out an intelligence-driven patient-centred cancer research roadmap for Europe.

The high-resolution cancer research data and intelligence we have generated shine a penetrating light on current activities, captured through different metrics including by region, by disease burden, by research domain, by impact, while also capturing granular data on research collaboration, gender of researchers and research funding. This has facilitated identification of those areas that are perhaps over-emphasised in current cancer research in Europe, while also highlighting those domains that are underserved.

Our detailed intelligence emphasises the need for more information and data-driven cancer research strategies and planning going forward. A particular focus must be Central and Eastern Europe, as our intelligence emphasises the widening gap in cancer research activity, capacity and impact compared with the rest of Europe. Citizens and patients, no matter where they are, must benefit from advances in cancer research. Our intelligence also highlights that the narrow focus on discovery science and biopharmaceutical research in Europe needs to be widened to include such areas as prevention and early diagnosis, treatment modalities such as radiotherapy and surgery and a larger concentration on developing a research and innovation strategy

for the 20 million Europeans living beyond a cancer diagnosis. Our data highlights the important role of Comprehensive Cancer Centres in driving the cancer research agenda

Critical to a functioning cancer research strategy and its translation into patient benefit is the need for a greater emphasis on health policy and systems research, including implementation science, so that the innovative technological outputs from cancer research have a clear pathway to delivery. This European Cancer Research Commission has identified 12 key Recommendations within a Call to Action to “Reimagine Cancer Research and its Implementation in Europe” to help achieve our ambitious 70:35 target; 70% average survival for all European cancer patients by 2035.

Cancer Research in Europe: Setting the Scene

Cancer Research in Europe in the meta-COVID era

We have reached a critical inflection point for cancer research in Europe. Our challenge is unequivocal - how best can research play a transformative role in promoting more effective prevention, facilitating earlier diagnosis, delivering better, safer and potentially more affordable treatments and ensuring enhanced quality-of-life for current patients and those living beyond cancer? Furthermore, how do we address this challenge through the prism of the significant impact of the COVID-19 pandemic and other externalities (e.g. Brexit, the Russia-Ukraine war, economic recession)?

Crucial to informing a person-centred ambitious cancer research agenda for Europe is the need for accurate, timely, granular data that capture the current landscape of research activity and highlight the gaps that need to be addressed. Too often opinion, even if expert, has trumped data in the genesis and implementation of cancer research policies. In this *Lancet Oncology European Groundshot Commission on Cancer Research*, we have first focussed on generating the data to shine a penetrating light on the current European cancer research landscape, highlighting its strengths but most particularly capturing its weakness, contrasting areas that have perhaps received an over-emphasis of effort with those which have been underserved. Analysing these data and deploying the resulting intelligence underpins a series of Recommendations and a Call to Action, which if acted upon, will help nurture a cancer research culture that delivers pragmatic solutions for Europe.

One unintended consequence of the COVID-19 pandemic, with rapid repurposing of health services and introduction of national lockdowns, has been the adverse impact that these measures, and their continuing legacy, have had on cancer services, on cancer research and most importantly on cancer patients.¹⁻⁴ Just to emphasise the scale of the problem, we estimate that ~1 million cancer diagnoses may have been missed across Europe during the pandemic.⁵ There is emerging evidence of major stage-shifts as a result of significant delays in cancer diagnosis and treatment, which will continue to stress European cancer systems for years to come.⁶ These issues will ultimately compromise survival and contribute to inferior quality-of-life for many European cancer patients. COVID has regrettably exposed a lack of resilience in

cancer health systems which if not addressed as a matter of urgency, will prompt a cancer epidemic over the next decade.⁷

Much of the success achieved in improving cancer outcomes over the last decades in Europe may be reversed by the impact of the pandemic.⁸ Crucially, in the context of this *Lancet Oncology Commission*, there has been an unsettlingly negative impact on cancer research, with significant reductions in cancer clinical trial activity, disruption to discovery cancer research and major reductions in cancer research funding.⁹

Against this backdrop, the *Lancet Oncology Commission* provides crucial intelligence on the current landscape of cancer research across Europe, exposes the key gaps and demands a re-prioritisation of European cancer research agendas over the next decade. Critically, we focus on those gaps and inequalities in cancer research, that if addressed, would create a more effective cancer research ecosystem, significantly shifting the dial and reimagining cancer research and its implementation across Europe. Simply continuing to dedicate resource and effort to a narrow research agenda is no longer desirable or viable – we must follow the data and act on what they reveal.

Cancer Research Domains of Particular Strength in Europe: Some Examples

There are many research domains where Europe can be categorised as world-leading. The European continent (not just the EU27) is a global leader in cancer discovery science. Strengths are evident in molecular, cellular and structural cancer biology, modelling, diagnostics and early detection, new medical technologies and personalised treatments, precision oncology, vaccines, immunotherapies and drug-antibody conjugates, and paradigmatic shifts in neo-adjuvant therapy, especially for immunotherapy. European cancer epidemiology research and deployment of population-based cancer registries have been crucial in a data-driven approach to understanding cancer and enhancing cancer outcomes.

Cancer Registries: More than 180 cancer registries are in operation across Europe, in over 30 countries, coordinated by the European Network of Cancer Registries.¹⁰ In most countries, cancer registration covers the entire national population, and is a statutory requirement. This provides a comprehensive picture of Europe's cancer

burden, but problems in accessing the data can make it difficult for researchers to produce reliable information in a timely fashion. The COVID pandemic has demonstrated that governments can ensure rapid access to data, when they perceive a pressing need. The European Centre for Disease Control¹¹ was able to produce daily updates of the numbers of cases and deaths from COVID within 2-3 days of their occurrence. Population-based cancer registries represent key enabling infrastructure to help define cancer inequalities, evaluate the impact of cancer prevention research strategies and determine effectiveness of national health systems in providing best care for cancer patients, regardless of their socio-economic status.

There is a strong public health case for ensuring that high-quality data on cancer in all European countries are as up-to-date as possible, and that they are made available for research in compliance with national laws and the EU General Data Protection Regulation (GDPR),¹² without unnecessary constraints. GDPR is not sufficiently well understood and in some countries its interpretation can be restrictive for research. We need a pragmatic approach to ensure protection of the individual's rights while also making data available for bona-fide research. Without this access to data intelligence, our ability to address the challenges of the COVID pandemic would have been severely compromised.⁵

Cancer Model Systems: The discovery/development of organoids as a model system to elucidate critical drivers of cancer, has allowed precise definition of distinct mechanisms of tumour cell killing and helped determine emerging drug resistance.¹³ Creation of "living biobanks" for multiple tumour types provides an excellent platform for driving cancer research and innovation.^{13,14} Appropriate well-characterised model systems have been critical drivers in the rapid development of drug-sensitivity screening models, with predictive value in multiple tumour types, underpinning innovative precision oncology and immunotherapy research.^{13,15,16}

In parallel, creation/deployment of a variety of animal model systems that recapitulate the tumour biology of multiple cancer types, facilitated evaluation of innovative treatment modalities at the pre-clinical stage. Europe has shown particular strengths and pursued innovation in animal models, particularly Genetically Engineered Mouse Models (GEMMs) and Patient-Derived Xenographs (PDXs).¹⁷ The importance of

animal model systems and their relevance to cancer is supported by the UK's Medical Research Council (MRC) recent announcement of a multi-million investment in a National Mouse Genetics Network, with cancer as a key cluster.¹⁸

Early Detection Research: The NELSON randomized trial in lung cancer has been pivotal, because of the convincing early detection rates achieved, and their impact on survival.¹⁹ New European-driven developments in ultra-thin rapid next-generation CT-scanning and AI-enhanced early detection (and prediction)²⁰ will further empower robust early detection, enhanced by robotic read-out systems and machine learning (ML) approaches that provide increasing precision/speed in early cancer detection. While this will require investment, it will subsequently be accompanied by a lowering of costs, driving the dual imperative of saving people's lives, while delivering value-based care.²¹

Cancer Diagnostics and Precision Oncology: There has been a significant push in Europe to embrace new medical technologies, developing and deploying innovative tools to enhance cancer diagnosis and treatment. Cancer biomarkers and genomic testing are critical enablers to unlock the promise of precision oncology. A robust cancer biomarker infrastructure must be embedded across health systems, to ensure their deployment as innovation drivers Europe-wide. Cancer biomarkers must also be considered in the context of the In Vitro Diagnostics Regulation, which may still pose certain challenges.²² Embedding cancer biomarkers within real-world oncology delivery and providing genomic testing across Europe, whilst ensuring that inequity gaps for patients are narrowed, not widened, must be the goal.²³ Critically, cancer patients must be at the centre of this biomarker-driven precision oncology research agenda, with research on value-based care informing appropriate biomarker use.

If deployed appropriately, cancer biomarkers can reduce costs by ensuring the right treatment, for the right patient, at the right dose, at the right time, sparing cancer treatment sequelae for those who gain no therapeutic benefit. Our recent health economic analyses have underlined the potential for cancer biomarkers to deliver value for money.²⁴⁻²⁶ However, we also found a paucity of studies employing detailed health economic analysis to inform the feasibility of incorporating cancer biomarkers/genomic testing into the clinic, highlighting the need for wider deployment

of health economic evaluation to inform value-based care. Precision diagnostics can also help target interventions to the most significant areas of disease.²⁷

Radiation Oncology: Europe's radiotherapy research agenda is highly focused on precision radiation therapy development. For instance, new-generation MRI-guided radiotherapy²⁸ or FLASH therapy²⁹ systems both search for the optimal balance between treatment toxicity and tumour control. This continuous quest for better-tolerated radiation treatments not only allows their integration in combination with new drugs, but has also facilitated highly hypo-fractionated delivery, which has become standard-of-care in breast/prostate cancer, thanks to large randomised European clinical trials.³⁰ This also has allowed expansion of radiotherapy to new patient populations, such as in the radical approach to oligometastatic disease with stereotactic body radiation therapy (SBRT).³¹ Shortening radiotherapy delivery through hypofractionation based on unique radiobiological profiles of different tumour types has profoundly enhanced radiation therapy delivery, with positive impact on patient/societal burden. Europe's commitment to practice-changing RCTs³² has enabled radiotherapy to be reactive to the pandemic's impact, facilitating changes in practice-of-care to enable continuation of services during the pandemic and subsequent management of the cancer backlog.

Vaccine development: Overall, there are substantial strengths in cancer vaccine expertise across Europe. Successful development of the preventative Human Papilloma Virus (HPV) vaccine and its implementation to protect girls from cervical cancer (and more recently both sexes from HPV-driven cancers such as oropharyngeal and anal cancers) had its origins in the pioneering research of 2008 Nobel Prize winner Harald Zurhausen . More recently, Europe has been at the forefront of COVID vaccines development, deploying mRNA personalized vaccine approaches for vaccination strategies in solid tumors.³³

Tumour Immunology and Immunotherapy: Tumour immunology/immunotherapy are further examples of recognised research strengths in Europe. The early work on anti-PD1 (nivolumab, pembrolizumab), is both a seminal development and an exemplar of European research strength.³⁴ Recognition of the importance of immunogenic cell death has been pivotal, particularly for classifying chemotherapeutic drugs and

enhancing combination strategies.³⁵ Europe is also a global leader in determining the impact of the microbiome on cancer treatment efficacy, in particular treatments employing immune-checkpoint inhibitors.³⁶⁻³⁹ Discovery science has informed clinical trials, opening up microbiome-management approaches to optimise anti-tumour responses.⁴⁰ Characterising the immune component of the tumour micro-environment has been critical in developing tumour “immunoscores”;⁴¹ detailing immune-enhancing and immunosuppressive components fundamental to our understanding of the immune environment. Manipulation of the immune system and the tumour microenvironment represent pivotal targets in cancer therapy development.⁴²

Immunotherapy is currently undergoing its next revolution, Translating discovery science in advanced disease in melanoma and its roll-out in multiple tumour types represented the first paradigm shift; rapidly followed by development of adjuvant therapy approaches, initially in stage-III melanoma patients.⁴³ This neo-adjuvant immunotherapy paradigm is achieving highly significant reductions in clinical relapses, more cures, shorter treatment cycles, and less surgery.⁴⁴ It has been deployed effectively to avoid rectal cancer surgery in almost all patients,⁴⁵ with promising results for head and neck,⁴⁶ bladder⁴⁷ and locally-advanced lung cancer.⁴⁸

Cancer Research Challenges in Europe

While we have reflected on some exemplars of pre-existing research excellence and front-line innovation, there are a number of substantial research challenges that must also be considered and addressed. The focus of this *Lancet Oncology European Groundshot Commission on Cancer Research* is to identify and codify these challenges and utilise the intelligence revealed to propose a broader, more person-centred data-informed cancer research agenda for all of Europe, not just the EU27. Cancer prevention research, for example, has not had the attention (nor the funding) it deserves, given its potential impact on cancer control.⁴⁹ Screening recommendations from 2003 have not been fully implemented, emphasising the dearth of national implementation science programmes to address this deficit.

Similarly, our ability to convert research discovery into therapeutic innovation is compromised by regulatory, implementation and scale-up challenges.⁵⁰ More support

is required for both academic-led clinical trials/and RWE studies. Health services research and implementation science are critical to ensuring translation of research into clinical practice, but research focus and funding for these two critical areas has been woefully lacking. Overall, this lack of support is curtailing our ability to deliver new diagnostics and therapeutics that can be sustainably and equitably embedded across European health systems. Crucially, despite the 20 million European citizens living with and beyond cancer,⁵¹ there remains a distinct lack of focus on developing research programmes that address the physical, psycho-social and financial needs of cancer survivors.

From an infrastructure perspective, significant gaps exist. We must occupy the vanguard of the digital health revolution, ensuring well-structured data-warehouses, databanks and IT-systems to support rapid deployment of ML and accelerated analytic approaches. Europe does have world-leading excellence in data science, including the pioneering work of the European Bioinformatics Institute and Health Data Research UK,^{52, 53} but what is needed is the creation of pan-European linked highly-curated datasets to enable national evaluation of practice, policy and performance.

We need to facilitate precise analysis of the impact of new cancer technologies on health systems, on the real-world impact of new treatments, and on new prevention and life-style adaptation strategies. These developments are currently hampered by Europe's fragmented health informatic architecture. However, a great advantage that we must build on is that research policies are defined and research funding is allocated both at national and at European level, providing an opportunity to break down traditional silos and enhance the value of cancer research and its translation across Europe. This is particularly relevant, given the opportunities already highlighted (Europe's Beating Cancer Plan, EU Cancer Mission), as well as other opportunities through Horizon Europe's research funding programmes. Critical to this is the need for the bioinformatic, statistical and advanced data analytics skills and frameworks to drive a digital health agenda that places significant emphasis on data intelligence and its deployment to underpin cancer research and its real-world translation for the benefit of human health and wellbeing. With our push for federated datasets and the

ongoing development of the European Health Data Space,⁵⁴ Europe is ideally positioned to be a world leader in cancer health data science and its application.

Another critical gap is the poor quality of RWE studies,⁵⁵ reinforcing the need for better data strategies and systems for post-marketing studies. Through more data-empowered morpho-molecular analysis, coupled with linkage to clinical information, we are realising the unique nature of every cancer patient. Consequently, the classical research paradigm will undoubtedly shift in the near future, to one where collecting and analysing RWD from all oncology patients is the norm.^{56, 57} In this context, new financing models such as coverage linked with evidence development, may aid evidence generation (both clinical and economic), to support formal reimbursement schemes in the real-life setting.⁵⁸

Cancer Research in Europe – the Political Opportunity

For many European countries, cancer is the leading cause of premature mortality/morbidity, and a major economic burden for citizens and societies. The human and financial costs of cancer to Europe and its citizens will only continue to grow. Although Europe provides some of the best cancer care in the world and conducts high-quality globally-recognised cancer research, there are notable disparities in access to and delivery of optimal cancer control, coupled with a need to ensure that cancer research and innovation address these disparities, so as to reduce the inequalities divide between and within European countries. European cancer research strengths are currently unevenly distributed and do not necessarily align with the cancer priorities of individual European countries, an area we explore in more detail in this *Commission*.

Despite these challenges, there have been encouraging chinks of light within the overall European cancer control and research landscapes. Crucially, European Commission President Ursula von der Leyen has championed the need for a clearer strategic focus on health, exemplified by her call for a stronger European Health Union. Previous incumbents of her office have rather shied away from this strategic focus, relying instead on the oft-used phrase “health is a national competency”. Variations in survival, however, suggest that relying on national competency alone is not in the best

interests of European citizens. If there is one irrefutable truth that the current pandemic has taught us, particularly in the context of the rightly-praised collaborative COVID vaccine development effort and the rapid delivery of effective vaccines to European citizens, it is that collaboration between countries, jurisdictions and sectors is absolutely essential.

