

STUDY

Requested by the ENVI committee



Strengthening Europe in the fight against cancer

Going further, faster



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Abstract

This study provides an overview of the current state-of-play in Europe in respect to the fight against cancer.

It focuses in particular on four main areas: causation of cancer; cancer screening and early diagnosis; access to cancer treatment, care and research; and rare and childhood cancers. It provides key findings and recommendations in each of these areas.

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LIST OF ABBREVIATIONS

AI	Artificial Intelligence
CanCon	Cancer Control Joint Action
CAR-T cells	Chimeric Antigen Receptors-T cells, a type of modified immune cell used in cancer immunotherapy
DNA	Deoxyribo-Nucleic Acid
EC	European Commission
EMA	European Medicines Agency
ERNs	European Reference Networks
EU	European Union
GDPR	General Data Protection Regulation
HBV	Hepatitis B Virus
HPV	Human Papillomavirus
HTA	Health Technology Assessment
IARC	International Agency for Research on Cancer
IT	Information Technology
JARC	Joint Action on Rare Cancers
JRC	Joint Research Centre
NCCPs	National Cancer Control Plans
NGOs	Non-governmental organisations
RARECARE	Surveillance of Rare Cancers in Europe
RARECAREnet	Information Network on Rare Cancers
R&D	Research and Development
UK	United Kingdom
US	United States
UV	Ultraviolet
WHO	World Health Organisation

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EXECUTIVE SUMMARY

Nearly 3 million new people are diagnosed with cancer each year in the EU. Cancer is caused by mutations in cells of the body, allowing them to chronically proliferate and to form tumours able to invade the body of the host through metastases. Uncontrolled growth of the cancer cells may eventually result in organ failure and death. Cancer is responsible for more than 1.2 million deaths in the EU each year. However, growing access to multidisciplinary cancer care and innovation in all treatment modalities, including radiation therapy, surgery and chemotherapy, are helping to improve survival rates for many tumours. Latest figures from WHO estimate almost 10 million people in Europe are surviving more than 5 years after cancer diagnosis.

Around 40% of all cancers are currently preventable in Europe, i.e. associated with modifiable risk factors. **Tobacco use, and in particular cigarette smoking, is by far the single largest preventable cause of cancer in the EU.** It is followed by other life-style related factors (such as being overweight or obese, maintaining poor dietary habits, lack of physical activity and alcohol consumption) and infections by carcinogenic viruses or bacteria (notably Human Papillomavirus (HPV), Hepatitis B and C Viruses (HBV & HCV) and *Helicobacter pylori*). Environmental factors (UV and ionising radiation; pollution), occupational factors (such as exposure to asbestos or heavy metals), and medical or reproductive factors (no breastfeeding, postmenopausal hormonal replacement use and carcinogenic pharmaceutical drugs) are also known to be associated with cancer development.

Primary prevention interventions, aimed at preventing the onset of cancer through action on modifiable risk factors, are the most cost-effective strategy in the control of cancer. Approaches notably include population-wide awareness campaigns, such as the European Code Against Cancer, and legislative or regulatory initiatives, such as discouraging tobacco use and banning artificial tanning devices. Furthermore, vaccination against carcinogenic viruses, such as HPV, has the potential to eliminate a category of cancer as a public health problem and are therefore recommended to be universally implemented in EU Member States.

Secondary prevention through screening and early diagnosis of cancer is also vital to improve outcomes of affected patients. The **Council of the European Union issued in 2003 a set of recommendations on the establishment of organised breast, cervical and colorectal cancer screening programmes** in EU Member States. Despite a number of initiatives since 2003, **their implementation is still far from complete and there remain significant inequalities in access to quality-assured cancer screening** across the EU. Furthermore, there have been growing calls for an update of these 2003 recommendations, in order to factor in recent scientific and technological developments in respect to cancer screening.

Beyond screening, significant challenges remain in respect to early diagnosis of cancer. **To achieve improved levels of early diagnosis of cancer, the public must be assisted in gaining sufficient awareness of potential cancer symptoms**, overcoming fear or stigma associated with cancer and accessing appropriate healthcare advice. This requires primary **healthcare professionals to possess the clinical skills and knowledge to identify potential symptoms** described or presented by patients and ensure timely referral to specialist cancer services. Another critical element of early diagnosis is **accurate clinical evaluation, diagnosis and staging**, which again requires appropriate expertise. Main perspectives in this respect include addressing shortages in the pathology workforce, supporting investments in new diagnosis technologies and creating quality indicators for improved timeliness of cancer patient referral.

Cancer treatment is multimodal. Key modalities of cancer treatment include non-systemic treatments, such as radiation therapy and surgery, and systemic treatments through pharmaceutical agents. **There is a need to address inequalities in access to all forms of cancer treatment.**

Among core needs to be met in respect of surgery, radiation therapy and interventional oncology are proactive support in achieving European level harmonisation and recognition of training and qualifications, and stronger investment in clinical research, both of which might be addressed in the context of an emerging Europe's Beating Cancer Plan and the Cancer Mission of the Horizon Europe research and innovation programme (hereafter referred as the "EU Cancer Mission").

The area of **cancer medicine** is undergoing rapid development and change, not least as a result of advances in personalised therapy and precision oncology. The advent of CAR-T cell therapy (treatment in which a type of immune cells, the so-called T cells, are collected from the patient and changed in the laboratory so they will attack cancer cells) has been a prominent example in this regard. This, in turn, has been driving demands for change in terms of both regulatory approval mechanisms and in respect to pricing and reimbursement strategies for such new treatments. In this respect, **the new EU Pharmaceutical Strategy should be ambitious in achieving a timely update of both regulatory and incentive models. The delay in passing into legislation the European Commission's proposal for improving Member States' cooperation on Health Technology Assessment must end.** Continued delay represents a serious frustration of a common will for its implementation. To achieve longer term resolution of the persisting problem of **cancer medicines shortages**, the EU Pharmaceutical Strategy should:

- strengthen EU pharmaceutical legislation in respect to notification of shortage;
- provide clearer guidance to Member States on the operation of parallel trade;
- bring better information sharing between countries in respect to shortage management and prevention; and
- encourage improved procurement procedures for generic medicine.