This re-orientation of the narrative, championing enhancement of our cancer health and well-being as part of a pan-European effort, was recently reinforced by the conclusions of the Conference on the Future of Europe, calling for more pan-European cooperation in health care and research (**Panel 1, appendix p5**)⁵⁹ A stronger European Health Union beyond the political boundaries of the EU27, with an emphasis on greater health resilience and integrated research, a “health in all policies” approach and a data-informed, citizen-focussed research-driven agenda such as what we are proposing, are what is urgently required to address the challenges that cancer poses. Putting patient- and citizen- focussed (and approved) research at the heart of a pan-European cancer strategy will be a critical driver of enhanced health outcomes.

Early in her tenure, the European Commission President tasked her Health and Food Safety Commissioner Stella Kyriakides with developing an ambitious plan for cancer, emphasising the importance of tackling this devastating disease that was diagnosed in 2.7 million citizens and led to >1.3 million deaths in the EU in 2020.⁶⁰ Following a period of development and a degree of consultation, an overarching Europe Beating Cancer Plan was launched by Commissioner Kyriakides on the eve of World Cancer Day, 2021. The Plan has four key pillars - prevention; early detection; diagnosis and treatment; and quality-of-life. Progress within these four pillars will be achieved through implementation of ten key Flagship Initiatives (**Panel 2, appendix p6**), and a series of accompanying supporting actions. On 16th February 2022, the European Parliament ratified Europe’s Beating Cancer Plan, the first time that Europe has developed a consolidated approach to address this deadly disease that is overtaking cardiovascular disease as the most common cause of premature death in Europe.

From a research perspective and thus of critical importance to this *Lancet Oncology Commission*, cancer was also selected as one of five research “missions” of the EU, emphasising the importance placed on cancer research as integral to national cancer

control planning. Irrefutable evidence generated by members of this *Commission* and by others indicates that those patients treated in research-active hospitals have significantly better outcomes than those who are not.⁶¹ The interim report of the Cancer Mission Board “*Conquering Cancer: Mission Possible*” was published towards the end of 2020.⁶² A number of key research themes were identified, echoing the pillars of Europe’s Beating Cancer Plan: Understanding of cancer; Prevention and early detection, Diagnosis and treatment, and Quality-of-Life for patients and their families, supported by a series of activities (**Panel 3, appendix p7**). Additionally, the Cancer Mission espouses a set of guiding principles (**Panel 4, appendix p8**) - noble ambitions, but they must be underpinned by an appropriate critical evidence base, as we have sought to do in this *Lancet Oncology Commission*.

Politically, as Europe’s Beating Cancer Plan and the Cancer Mission were being developed and socialised, a significant focus on cancer also emerged within the European Parliament. The European Beating Cancer Committee (BECA) hearings received substantial evidence submissions from stakeholders from across the cancer community. Establishment of a new cross-party European Parliament *Challenge Cancer Intergroup*, with secretariat provided by the European Cancer Patient Coalition (ECPC), (Europe’s largest umbrella cancer patient advocacy organisation), provides a complementary voice to the already-existing *Members of the European Parliament Against Cancer (MAC)*. These two cross-party European Parliamentary groups emphasise the commitment of MEPs to cancer issues. Political support is critical in driving a cancer research agenda as Europe navigates turbulent economic, social and political waters in the wake of the COVID-19 pandemic, the Russia-Ukraine war and economic contractions.

The aims and specific objectives of Europe’s Beating Cancer Plan and in particular the Cancer Mission echo the US Cancer Moonshot,⁶³ with its aspiration “*to accelerate efforts to prevent, diagnose and treat cancer*” and perhaps more controversially “*achieve a decade of progress in just 5 years,*” as articulated in a previous Lancet Oncology Commission “*Future Cancer Research Priorities in the USA.*”⁶⁴ On Wednesday 3rd February 2022, US President Joe Biden announced the re-ignition of the Moonshot (Cancer Moonshot 2.0 if you like), with an aim of reducing cancer deaths by 50% in the next 25 years.⁶⁵ But does Europe really need another Cancer Moonshot?

In developing the *Lancet Oncology European Groundshot Commission on Cancer Research*,⁶⁶ we argue that a more citizen- and patient- focussed, less techno-centric cancer research approach is more appropriate to the challenges that cancer poses for Europe. Cancer research prioritisation for Europe must reflect what is happening on the ground (hence the European Groundshot) empowering a more holistic person-focussed cancer research agenda and informing cancer research priorities and their implementation across all of Europe.

The *Lancet Oncology Commission* is supported by a significant number of new analyses, uncovering novel insights, combined with intelligence recently generated by members of the *Commission*. Crucially, this cancer research intelligence has been enhanced with significant input from members of the Focussed Topic Networks⁶⁷ of the European Cancer Organisation (E.C.O). E.C.O. is the largest multi-professional cancer organisation in Europe, bringing together >40 European health and care professional societies and 20 cancer patient advocacy groups as the authoritative, united policy voice of the European cancer community. Initially, E.C.O. established eight Focussed Topic Networks in areas of strategic relevance – Prevention, Early Detection and Screening; HPV Action; Health Systems and Treatment Optimisation; Quality Cancer Care; Digital Health; Workforce; Survivorship and Quality of Life; and Inequalities.⁶⁷ The COVID pandemic prompted E.C.O to establish a Special Focused Network on the Impact of COVID-19 on Cancer⁶⁸ and in response to the Russia-Ukraine war, E.C.O. joined with the American Society of Clinical Oncology (ASCO) to form an E.C.O-ASCO Special Network on the Impact of the War in Ukraine on Cancer.⁶⁹ The ten Focussed Topic Networks which have inputted to this *Commission* are highlighted in **Figure 1**.

Additionally, there have been major contributions through specific partnerships with pan-European organisations including ECPC; the European Academy of Cancer Sciences ((EACS) a pan-European body which convenes clinicians and scientists to provide evidence-based advice to underpin cancer policy in Europe); the Organisation of European Cancer Institutes ((OECI), a cancer research network that promotes greater cooperation among European Cancer Centres and Institutes); and the International Cancer Research Partnership ((ICRP), a unique alliance of >150 cancer

research organizations that maintains the only public repository of publically-funded cancer research globally).

A significant challenge for Europe, both for the Beating Cancer Plan and the Cancer Mission, are the inequalities that persist in many aspects of cancer health systems and services, including screening, diagnosis, treatment, and supportive care, particularly in Central and Eastern European (CEE) countries. Illuminating such inequalities within national cancer research agendas is critical for developing new policies that deliver better patient outcomes.

A Person-Centred European Cancer Research Agenda

The *Lancet Oncology European Groundshot Commission on Cancer Research* is also informed by a number of patient-enabled initiatives driven by the European cancer community. A project by the European Cancer Concord, a pan-European collaborative group of patients and health professionals, gathered and analysed comprehensive data from across Europe, facilitating characterisation of Europe's key cancer inequalities.⁷⁰ This led to development of the *European Cancer Patient's Bill of Rights*⁷¹ (**Panel 5, appendix p9**), launched with cross-political party support in the European Parliament on World Cancer Day 2014. The Bill of Rights, co-created by patients and health professionals, was developed as a catalyst for change and an empowerment tool for cancer patients across Europe. One of its three components was a commitment to optimal cancer care, underpinned by research and innovation (see **Panel 5, appendix p9**, 2nd Article of the Bill of Rights). The Bill of Rights and its implementation across Europe received the prestigious 2018 European Health Award at Gastein.⁷²

Congruent with development of the *Bill of Rights* was the launch of the *Europe of Disparities in Cancer* initiative (**Panel 6, appendix p10**),⁷³ led by ECPC, with input from European health professionals. This initiative forms the bedrock of ECPC's cancer inequalities agenda. A critical evidence-informed output in the context of this *Lancet Oncology Commission* is the policy paper on tackling social determinants in cancer prevention, cancer research and cancer control in Europe,⁷⁴ published through CanCon, the EU Joint Action on Cancer Control.

The 70:35 Vision for Cancer Control and Research in Europe

The initiatives described above, with their citizen- and patient- driven focus on addressing cancer inequalities, have been instrumental in developing an overarching new vision for cancer research and control in Europe, the 70:35 Vision. This Vision was co-created with multiple stakeholders through consultation and data-enabled research, evaluating different scenarios, which, if realised, would help reduce lives lost due to cancer. This analysis culminated in a proposed target of an average of 70% 10-year survival for patients treated for cancer in Europe by 2035.⁷⁵ Research and innovation form a critical pillar to support delivery of this 70:35 vision (**Panel 7, appendix p11**).

In this *Lancet Oncology Commission*, we have collected and analysed high resolution data on cancer research activity and its funding in Europe, with a particular emphasis on CEE countries. This high-quality intelligence provides the narrative for current cancer research being performed in Europe and informs our 12 Recommendations framed within our Call to Action. It is also a key driver of a citizen- and patient- centred research-informed Call to Action to ensure that the European cancer research agenda (and more importantly its implementation and monitoring) addresses the challenges that European citizens face in their daily lives, including a burgeoning East-West divide in cancer research.

Methodology

Definitions of Europe

The different definitions of Europe employed in this *Lancet Oncology Commission* are indicated in **Table 1(appendix p42)**

European Cancer Outcomes

Determining inequalities in cancer survival

Data from population-based cancer registries across Europe provide comprehensive intelligence that facilitates estimation of survival for cancer patients. These data are an important metric for the overall effectiveness of a country's/region's health system

in managing cancer, from early diagnosis through treatment delivery to final outcome.⁷⁶ For this *Lancet Oncology Commission*, survival estimates were provided by the third cycle of the CONCORD programme,⁷⁷ which analysed individual records for 37.5 million patients diagnosed with one of 18 common cancers world-wide, including ~15 million cancer patients diagnosed in Europe. Data were provided by 157 population-based cancer registries in 31 European countries, 22 of which provided data with national coverage. We estimated 5-year net survival, i.e. the cumulative probability of surviving up to 5 years since diagnosis after correcting for other causes of death (background mortality).^{78,79} Survival estimates were age-standardised using the International Cancer Survival Standard (ICSS) weights for adults⁸⁰ and children.⁸¹

Determining inequalities in Cancer Mortality

Official death certification data for 22 cancer anatomical sites and estimates of resident populations, based on official censuses, for European countries, were extracted from the World Health Organization (WHO) database.⁸² All cancer deaths were recoded according to the 10th Revision of the International Classification of Diseases.⁸³ Age-specific rates for quinquennia of age (from 0-4 to 85+ years) were computed. Age-standardized mortality rates per 100,000 person-years, based on the world standard population were obtained for each calendar year and sex, and for western and CEE regions, separately. The number of avoidable deaths in 2016 in CEE countries was estimated by applying the age- and sex-specific western European rates to the corresponding CEE populations. Similarly, avoided deaths from all cancers combined over the period 1991-2016 were estimated by applying the 1990 peak age-specific mortality rate to the population of the successive calendar periods and comparing the resulting numbers of deaths to the observed ones.

European Cancer Research Landscape

Bibliometric Analysis of European Cancer Research Outputs

Cancer research papers (articles and reviews) were identified in the Clarivate Core Collection Web of Science (WoS) Database (Db) through a complex filter with the names of 396 specialist oncology journals and 384 title words/phrases as previously described.⁸⁴ The filter was calibrated and had a precision, *p*, of 0.95 and a recall, *r*, of

0.98. Additionally, we identified biomedical research papers with a second filter, containing a list of 172 address words/contractions in oncology. Numbers of papers in each subject area, year-by-year, from the world, the 44 European region countries as a group **Table 2, appendix p43**), and from each of them individually, were extracted to underpin our landscape mapping analysis.

Sets of papers were further analysed with a series of sub-filters based on title words, and on names of specialist journals. Identified papers captured cancer research outputs across 14 research domains (**Table 3a, appendix p44**), such as genetics and surgery, but also including domains such as paediatrics (childhood cancers). They also identified papers relating to 17 anatomical cancer sites (**Table 3b, appendix p44**) e.g. breast, lung, colon etc. For each of these 31 subject areas, annotated with tetragraph and trigraph codes, we determined numbers of papers from each of the 44 European region countries in the 12-year period (2009 – 2020), and from the European region as a whole. These data allowed comparison of the amount of research on each anatomical site with the relevant disease burden (in DALYs) for the European region as a whole. It also provided potential for data intelligence to determine which European countries had tailored their cancer research portfolio to take proportional account of the cancer burden distribution between anatomical sites. Tinting of the cells (**Tables 4, 5a, 5b, 6, appendix pp45-48**) is based on a five point Likert significant statistical scale, ranging from very weak (pink) through to very strong associations (dark green).

Patterns of International Cooperation

EU-wide activities have already stimulated much co-authorship in cancer research within the region - and not just between the 27 Member States (MS). We sought to determine the pattern of international collaboration for the ten countries with the largest output of cancer research papers (at least 18,000 over the 12-year study period). For each country, we compared the numbers of papers published in cooperation with each of the other nine countries, and with nine non-European countries, as a percentage of the totals of its international papers with the percentage presence of each country in world cancer research *minus* the contribution of the original country. For example, of 42,812 German papers with international collaboration, with a total of 118,719

individual country contributions, Sweden co-authored 3,899 (3.28%), but South Korea only 1,125 (0.95%). Of 1,196,119 cancer papers *without* a German author, and with a total of 1,491,804 national contributions, Sweden contributed 17,653 (1.18%) and South Korea 54,180 (3.63%). So Sweden was a preferred partner of Germany by a factor of $3.28/1.18 = 2.8$, but for South Korea the ratio was $0.95/3.63 = 0.25$, so it was non-preferred.

Actual Citation Impact

Citation counts for each paper (2009-20), year by year, were downloaded from WoS. Five-year citation counts (Actual Citation Impact, ACI) beginning in the publication year were calculated. A five-year window was used as a compromise between the need for immediacy (i.e., citations for recent papers) and stability (i.e., inclusion of the peak year for citations, usually the second or third year after publication).

Cancer research activity by gender

Gender of authors was captured through <https://gender-api.com> as previously described.⁸⁵ This assigns sex of names across Europe from a database of 4 million names, categorising them into regional- or country-level coding. Gender of project principal investigators was determined using <https://gender-api.com>, ORCID (<https://orcid.org/>) and internet searches when first names were not provided.

European Cancer Research in Comprehensive Cancer Centres

Bibliometric Analysis of Research Outputs for the Organisation of European Cancer Institute (OEI) Centres

Our filter was applied to WoS, and the numbers of papers, year by year, determined for the world; the European Union (EU27), plus Iceland, Norway, Switzerland, Turkey and the UK, and for the group of 19 European countries (EU19) with one or more OEI-accredited centres. These were: Belgium, Czech Republic, Denmark, Estonia, Finland, France, Hungary, Ireland, Italy, Lithuania, Netherlands, Norway, Portugal, Romania, Spain, Slovenia, Sweden, Turkey, and the UK, The 51 OEI cancer centres are listed in **Table 7 (appendix p49)**. To determine the amount of collaboration, sums of the outputs of the three latter groups of individual countries/centres were compared

with totals for each group. We also applied sub-field filters to each of the four entities that identified papers in different research domains and different anatomical sites (**Table 8 (appendix p50)**). These mainly consisted of lists of title words, and (for some sub-fields), journal name-strings. They were combined into a series of search statements that could be applied directly to WOS, in combination with cancer research and appropriate geographical filters.

Cancer research funding in Europe.

Cancer Research Funding

Projects supporting principal investigators in European countries (**Table 17 appendix p52**) between 2010 and 2019 (inclusive) were extracted from the ICRP database⁸⁶ (n=20761, total value €10.8 billion (B)) or provided in Excel by partner organizations whose historic data was not yet included in the database due to GDPR or other constraints. To complement ICRP data, Framework Programme 7 (FP7) and Horizon 2020 (H2020) projects active in calendar years 2010-2019 inclusive and relevant to cancer research (keyword search using terms cancer, oncol*, malign*, tumor*/tumour*, *oma, melanom*,leuk*) were extracted from the EU CORDIS database⁸⁷ (2010-2019, n=3212, total value €5.4bn - only project funding to partners in European countries was included) and projects funded by the Swedish Research Council (2016-2019, n=471, total value €0.5bn) were extracted from WorldReport.⁸⁸ Other cancer-relevant projects from WorldReport were already included in the ICRP database. For non-ICRP data, manual review of projects with low numbers of keywords was conducted to exclude projects without a specific focus on cancer research. Non-ICRP projects were coded by ICRP to one or more CSO research domains and cancer anatomical sites.