To provide patients with **quality cancer care** means ensuring a balanced and comprehensive approach that enables them to access not only the core modalities of cancer treatment, but also the many other essential components that make up the foundation of high quality cancer care, including strong primary care, pathology, specialist cancer nursing, oncology pharmacy, palliative care, supportive care and psycho-oncology. All such elements of quality cancer care could be supported by: proactive assistance for the harmonisation and development of education and training requirements at the European level; and, official EU-level monitoring and reporting on patient access to these critical elements of cancer care across Europe, potentially via a suggested **European Cancer Dashboard**, supported through the new EU4Health funding programme. **Europe's Beating Cancer Plan should support the goal of at least one comprehensive cancer centre in each Member State, and one for every 5 million inhabitants in countries with a larger population.**

Legal and other tools should be leveraged to protect cancer patients and survivors from discrimination. This includes introducing **"the right to be forgotten"** (in respect to cancer survivor access to financial services) in all countries.

The possibilities of Artificial Intelligence and digital technology to enhance cancer care should be embraced and be firmly supported via EU initiatives focused on the digital economy and the Horizon Europe research and innovation programme.

Cancer research, and its translation into everyday clinical practice, is fundamental to ensuring continual improvements in cancer prevention, diagnosis, treatment and follow-up care for survivors. An underlying concept for developing Europe's translational research strength is the potential for wider application of the Comprehensive Cancer Care Network (CCCN) vision to not only improve delivery of cancer care, but also to advance Europe's network for practical cancer research.

Other opportunities for improving the landscape for cancer research that are highlighted in this report include: adoption of recommendations for improving **treatment optimisation research**; stronger promotion of opportunities for **drug repurposing research**; additional support for **research in respect of non-systemic/loco-regional cancer treatment**; greater adoption of **patient reported outcome measures** within prevailing regulatory structures; ongoing work to improve the **harmonisation and standards of European cancer registries**; and, addressing of the cancer research community's expressed complaints on **the burdens of the General Data Protection Regulation**.

Rare cancers represent a major public health concern in Europe, affecting an estimated 5.1 million of patients across Europe. Noting ongoing dramatic variations in survival across Europe, **sustained attention to rare cancer policy is required** within the context for the forthcoming Europe's Beating Cancer Plan, EU Cancer Mission and new EU Pharmaceutical Strategy.

The European Union is playing a central role in improving collaboration in respect to rare cancers via the construction and operation of "**European Reference Networks**". The ERNs are opening new possibilities for improving rare cancer treatment and care including via: sharing of clinical cases; rationalisation of patient referral; and, improved rare cancer management in small countries. Many further potential roles for the ERNs are suggested, including producing clinical practice guidelines for rare cancers, facilitating biobanking, and achieving efficiencies of scale in clinical trials. **However, to achieve this, ERNs must be supported by long term sustained funding.**

Paediatric cancers are jointly the first cause of death by disease in children older than 1 year in Europe. More than 35,000 cases are diagnosed annually and over than 6,000 young patients die each year. There are substantial inequalities in access to the best available care and expertise across Europe, causing up to 20% differences in children's survival rates among European countries.

Among very clear policy requirements is further attention to paediatric cancer research needs. These needs include research into genetic predisposition in paediatric cancers as a key pillar of a broader paediatric cancer research agenda. More generally, to redress unequal allocation of investment to paediatric cancer, a clear and specific EU funding stream should be dedicated to paediatric cancer research and budget allocations earmarked across all relevant EU programmes.

From a regulatory perspective, the EU Orphan Medicines Regulation (Regulation (EC) No 141/2000 on orphan medicinal products) **has been ineffective for paediatric cancer medicine development.** The EU regulatory environment should be revisited in this respect, to address the unmet needs of children and adolescents with cancer and make medicine development for this group faster, more efficient, and in line with the rate of innovation observed in the adult cancer sector.

While there are nearly half a million childhood cancer survivors in Europe, the majority are experiencing adverse long-term effects hindering their health, daily life and participation. Long-term follow-up of childhood cancer survivors is key to address this issue. In this regard, the EU co-funded **Joint Action on Rare Cancers has recommended the roll-out of a European Unique Patient Identifier, in order to ensure monitoring of long-term outcomes in childhood cancer survivors in a cross-border setting.**

1. CAUSES OF CANCER AND PRIMARY PREVENTION OF CANCER

1.1. Causes of cancer

KEY FINDINGS & RECOMMENDATIONS: CAUSES OF CANCER

According to latest estimates, nearly 3 million new people are diagnosed with cancer each year in the EU. Cancer can be defined as a disease of unwanted growth, where genetic mutations drive cells to grow and proliferate in an uncontrolled manner and to progressively acquire the hallmarks of a tumour, including the capacity to invade the body through metastases.

In 5 to 10% of cancer cases, cancer-causing mutations are known to be inherited from the individual's parents, causing individuals harbouring them to be affected by a genetic susceptibility to cancer. In all other cases, cancer is due to acquired mutations, arising during the lifetime of the individual in a particular tissue, as a result from exposure to environmental factors or random genetic events. It is usually not possible to know exactly why a certain patient has acquired such mutations and subsequently developed cancer; however, a number of cancer risk factors have been identified.

According to latest available estimates, around 40% of all cancers are currently preventable in Europe, i.e. known to be associated with avoidable (or modifiable) risk factors. **Tobacco use, and in particular cigarette smoking, is by far the single largest preventable cause of cancer in the EU, being responsible for 15-20% of European cancer cases.** It is followed by other lifestyle related factors (obesity, unhealthy diet, lack of physical activity and alcohol consumption) and by infections by carcinogenic viruses or bacteria (notably Human Papillomavirus (HPV), Hepatitis B and C Viruses (HBV & HCV) and *Helicobacter pylori*). Environmental factors (UV and ionising radiation; pollution of air, water and soil), occupational factors (such as exposure to asbestos) and other biological or internal factors (no breastfeeding, postmenopausal hormonal replacement use and carcinogenic pharmaceutical drugs) are also known to be associated with cancer development.