A list of funding organizations whose data were included in the analysis is indicated in **Table 18 (appendix, p53-54)**. Projects whose funding data were not in Euros ((Canadian Dollars (CAD), US Dollars (USD), Sterling (GBP), Swedish Kroner (SEK)) were converted to Euros using the 2019 average annual exchange rate,⁸⁹ to avoid trends solely due to currency fluctuations. Analyses represent the full value of the projects active in the relevant time frame. To complement the detailed analyses based on aggregated project-level data, estimates of overall cancer research funding by

other European cancer research funding organizations, for which project details were not found in the public domain, were sourced from internet searches for annual reports, using as a starting point the International Agency for Research on Cancer (IARC) list of global cancer research funders.⁹⁰ This approach was limited to data available in the public domain; for biomedical research funders, it was not always possible to identify spend that was specifically dedicated/relevant to cancer. A further limitation in capturing overall cancer research spend was that details of funding from pharmaceutical companies were generally not available in the public domain.

Cancer Prevention Research Funding

Analysis of cancer research funding for prevention builds on a previous mapping exercise using bibliometric data as the initial basis for creating a comprehensive database on all cancer research funding entities.⁹⁰ The database was updated to include the years 2019-2021, bringing the total number of cancer research funders identified in the World and in Europe to 4998 and 1477 respectively. A methodology based on a keyword analysis of all cancer research papers in the WoS from 2008 to 2021 was developed with cancer researchers to extract prevention research publications. A “bottom-up” approach was applied; funding acknowledgements were used to identify funders active in prevention research and assess current trends. For the purpose of this Commission, the following three areas were included: Aetiology, Prevention and Early Detection, Diagnosis, and Prognosis. Tertiary prevention was excluded.

Results

Mapping European Cancer Outcomes

Inequalities in Survival Between European Countries

Our overall findings indicated that survival varied substantially between European countries and regions. For several countries in Northern (Finland, Iceland, Norway, Sweden) and Western Europe (Belgium, Germany, Switzerland), age-standardised 5-year net survival for patients diagnosed during 2010-2014 was the highest in Europe for many of cancers evaluated. In contrast, survival was lowest in the majority of the CEE countries evaluated (Bulgaria, Poland, Romania, Slovakia and Russian Federation). However, in certain Southern (SE) and Eastern European countries, five-

year survival for liver, lung and pancreatic cancer was comparable with or higher than in Northern European (NE) countries. Denmark, which alone of the Nordic countries had previously exhibited poorer survival,⁹¹ is closing the survival gap with its Nordic neighbours; for patients diagnosed during 2010-2014, five-year survival in Denmark was among the highest in Europe for cancers of the rectum, breast (women), cervix and brain, as well as for lymphoid malignancies and melanoma of the skin. In the United Kingdom (UK), which like Denmark has also exhibited lower survival (EUROCARE; International Cancer Benchmarking Partnership (ICBP)),^{91,92} five-year net survival from the CONCORD programme for patients diagnosed during 2010-2014 with cancers of the stomach, pancreas, lung, ovary and brain was similar to that seen in certain CEE countries. Five-year survival in the UK was high in the European range only for melanoma. Europe-wide differences in survival were particularly marked for cancers of the oesophagus, stomach and rectum, melanoma and lymphoid malignancies, particularly for patients diagnosed during 2010-14 (**Figure 2a-c, Figure 3a-c, appendix pp23-30**).

Regional Variation in Survival within European countries

For a substantial proportion of cancers, five-year net survival also varied widely within countries (**Figure 4a-c, appendix pp31-34**). Regional variations in Southern and Eastern Europe (France, Italy, Poland, Spain, Russian Federation), were more pronounced than in Central Europe (Germany, Switzerland) and the UK. Five-year survival increased steadily for many cancers between 2000-2004 and 2010-2014, particularly for colon/rectal cancers, and lymphoid malignancies, but for some cancers (e.g. oesophageal, liver, pancreatic, lung), age-standardised five-year net survival still remains below 20%.

Inequalities in Cancer Mortality Across Europe

Cancer mortality has shown substantial variation across different EU countries. The highest mortality rates, particularly for men, have been recorded in Eastern Europe, with a greater than twofold difference in total cancer mortality between the highest (> 250 per 100,000 in men, in Hungary) and the lowest (~110 per 100,000, found in most Nordic countries, and in Switzerland).^{93,94} A significant proportion of the higher cancer mortality in Eastern Europe is due to lifestyle factors, (use of tobacco, consumption of

alcohol, and particular dietary choices);⁹⁵ however, part of the inequalities in cancer mortality in certain European countries reflects inadequate cancer management.⁹⁶

Previously, we used cancer registration data from EUROCare-5 and a modelling approach employing different survival scenarios to estimate the number of avoidable cancer deaths in the EU, based on survival estimates across EU countries. We found that, if 5-year cancer survival in EU countries where survival is currently low, mainly in Eastern Europe, could be raised to the median rate of survival of all EU countries, then ~50,000 additional cancer deaths would be avoided each year.⁹⁷ If cancer survival in all EU countries could be raised further to the level of the 75th percentile, then >100,000 cancer deaths would be avoided annually. These data were the critical evidence that informed our 70:35 Vision, 70% average survival for at least 10 years across the EU by 2035.⁷⁵ Here, we update these data analyses, with additional analyses specifically comparing Western and Eastern Europe to inform the *Lancet Oncology Commission* recommendations in relation to building research capacity and capability to help improve outcomes in all European countries.

Persisting East/West Differences Across Europe in Cancer Mortality

When CEE countries gained access to the EU in 2004, large differences were evident for total mortality, and cancer mortality in particular. Using the most up-to-date available data, we now investigate whether such a gap in cancer mortality has closed over recent years and estimate the potential number of avoidable cancer deaths, assuming that such a gap would be closed.

We present age-standardized mortality rates from cancer sites per 100,000 person-years in Western Europe (WE) and CEE, in 2010 and in 2016, together with number of deaths observed in 2016 and percent change between the two rates (**Table 9**). From 2010 to 2016, in men, mortality rates for all cancers combined declined from 131.5/100,000 to 122/100,000 (-7.1%) in WE, and from 177 to 168 (-5%) in CEE, i.e. there was a persisting 38% excess in CEE versus WE. Corresponding rates in women declined from 80.7 to 78 (-3.4%) in WE, and from 95.9 to 94.8 (-1.2%) in CEE (excess 22%).

In WE, male rates declined in most cancer sites (e.g. Hodgkin's Lymphoma (HL) (-22.9%), larynx (-17.3%), testis (-16.7%), stomach (-16%). Unfavorable patterns with documented rises in mortality were seen for pancreatic (+3.3%) and renal (+4.2%). Overall declines were smaller in women (-3.4%), due to persisting rises in tobacco-related cancers. Major decreases were observed in mortality from HL (-39.1%), thyroid (-16.7%), and stomach (-15.3%). Unfavorable trends were detected in lung (+6.2%), larynx (+5.3%), pancreas (+5%), oral cavity/pharynx (+3.7%/3%) and liver (+0.6%). Highest mortality rates were for breast (14.4/100,000), lung (14/100,000), and colorectal (8.9/100,000).

In CEE countries, greater variability was observed in both rates and trends. In men, major declines in rates were observed for HL (-22.9%) and stomach (-19.5%). Unfavorable patterns of mortality were registered for skin (+13.7%), multiple myeloma (MM) (+7.8%), Non-Hodgkin's Lymphomas (NHL) (+6.5%), liver (+6.1%), testis (+5.5%), bladder (+3.5%), and prostate (+1.3%). Similarly, in women, major declines in rates were observed in HL (-20.7%) and stomach (-18.5%). Increased mortality was registered for lung (+17.7%), bladder (+7.2%), oral cavity and pharynx (+14.4%), pancreas (+7.5%), oesophagus (+6.6%), MM (+6.2%), liver (+6.1%), skin (+4%), and breast (+2.6%).

In **Table 10**, we indicate predicted avoidable deaths from major cancer sites in 2016 in CEE countries, assuming they had the same mortality rates as WE. A total of 55,239 cancer deaths (40,804 men/14,435 women) would have been avoided in CEE countries in 2016. In **Figure 5**, we present the estimated avoided deaths from total cancer mortality in men and women from Western and CEE countries, between 1991 and 2016, applying the peak age-specific mortality rates in 1990 (light grey) as constant. In WE, we estimate a total of ~5 million avoided cancer deaths (over 3 million men and almost 2 million women), while only 62,000 (about 52,500 men and 9,700 women) avoided deaths were predicted in CEE countries. A total of approximately 55,000 deaths would have been avoided in CEE countries in 2016, if they had exhibited the same mortality rates as in the WE region.

For 2016, our current data indicate that the major differences between the two regions were observed in men for lung (30.8/100,000 men in West vs 47.1/100,000 in CEE

countries), colorectal (14.4 vs 21.7), oral cavity and pharynx (4.1 vs 8.5). Major differences between female rates were for stomach (2.5 vs 4.1), intestine (8.9 vs 11.2), and uterus (3.9 vs 8.5). In the early 2000's, total cancer mortality rates were 194/100,000 in CEE countries versus 155/100,000 in Western countries (25% difference) in men, and 104/100,000 in women in both the regions.

Mapping the European Cancer Research Landscape

In seeking to frame public policy for European cancer research, its prioritisation and its funding at national and supra-national (European Commission) levels, objective analysis is crucial to provide strategic intelligence to help inform political discourse on the relevance, prioritisation and implementation of research. Scientometrics (the analysis of scientific outputs) provides a well-validated tool to underpin both evidenced-based requirements analysis and criterion-based benchmarking for European cancer research.⁹⁸ Here, we deploy scientometrics to define the landscape of cancer research activity across Europe between 2009 – 2020, and use this granular intelligence to frame an evidence-based consideration of how best to ensure that the optimal cancer research is enacted within the Cancer Mission and robustly informs Europe's Beating Cancer Plan.

Cancer Research Activity by European Region

In the twelve years (2009-2020) leading up to the start of COVID-19 pandemic, the European region published 39.4% of all biomedical research, but only 33.8% of cancer research (**Figure 6a**). Its output of cancer research papers also grew more slowly (5.1% *per annum*) than that of the world (8.1% *p.a.*) (**Figure 6a**), suggesting that despite significant investment, total cancer research productivity in Europe has been contracting.⁸⁴ Why this is happening is illuminated by a sub-analysis of the outputs by high income 'old' European countries (EU15 pre 2004) and newer EU13 countries that joined post 2004 (EU13 post 2004). Our findings are stark. Whilst the wealthy EU15 countries have collectively enjoyed a doubling of cancer research activity during the study period, EU13 (CEE) countries have languished behind (**Figure 6b**). These data suggest that the actions started under EU Research Commissioner Philippe Busquin's European Research Area (ERA) and accelerated from the 6th European Framework research programme onwards, have not succeeded in delivering the trans-European

cancer research equity/equality that was part of their intended impact.⁹⁹ Therefore, there must be a renewed effort, through a combination of research capacity-building, directed funding and twinning approaches to enhance cancer research activity, its quality and its translation in CEE countries.

Cancer Research Activity in Central and Eastern Europe

Other work that we have completed on mapping cancer research in newer EU13 CEE countries suggests that certain countries are escaping this ‘low output’ trap e.g. Poland.^{100,101} As already indicated, the COVID pandemic has had a significant negative impact on cancer research activity and its funding in Europe (particularly from charity/non governmental organisation (NGO) sector), while both COVID and the Russia-Ukraine war are likely to have a major negative impact on research funding for cancer in the foreseeable future.¹⁰² Beyond just the capacity to retain an active research community due to these externalities, the low research activity of the EU13 that we highlight here (**Figure 6b**), is likely to have a direct impact on population cancer outcomes in these countries for many years to come.

Cancer Research Activity and Brexit

Additional to the pandemic and the Russia-Ukraine conflict, the impact of Brexit and the European Union’s contraction to EU27 on cancer research activity, previously articulated by us¹⁰³ has already been detrimental and will continue to negatively impact European cancer research outputs.¹⁰⁴ Additional to those data, which starkly delineated the detrimental impact of Brexit on cancer research and the cancer research workforce, the work that we present here is also revelatory, highlighting the significant gap in outputs when we compare EU28 (UK included) versus EU27 (UK not included) research activity (**Figure 6b**). The gap is sizeable, reflecting the fact that the UK is a significant powerhouse in European cancer research. As such and based on our data, the UK’s strong research outputs are unlikely to be compensated for by increased research activity, either collectively or individually within other EU27 MSs.

Paediatric Cancer Research Activity

Specific domains such as paediatric oncology research outputs (**Figure 6c, appendix p35**) are broadly in parallel with overall oncology outputs; however previous analysis

has shown that non-commercial domains such as European childhood cancer research networks have potentially fragile funding models.¹⁰⁵ lending support to the specific request for a paediatric cancer research uplift, as proposed by the International Society of Paediatric Oncology (SIOP),¹⁰⁶ and supported by this study. Our analysis provides a revealing picture of how different domains in adult versus paediatric cancers (for both solid and haemato-oncology tumours) are balanced across the EU's portfolio, building on our previous work with SIOP Europe (SIOPE), *The Lancet Commission for Sustainable Care for Children with Cancer in 2020*¹⁰⁷ and *The Lancet Oncology Series Improving Cancer Care for Children and Young Adults in 2013*.¹⁰⁸ Paediatric oncology is rightly embedded as a recognised domain for research prioritisation within the Cancer Mission.

Cancer Research Activity by Collaboration

When it comes to choice of countries with whom to collaborate, European countries tend to be governed by traditional ties - language, cultural background, geographical proximity. Within Europe, strong cancer research linkages were detected between most pairs of countries, while European interactions with countries in for example East Asia were much weaker (**Table 4, appendix p45**). Tinting of the cells shows which countries were preferentially chosen as partners by the ten European region countries. Thus, Iran was non-preferred by all ten European region countries except Turkey, while Turkey was non-preferred by all nine European countries. In contrast, Switzerland was a preferred partner by all the other nine countries, especially its neighbours with whom it shares common languages: Germany, Italy, France. The converse was also true. The UK was well represented in the research portfolio of its European partners, and it also favoured them, especially Sweden and the Netherlands, as well as Austria. Perhaps surprisingly, the USA is a non-preferred country for European countries, particularly compared with Canada, and even with Brazil.

Europe has seen a range of strategic collaborative initiatives, some of which have yielded significant impact. One initiative, the Ireland-Northern Ireland-US National Cancer Institute Cancer Consortium,¹⁰⁹ led to a doubling of joint cancer research outputs on the island of Ireland, a significant increase in field-weighted citations and a

series of joint research activities between cancer researchers on the island of Ireland and their US counterparts. These have delivered significant benefit to cancer systems and cancer patients on the island of Ireland over a 20+ year period, serving as a model for future cross-jurisdictional collaborative strategic approaches.¹⁰⁹

The recently established UK-USA axis on cancer research represents another important development,¹¹⁰ but for both the UK and US, the overall commitment to global cancer research remains very limited (<4% of overall research activity).¹¹⁰ In a similar way, Europe's commitment to collaborate with low- and middle-income countries (LMICs), in cancer research is also disappointingly low.¹¹⁰ Only 3.9% to less than 0.5% of Europe's research is co-authored with LMIC researchers. Thus, despite Europe's substantial expenditure on cancer research, its overall support of global cancer research has been extraordinarily poor, as has that of the US.¹¹⁰

Cancer Research Activity by Disease Burden

A further significant policy question that we have posed is to what extent European cancer research reflects both the burden of sites-specific cancers and overall Disability Adjusted Life Years (DALYs) lost to cancer, both overall in Europe and within individual countries/regions? For certain site-specific cancers, our data indicate that the research activity is commensurate with their burden across Europe, with some e.g. haematology (HAE) even having higher than expectational levels of research activity. However, major cancer anatomical sites such as lung and colorectal, irrespective of European region, are significantly under-researched when compared with their relative disease burdens, as too are hepato-biliary and upper GI cancers (**Figure 7, a-d**). Remarkably, patterns for anatomical site-specific research are similar for all groupings. For some under-researched anatomical cancer sites, the amount of research may be as little as one fifth of what would be proportionate e.g. lung cancer is responsible for 20% of DALYs, but only 4% of European oncology research is committed to lung cancer.

We have also conducted a more detailed analysis of the relative commitment of each European country to cancer research within major site-specific anatomical domains. This "deep dive" shows that relative strengths, and more importantly weaknesses,

are not a result of gaps in one or two countries' research activities, but rather reflect pan-European deficits (**Table 5a, 5b; appendix pp46-47**). Addressing such research deficits requires high-resolution strategic insight in order to understand potential causes and inform tangible solutions.¹¹¹ Such strategic mis-alignment is further reflected when we evaluate cancer research performance in individual European countries vis-à-vis overall cancer burden (as measured by DALYs), Whilst some countries have clearly developed national strategies that drive proportional levels of cancer research aligned to the countries' disease burden, where there are robust researchable questions as judged by researchers and funders, many have not, particularly CEE countries. Although many of this latter group are lower-middle income CEE countries, UK and Ireland are notable high income additions to this deficit in research proportionality (**Figure 8**).