Knowledge of cancer causative factors allows for the development of individualised cancer risk prediction and of risk stratification in cancer management, that is the development of distinct, risk-adapted strategies depending on the level of cancer risk of each individual. Such strategies can apply to both the prevention of the onset of cancer and its earlier detection; they are seen as a promising prospect to reduce the cancer burden and increase the cost-effectiveness of cancer management.

The EU should therefore support the integration of cancer risk prediction and risk stratification as stronger components of cancer control strategies. An EU Cancer Dashboard monitoring patient access to quality cancer care across Europe should include in its parameters access to genetic germline testing and to associated genetic counselling. The establishment and/or endorsement of clear guidelines at the European level may also prove instrumental in ensuring that healthy individuals and cancer patients benefit from the best clinical and ethical standards in respect to genetic testing.

1.1.1. Mechanisms of carcinogenesis

a. "Drivers of cancer": genetic mutations

Cancer can be defined as a disease of unwanted growth, where cells of an individual's body grow and proliferate in an uncontrolled manner. Carcinogenesis (i.e. cancer development) is primarily **caused by mutations** (abnormalities) in the DNA of cells in the body, affecting two main categories of genes:

- those involved in the stimulation or the inhibition of cell growth and division (known as proto-oncogenes and tumour-suppressor genes, respectively); and
- those involved in the control of DNA integrity (known as DNA repair genes)^{1,2}.

Mutations in proto-oncogenes and tumour-suppressor genes make cells prone to sustain chronic proliferation, while mutations in DNA repair genes cause them to harbour genomic instability, i.e. an increased tendency to acquire additional mutations, including some further nurturing carcinogenesis. Accumulation of these genetic alterations ultimately culminates in the development of a malignant tumour, i.e. a mass of cancerous cells able to grow and divide in an uncontrolled manner, as well as to invade nearby tissues of the body, in a process known as metastasis^{3,4}. They are therefore sometimes referred to as the "**drivers of cancer**"⁵.

b. Origins of cancer-causing mutations: genetic susceptibility and cancer risk factors

Depending on when/where they occur, two types of cancer-causing mutations can be identified: germline (inherited) mutations and somatic (acquired) mutations.

i. Germline mutations and genetic susceptibility to cancer

Cancer-causing mutations can be inherited from the individual's parents, meaning that they are present in the reproductive cells of the parent(s) and are therefore incorporated into the DNA of every cell in the body of the offspring. Individuals harbouring such mutations are therefore affected, from birth, by a **genetic susceptibility to cancer**, the extent of which depends on the mutation(s) involved. Although these hereditary factors are implicated in cancer development, they only contribute to **5-10% of cancer cases**^{6,7,8}.

¹ European Code Against Cancer's factsheet about the causes of cancer: <https://cancer-code-europe.iarc.fr/index.php/en/about-cancer/what-causes-cancer> (accessed March 2020).

² US National Cancer Institute's factsheet about the causes of cancer: <https://www.cancer.gov/about-cancer/understanding/what-is-cancer> (accessed March 2020).

³ See US National Cancer Institute's definition of a malignancy: <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/malignancy> (accessed May 2020).

⁴ Malignant tumours are defined as opposed to benign (i.e. non-cancerous) tumours, which failed to acquire key hallmarks of cancer, such as the capacities to grow in an indefinite manner and to invade nearby tissues. See US National Cancer Institute's definition of a benign tumour: <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/benign-tumor> (accessed May 2020).

⁵ US National Cancer Institute's factsheet about the causes of cancer: <https://www.cancer.gov/about-cancer/understanding/what-is-cancer> (accessed March 2020).

⁶ Schüz J., Espina C., Wild C.P., Primary prevention: a need for concerted action. *Mol Oncol.* 2019 Mar; 13(3): pp. 567-578.

⁷ Lichtenstein P., Holm N.V., Verkasalo P.K. et al., Environmental and heritable factors in the causation of cancer—analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med* 2000 Jul 13; 343(2): pp. 78-85.

⁸ Mucci L.A., Hjelmborg J.B., Harris J.R. et al., Nordic Twin Study of Cancer (NorTwinCan) Collaboration (2016) Familial risk and heritability of cancer among twins in Nordic countries. *JAMA.* 2016 Jan 5; 315(1): pp. 68-76.

These germline mutations increase the risk for individuals harbouring them to develop cancer, in some cases with a very high penetrance⁹, close to 100% (e.g. hereditary retinoblastoma¹⁰). Two categories of germline mutations can be distinguished:

- hereditary cancer predisposition syndromes, where individual mutations associated with a high cancer risk can be identified, such as Lynch syndrome (hereditary colorectal cancer caused by mutations in DNA repair genes) or hereditary breast cancer (notably caused by mutations in tumour-suppressor genes, such as BRCA1 and BRCA2); and
- polygenic cancer predisposition, where the accumulation of a number of mutations individually associated with a low to moderate cancer risk into the DNA of members of a single family result in a high cancer incidence¹¹ among them; this accumulated risk is referred to as an individual's polygenic risk score.

Importantly, as a consequence from these genetic risk factors, **cancer tends to aggregate in families**^{12,13} or in other population groups with a relative genetic homogeneity, such as those affected by cancer-associated "founder mutations"¹⁴, e.g. breast cancer-associated mutations in women of Ashkenazi Jewish ancestry¹⁵. Therefore, a "**positive cancer family history**", i.e. the fact of having one or several of one's family members previously affected by a cancer, or the belonging to a population affected by known cancer-associated founder mutations, **has to be considered as a "cancer risk indicator"**.

It should however be emphasized that the positive cancer risk family history is not a generally sensitive tool, e.g. in cases of small family size. An **early age at cancer diagnosis** for that cancer type and the **occurrence of multiple primary tumours** can also indicate that the affected cancer patient was harbouring genetic predisposition to cancer. In this case, the patient's healthy relatives may be affected by the same genetic disorder and therefore also have an increased risk of developing cancer.

Together, these indicators can justify performing genetic testing to confirm the suspected presence of cancer-associated germline mutations and ultimately implementing risk-adapted strategies for cancer prevention and earlier detection¹⁶.

⁹ Penetrance is defined in epidemiology as the proportion of individuals with a specific disease-associated genotype (i.e. one or several genetic mutations associated with higher risk of developing the disease) who also express corresponding disease phenotype (i.e. develop the corresponding disease).

¹⁰ See the American Cancer Society's factsheet about the causes of retinoblastoma: <https://www.cancer.org/cancer/retinoblastoma/causes-risks-prevention/what-causes.html> (accessed May 2020).

¹¹ Incidence is defined in epidemiology as the number of new individuals developing a disease during a particular time period (such as one year).

¹² Frank C., Sundquist J., Yu H. et al., Concordant and discordant familial cancer: Familial risks, proportions and population impact. *Int J Cancer*. 2017 Apr 1; 140(7): pp. 1510-1516.

¹³ Yu H., Frank C., Sundquist J. et al., Common cancers share familial susceptibility: implications for cancer genetics and counselling. *J Med Genet*. 2017 Apr; 54(4): pp. 248-253.

¹⁴ Founder mutations are defined as genetic alterations observed with high frequency in a group that is or was geographically or culturally isolated, in which one or more of the ancestors was a carrier of the altered gene. See US National Cancer Institute's definition of founder mutations: <https://www.cancer.gov/publications/dictionaries/genetics-dictionary/def/founder-mutation> (accessed May 2020).

¹⁵ See US Centers for Disease Control and Prevention's factsheet about Jewish women and BRCA gene mutations: https://www.cdc.gov/cancer/breast/young_women/bringyourbrave/hereditary_breast_cancer/jewish_women_brca.htm (accessed May 2020).

¹⁶ See section 1.1.3. about cancer risk prediction and risk-adapted strategies in cancer.

ii. *Somatic mutations and cancer risk factors*

In the vast majority of cases, cancer is due to somatic (acquired) genetic **mutations, i.e. mutations arising during the lifetime of the individual in a particular tissue, as a result from exposure to environmental factors** or random mutational events associated with DNA replication^{17, 18, 19, 20, 21, 22}.

It is usually not possible to know precisely why a certain patient has acquired cancer-causing somatic mutations and subsequently developed cancer. Nevertheless, **epidemiological studies have allowed the identification of suspected cancer risk factors**, which, through a variety of mechanisms, disrupt the functioning of the individual's cells and favour carcinogenesis²³.

Importantly, **the confirmation of these risk factors**, leading to further research into primary prevention measures, **requires the conduct of rigorous scientific risk assessment**, including regarding the existence of sufficient evidence of the agent's carcinogenicity in humans, in order to appraise the potential impact of the exposure to the potential risk factor of interest upon a defined population. The International Agency for Research on Cancer (IARC) Monograph programme on the identification of carcinogenic risks to humans, which regularly publishes and updates, based on latest available scientific evidence, lists of confirmed or suspected carcinogens, is a global reference in this respect^{24, 25, 26, 27}.

c. *"Hallmarks of cancer": key steps of the carcinogenesis process*

Importantly, healthy individuals benefit from a number of defence lines against carcinogenesis, both at the cell-intrinsic level (i.e. contained within all cells of the body, preventing them from acquiring above described cancer-causing mutations and from becoming cancerous) and at the cell-extrinsic level, through cancer immunosurveillance performed by specific immune cells. Therefore, **carcinogenesis is a complex multi-step process requiring a group of previously normal cells to overcome this wide range of barriers**. Progress in genetics and molecular biology in the past decades have refined the understanding of this process, leading to the identification of a set of **key traits required to be acquired a cell and a tumour to fully develop into cancer**, known as the **"hallmarks of cancer"**. While six such "hallmarks" were initially identified in a landmark article published in 2000²⁸, a revised list of 10 requirements was produced in 2011 by the same authors, factoring in further progress in cancer research.

¹⁷ Schüz J., Espina C., Wild C.P., Primary prevention: a need for concerted action. *Mol Oncol.* 2019 Mar; 13(3): pp. 578-567.

¹⁸ Klutstein M., Moss J., Kaplan T. et al., Contribution of epigenetic mechanisms to variation in cancer risk among tissues. *Proc Natl Acad Sci U S A.* 2017 Feb 28; 114(9): pp. 2230-2234.

¹⁹ Nowak M.A. and Waclaw B., Genes, environment, and "bad luck". *Science* 2017 Mar 24; 355(6331): pp. 1266-1267.

²⁰ Tomasetti C. and Vogelstein B., Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. *Science* 2015 Jan 2; 347(6217): pp. 78-81.

²¹ Tomasetti C., Li L. and Vogelstein B., Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention. *Science* 2017 Mar 24; 355(6331): pp. 1330-1334.

²² Wild C.P., Espina C., Bauld L. et al., Cancer Prevention Europe. *Mol Oncol.* 2019 Mar; 13(3): pp. 528-534.

²³ See section 1.1.2. about modifiable cancer risk factors.

²⁴ Schüz J., Espina C., Wild C.P., Primary prevention: a need for concerted action. *Mol Oncol.* 2019 Mar; 13(3): pp. 567-578.

²⁵ International Agency for Research on Cancer (IARC)'s Monographs on the identification of carcinogenic hazards to humans. List of classified agents, Volumes 1-125: <https://monographs.iarc.fr/agents-classified-by-the-iarc/> (accessed June 2020).

²⁶ Coglianò V.J., Baan R., Straif K. et al., Preventable exposures associated with human cancers. *J Natl Cancer Inst.* 2011 Dec 21; 103(24): pp. 39-1827.