Cancer Research Activity by Gross Domestic Product

Broadly speaking, the level of cancer research outputs across Europe follows the country's wealth ($r^2 = 0.94$) (**Figure 9, appendix, p35**), with four nations (UK, Italy, France, Germany) collectively dominating. A combination of huge national investment and collaborations between comprehensive cancer centres in these countries have acted as potent drivers of research activity.¹¹² In spite of the overall strength of this "top four", many other countries and groupings within Europe also deliver highly-cited cancer research (**Figure 9, appendix, p36**), However, the impact of the low volumes of research being produced by EU13 i.e. mainly CEE countries, remains poor.

Cancer Research Activity by Research Domain

For the five largest cancer research domains (genetics (GENE), prognosis (PROG), surgery (SURG), systemic treatment (CHEM), and pathology (PATH), there is a fairly even distribution of research between leading high-income European countries. However, surgery continually lags behind other modalities in research effort overall. In epidemiology (EPID), the four Scandinavian countries, followed by the Netherlands and the UK, have a high relative commitment. (Iceland is even more committed, RC = 5.21). In clinical research, including clinical trials (CLIN), Belgium and Switzerland show the highest relative commitment; In palliative care (PALL), Norway, Ireland, and

Denmark show the highest relative commitment, and could perhaps assist the southern Mediterranean countries of Spain, Italy and Greece. Ireland's strength may reflect the All-Ireland Institute of Hospice and Palliative Care, a product of the above-mentioned Ireland-Northern Ireland-US National Cancer Institute Cancer Consortium.¹⁰⁹

The Impact of European Cancer Research

The impact of cancer research from certain European countries e.g. Netherlands, Germany, UK, as measured by ACI, has been consistently on par with that of the USA (**Figure 10a, 10b**). The most striking finding, however, is for the EU13, which, in addition to low research volumes, also have a low research impact, again reflecting the uneven progress in building cancer research capacity and capability across Europe). Furthermore, the global expansion of cancer research means that Europe cannot take for granted that its research will continue to be high impact.

Cancer Research Activity by Gender

Finally, in this particular analysis section of *The Lancet Oncology Commission*, we address a very significant research policy topic that has arisen in the last decade, the question of gender equality (or more precisely its lack) within research, here focussing on cancer research. Although we show that all European countries have improved over time, now performing at or above the world average for gender equality in cancer research outputs, the EU13 (CEE), and research groups in Nordic and Benelux countries have done the most to promote women, with the highest levels of women in both first author and last (senior) author positions (**Figure 11a, b**). However, women in last (senior) author positions still only make up a third of all authors for those European countries contributing the most cancer research outputs (**Figure 11b**). In Germany, a recognised powerhouse of European cancer research, the number of females in senior author positions is disappointingly low, less than 25%.

The gender of principal investigators in Europe was also determined for 22,291 projects in the ICRP database for which investigators' first names could be identified. The majority of principal investigators were men (65%) with only 35% women, reflecting the gender inequality results of the analysis of senior authors.

Comprehensive Cancer Centres and Comprehensive Cancer Infrastructures

Driving the Research Agenda

Comprehensive Cancer Centres (CCCs) (**Panel 8**) and Comprehensive Cancer Infrastructures have a key role to play in European cancer research and care agendas. The EU's Mission Board has recommended the establishment of “a *Network of Comprehensive Cancer Infrastructures within and across all EU Member States to improve the quality of research and care*”.¹¹³ Additionally, Comprehensive Cancer Infrastructures need to be underpinned by quality standards and accreditation processes, for both cancer research and cancer care. The aspirations espoused in the EU Cancer Mission are complemented by the Flagship Initiative 5 of Europe's Beating Cancer Plan¹¹⁴ (**Panel 9, appendix p12**). Allied to these statements, the ‘Porto Declaration’ of May 2021 indicates that an enhancement of the European cancer research infrastructure, with better connection of comprehensive cancer centres, could help enable “a *ten-year cancer-specific survival for 75% of patients diagnosed in EU member states with a well-developed healthcare system*”,¹¹⁵ echoing our 70:35 vision.

CCCs as Research Hubs and Research Drivers

A total of 51 CCCs and large clinical centres in 19 European MSs have been accredited by OEIC to date (**Table 7, appendix p49**). There are 12 centres in Italy and eight in France, but in ten countries, there is only a single accredited centre. Mapping of existing structures for translational, clinical and outcomes research shows that CCCs and large clinical centres are key drivers of research (the first 40 centres accredited by OEIC produce ~12,400 peer reviewed papers annually).¹¹⁶ Additionally, within the German Cancer Aid/German Cancer Society accreditation programmes, there are 14 designated “Oncologische Spitzenzentren,” each with a high degree of cancer research.¹¹⁷ Furthermore, EACS has developed a Designation of Research Excellence for CCCs, which has to date designated two centres¹¹⁸ Disease-specific

accreditation programmes are also available from professional organisations: breast (European Society of Breast Cancer Specialists (EUSOMA)),¹¹⁹ neuro-endocrine (European Neuroendocrine Tumour Society (ENETS)),¹²⁰ and prostate (European Association of Urology (EAU)),¹²¹ while the European Society of Medical Oncology (ESMO) leads an accreditation programme in palliative care.¹²²

A number of European networks of CCCs have been formed to address specific research areas and their translation. These include Cancer Prevention Europe, bringing together ten major centres with a focus on cancer prevention;¹²³ Cancer Core Europe, linking seven CCCs to help drive a precision oncology agenda, with a particular focus on early-phase clinical trials¹²⁴ and the European Organisation for Research and Treatment of Cancer (EORTC), aligning multiple stakeholders for delivery of high-quality translational and clinical trial research.¹²⁵

Capturing the research activity of OEI centres

Outputs of papers for each of the four groups (World, EUR32, EUR19, OEI), year-by-year, are presented in **Table 11 (Appendix p51)**. European research output has grown more slowly than that of the world, reflecting the rapid increase in papers from China. However, growth in outputs for the 51 OEI-accredited centres as a grouping has increased slightly faster than the world as a whole, now accounting for 6.6% of world output (up from 6.3% in 2012), and an increasing share of the output of the 19 European countries in which they are located (28.0% in 2021 (up from 22.2% in 2012)).

Overall, OEI-accredited centres accounted for over one quarter of the total for the top 19 European countries by output (**Table 12**), but this varied greatly, with Nordic countries at 50% and CEE countries at <15%. The sum of the outputs of the 51 OEI accredited centres exceeded the total by 68%, representing papers with authors affiliated to different OEI-accredited centres (thus, collaboration) but because there are many more centres than countries, this figure cannot be directly compared with the 30% for the 19 countries individually. The sum of the outputs is much larger than the corresponding figures for European countries as a whole (EUR32) (+ 40%) and the world (+34%), with 199 countries in the WoS data. This suggests that membership

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of the OECl accreditation programme correlates to more collaboration between centres than is the case between individual EU countries.

By research domain for OECl-accredited centres, **(Table 13)** clinical trials are the most highly represented, followed by targeted therapy, epidemiology, and radiotherapy. However, the centres collectively do relatively little research on quality-of-life. This domain, together with screening and palliative care, is neglected. For research on cancer anatomical sites **(Table 14)**, differences are less than those by research domain; they show a welcome focus of OECl-accredited centres on oesophageal and lung cancers, which are often relatively neglected in Europe **(Figure 7a-d)**. OECl-accredited centres' concentration on breast and skin cancers relative to that of the world, reflects the greater burden associated with these cancers in Europe.

A key question in cancer research is the value of comprehensiveness, or concentration of resources, versus more distributed research networks. Our data indicate a faster growth in cancer research outputs over the last 9 years from larger centres, which tend to be those who elected to go for OECl certification and have been accredited. OECl-accredited centres saw a 100% growth of relevant cancer research publications from 2012-2021, compared to a 59% growth in the EUR32 group **(Table 11 (appendix p51))**. As a result, the proportion of cancer research papers from OECl-accredited centres within the EUR19 group rose from 22.2% to 28.0%. This confirms what OECl has observed during its accreditation processes. Larger CCCs, often supported by a targeted-enabling central budget, are able to galvanise the full resources of universities/institutes, spurring collaborations between physical sciences, mathematics, engineering and biosciences, increasing the reach of the research. OECl has seen a growth in the number of university hospitals establishing formal CCCs with a central governance, bringing together high-quality clinical care, clinical research, and translational research, and in many cases, discovery science.¹²⁶

Geographical differences within the EUR19 were also observed **(Table 12)**. But the number of papers per annual GDP in both the two country and five country groups show a remarkable congruence, ranging from 24 papers per billion euros GDP in France to 45 papers in Italy, albeit that the euro purchasing power in those country groups has not been adjusted for. Scientific outputs of CEE countries comes out at

above the average for European countries, which is a promising development. Networking between centres is vital to cancer research; it is now universally acknowledged that key scientific challenges cannot effectively be tackled by cancer centres/institutes acting alone. These collaborations involve investigators in multiple locations with a team science mentality, for example performing deep -omics studies at scale, and publishing results of clinical trials involving large numbers of patients from multiple sites.

Clinical Research in Comprehensive Cancer Centres

Critical mass and integration are also important for maintaining a throughput of high quality clinical trials, focussing on investigator-led studies. Not only are numbers of eligible patients within the network vital, but also protected time for academic clinicians, supported by a team of research nurses, study coordinators and other professionals. These resources are generally more available in larger CCCs. This is confirmed by our findings (**Table 13**); a higher preponderance of OECl-certified CCCs significantly exceeding EUR32/EUR19 outputs in Clinical Trials (Phases 1-3); targeted therapies including immuno-oncology; genetics and discovery science; radiotherapy and epidemiology. One surprise is the lower ratio of surgical studies, which may be from University Hospitals not yet formed into CCCs or part of the OECl network.

Regarding clinical trials overall (**Figure 12 (A, B)**), in 48 accredited OECl centres, the number of open clinical trials and patients recruited is presented in two designated groups: OECl CCCs and OECl Cancer Centres (CC). In the 31 CCCs, there is a large throughput of prospective interventional clinical trials, recruiting significant numbers of patients, with a median of 534 patients annually. This is 3.8 times greater than their CC counterpart, even without addition of observational or biomarker-driven studies. CCCs enrolled around 10% of new patients to prospective interventional trials, compared to 3.4% within CCs (**Figure 12C**). Phase I and I/IIA trials are especially concentrated in the large CCCs (**Figure 12D**), with the critical mass of expertise and patients to conduct such studies. The median CCC conducted 23 early phase studies, compared to the CC median of 2. The very largest CCCs have around 100 open Phase I/IIA studies at any one time.

Research budgets of CCCs and CCs, adjusted by purchasing power parity in the country in which the centre is located, are commensurate with the volume/spread of clinical research in the two groups, with median annual research budget of CCCs (€26.3M) 5 times greater than the median CC (**Figure 13C**). However, some quite large cancer centres in Europe devote comparatively few financial resources to research, with concomitantly lower clinical research outputs (**Figures 13A,13B**).

The Funding of European Cancer Research

Public sector/governmental funding for cancer research in Europe

The Cancer Mission, the European Beating Cancer Plan, the EU for Health Programme, Horizon Europe and others all provide significant opportunities for research funding at supra-regional level. But it is important to learn from previous funding activities and align future resources to disease and research domains where they are most needed, heeding our intelligence on the European cancer research landscape. National Funding Agencies should also align their funding schemes to relevant “in country” research priorities.

Collaboration, including strategic partnerships between research funding organizations, is becoming increasingly important internationally, allowing coordination of investment in common identified priority areas, reducing duplication, and fast-tracking better outcomes. The International Cancer Research Partnership (ICRP) is an alliance that in 2022 includes more than 150 cancer research organizations from the USA, Canada, Europe, Japan, South Africa and Australia. ICRP maintains the only public source, worldwide, of current and past grants, totalling more than \$100bn US dollars (USD) in cancer research funding since 2000. ICRP member organizations submit project-level data for their research portfolios to the ICRP database,⁸⁶ including PI name, host institution, city, country, funding organization, project title, abstract, start and end date, and total funding amount. Each project is assigned to one or more cancer anatomical sites and research domain. The research domain classification (CSO) includes 34 codes, grouped into six categories (Biology; Aetiology; Prevention; Early Diagnosis and Prognosis; Treatment and Survivorship and Cancer Control). All fields (with the exception of funding amount) are

visible on the ICRP public website; funding amount is visible to partners who contribute data. It is estimated that ICRP captures over 60% of global cancer research funding.

Overview of European public sector/governmental funding for cancer research

From 2010-2019, a total of 24,394 individual projects (total value €16.7 Billion (B)) were identified in the ICRP Database that could be coded to cancer anatomical site and research domain (**Figure 14**). From internet searches of annual reports, we estimate that an additional €4B of European cancer research was also funded during this period, but could not be analysed in detail, as project-level data could not be sourced. Thus, the overall public sector funding for European cancer research (government or philanthropic) was estimated at €16B-€21B over the 10-year period (**Figure 14**).

European Cancer Research Funding by Research Domain

Analysis of European cancer research funding by research domain (**Figure 15**) indicated that between 2010-2019, treatment (CSO5) received the highest level of investment, closely followed by biology (CSO1). Prevention (CSO3) received the least investment. Between 2010 and 2019, the pattern changed (**Figure 16, appendix p37**), with increases in funding proportion to Diagnosis, Detection and Prognosis (CSO4) (from 19% to 23%), and Treatment (CSO5) (from 27% to 32%), suggesting that the research portfolio is becoming more translational/clinical. Funding for Biology (CSO1) and Aetiology (CSO2) decreased, (from 34% to 29% for Biology, and from 11% to 6% for Aetiology). Investment in Cancer Control and Survivorship research (CSO6) increased by 1.5 percent (5.6% to 7.1%), an encouraging trend. Research into primary prevention (CSO3) was very low, <4% of the overall European cancer research portfolio. However, there was a very small increase in the percent investment for Prevention research from 3.4% (2010) to 3.7% (2019). The research domain profile was similar for the international portfolio¹²⁷ (**Figure 15**), with a higher emphasis on discovery biology, diagnosis and treatment than on aetiology, prevention and cancer control/survivorship, reflecting our findings on cancer research outputs.

European Cancer Research Funding by Cancer Anatomical Site

Investment in non-site-specific research was highest (>50%) (**Figure 17 appendix p38**); this included either basic/discovery research, or research relevant to multiple cancer sites (e.g. pain control/palliative care). 48% of codeable projects were related to specific cancer anatomical sites. **Figure 18** illustrates the percent investment by cancer anatomical site, compared to incidence and mortality trends for those cancer sites in Europe.⁶⁰ Breast cancer research received the highest level of investment (18% of site-specific investment), followed by colorectal cancer (12%) and leukaemia (12%). The pattern of investment showed broad correlation with cancers of high incidence/mortality (**Figure 18**), but with some notable outliers (lung, bladder, stomach, pancreas) where percent investment was significantly lower than percent mortality, again reflecting our intelligence from mapping the cancer research landscape by publication output.

Our evaluation of European cancer research spend does have some limitations. At least €4bn (approximately 18%) of investment could not be analysed in-depth, as project-level data were not available in the public domain. Investment by country is included (**Table 19, Appendix pp55-56**), along with estimates of additional funding for cancer research that could not be coded in detail. A full picture of the European research portfolio will be invaluable in understanding more precisely the impact of COVID-19 on cancer research investment and capacity.

Who Funds Cancer Prevention Research in Europe?

Our analysis reveals that 11% of cancer research papers published between 2008 and 2021 focussed on prevention research, supported by 243 European funders, representing 16% of all European cancer research funders (**Figure 19a, b, appendix p39**). European not-for-profit prevention research funding organizations accounted for 45% of total spend (**Figure 20a**). Governmental sources (including the European Commission) represent 31% of cited organizations, but received 48% of funding acknowledgements in our dataset (**Figure 20b**). While a direct link between funding acknowledgements and funding received cannot be established, it nevertheless provides indirect intelligence of which funder may be supporting relatively more or less research in cancer prevention, compared with other research domains. Thus, government funders support more cancer prevention research than typical not-for-

profit organizations. Maybe unsurprisingly, only 8% of prevention research funders are for-profit entities, while they account for 17% of funders of all cancer research (**Figure 20a**).

Cancer prevention research funders are present in 23 European countries (94% EU). Number of funding acknowledgements per country were compared as an indicator of overall spend on cancer prevention research. UK, Germany and Italy are the three most acknowledged countries in cancer prevention research publications. Restricting the scope of funding acknowledgments to not-for-profit organizations, UK, Spain and Sweden are the most active in cancer prevention research (**Table 15**).