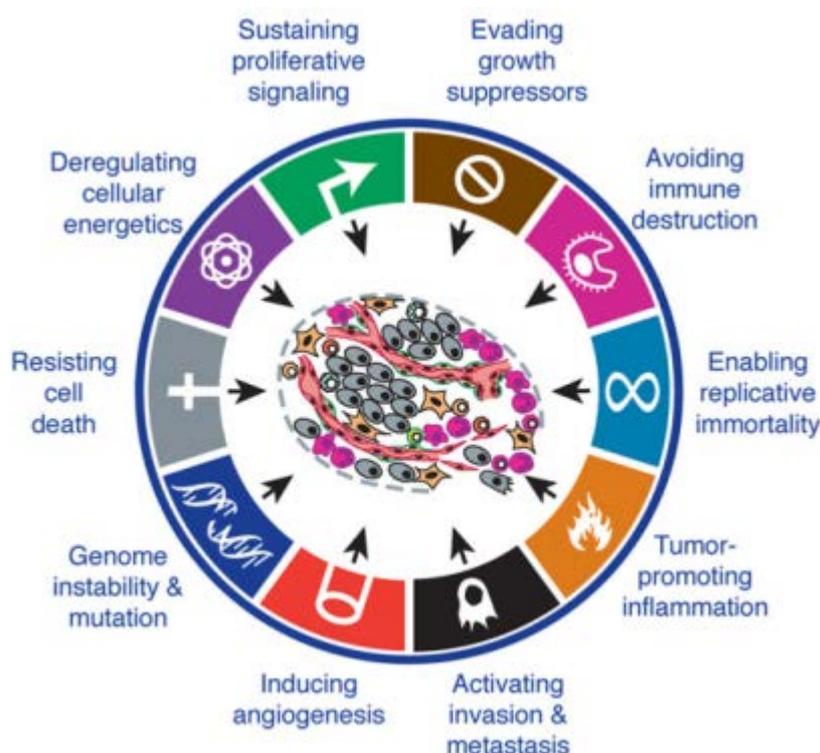
²⁷ Pearce N., Blair A., Vineis P. et al., IARC monographs: 40 years of evaluating carcinogenic hazards to humans. *Environ Health Perspect.* 2015 Jun; 123(6): pp. 14-507.

²⁸ Hanahan D., Weinberg R.A., The hallmarks of cancer. *Cell.* 2000 Jan 7; 100(1): pp. 57-70.

The 10 hallmarks of cancer include:

- two "enabling characteristics", underlying the capacity for cells and tumours to acquire their cancer features (genome instability and tumour-promoting inflammation); and
- eight functional "hallmarks", allowing cancer cells to survive, proliferate and disseminate²⁹.

Figure 1: The hallmarks of cancer



Source: Adapted from Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011 Mar 4; 144(5): pp. 74-646.

Tumours formed through this process of carcinogenesis have a **very wide range of impacts on the physiology of the affected individual**, including, if they are not treated successfully, **multiple organ failure and death**.

d. Heterogeneity of cancer: main types of cancer and associated cancer burden

The above described process of carcinogenesis results in the **development of a very wide variety of cancer types**. Increasing knowledge of the biology of cancer and molecular characterisation of tumours are revealing the extent of this heterogeneity, leading to the identification of hundreds of specific cancer types.

These cancer types are primarily distinguished on the basis of the anatomic site of the tumour, i.e. the organ in which carcinogenesis primarily occurs. In the EU, the organs most commonly affected by cancer are **breast, colorectum, prostate and lung, with more than 300,000 new cancer cases each in 2018**. Of these cancers, **lung cancers are the deadliest, accounting for more than 150,000 yearly**

²⁹ Hanahan D., Weinberg R.A., Hallmarks of cancer: the next generation. *Cell*. 2011 Mar 4; 144(5): pp. 74-646.

deaths in the EU, followed by far by breast and pancreas cancers, which are associated to more than 80 000 deaths in 2018 in the EU (see Annex 1³⁰).

Cancer types are further distinguished and named according to the cell type in which abnormal proliferation primarily occurs. Epithelial cells, i.e. covering the inside and outside surfaces of the body, are the most commonly involved, accounting for an instance for the large majority or the totality of breast, colorectum, prostate and lung cancers; in this case, the tumour is called a **carcinoma**. However, a wide range of other cell types can be affected by malignant proliferation; these notably include:

- bone and soft tissues, including muscle, fat, blood vessels, lymph vessels and fibrous tissue (in the case of **sarcomas**);
- blood-forming cells in the bone marrow (in the case of **leukaemias**);
- differentiated immune cells such as T and B lymphocytes (in the case of **lymphomas**), or plasma cells (in the case of **multiple myelomas**); and
- melanocytes, i.e. specialized skin cells responsible for the production of melanin (in the case of **melanomas**)³¹.

Finally, the genetic changes underlying carcinogenesis in the affected individual can also serve to further separate cancer types and have impacts on both the physiopathology of the patient and the treatment that he/she may, or may not, benefit from to get his/her cancer cured.

In total, all these cancers affect nearly 3 million new individuals each year in the EU and are responsible for 1.2 million deaths.

1.1.2. Modifiable cancer risk factors

According to latest available estimates, **around 40% of all cancers are currently preventable in Europe, i.e. known to be associated with avoidable (or modifiable) risk factors**^{32,33,34}. As shown in Figure 2, such risk factors include, from highest to lowest attributable fraction of the cancer burden:

- lifestyle-related factors: tobacco and smoking, being overweight or obese, having poor dietary habits, conducting low levels of physical activity and over-consuming alcohol;
- infections by carcinogenic viruses or bacteria, notably Human Papillomavirus (HPV), Hepatitis B and C Viruses (HBV & HCV) and *Helicobacter pylori*;
- environmental factors: ultraviolet (UV) and ionising radiation, pollution of air, water and soil, and naturally occurring carcinogens;
- occupational factors, such as exposure to asbestos or heavy metals; and

³⁰ Epidemiology of most common cancers in 2018 in the EU. Data extracted from IARC Global Cancer Observatory, available at: <https://gco.iarc.fr/> (accessed June 2020).

³¹ "What Is Cancer?" factsheet on the US National Cancer Institute's website: <https://www.cancer.gov/about-cancer/understanding/what-is-cancer> (accessed June 2020).

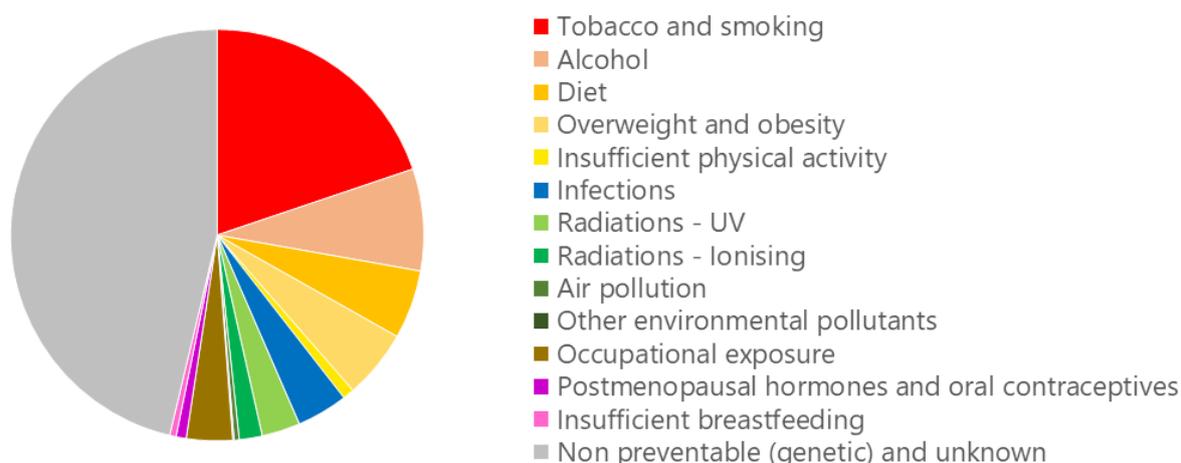
³² Brown K.F., Runggay H., Dunlop C. et al., The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. *Br J Cancer*. 2018 Apr; 118(8): pp. 1130-1141.

³³ IARC (2018). Les cancers attribuables au mode de vie et à l'environnement en France métropolitaine. Lyon: International Agency for Research on Cancer. Available from: http://gco.iarc.fr/resources/paf-france_fr.php (accessed May 2020).

³⁴ Islami F., Goding Sauer A., Miller K.D. et al., Proportions and numbers of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. *CA Cancer J Clin*. 2018 Jan; 68(1): pp. 31-54.

- medical or reproductive factors: reproductive and hormonal factors (not breastfeeding, postmenopausal hormonal replacement use) and carcinogenic pharmaceutical drugs³⁵.

Figure 2: Causes of cancer – fractions of cancer cases attributable to modifiable risk factors



Source: IARC (2018). Les cancers attribuables au mode de vie et à l'environnement en France métropolitaine. Lyon: International Agency for Research on Cancer. Available from: http://qco.iarc.fr/resources/paf-france_fr.php.

Note: Data shown correspond to population attributable fractions calculated for the main identified modifiable cancer risk factors, for the French population among adults over 30, in 2015. Although precise figures may differ from country to country, orders of magnitude are valid for the entire EU.

This potential for prevention shows extremely wide variability between cancer types, ranging from an estimated 100% of preventable cancers in the case cervical cancer (caused by HPV infection) to 0% for prostate and brain cancer, for which there is still no modifiable risk factor identified (see Annex 2³⁶).

Of note, given the long latency between exposure of individuals to most of these cancer risk factors and cancer development (10-20 years), it should be kept in mind that this data does likely not reflect recent evolutions in the exposure to some risk factors, such as air, water and soil pollution³⁷.

a. Lifestyle-related cancer risk factors

i. Tobacco and smoking

The tobacco epidemic is one of the biggest public health threats the world faces today, killing more than 7 million people a year worldwide³⁸. Europe has the highest levels of tobacco use in the world. Regional estimates suggest that around 29% of people over the age of 15 years use tobacco products,

³⁵ World Cancer Report 2014. Geneva, Switzerland: World Health Organisation, International Agency for Research on Cancer, WHO Press, 2015.

³⁶ Population attributable fractions to all risk factors (i.e. share of preventable cancers) among the most common cancer types in Europe. Data on estimated incidence in 2012 retrieved from International Agency for Research on Cancer's Global Cancer Observatory (<https://qco.iarc.fr>) and on risk factor attributable fraction retrieved from Brown KF, Rumgay H, Dunlop C, et al. The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. *Br J Cancer*. 2018 Apr; 118(8): pp. 1130-1141.

³⁷ Schüz J., Espina C., Wild C.P., Primary prevention: a need for concerted action. *Mol Oncol*. 2019 Mar; 13(3): pp. 567-578.

³⁸ WHO report on the global tobacco epidemic 2017. Geneva: World Health Organisation; 2017, available at: https://www.who.int/tobacco/global_report/en/ (accessed June 2020).

with a higher consumption among men than women^{39,40}.

Tobacco use, and in particular cigarette smoking, is the single largest preventable cause of cancer in the European Union (EU). All tobacco products contain a wide range of carcinogens; tobacco consumers are also exposed to nicotine, leading to tobacco addiction in many users⁴¹.

Tobacco use causes cancer in multiple organs and is the main cause of tracheal, bronchial and lung cancer, responsible for approximately 90% of deaths from these cancers^{42,43}. In 2018, about 313,000 new cases of lung cancer and 258 000 lung cancer deaths were reported in the EU⁴⁴. In total, according to latest estimates, around **15-20% of cancer cases^{45,46} and 27% of cancer deaths^{47,48} are currently attributable to tobacco use in Europe.** Beyond, smokers also suffer from increased risks of cardiovascular and respiratory diseases; half of them die prematurely (from 14 years on average). Overall, tobacco consumption is responsible for nearly 700,000 deaths in the EU every year⁴⁹.

Of note, tobacco use also include the use of smokeless tobacco products, a heterogeneous category, which are also carcinogenic but cause a lower burden of cancer deaths than cigarette smoking.