Another element of the European cancer prevention research landscape is the absence of prevention research infrastructures. At European and national levels, infrastructure for cancer prevention tends to be fragmented. There are few examples of cancer prevention research centers. Out of the 32 European research networks identified, only two are involved in (but not dedicated to) prevention research, reflecting wider structural issues where major CCCs are heavily focused on discovery science and biopharmaceutical research, including clinical trials.

Is Europe Leading the Way in Cancer Prevention Research?

A comparison between global and European prevention research funding indicates that Europe does slightly better, with more European cancer research funders in prevention research (16%) than in the World (12%) (**Figure 21a, 21b; appendix p39**). European not-for-profit organizations are also more involved in prevention research, accounting for 45% of European cancer prevention research funders (**Figure 20a**) and representing 13% of all European not-for-profit organizations funding cancer research (**Figure 21b, appendix p40**). In comparison, 34% of cancer prevention research funders in the World are not-for-profit entities (**Figure 20a**), representing only 7% of all not-for-profit organizations funding cancer research (**Figure 21a, appendix p40**). European not-for-profit organizations are acknowledged in 31% of cancer prevention research papers; this percentage drops to 20% for the World (**Figure 20b**).

The total number of European funding sources for cancer prevention research has more than doubled since 2008, resulting in a proportional increase in prevention

research publications. This is primarily due to the multiplication of not-for-profit organizations and governments involved in prevention research, as the number of other types of funding e.g. industry has stagnated. However, while interest in prevention research is growing globally, the last six years have seen a slowdown in the growth rate and spend by European cancer prevention research funders (**Figure 22**).

Primary Prevention: a (Consistently) Neglected Research Area

A break-down by research domains within cancer prevention reveals that secondary prevention is the most funded area (52% of European cancer prevention research funders), closely followed by aetiology (47%) (**Figure 22a**). Primary prevention is the least-funded area, though higher in Europe (25%), compared to the World (20%) (**Figure 23a, appendix p40**). Thus, <4% of the 1477 European cancer research funders identified are interested in primary prevention research, concordant with our bibliometric analysis and reflecting long-term failure of research funding organisations to properly balance their research portfolios and funding. Not-for-profit funders represent 45% of secondary prevention funders, acknowledged in 32% of secondary prevention research papers (**Figure 23b, 23c; appendix p41**). In contrast, they are acknowledged in only 12% of primary prevention research papers. Governments (including the European Commission) are active in primary prevention, with 56% of primary prevention funders identified as governmental entities and 86% of primary prevention research papers containing government funding acknowledgements.

Strengthening Cancer Services and Systems Research for Europe

Ensuring Precision Oncology Research is Part of a Broader Research Portfolio

The 'pharmaceuticalisation of cancer care' across Europe¹²⁸ risks being somewhat reductionist in pursuing improving outcomes, pivoting research and public sentiment away from the evidence-based reality that early diagnosis, high-quality surgery and radiotherapy (de facto focusing on the precise delivery of cancer treatment), and health systems research contribute as significantly to better, more equitable and affordable cancer outcomes for populations. Precision oncology has a critical place in this new research paradigm,^{129,130} as evidenced by, for example, the impact of immune-oncology, but needs to be proportionate and contextualised to its contribution

to improving population outcomes. The new generation of precision oncology medicines, including immune-oncology are exciting and indicate clear potential; genuine advances were presented at the ASCO Conference in Chicago in June 2022, but these new agents are also expected to collectively contribute to 70% of total cost of active care in Europe by 2025,¹³¹ reopening the price/cost versus value debate. Furthermore, there is now ample evidence that a substantial proportion of research in precision biopharmaceuticals is not delivering new pharmaceutical technologies with clinically-meaningful benefit.¹³²

An overemphasis on precision oncology also risks reinforcing the notion that achieving the best for patients can simply be addressed by ensuring cutting-edge technologies are available,¹³¹ ignoring the wider social and economic contexts within which people live and which will ultimately influence their outcomes.^{132,133} Accumulating evidence shows that novel biopharmaceutical treatments tend to deliver value more at the margins and may not contribute significantly to reducing cancer mortality at population level,¹³⁴ Investing more in biomedical research and technologies, without building the wider cancer research base, is therefore unlikely to deliver better, more affordable, more equitable progress in European cancer outcomes.¹³⁵

The Value of Health Systems/Implementation Science Research

Health systems fund, organise and deliver cancer care. The wider political, economic and societal context within which they are embedded define the accessibility, affordability, equity and outcomes of cancer control interventions^{136,137} These aspects set the parameters for policies/strategies that help protect people's health (e.g. legislation on unhealthy commodities such as tobacco and alcohol); define options and ensure access to early detection and prevention (e.g. HPV vaccination); determine when and how people seek care, what treatments are available and where, who gets these treatments, their cost and cost-effectiveness, and the quality of care delivered. Health systems research frames the science by defining research ecosystems and prioritising what will help realise the greatest improvements in patient outcomes.¹³⁸

Health systems, and the cancer services and systems within them are complex. To address the myriad factors which influence patient outcomes at the individual and population level, requires a more balanced research portfolio which prioritises health policy and systems research (HPSR), as well as implementation science. This would enable a deeper understanding of the multiple factors acting at different levels, their interconnections, and the priorities, agency and the power of the various actors within and across systems that influence cancer outcomes.¹³⁴ This requires convening a wide range of scientific disciplines and professions, from political science to applied health services research, implementation science to epidemiology, geography to economics and anthropology to behavioural psychology. However, most cancer research funders do not consider these domains a priority for funding. Strategic imbalances in funding and policy exist, leading to a devaluation of global cancer care due to a focus on marginal gains. Prioritisation and targeted investment could serve to address this imbalance.

There is an emerging understanding of political economy and its importance to ensuring equitable, efficient cancer care, research delivery and sustainable funding e.g. HTA, commissioning and reimbursement systems, and pharmaceutical regulation.¹³⁹ However, the benefits for outcomes, affordability and equality achieved by implementing multi-layered governance from mandated clinical practice guidelines through to sophisticated HTA mechanisms, coupled to pricing and reimbursement models, are not being universally replicated across all European countries.¹⁴⁰

Implementation Science as a Driver of Innovation

No innovation improves patient care and outcomes without first navigating its way through the health system. Implementation and scale-up, both intrinsic aspects of health systems strengthening, further determine whether an innovation is affordable and pro-equity. Yet in a system where you “pay to play” so to speak, global cancer research largely focuses on discovery science and systemic therapies.^{3,141} A recent analysis reviewing publication outputs in lung cancer found that 60% of research focused on systemic therapies and discovery science research, compared to 8% on radiation research, 4% on early diagnosis and 2% on screening research.¹⁴²

What gains could potentially be made from a greater emphasis on implementation science for early diagnosis and more effective curative loco-regional treatments? Improving our understanding of how to minimise disparities in access to care through health services research, could make a huge difference to population-level survival, yet for example only 2% of radiation research is devoted to this area.³⁰ There is an urgent need for cancer research funders, particularly federal and philanthropic, to re-assess the balance of their research portfolio investments and their overall strategic direction. Promising areas like precision oncology will only prosper and deliver within a fully-fledged health system, informed by health systems/ implementation science research.

Prevention, Screening and Early Diagnosis Research

Primary prevention.

Our findings on cancer prevention, particularly primary prevention underfunding, led to additional analysis on cancer prevention and implementation science. A sample of 2000 European cancer prevention research papers from the last five years was checked and coded to identify implementation science projects. Only 7% of European cancer prevention research papers were classified as implementation (9% in the World), demonstrating that cancer prevention research, and especially implementation science, remain underfunded, in comparison to other research areas. This imbalance must be rectified.

Research to Promote Early Detection of Cancer

While enhancing cancer prevention research is a critical (but under-resourced) component to primary prevention policy development across Europe, it must be accompanied by a clear strategic focus on research that improves secondary prevention, through earlier detection of cancer. When identified at an earlier stage, cancer is more curable and less expensive to treat. Additionally, health systems which deliver early detection through cancer screening and early diagnosis will ensure more cost-effective cancer control for citizens, patients and society. Importantly, it is estimated that up to one third of cancer cases in Europe can be positively impacted by an early detection approach, including some of the commoner causes of cancer

mortality, (breast, colorectal).¹⁴³ IARC estimates that women who attend breast cancer screening appointments have a 40% reduction in their risk of dying from breast cancer,¹⁴⁴ with over 21,000 deaths prevented annually.¹⁴⁵ Secondary prevention also makes sense from a health economic perspective; the total cost associated with managing late-stage colorectal cancer is ten times higher than for early-stage disease,¹⁴⁶ although comprehensive early detection/screening programmes may shift resource needs (e.g. impacting on loco-regional treatment strategies).

Disparities in Cancer Screening

In 2003, the European Council of Health Ministers issued recommendations for the implementation of cancer screening programmes to reduce the burden of certain cancers in Europe.¹⁴⁷ These recommendations included a shared commitment by EU MSs to implement systematic population-based screening programmes for breast, colorectal (respectively the third and second leading cause of death due to cancer in the EU) and cervical cancer. These three cancers are collectively responsible for nearly 300,000 deaths in the EU annually. As of 2020, 25 EU countries had introduced population-based screening for breast, 22 for cervical and 20 for colorectal.¹⁴⁸ It is an indictment of European cancer screening policies and the lack of implementation research that population-wide screening programmes are not universal in all European countries, leading for example to cervical cancer mortality over four times the EU average in Romania.¹⁴⁹

Coverage of respective target populations by screening also remains very low, at 14% on average across the EU for colorectal cancer.¹⁵⁰ Wide disparities exist, both across European countries, with breast cancer screening coverage for instance ranging from 6 to 90%,¹⁵¹ and across social groups, as women of lower socio-economic status have less access to screening. Over 12,000 deaths could be avoided annually from breast cancer, if maximal coverage was achieved throughout the EU.¹⁴⁵ Cancer screening programmes achieving the best coverage were also those with the most rapid recovery from the pandemic, showing how best practices in screening precipitate more equitable citizen access and increased resilience to health crises.

Disappointingly, all screening rates show wide variability between European countries and, in some cases, between specific regions within-country. In countries where population-based cancer screening programmes were actively implemented, examination coverage rates ranged between 17%-84% (breast), 1%-53% (colorectal), and 4%-71% (cervical).¹⁵² However, such research, illuminating these differences, is essential for leveraging political and social change.

There have been significant considerations on developing additional cancer research screening programmes for other cancer anatomical sites, with a particular focus on lung cancer. While CanCon have indicated that further evidence is required,¹⁵³ recent research studies by European disease-based communities have provided evidence to support the case for low-dose computed tomography (CT) screening for lung cancer.¹⁵⁴ The development and roll-out of lung cancer screening would help in tackling the leading cause of cancer death in the EU, responsible for an estimated 296,140 deaths in 2018¹⁵⁵ but requires investment in national systems and implementation science research to succeed.

Early Diagnosis of Cancer

Despite many public health efforts, awareness of cancer warnings signs remains low among the public.¹⁵⁶ A more prominent role for primary care providers in the research agenda is essential for successful implementation of early detection strategies.¹⁵⁷ Currently, >75% of cancer cases are not detected through a screening approach; including 40 of the most frequent and more lethal cancer types. Worryingly, a pan-European survey of >4,000 patients with cancer, revealed that for 30% of those patients whose cancer was detected outside of screening, their original diagnosis was not cancer, sometimes on multiple occasions,¹⁵⁸ emphasising the challenges for effective early cancer detection.

From a research perspective, risk-based early detection to help diagnose cancer is attractive, helping deliver earlier, better and more equitable cancer diagnostic capacity for European citizens. For breast cancer, incorporation of genetic risk prediction based on family history and polygenic risk scores¹⁵⁹ can be effective, from clinical, and

health economic perspectives. For colorectal cancer, employing the Faecal Immunochemical Test (FIT) as a decision tool for triaging patients for colonoscopy was successfully employed to ensure early detection of colorectal cancer, despite the impact of COVID-19 and national lockdowns on the urgent diagnostic pathway.¹⁶⁰⁻¹⁶² Not only did this approach help save lives, it also allowed colonoscopy capacity to be managed more efficiently.¹⁶² In lung cancer, low-dose computed tomography (LDCT), can be targeted to at-risk populations.¹⁶³ Self-collection approaches for screening (e.g HPVCheck)¹⁶⁴ are increasingly being adopted. However, all these diagnostic innovations need rigorous pre-clinical and clinical evaluation, much of which is becoming increasingly complex, requiring larger (pan European) populations to rapidly validate.

Beyond this type of research, there is also a need for better studies addressing patient pathways to diagnosis. In an All.Can survey, >25% of surveyed cancer patients and their care givers highlighted that diagnostic pathways were a major issue for patients, negatively impacting on their experience of cancer care.¹⁵⁹ There is a wider research need to examine the cancer workforce perspective in this area; general practitioners, nurses and allied healthcare professionals, pathologists and clinical scientists all play a pivotal role in helping to deliver accurate and timely cancer diagnosis. However, workforce shortages for these disciplines are significant, for example in pathology capacity, as we previously highlighted in the *Lancet Series on Pathology and Laboratory Medicine*.¹⁶⁴ Cancer nursing shortages have also been highlighted and need to be addressed.¹⁶⁵

Secondary Prevention: Human Papillomavirus (HPV) and Research

HPV causes ~5% of all cancers in women and men worldwide.¹⁶⁶ From a European perspective, ~2.5% of cancers are attributable to HPV. Widely recognised as the causative agent in cervical cancer; it is also involved in the aetiology of anal, oropharyngeal, penile, vaginal, vulval and potentially other cancers. There are around two hundred different types of HPV; twelve are associated with a high cancer risk.¹⁶⁷ HPV is responsible for ~87,000 of cancers across the WHO European region.¹⁶⁸

Recently, there has been a marked increase in the incidence of oropharyngeal cancers, particularly in men.¹⁶⁹ In the US, HPV-positive oropharyngeal cancer has overtaken cervical cancer as the most common HPV-associated cancer type.¹⁶⁸ Dentists and dental hygienists also have an important role to play in opportunistic detection of oral lesions associated with oropharyngeal cancer, but more research is required to precisely delineate the benefits. The worrying recent increase in oropharyngeal cancer detection may reflect the indirect impact of the pandemic when dental surgeries were shut, often for many months.

From a screening perspective, HPV testing is recognised through the *European Guidelines for Quality Assurance in Cervical Cancer Screening* as the most accurate and effective method of cervical cancer screening,¹⁶⁹. Research has shown that cervical cancer screening can reduce cervical cancer mortality by up to 90%,¹⁷⁰ and this has spurred a range of new implementation research programmes across Europe.

An impressive 100% vaccine effectiveness has been demonstrated over 12 years in four Nordic countries; no cases of high-grade cervical dysplasia were found in a large sample of vaccinated women.¹⁷¹ Incidence of genital warts (also caused by HPV) has also been significantly reduced by HPV vaccination.¹⁷² The US Food and Drug Administration (FDA) has approved vaccination as a means of preventing head and neck cancers caused by HPV.¹⁷³ Vaccinating both sexes provides an effective and faster approach to preventing or reducing the incidence of cancers and other HPV-related diseases (**Panel 10, appendix p13**). A universal approach could make the elimination of HPV-driven diseases possible, even with moderate levels of vaccination uptake (50-75%) across Europe.^{168,174} The European Centre for Disease Prevention and Control (ECDC) has indicated that universal vaccination is a cost-effective option to prevent all diseases where HPV is implicated.¹⁷⁵ emphasising the importance of research that spans across domains, in this instance including health economics.

Research indicates that there is wide variation in European citizens' perceptions on the safety of HPV vaccination. In Northern Europe, 73% of people believe that vaccines are safe, but this drops to 59% in Western Europe and a lowly 40% in Eastern Europe.¹⁷⁶ 'Vaccine hesitancy' is linked to a number of factors: insufficient and

inadequate information about vaccination; misinformation about potential side effects; issues around trust in health authorities, doctors and new vaccines; and a perception of low vaccine effectiveness.¹⁷⁷ However, these views may change given the recent UK data showing clear HPV vaccine efficacy,¹⁷⁸ along with the recent success of COVID vaccines.

Many people currently lack basic knowledge about HPV and its associated risks. In the UK, despite HPV systematic cervical cancer screening since 1988 and vaccination for girls from 2008, a survey found that only 37% of participants had even heard of HPV.¹⁷⁹ Of these, 70% were aware that HPV could be transmitted during sex, and ~40% recognised that HPV could cause oropharyngeal cancer, but only 64% were aware of the existence of a vaccine that could prevent HPV-associated disease. A study of 17,000 Europeans across ten countries found that 70% of participants were not aware that HPV could cause cancer in males.¹⁸⁰ These findings clearly support the need for education and policy research to determine ways to reduce inequity, coupled with the need for research to challenge disinformation around HPV vaccination.

Prioritisation of Radiation Therapy and Surgical Oncology Research in Europe

Radiotherapy and surgery are essential treatment modalities to help improve cancer outcomes, exert improved cancer control, and deliver appropriate palliation. Over 50% of cancer patients have an evidence-based intervention with radiotherapy and/or surgery at least once in the course of their disease.¹⁸¹ However, there is a paucity of research focus/funding for these two important domains.

Gaps in Radiation Oncology Research

While radiation therapy is a core component of modern cancer treatment, the data that we have presented highlights a lack of prioritization of radiation research relative to research on other cancer treatment modalities, particularly systemic therapy and precision oncology. Additionally, radiation research tends to be somewhat unbalanced. Previous analysis from a global perspective has shown that ~50% of all publications in this domain relate to radiation therapy preparation/delivery, combined-modality regimens, and dose fractionation studies, with very little focus on health services research, palliative care, and quality-of-life studies.⁵⁰ Trial-related

publications represented only 5.1% of total radiation research output. Randomized clinical trials are often difficult to execute - due to the complexity of radiotherapy innovations, high up-front investments for new technologies and strong operator dependency. These challenges are further intensified by the limited research budgets available for radiation oncology research,⁵⁰ and in the challenge of implementing the evidence into clinical practice.¹⁸² An anonymous, electronic survey, distributed to radiation oncologists through the European Society for Radiotherapy and Oncology – Global Impact: Radiation in Oncology (ESTRO-GIRO) initiative, revealed significant variation in hypofractionation, especially across specific curative approaches and between geographical regions, in spite of the available literature evidence.¹⁸³

To assure access to the most optimal radiation treatment for each cancer patient in Europe, a dual focus is required: one on treatment optimization, with the aim to guarantee best clinical outcomes and quality-of-life for the individual patient; one on health system optimization, guaranteeing equitable access to valuable innovations, considering the societal perspective. Beyond the need for research that deepens our understanding of how new radiotherapy interventions impact patient benefit, there is also the need to perform research defining the value of these radiotherapy innovations, to support their implementation in the clinic. Focusing on health services research and implementation science approaches to address inequalities across Europe is urgently required, as these research domains have been underrepresented in radiation and radiotherapy research.

Since 2012, the ESTRO Health Economics in Radiation Oncology project (ESTRO-HERO) has focussed on health systems research, developing an evidence-base for radiotherapy availability, access, cost and reimbursement across European countries.^{181,184} To foster the diffusion and clinical implementation of innovative radiotherapy interventions, ESTRO-HERO is now developing an evidence-based value framework for radiation oncology.¹⁸⁵ which requires a greater focus on the patient perspective, considering the broad spectrum of endpoints most relevant to patients undergoing radiotherapy; as well as a more blended approach to evidence-generation, diversifying for new radiotherapy technologies, techniques and treatments.¹⁸⁶ Alternatives to RCTs have been suggested and are under evaluation,

such as the model-based approach in proton-beam radiotherapy,¹⁸⁵ the R-IDEAL framework developed for MR-guided radiotherapy¹⁸⁶ the embedding of randomization into prospective cohort studies¹⁸⁷ or the collection of RWE.⁵⁸

In the context of Europe's Beating Cancer Plan and the Cancer Mission, the need to collect radiation-relevant information deploying data analytics and AI approaches is evident. Such data should inform research developing predictive models for radiation treatment outcomes, empowering a more tailored and personalised approach for each patient's treatment. There is a need to evaluate new radiotherapy technologies and treatment modalities that are emerging, also from the patient perspective, to ensure that radiotherapy innovations are accessible across Europe. Analysis of data from both clinical trials and in the "real world" will allow information on therapeutic efficacy and effectiveness, while quality-of-life and patient-reported outcomes should be captured and assimilated. Turning this data into intelligence will both facilitate the best therapy for each patient but also allow patients' quality-of-life readouts to inform future research priorities for patients living beyond cancer.

Gaps in Surgical Oncology Research

Cancer surgery remains a critical yet underdeveloped domain for research. Through a services/systems lens, the World Bank's Disease Control Priorities 3 (DCP3)¹⁸⁸ focused on the trade-offs between centralized and de-centralized approaches to cancer surgery and capacity- and capability-building for the breadth of the surgical workforce needed to deal with cancer, including the challenges, both economic and practical, of scaling up different models.¹⁸⁹ However, *The Lancet Oncology Commission Global Cancer Surgery: delivering safe, affordable, timely cancer surgery*¹⁹⁰ took a deep, broader strategic view, highlighting both care and research needs and deficits and finding that >80% of people diagnosed with cancer worldwide requiring a surgical procedure at some point in their treatment; ¾ of cancer surgery are judged to be unsafe, not delivered, or unaffordable.¹¹¹ This current *Commission* found dramatic deficiencies in the research ecosystem to support cancer surgery.

Across Europe, cancer research funding organisations have failed the challenge of delivering more surgical oncology research. Perusal of the EU Clinical Trials register

reveals that surgical oncology comprises only 6.1% of cancer clinical trials. Funders are increasingly inward-looking, focused on discovery cancer science and biopharmaceutical research¹¹¹ Additionally, <4.5% of cancer research activity over the last decade was in collaboration with LMICs (of this cancer surgery research was <0.1%). Furthermore, there is little evidence that cancer surgery and surgical research are priorities commensurate with the surgical need.¹⁸⁹ Reflecting on previous analysis in 2012 where, based on bibliometrics, <5% of total global (including European) cancer R&D expenditure was on surgery,¹⁹¹ little has changed. Our updated 2022 analysis found almost no progress. Instead, research funding organisations and advocacy groups continue to focus on access to cancer medicines. The realpolitik of cancer surgery is that it remains marginalised, politically, on the European stage. However, with the rise of new advocacy movements, for example global diagnostics,^{164,192} the opportunity exists to re-integrate cancer surgery as part of a broader political discourse, reflected in Europe's Beating Cancer Plan focus on enhancing surgical oncology and emphasising its position as a pillar of cancer treatment.

European cancer surgical research has, however, innovated in numerous areas, for example in the impact of technology, in particular robotics and to a lesser extent minimally-invasive surgery. Technology innovation is fundamental to cancer surgery; however, robotics has had a highly disruptive impact on services and systems. What data we have, mainly from Nordic countries and the UK, strongly suggests that these novel technologies, if not properly implemented in a managed cancer care system, can be anti-equity, distorting cancer surgical systems which then adapt to deliver these high-cost, high-end technologies.¹⁹³ Technological innovation has often come at the expense of surgical systems' strengthening, primarily due to the failure to bring cancer surgery into the orbit of HTA and more managed systems planning.⁵⁰

Cancer surgery has, however, been a rich area for health services/policy research in Europe, with a long history of research into performance metrics, models of care, and surgical workforce. These analyses have helped underpin policy intelligence for national planning, reflecting the importance of a broad surgical oncology research strategy, embracing technological innovation and health systems research.¹⁹⁴ Surgical innovation, for example the development of Total Mesorectal Excision for

rectal cancers, has delivered stunning improvements in patient outcomes, reflecting a critical modality for future EU research strategies that can deliver significant population outcomes improvements.¹⁹⁵

Ensuring a Person-Centric Approach to Cancer Research and its translation

The European Code of Cancer Practice

A patient-centred approach to cancer research is crucial to bridging health research, policy, and clinical practice. In the Introduction to this *Lancet Oncology Commission*, we highlighted how the *European Cancer Patient's Bill of Rights* and the *Europe of Disparities in Cancer* initiatives articulated and supported the need for patient-centred cancer care and research across Europe. Continuing this theme, the recent establishment of the *European Code of Cancer Practice* places patients at the centre of both cancer control and cancer research agendas in Europe. The *European Code of Cancer Practice* (**Figure 24**)¹⁹⁶ is a citizen and patient-centred initiative, highlighting the core requirements that people should expect, in order to receive good quality clinical cancer care which also involves access to cancer research e.g. clinical trials.

The Code sets out a series of ten key overarching rights (**Panel 11**),¹⁹⁷ signposting what European patients should expect from their health system, including cancer research as a critical component of their care. The Code has been co-produced by a team of cancer patients, cancer professionals and patient advocates, to underpin a framework for the delivery of optimal cancer care and patient-centred cancer research. The ten rights provide specific support for the cancer patient and their family/carer and are articulated in detail in **Panel 12, appendix p14-15**.¹⁹⁷ Legitimacy of each of these ten rights is underpinned by a combination of the best available medical literature, evidence-based guidelines and research intelligence,^{197,198} including the *Essential Requirements for Quality Cancer Care (ERQCC)*.¹⁹⁹

The Code has been translated into 28 languages, facilitating its dissemination and deployment across Europe. EU Health and Food Safety Commissioner Kyriakides has committed to use her office to support dissemination of the *European Code of Cancer Practice*; providing both an endorsement of the Code's relevance and impact in Europe, as well as an invaluable support for its widespread dissemination and

implementation. The ten rights of the Code align to E.C.O.'s Focussed Topic Networks (Figure 1).

Living Beyond Cancer

Research on Cancer Survivorship

As 5-year and 10-year cancer survival from many cancers have improved substantially, there is a need for greater focus on ensuring that those living beyond cancer attain a better quality-of-life, both physically and psychologically, including addressing the challenges of social and economic exclusion e.g. inability to access bank loans. In Europe, research must focus on these survivorship challenges. There are 20 million European citizens living beyond a cancer diagnosis and this will continue to rise.⁵¹ Improvements in survival are juxtaposed with a range of issues, either as a consequence of the cancer itself (or its comorbidities), or of the treatment the patient received to control their cancer. The European research agenda needs to encompass a wide range of biomedical and socio-economic survivorship challenges: physical (e.g. side effects, complications, chronic pain, co-morbidities) psycho-social (e.g. cancer distress, cancer stigma, professional and financial (e.g. loss of employment, impact on relationships, including intimacy and fertility).²⁰⁰

Comorbidities are particularly common in cancer patients, with research indicating that the majority of cancer patients report at least one comorbid condition.^{200,201} From a psycho-social perspective, the evidence indicates that psycho-oncology research must be an integral component of the comprehensive multidisciplinary approach to survivorship.^{202,203} Unfortunately, management of the long-term impacts of cancer and its treatment is not consistent across European countries, emphasising the need for widening of the cancer survivorship research agenda. There is a need for a research-to-policy strategy that is patient-centred, (**Panel 13, appendix p16**).²⁰⁴ We also need new research-informed approaches to survivorship care. This includes developing risk-stratified pathways that optimize coordination between cancer specialists and primary care physicians, based on the “whole person” needs of the individual.²⁰⁵

In association with EACS and ECPC, we focus on delineating specific survivorship research and innovation challenges that Europe is currently facing and propose tangible solutions that can be embedded within an overarching cancer survivorship framework. Previously, we performed in-depth analysis of the state-of-the-science in cancer survivorship and identified specific research domains that should be developed,^{51,206,207} in order (as part of a wider focus on cancer research) to embed cancer survivorship research as an active component of the Cancer Mission.²⁰⁷ We have prioritised three distinct Cancer Survivorship Research and Innovation Pillars (**Panel 14, appendix p17**) that we propose should be the thematic areas of particular focus. Within these pillars, we highlight the challenges (**Panels 15-17, appendix pp18-20**) and propose a series of recommended solutions to firmly empower cancer survivorship research and innovation.

Pillar One: The Medical Cancer Survivorship Research and Innovation Pillar

Ten challenges have been identified (**Panel 15, appendix p18**). Addressing the lack of cancer survivorship research integration requires a commitment that is resourced within the overall European cancer research agenda. This is best achieved by creating a European Cancer Survivorship Research and Innovation Plan, embedded within the Cancer Mission and aligned to our 70:35 Vision. Prioritisation of its themes should be informed by a comprehensive mapping exercise of existing cancer survivorship research activities, identifying, quantifying and prioritising specific survivorship research gaps. Prioritisation must clearly align to survivors' specific challenges (in areas such as mental health; reconstructive surgery; fertility preservation; active rehabilitation), Cancer survivors must be empowered as "active participants" rather than "passive recipients" in research and innovation to enhance their quality-of-life.

Pillar Two: The Socio-Economic Cancer Survivorship Research and Innovation Pillar

Six challenges have been identified (**Panel 16, appendix p19**). Research on identifying determinants of cancer inequalities linked to social rehabilitation of cancer survivors, including disparities present across Europe (in particular in CEE countries) should be prioritised. From a quality-of-life perspective, a combination of maximising use of existing approaches and creating/evaluating new research tools will permit

granular assessment of the quality-of-life of cancer survivors, help identify social determinants of health and how cancer survivors can return to normal living.

Financial challenges of cancer must also be addressed. Research is required on precise economic evaluations of direct and indirect costs to those living with and beyond cancer (including levels of financial toxicity experienced by survivors and their families); aligning this to the proposed European Cancer Inequalities Register²⁰⁸ can help promote distinct actions to address this area of increasing relevance. Social issues such as access to work, education, insurance, loan, mortgage and the impact of financial toxicity must be prioritised within the research and innovation agenda.

Pillar Three The Politico-Legal Cancer Survivorship Research and Innovation Pillar

Five challenges have been identified (**Panel 17, appendix p20**). Increasingly, it is important to characterise any legal aspects of discrimination for cancer survivors, deploying this intelligence to inform research on discrimination and how it can be mitigated. The *Right to be Forgotten*²⁰⁹⁻²¹¹ with its key roles in sparing cancer survivors the challenges of potential financial toxicity, while promoting reintegration, equality and social inclusion must be adopted across all European countries and jurisdictions. It is currently embedded in 6 European countries (France, Belgium, The Netherlands, Luxembourg, Portugal, Romania); it needs to be universally accepted in all European countries, as all cancer survivors require access to financial services without discrimination once declared “cured”. Equal access to financial services should not depend upon a person’s “post code”.

Defining and mitigating the stigmas associated with cancer is an increasingly relevant research area and must be pursued, promoting a cultural shift to a more active survivorship-focussed approach. Investigating the potential role of comprehensive survivorship clinics should be prioritised. Additionally, consideration of how survivorship care should be organized, without disrupting the medical units dealing with patients who still require active treatment should be considered. Specialised multidisciplinary teams in survivorship should be created and their expertise and activities promoted. Empowerment is also critical and should be supported through

patients' self-management. One size does not fit all, so flexibility is required. We need to deliver for all cancer survivors, Europe-wide.

The Critical Importance of Data for European Cancer Research

If there is one important lesson for European cancer research that we have learned during the COVID-19 pandemic, it is the critical role of data and its conversion into intelligence to inform policy and practice. Data and health intelligence are embedded in the public consciousness and have become part of our daily norm. As a society, we are now more familiar with data; be it daily numbers of people infected with SARS-CoV-2, percentage of the population vaccinated, or sadly, COVID death numbers. But data are not just being deployed to help mitigate the direct impact of COVID-19. They have also highlighted the indirect impact of the pandemic on life-threatening diseases such as cancer.

Given data science's crucial role in unravelling the indirect impacts of the COVID pandemic on cancer, a critical component of the European cancer research effort must focus on empowering the responsible and effective use of health-relevant data, including building capacity and capability of cancer registries. Building a citizen-centred cancer knowledge network must be our goal.²¹² We now inhabit a digital society; we must explore ways to better harness the power of data, while ensuring that they are used in a safe and trustworthy manner.²¹³ Data intelligence and their comparability are pivotal to this *Lancet Oncology Commission*, informing the research that underpins development of better approaches to ensure optimal cancer control for European citizens. Combining multi-modal data sources and employing this improved intelligence to drive research and innovation, must be central to efforts to deliver better outcomes and fair value for citizens/patients, for clinicians, for researchers and for economic/societal development across Europe. In particular, the ability to collate, access and use data to inform tumour site-specific national audits, and trans-national care audits e.g. for rare cancers, will need to be a major fulcrum of European cancer research, if health systems are to improve care access, quality and outcomes.

Externalities Impacting the Cancer Research Agenda

Externalities will have a major influence on the future of European cancer research. We have yet to fully understand the triple impact of the pandemic, Brexit and the Russia–Ukraine war on investment in, and commitment to cancer research across Europe. There may be implications for the European Commission’s ability to continue to support the Cancer Mission at the intended and required level. Economic shocks from the pandemic and the war are having profound impacts on the cost-of-living, which directly alters our population’s philanthropic behaviours. **(Panel 18, appendix p21)** Thus, we may see a huge contraction in donations for investment in cancer research, severely damaging our aspirations.