Smoking generates second-hand smoke (SHS), an established cause of lung cancer; inhalation of SHS by non-smokers is not yet completely abolished in indoor workplaces or indoor public places, and much more present in the homes of smokers⁵⁰.

ii. *Obesity, diet and physical activity*

Obesity and cancer causation

It is estimated that over half the population of the EU is overweight or obese due to an imbalance between energy expenditure and energy intake. This is related to an obesogenic environment of sociocultural, economic and marketing challenges to the control of body weight. **Excess body fat is associated with nine cancer sites** (oesophagus, colorectum, gall bladder, pancreas, postmenopausal breast, endometrium, ovary, kidney and prostate [advanced stage])⁵¹, accounting for an estimated

³⁹ WHO global report on trends in prevalence of tobacco smoking 2000–2025, second edition. Geneva: World Health Organisation; 2018 (<https://www.who.int/tobacco/publications/surveillance/trends-tobacco-smoking-second-edition/en/>; accessed June 2020).

⁴⁰ WHO (2019) European tobacco use: Trends report 2019, available at: <http://www.euro.who.int/en/health-topics/disease-prevention/tobacco/publications/2019/european-tobacco-use-trends-report-2019-2019> (accessed June 2020).

⁴¹ Leon M.E., Peruga A., McNeill A. et al., European Code against Cancer, 4th Edition: Tobacco and cancer. Cancer Epidemiol. 2015 Dec; 39 Suppl 1: pp. 33-520.

⁴² Association of European Cancer Leagues (ECL)'s Vision paper about the European Beating Cancer Plan: European Code Against Cancer: https://www.iccp-portal.org/sites/default/files/resources/ECL-vision-EU-Beating-Cancer-Plan_final.pdf (accessed June 2020).

⁴³ WHO (2019) European tobacco use: Trends report 2019: <http://www.euro.who.int/en/health-topics/disease-prevention/tobacco/publications/2019/european-tobacco-use-trends-report-2019-2019> (accessed June 2020).

⁴⁴ Data on lung cancer incidence and mortality in 2018 in the EU extracted from the IARC Global Cancer Observatory: <https://gco.iarc.fr>.

⁴⁵ Brown K.F., Rumgay H., Dunlop C. et al., The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. Br J Cancer. 2018 Apr; 118(8): pp. 1130-1141.

⁴⁶ IARC (2018). Les cancers attribuables au mode de vie et à l'environnement en France métropolitaine. Lyon: International Agency for Research on Cancer. Available from: http://gco.iarc.fr/resources/paf-france_fr.php (accessed May 2020).

⁴⁷ Association of European Cancer Leagues (ECL)'s Vision paper about the European Beating Cancer Plan: European Code Against Cancer: https://www.iccp-portal.org/sites/default/files/resources/ECL-vision-EU-Beating-Cancer-Plan_final.pdf (accessed June 2020).

⁴⁸ WHO (2019) European tobacco use: Trends report 2019: <http://www.euro.who.int/en/health-topics/disease-prevention/tobacco/publications/2019/european-tobacco-use-trends-report-2019-2019> (accessed June 2020).

⁴⁹ <https://www.europarl.europa.eu/news/en/headlines/society/20160518STO27901/700-000-deaths-a-year-tackling-smoking-in-the-eu>.

⁵⁰ Leon ME, Peruga A, McNeill A, et al. European Code against Cancer, 4th Edition: Tobacco and cancer. Cancer Epidemiol. 2015 Dec; 39 Suppl 1: pp. 33-520.

⁵¹ Anderson A.S., Key T.J., Norat T. et al., European Code against Cancer 4th Edition: Obesity, body fatness and cancer. Cancer Epidemiol. 2015 Dec; 39 Suppl 1: pp. 45-534.

5-6.5% of the European cancer burden^{52,53}.**Diet and cancer causation**

In addition to the significant impact of diet on body fatness, a risk factor for several cancers, experimental studies have indicated that **diet may also influence the cancer process in a number of other ways**; an estimated **additional 4.5-5.5% of the European cancer burden** is thought to be attributable to these further impacts of diet on cancer causation^{54,55}.

Prospective studies have shown that dietary patterns characterised by higher intakes of fruits, vegetables, and whole-grain foods, and lower intakes of red and processed meats and salt, are related to reduced risks of death and cancer, and that a healthy diet can improve overall survival after diagnosis of breast and colorectal cancers. There is evidence that high intakes of fruit and vegetables may reduce the risk of cancers of the aerodigestive tract, and that dietary fibre protects against colorectal cancer.

Red and processed meats increase the risk of colorectal cancer. Diets rich in **high-calorie foods, such as fatty and sugary foods**, may lead to increased calorie intake, thereby promoting obesity and leading to an increased risk of cancer. There is some evidence that **sugary drinks** are related to an increased risk of pancreatic cancer⁵⁶.

Physical activity and cancer causation

Physical activity is a complex, multidimensional behaviour, the precise measurement of which is often challenging. Nonetheless, representative survey data show that 35% of the European adult population is physically inactive.

Inadequate levels of physical activity are disconcerting, given substantial epidemiologic evidence showing that **physical activity is associated with decreased risks of colon, endometrial, and breast cancers**. For example, insufficient physical activity levels are thought to cause 9% of breast cancer cases and 10% of colon cancer cases in Europe. Conversely, insufficient physical activity is considered to **account for around 0.5-1% of the European cancer burden**^{57,58}.

In recent years, sedentary behaviour has emerged as a potential independent determinant of cancer risk. In cancer survivors, physical activity has shown positive effects on body composition, physical fitness, quality of life, anxiety, and self-esteem.

Physical activity may also carry benefits regarding cancer survival, but more evidence linking increased physical activity to prolonged cancer survival is needed⁵⁹.

⁵² Brown K.F., Rumgay H., Dunlop C. et al., The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. *Br J Cancer*. 2018 Apr; 118(8): pp. 1130-1141.

⁵³ IARC (2018). Les cancers attribuables au mode de vie et à l'environnement en France métropolitaine. Lyon: International Agency for Research on Cancer. Available from: http://gco.iarc.fr/resources/paf-france_fr.php (accessed May 2020).