Impact of the COVID-19 Pandemic on Cancer

By many measures, the COVID-19 pandemic has had a grave impact on Europe, both directly – most European countries have experienced high per capita COVID-19-related mortality and morbidity and indirectly - through its impact on non-COVID healthcare. At the nadir of the first pandemic wave (March-April 2020), we collected and evaluated near real-time data from hospital trusts across the UK, measuring the impact of the pandemic on cancer diagnostic and treatment pathways.²¹⁴ Specifically, we focussed on 2 Week Wait times (a surrogate for urgent referrals) and chemotherapy delivery (measuring cancer treatment pathway robustness). Delays uncovered were extremely worrying; seven out of ten citizens were either unwilling to see their doctor for fear of catching COVID, or unable to access GP/specialist cancer services. While not as dramatic, the impact on treatment was also significant; four out of ten cancer patients experienced delays in delivery of their chemotherapy. These data were the first in the UK to show the indirect impact of the pandemic on cancer and contributed to the decision to restore cancer services. A number of other studies also highlighted the critical role of data intelligence in influencing policy,^{5,215-217} including rescinding the decision in relation to colorectal cancer screening delay²¹⁷, while projections on the impact of the pandemic are proving accurate (and may indeed be under-estimates). Worryingly, the cancer backlog (in both diagnosis and treatment) continues to be significant, staff are still under strain following the pandemic, and many are choosing to leave or retire. Such studies reflect the power of data intelligence, cancer health policy and systems research in informing national planning.

At a European level, these salutary data prompted E.C.O. to establish a Special Focussed Network on the Impact of COVID-19 on Cancer. Extending our data analysis revealed the disastrous impact across the European continent (**Figure 25**)⁵ - 100 million missed screening tests, up to a million citizens who may have an undiagnosed cancer, significant delays/reductions in treatment (particularly systemic therapy, surgery) and significant impacts on cancer clinical trial activity and cancer research programmes. Impact on the cancer workforce is also revealing, with four out of ten cancer healthcare workers feeling burned-out due to their Herculean efforts, not only to control cancer, but also to contribute to infection control efforts of a beleaguered health system. Additionally, the analysis shows that three out of ten cancer healthcare workers exhibited symptoms of clinical depression.

These compelling data prompted E.C.O. to launch a *Time To Act* Campaign with the strapline “Don’t let COVID stop you from tackling cancer.”⁵ Translated into over 30 languages, this campaign was launched at European level in Brussels in May 2021 and has now been launched nationally in 12 European countries. It is accompanied by a Time to Act Data Navigator (**Figure 26**), facilitating evaluation of the impact of COVID on cancer by tumour subtype, by country or region, by treatment modality etc., providing an extremely informative tool for the European cancer community.⁵ Both European Commission President von der Leyen and European Commissioner for Health and Food Safety Kyriakides highlighted *Time to Act* and referenced its sobering statistics.^{218, 219} These data are also emphasised in the Special Committee on Beating Cancer (BECA) report.⁵ At all national *Time to Act* launches, Ministers of Health participated and were very supportive of the campaign, while presentation of local research data confirmed the substantial impact of the pandemic on cancer patients/cancer healthcare systems in different European nations, highlighting the need for pan-European solidarity. Recognising the impact of the campaign, *Time To Act* received the prestigious [Excellence in Communicating and Using Data Award](#) at the 2022 [Communiqué Awards](#), which highlights best practices in healthcare messaging across Europe.

Patient advocacy organisations have also been active in research utilising data to help define the impact of the pandemic on cancer patients, surveying their own patient

communities, to gain insights on the impacts on patients and care givers²²⁰ and cancer charities.²²¹

The pandemic has had a chilling effect on cancer research across Europe; laboratories were shut and clinical trials delayed/cancelled in the first pandemic wave. This persisted for many months due to further waves and full/partial lockdowns in certain European countries. Whilst the medium-term impact of COVID-19 remains unclear, research data that we and others have generated suggest significant negative impacts, particularly on CEE countries.⁵ The pandemic has highlighted that cancer research and cancer care are complex adaptive systems, easily disrupted by systemic shocks. Patient outcomes can rapidly change for better or worse, requiring national systems to constantly check and adapt their planning. Our work has exposed a more general weakness in European research ecosystems that, in many cases, are not capable of extracting actionable intelligence from health information systems to inform research activities. The pandemic has also shone a light on the gulf between countries that have built clinical research ecosystems and deliver outputs such as national audits, and those that have not. Yet, investment in these data research infrastructures remains challenging in many European countries. To put their value into context, the cost for developing a cancer audit research ecosystem is ~€2M euros over five years, 0.002% of the median estimated cost for developing a new therapeutic agent (>€9100M).

The Impact of the Russia-Ukraine war

The invasion of Ukraine by Russia (February 24, 2022) has added to the impact of the pandemic on European health systems, creating a massive humanitarian crisis. The impact of this conflict comes on top of eight years of low-level war by Russian-backed forces in the Eastern Donbas region, which had already created huge challenges for healthcare systems in Ukraine. The impact of Ukrainian refugees in Europe is creating new difficulties for cancer systems capacity, especially for CEE countries. Recognising these challenges and the need to provide much-needed support, E.C.O and ASCO established a joint E.C.O-ASCO Network on the Impact of the War in Ukraine on Cancer, leading to a series of activities including cancer data intelligence

gathering in Ukraine and surrounding countries to inform actions on issues including medicines shortages, diagnostic and treatment capacity.

Whilst there has been much discourse on the Russia-Ukraine war, what has gone relatively unnoticed is its profound impact on clinical cancer research. Both Ukraine (lower-middle income) and Russia (upper-middle income) are unusual in their significant global impact on cancer research. Both are two of the largest contributors to clinical cancer research in the world, especially industry-sponsored clinical research. Our analysis (**Table 16**) indicates that between 2014 and 2017, a total of n=636 cancer Randomised Control Trials (RCTs) were published. Ukraine contributed to n=39 of these RCTs, one of the highest lower-middle income contributors (out of a total of 136). Countries in the upper-middle income category contributed to n=182 cancer RCTs. Russia was by far the largest contributor (n=115 cancer RCTs). At the start of the war, analysis of the ClinicalTrials.Gov website indicated that Ukraine had n=245 active pharmaceutical cancer clinical trials, with 127 actively recruiting. Corresponding figures for Russia were n=667 and 352, respectively, emphasising the significant impact that the Russia-Ukraine war will have on cancer clinical trials activity in Europe.

For Europe, the conflict also emphasises the complex and political nature of pharmaceutical-driven research, as multinational corporations have come under increasing pressure to withdraw all engagement with Russia. Major pharmaceutical companies such as AstraZeneca, Pfizer, Glaxo Smith Kline *et al* have stopped new investment/new clinical trials in Russia, but continue both pre-existing trial recruitments and supplying standard cancer medicines as per contractual arrangements. This European conflict highlights the need for, (a) much better cancer intelligence beyond disease burden (infrastructure, cancer care workforce, mapping patient pathways, etc) across EU national boundaries and, (b) a greater focus on building clinical research capacity and capability that can support other European countries.

Safeguarding Europe as a Global Leader in Cancer Research

Europe is part of a global research community and the next decade will witness major expansions in countries across the world working in cancer research. China and India

have significantly increased their research imprint,^{222,223} the former being particularly dominant, globally, in lung cancer research and discovery science, driving a revolution in immuno-oncology drug development.^{142,224} Such research activities are both disruptive and opportunistic for Europe. More widely, the Middle East and Latin America are also ramping-up cancer research activities, providing wider opportunities for European trans-national engagement.^{224,225} In Sub-Saharan Africa, the challenges are different; countries on this continent require a higher level of capacity and capability building, with broader collaborative networks to enhance cancer research methodological skills from biostatistics to clinical trial design, as well as discovery science techniques.²²⁶ All evidence shows that regions and countries that are outward-looking and engaged produce better, higher impact research.

One area where Europe's research expertise would be beneficial is in the area of geriatric oncology, ensuring that ageism is not a factor in research and care delivery in older adults.²²⁷ The International Society of Geriatric Oncology Priorities Initiative highlights research as one of its four key priorities,²²⁸ emphasising its importance for older adults with cancer, who represent a major and rapidly growing demographic in global epidemiology.

A stronger focus on global cancer is crucial for Europe, catalysing its own research agenda but also in solidarity with countries faced with their own unique challenges as they look to deliver innovative, effective cancer research. However, European cancer research funding organisations are failing to realise this potential or honour their global commitments to cancer control that they so often espouse.¹¹¹ We need a new strategic pact that focuses funds and effort on the wider global cancer agenda, rather than wealthy-to-wealthy country co-operation. Multiple *Lancet/Lancet Oncology* Commissions, as well as recent significant multi-stakeholder strategic reviews,²²⁹ have created the opportunity for Europe to engage more widely and this *Commission* emphasises an unrivalled global opportunity that needs to be grasped. However, the opportunities for Europe to engage in global cancer can only be realised through better funder-to-funder collaboration as well as trans-national joint ventures to strategically address research capacity and capability in specific countries and regions. Across the

world, many research projects, supported by different EU countries run in parallel, with little strategic co-ordination.

Recommendations and Call to Action

This *Lancet Oncology European Groundshot Commission for Cancer Research* has employed an evidence-based approach to capture and analyse information on key areas of relevance across the cancer continuum including survival, mortality, research activity, research funding, cancer prevention and control, cancer treatment, survivorship, quality-of-life and the impact of external factors including the COVID pandemic, Brexit and the Russia-Ukraine war. Gaining this more granular understanding of the European cancer research landscape, its strengths and in particular its weaknesses, has empowered us to deploy this intelligence to inform a series of 12 Recommendations (**see Panel 19**), underpinning a *Call to Action* to ensure that cancer research is a pivotal driver of enhanced cancer control and improved quality-of-life for cancer patients and those living beyond cancer across Europe. Our recommendations are grouped under three thematic areas, informed by our interpretation of the data and intelligence we have generated through this *Commission*:

- *Closing the European Cancer Research Divide*
- *Addressing the Gaps in European Cancer Research and its Funding*
- *Responding to Current and Future challenges*

For each of the 12 Recommendations, we provide an indication of how they can be achieved and a time-frame for their implementation through a Call for Action (**Panel 19**).

Closing the European Cancer Research Divide

Recommendation 1: Develop an implementation science focused research and innovation plan, to help deliver a European 70% average ten-year survival for all cancer patients by 2035

Recommendation 2: Embed the principles of equity and equality within the European cancer research agenda, so that all citizens and patients, no matter where they live, will benefit equally from advances in cancer research

Recommendation 3: [As a matter of urgency, develop resourced time-bound European and national action plans to increase cancer research capacity and capability in Central and Eastern European countries by 25% by 2025](#)

Overall, our data emphasise that population-based intelligence is crucial to help in the precise delineation of the cancer inequalities that persist across Europe and in the development of intelligence-driven research solutions to address these inequalities. Information on crucial factors such as stage at diagnosis, treatment delivered, lifestyle behaviours and socio-economic status, should be routinely collected nationally and shared Europe-wide, in order to both quantify their impact on survival and illuminate a pathway to narrow the inequalities divide, particularly in CEE countries.

Diverging patterns in cancer mortality between Western and CEE countries have continued to persist and - if anything – have increased over the last decade. There has been little evidence of this gap in cancer mortality being closed, though overall mortality has declined across Europe's geographic regions and countries. Our data emphasise the need to prioritise cancer research and cancer control activities as rapidly as possible in CEE countries.^{101,230} Persisting unfavorable patterns in exposure to major cancer risk factors, including tobacco, alcohol, and aspects of diet, together with residual environmental disadvantages explain part of the persistent gap.²³¹⁻²³³ However, delays in implementing research discoveries into screening and early diagnosis activities are also evident, together with delayed and inadequate adoption of modern therapeutic approaches for cancers amenable to treatment,²³³ a deficit which must be addressed as a matter of urgency. Ensuring equitable cancer research activity across Europe is also critical, particularly given that research-active hospitals and cancer centres achieve better cancer outcomes than those which do not prioritise research within their remit.

Another area that our research has uncovered as crucial to a robust European cancer research agenda is data – and more specifically turning that data into intelligence to inform European cancer research priorities. Use of near real time data is crucial – we must ensure that the data that drive our research and innovation and their translation into benefit for cancer patients are available and analysed in a timely fashion, such that up-to-date data intelligence informs our research and innovation efforts.

Addressing the gaps in European cancer research and its funding

Recommendation 4: Cancer research funding organisations and Europe's Cancer Mission must double the European cancer research budget to €50 per capita by 2030 and commit to supporting underserved research domains

Our analysis indicates that the total amount of investment in cancer research in Europe, excluding the private sector (e.g. pharmaceutical industry) is ~€20-22B (2010-2019). The minimum equivalent figure for the USA over the same time period was \$80.5B (around €76B), an almost four-fold difference. Looking at investment per head shows an even wider gap - for Europe, the figure over this period was ~€26 per head, a logfold lower than the US investment (minimum €234 per head). There is an urgent need to make significant additional investment in cancer research in Europe, in order to narrow the overwhelming gap in spend per head between two international powerhouses of cancer research. So what is possible in terms of an uplift in cancer research spend? The UK's National Cancer Research Institute (NCRI) has tracked cancer research investment by UK funders since 2002;²³⁴ the initial reported investment of £298m in 2002 doubled to £601m by 2011. The average annual UK increase in investment was approximately 5% until 2019.

Efforts to increase investment may however be hampered by the impact of the pandemic on cancer research funders, particularly the charitable sector, whose available funds to support cancer research have, and will be badly affected by the pandemic.²³⁵ Recent analysis by the NCRI (UK) showed that in 2020/21, funding for UK cancer research dropped by 9%; fewer new cancer research projects were funded.²³⁶

Our data and intelligence indicates that European cancer research is largely dominated by discovery science, including biomarker research, and research into systemic therapy (**Table 6, appendix p48**). The emergence of translational cancer research as a major domain in the 2000's²³⁷ has tended to 'capture' European cancer research, including public sector-funded research, within a more private-sector driven discovery science and biopharmaceutical paradigm.²³⁸ Whilst there are considerable country-to-country differences by research domain, Europe is particularly strong

(committed) in clinical trials, driven by research into targeted (systemic) therapies and, although volumetrically low, Europe has also made significant strides in driving forwards quality-of-life research activity (**Table 6, appendix p48**), a direction of travel to be welcomed.

However, for surgery and radiotherapy, currently the most effective treatments in controlling cancer, a significant number of countries are under-committing to these research domains (surgery: Denmark, Finland, Portugal; radiotherapy: Greece, Israel, Finland, Czech Republic, Portugal, (**Table 6, appendix p48**)). This direction of travel appears to be global,¹⁹¹ with discovery science and biopharmaceutical research becoming the dominant spheres of cancer research, irrespective of income group.

Healthcare systems are faced with the continual challenge of ensuring high-quality discovery science and applied research ultimately influences practice. It can take 17-20 years to get clinical innovations into practice; <50% make it to the clinic. Improving this damning statistic requires greater investment in implementation science – the second translational gap - which seeks to test strategies to enhance clinical innovation adoption, by considering health system dynamics and actors (patients, clinicians, providers, policy environment, industry) which could impede or facilitate evidence adoption, deploying this intelligence to ensure clinical- and population-level implementation of research discoveries. Allied to this requirement for a bigger focus on implementation is the need to have access to intelligence from social and political science as well as cancer science. We are entering an era where RWE will be crucial to drive implementation of innovation, so we must ensure that Europe has sufficient digital maturity to collect, analyse and link these data to inform the rapid adoption of research and innovation within cancer health systems.

There are evidence-based and cost-effective preventive interventions available for cancer. The current privileged focus on biopharmaceuticals is not a long term cost-effective approach to cancer control policy, unless complemented with public health strategies for cancer prevention. Reducing the number of people developing cancer should result in greater resources being available to provide those patients who require treatment with the most effective therapies available. Increased funding in critical research areas - cancer prevention and implementation science research,

would yield significant return on investment. A more systematic and structured approach to cancer prevention in Europe would have a major impact at the public health, societal and economic level.

Recommendation 5: European cancer research funders and the European cancer research community must mitigate the impact of Brexit and other political challenges on European cancer research

Successful cancer research activity that we have documented for the most powerful high-income countries is counterbalanced by clear stagnation for many other countries in the CEE region. There have been huge increases in cancer discovery science and biopharmaceutical-centred research, placing individual countries and, collectively, Europe on an equal strategic footing with the USA. However, this success has been achieved at the cost of leaving many other important domains of cancer research far behind. Taken together, the strategic analysis which we have undertaken and the results that we have generated, reflect a potential mismatch with public rhetoric and the wider needs for improving patient and population outcomes which are affordable and equitable. The cancer research archaeology that we have defined provides objective data for considering today's European cancer research landscape, and how this can inform the most effective implementation of the Cancer Mission and Europe's Beating Cancer Plan going forward.

The data generated clearly indicate a significant gap between research outputs from EU28 (including the UK) and EU27 (excluding the UK), one that is extremely unlikely to be bridged by increased research activity from the remaining EU27. Disappointingly, at time of writing, it appears the UK will not participate in EU funding programmes going forward. If the UK is not involved in EU collaborative cancer research and not part of Horizon Europe's research community, this will have an extremely detrimental effect on European cancer research activity and quality moving forward. Ultimately, cancer patients will pay the price for this decision in terms of healthcare outcomes. Lobbying to reverse this insular decision must be a matter of priority among the cancer research community. It will also be important to consider maximising the involvement of other non-EU European countries in European cancer initiatives, like Switzerland and Norway.

Recommendation 6: The European cancer research community must develop proactive mechanisms to enhance gender equality in cancer research

Our data on female first and last (senior) author cancer research publications from European researchers clearly illustrate the significant gender gap that exists in the European cancer research community. While both CEE and Nordic countries show better gender ratios in first and last author publications, the performance by cancer research powerhouses such as Germany is disappointing. A similar gender disparity is seen in cancer research leadership as judged by our data on successful competitive research funding. Delving deeper into the reasons for better performance in terms of gender balance in certain European countries/regions and developing mitigation strategies based on this intelligence will hopefully improve the gender balance in cancer research outputs and cancer research leadership in Europe. This could be assisted by embedding programmes that provide formal leadership training for women within both research and oncology workforces.

Recommendation 7: European cancer funders and policy makers must mandate a step change in cancer prevention, cancer screening and early cancer detection research in order to reduce the burden of cancer for European citizens

In 2019, E.C.O.'s Focussed Network on HPV launched a resolution to achieve the elimination of cancers caused by HPV.²³⁹ Critically, this included supporting research priorities such as new vaccine and screening technologies, as well as ensuring best care and treatment modalities. More research is needed to improve the early detection of non-cervical cancers caused by HPV. Research is also required relating to the vaccination of women found to be HPV-positive at cervical cancer screening, as this could provide a potential pathway way to interrupt viral transmission in the community.

In combatting HPV-driven cancers and championing a research-underpinned prevention-led approach for their elimination, Europe has an unrivalled opportunity to be a global research leader and to demonstrate what can be achieved when countries work together to achieve a major public health goal. E.C.O.s HPV Action Network is an exemplar model to build on.

Since the 2003 Council recommendations on cancer screening, a number of scientific/ technological developments have emerged in breast, colorectal and cervical cancer screening. These include new screening tests, such as full field digital mammography, or supplemental magnetic resonance imaging (MRI) in women with extremely dense breast tissue,²⁴⁰ faecal immunological test and/or endoscopy for colorectal screening and HPV testing for cervical cancer screening.¹⁶⁹ We view the development of risk-adapted screening approaches, particularly ones incorporating distinct strategies according to risk profile of screened individuals, making use of the latest technological developments, as a critical component of 21st century screening research programmes.

Development of new tests and new approaches are helping to drive cancer screening and early diagnosis agendas. A good example is HPV DNA testing, which is now showing better results than pap-smear screening for cervical cancer screening.¹⁶⁹ Cervical cancer early diagnosis is also being enhanced by the provision of self/home-based screening tests. FIT for colorectal cancer screening helps reduce the invasiveness of the procedure, which translates into a significant improvement in screening adherence. A significant new development has been the use of liquid biopsies, where detection of circulating cancer cells or tumour DNA in blood can underpin the early diagnosis of multiple cancers.²⁴¹ Combining this with multi-cancer detection approaches represents a significant European research opportunity to underpin more accurate early diagnosis.²⁴²

Crucially for all approaches to enhance screening, early detection and accurate cancer diagnosis, we need to understand in more detail from a behavioural perspective why a European citizen does or doesn't attend their scheduled screening appointment, does or doesn't come forward with suspicious symptoms, does or doesn't engage with cancer patient pathways. Social science research to understand behavioural choice, cultural constraints and previously unrecognised barriers, particularly for disadvantaged/ underserved communities is critical to move the dial and enhance the early diagnosis of cancer across Europe.

Recommendation 8: European cancer funders and policy makers must continue to establish research driven EU Network of Comprehensive Cancer Centres and other relevant Networks

The European Commission is currently addressing the question of inequalities in a number of ways. Some are to map research capabilities and capacities. Others are to foster collaborations in smaller groupings, for instance twinning cancer centres in widening participation countries with more established CCCs or fostering team science. A third arm is to create an EU network of certified CCCs, and to build research capacities and capabilities in MSs. However, at the moment such initiatives lack hard evidence as to whether managed processes of spreading resources will deliver better science for the benefit of cancer patients Europe-wide. Our data capture the impact both individually and collectively that CCCs are having, emphasising the benefits of a network approach. Integration within and between CCCs needs to be achieved at multiple levels. For governance, a critical component is a CCC Board, bringing together cancer research leaders with clinical leads in cancer and patient advocates. At an organisational level, researchers need to be integrated with clinical colleagues; formally through programme structures, or through multi-disciplinary teams; informally, through colloquia, regular meetings and seminars highlighting science and clinical challenges; or through incentivised collaborations such as pump-priming grants offered only to clinical groups working with laboratory colleagues. Patients and patient advocates need to be embedded into this structure.

A critical component of this Comprehensive Cancer Infrastructures approach will be addressing the inequalities being experienced across Europe; in prevention, diagnosis, in treatment and care, and in access to clinical trials. A crucial infrastructural need to help achieve this goal is strengthening the quality of translational, clinical and outcomes research/implementation science and ensuring that they are integrated with clinical care delivery. Patients who are diagnosed and treated in research active cancer centres (including, but not limited to, CCCs) have better access to advanced diagnosis and therapy, and to clinical trials, reflected in better outcomes than those patients treated in general hospitals.^{61,243} Europe's Beating Cancer Plan aims to ensure that 90% of eligible patients have access to CCCs by 2030. Currently, a number of MSs have no accredited CCCs and many do not yet have regional/local

networks linking cancer research and care, organised around CCCs. A mapping exercise in 2017, performed as part of the EU Joint Action on Rare Cancers,²⁴⁴ showed that only 13 MSs had Cancer Networks covering the whole country.

Development of an EU Network of Comprehensive Cancer Centres also provides an opportunity to ensure underpinning laboratory infrastructure is in place to help drive discovery research and its translation, at scale. Additionally, in order to have maximum reach within countries as part of the envisaged infrastructure, effective local cancer networks will be required, supplemented by extended multi-disciplinary teams and digital and video-consultation infrastructure. A variety of funding sources could be deployed to help support the establishment of this EU Network of Comprehensive Cancer Centres. Strengthening research excellence will also require collaborative infrastructures across Europe, drawing on different aspects of the Cancer Mission and the Europe's Beating Cancer Plan.

Recommendation 9: [As a matter of urgency, European cancer funders and policy makers must establish a European Cancer Survivorship Research and Innovation plan to guide policy that will help enhance the lives of the 20 million European citizens living with and beyond cancer](#)

As already highlighted, to date European scientific and clinical communities have tended to focus more on research into the diagnosis and treatment of cancer, rather than the more holistic challenge of living with and beyond cancer. However, as indicated in the European Code of Cancer Practice, ~20 million European citizens have survived a diagnosis of cancer;^{51,196} it is incumbent upon the European cancer community to significantly enhance our engagement with cancer survivors and promote and instigate a cancer survivorship research agenda, in order to ensure that the specific challenges and needs of those living with and beyond cancer are adequately addressed. Survivorship, rehabilitation and reintegration into society are key pillars of the European Code of Cancer Practice; it is imperative that each cancer patient have a survivorship care plan, underpinned by research. Our recently published study highlights the importance of capturing detailed European data on cancer care and quality-of-life for cancer survivors.⁵¹ A cancer survivorship, rehabilitation and reintegration plan for patients should also take into account the

crucial role of caregivers in helping secure the well-being of those living with and beyond a cancer diagnosis.

Interdisciplinary survivor-centred research must be promoted and should include development of new tools to facilitate survivorship research. The paucity of specific research programmes for childhood, adolescent and young adult survivors should be addressed through age-adapted research programmes that best meet the needs of this demographic. The needs of the palliative care community should also be addressed, through promotion of research early across the full spectrum of palliative care. All approaches should underpin best-practice sharing and promotion of survivorship research and innovation across Europe, aligning and empowering all stakeholders in a unity of purpose to help achieve the 70:35 Vision.

As part of our recommendations, we call for establishment and implementation of a European Cancer Survivorship Research and Innovation Plan to ensure a research-informed approach for those living with and beyond cancer. Additionally, in order to ensure that the 20 million voices are heard, we call for establishment of a European Cancer Survivorship Day.

Responding to Current and Future Challenges

Recommendation 10: The European cancer research community must accelerate the research response to the indirect impacts of the COVID-19 pandemic on cancer, with particular emphasis on the deployment of accurate, timely cancer intelligence to build future resilience

The COVID-19 pandemic and the associated disruptions to cancer systems have dramatically impacted cancer care. In the context of the *Time To Act* campaign on the impact of COVID-19 on Cancer, we estimate that 100 million cancer screening tests were not performed in Europe, while urgent referrals of suspected cancer patients were cut by up to half. As a result of this cancer backlog, one million cancer patients could be undiagnosed in Europe. At national level, as shown by the 'Cancer and COVID-19 Data Navigator',²⁴⁵ the impact of the pandemic on cancer screening programmes has seen a 70% reduction in European countries such as Austria,

Belgium, Czech Republic and Poland. The disruptions to screening, early diagnosis, and timely treatment are all expected to lead to significant future excess mortality from cancer.

More broadly, the COVID-19 pandemic has focussed a spotlight on the substantial opportunity cost from current investments in cancer research, without a transparent and robust approach to linking this research to better, affordable, more equitable outcomes. The UK's NHS Cancer Drugs Fund and the diffusion of robotic surgery across European cancer care systems are examples of how high-cost techno-centric research have tended to drive the political narrative of European cancer research, divorced from the perspective of value and affordability.^{246,247} There has been a relentless narrative about innovation in cancer research, without wider consideration of research into the enabling environment, i.e. research translation into clinical practice, services, systems and policy. In the meta-pandemic era, given fiscal contractions across all countries, the need to inform European cancer services with research-empowered evidenced-based policy and a robust consideration of the ever-rising burden and costs of care is essential. New research initiatives must focus on increasing the value of care (outcomes relative to cost) across the cancer pathway, minimising waste and supporting responsible integration of innovation.

More fundamentally, the economic impact of the COVID-19 pandemic has resulted in an unprecedented economic contraction in 2020, with EU real GDP falling by 6.1%, more than during the global financial crisis of 2008. This current crisis calls for an urgent recalibration of public sector cancer research support to widen strategies beyond discovery science and biopharmaceutical research. Such a narrow focus is likely to be a significant indirect contributing factor to poorer outcomes. Why? It is clear from a wide variety of research outputs over the last two decades that good outcomes are directly linked to research activity but that this research activity needs to be broad, covering domains from public health and cancer through to surgery, radiotherapy and palliative care. Why is this important for patient outcomes? Because improving patient outcomes is critically empowered by a research-active health system that supports a wide range of fundamental/discovery and applied cancer research and their transition into patient-centric translation.

Aside from strategic questions about where Europe should now focus, COVID-19 has exerted a further downward pressure on cancer services and systems across Europe. The OECD report *Health at a Glance: Europe 2020*²⁴⁸ reflects the fact that many European countries were ‘burning hot’ (i.e. over-capacity) even prior to the pandemic. Critically, there was no capacity to expand or headroom to absorb systemic shocks. The pandemic has not just illuminated these deficits, but has also acted as an additional weight on the entire cancer ecosystem, from social determinants to survivorship and end-of-life care (**Panel 18, appendix p21**). Routine referrals during the pandemic collapsed in most European countries, such that fewer cancers were detected and that those that are eventually detected are at a later stage, meaning worse prognosis. In addition to directly worsening outcomes, this will lead to sicker, more advanced cancer patients needing treatment which has a higher care burden, which, when added to an already overheated system, is likely to indirectly worsen overall patient outcomes. This includes attention being paid to gaps in the cancer workforce and the need to support innovative clinical roles.^{165,249}

Such systemic effects have two downstream impacts on research. The first is to reduce the headroom for clinical cancer research, as capacity and funding are potentially diverted into routine care; the second is a political-policy mismatch. This is why the over-focus on discovery science and biopharmaceutical research does not lead to better population outcomes. If the pandemic has had the damaging impact that our data intelligence suggest, then Europe will see a significant decline in its cancer outcomes over the next 5-10 years, which needs to be addressed as a matter of the greatest urgency. Thus, now more than ever, there is a critical need to ensure that cancer is appropriately protected and prioritised within current and future European research agendas. Cogent solutions must be realised and acted upon that will translate the high quality cancer research that is currently being performed in Europe (and must continue to be delivered going forward), into improved outcomes for patients and make a significant contribution to healthier and more productive societies. It is critical that we redouble our efforts to ensure that cancer does not become the forgotten “C” in the fight against COVID.

Recommendation 11: As a matter of extreme urgency, the European cancer community must address how research can help mitigate the impact of the Russian–Ukraine war

Clinical cancer research finds itself in uncharted territory. The conflict-induced loss of cancer centres in Ukraine which are such major recruiters to global RCTs will have a significant impact. Many major clinical trials will be delayed, as new centres of varying capacity are incorporated and some will undoubtedly fail to recruit. Many of the cancer trials in Ukraine also had participation of major centres in CEE countries such as Romania (**Table 16**). If such trials are stopped, this will further reduce infrastructural investment and debilitate cancer clinical trial activity in CEE countries. More long term, it is not clear whether industry will consider it too high-risk to place cancer clinical research in CEE countries bordering Ukraine, particularly if, as the US National Intelligence Estimates suggest, we face a long drawn-out war of attrition. Such a cessation of private sector investment could be hugely damaging to cancer research ecosystems in CEE. Whilst this is understandably not the major focus for the European Commission at this moment of writing, it is clear that for the Cancer Mission to succeed, it will require that these externalities, which fall heaviest on CEE countries, are central to informing strategic planning and funding going forward.

Recommendation 12: European cancer research funders and policy makers must commit to empowering European cancer researchers in driving an equitable global cancer research agenda, with particular emphasis on Low and Middle Income Countries

While much of the focus of the cancer community in Europe has been directed towards refining and enhancing the European cancer research effort, Europe also has a substantial opportunity to provide international leadership and deliver tangible actions to address the challenge of cancer globally. We need to significantly increase cancer research collaborations between Europe and the rest of the world, in particular co-creating a broad portfolio of research activities across the LMIC continuum, where without immediate action nearly 70% of global cancer deaths will occur by 2040.¹¹⁰ Currently, we collectively devote <4.5% of our cancer research to activities with LMICs, a paltry figure for areas of the world where the research need is greatest. We

have a global responsibility to develop meaningful cancer research partnerships, enhancing research outputs to help address the increasing cancer burden that LMICs face.

Reimagining Cancer Research and its Implementation in Europe: A Call To Action

It has been a brutally challenging few years since the start of the COVID-19 pandemic for the European cancer community as it sought to deliver optimal cancer care and produce high-quality cancer research under unprecedented pressures. The impact at the time of writing of this Commission is far from over. The pandemic has highlighted a lack of systems resilience, prompting much reflection on whether the ways in which we delivered cancer care and research pre-COVID best served our citizens, patients and society. It has become rapidly clear that returning to the 'old' normal will simply not be good enough. Building back better 'post pandemic' for cancer care, research and education that truly has patients and society at the heart, will require renewed focus, drive and creativity.

In cancer research, there is an unrivalled opportunity to embrace the "build back better" mantra. In this *Lancet Oncology Commission*, we position future European cancer research endeavours as a Groundshot^{66,250} and we present our Recommendations within a Call to Action to "*Reimagine Cancer Research and its Implementation In Europe*" (**Panel 19**). The research response to COVID and its rapid transition to clinical care has been revelatory, particularly in the development and approval of the myriad of vaccine options and rapid testing platforms that have brought us to a better place, as citizens, as patients and as societies. We now have the opportunity to deploy a similar approach in cancer as we have done with COVID. *Follow the science, follow the data* must become our modus operandum. Reimagining cancer research and its implementation provides us with an opportunity to think differently, to embrace a more holistic end-to-end approach, by working closely with patient groups and the cancer workforce to nurture true pan-cancer innovation, and to be unencumbered by barriers or pressure points that would previously have prompted paralysis. While the data and intelligence that we have generated has highlighted the particular challenges that we face in Central and Eastern Europe, a

focus on research capacity building, directed funding and twinning approaches to enhance cancer research activity, its quality and its implementation in CEE countries has the potential to be transformational. Coupled with a more nuanced and much broader portfolio of research and empowered by the ethos of implementation that we have articulated within this *Lancet Oncology Commission*, we can start to reimagine a more equality-focussed, people-centred, data-enabled cancer research ecosystem that mandates that the best science and most promising innovation are delivered at pace and at scale so that our European 70:35 Vision is delivered.

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