⁵⁴ Brown K.F., Rumgay H., Dunlop C. et al., The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. *Br J Cancer*. 2018 Apr; 118(8): pp. 1130-1141.

⁵⁵ IARC (2018). Les cancers attribuables au mode de vie et à l'environnement en France métropolitaine. Lyon: International Agency for Research on Cancer. Available from: http://gco.iarc.fr/resources/paf-france_fr.php (accessed May 2020).

⁵⁶ Norat T., Scoccianti C., Boutron-Ruault M.C. et al., European Code against Cancer 4th Edition: Diet and cancer. *Cancer Epidemiol*. 2015 Dec; 39 Suppl 1: pp. 66-556.

⁵⁷ Brown K.F., Rumgay H., Dunlop C. et al., The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. *Br J Cancer*. 2018 Apr; 118(8): pp. 1130-1141.

⁵⁸ IARC (2018). Les cancers attribuables au mode de vie et à l'environnement en France métropolitaine. Lyon: International Agency for Research on Cancer. Available from: http://gco.iarc.fr/resources/paf-france_fr.php (accessed May 2020).

⁵⁹ Leitzmann M., Powers H., Anderson A.S. et al., European Code against Cancer 4th Edition: Physical activity and cancer. *Cancer Epidemiol*. 2015 Dec; 39 Suppl 1: pp. 55-546.

iii. Alcohol

Alcohol consumption is a public health problem in Europe, contributing to a vast number of chronic conditions and injuries and being the third leading risk factor for disease and mortality in Europe⁶⁰.

Ethanol and acetaldehyde contained in alcoholic beverages are classified as carcinogenic to humans by the IARC Monographs on the identification of carcinogenic risks to humans⁶¹; a **causal relationship** has been established for consumption of alcoholic beverages and cancers of the oral cavity, pharynx, larynx, oesophagus, liver, colorectum and female breast.

The higher the amount of alcohol consumed, the higher the risk of developing cancer. In Europe, an estimated **10% of all cancer cases in men and 3% of all cancer cases in women are attributable to alcohol consumption⁶².**

b. Infection by carcinogenic viruses or bacteria

Chronic infections with viruses or bacteria have been identified as strong risk factors for specific cancers. In total, 11 infectious agents are recognised as confirmed carcinogens by the IARC⁶³, most often with a very high relative risk (>10) for infected individuals to develop cancer, as compared to their non-infected counterparts⁶⁴. Four of these infectious agents are individually associated with significant cancer burden in Europe and make up the quasi-totality of all European infection-associated cancers:

i. Human Papillomavirus (HPV) and cancer causation

Human Papillomavirus (HPV) corresponds to a large group of over 100 viral subtypes, collectively responsible for a very commonly sexually transmitting infection: up to 90% of sexually active women and men will acquire HPV at some point of their lives⁶⁵. Infection typically resolves asymptotically within 1–2 years, but certain HPV subtypes can cause a wide range of cancers over extended time periods in individuals in whom HPV infection is not cleared by the immune system⁶⁶.

HPV is currently the largest cause of infection-associated cancers in Europe, accounting alone for an estimated 1.8% of the European cancer burden⁶⁷ and 3.8% of the global cancer burden. It is **responsible for all cases of cervical cancer and of anal squamous cell carcinoma**, as well as for various proportions of other genital cancers (25% of vulva carcinomas, 53% of penis carcinomas and 78% of vagina carcinomas), 30% of oropharyngeal cancers and 2% of oral cavity and larynx cancers

⁶⁰ Association of European Cancer Leagues (ECL)'s Vision paper about the European Beating Cancer Plan: European Code Against Cancer: https://www.iccp-portal.org/sites/default/files/resources/ECL-vision-EU-Beating-Cancer-Plan_final.pdf (accessed June 2020).

⁶¹ International Agency for Research on Cancer (IARC)'s Monographs on the identification of carcinogenic hazards to humans. List of classified agents, Volumes 1-125: <https://monographs.iarc.fr/agents-classified-by-the-iarc/> (accessed June 2020).

⁶² Scoccianti C., Cecchini M., Anderson A.S. et al., European Code against Cancer 4th Edition: Alcohol drinking and cancer. *Cancer Epidemiol* 2016 Dec; 45: pp. 181-188.

⁶³ International Agency for Research on Cancer (IARC)'s Monographs on the identification of carcinogenic hazards to humans. List of classified agents, Volumes 1-125: <https://monographs.iarc.fr/agents-classified-by-the-iarc/> (accessed June 2020).

⁶⁴ World Cancer Report 2014. Geneva, Switzerland: World Health Organisation, International Agency for Research on Cancer, WHO Press, 2015.

⁶⁵ European Cancer Organisation. Eliminating HPV-caused cancers and diseases in Europe: Case for Action. <https://www.european-cancer.org/resources/51:eliminating-hpv-caused-cancers-and-diseases-in-europe-case-for-action.html> (published December 2019; accessed June 2020).

⁶⁶ Wild C.P., Weiderpass E., Stewart B.W., editors (2020). World Cancer Report: Cancer Research for Cancer Prevention. Lyon, France: International Agency for Research on Cancer.

⁶⁷ IARC (2018). Les cancers attribuables au mode de vie et à l'environnement en France métropolitaine. Lyon: International Agency for Research on Cancer. Available from: http://gco.iarc.fr/resources/paf-france_fr.php (accessed May 2020).

among the world population⁶⁸. Importantly, **20-30% of HPV-caused cancers therefore occur in men**, with an increasing trend⁶⁹.

12 HPV subtypes have been classified as confirmed carcinogens by the IARC⁷⁰. Of note, the extent of the cancer risk associated with each of these subtypes may differ, with two of them (HPV16 and HPV18) being responsible for most cervical cancers⁷¹; this has important consequences in terms of HPV vaccine design.

ii. *Helicobacter pylori* and cancer causation

Helicobacter pylori mainly infects children via oral-oral or faecal-oral routes, with a decreasing prevalence⁷² trend in developed countries; it causes chronic inflammation of the stomach and slowly leads, decades later, to the development of two stomach cancer types in a small proportion of infected individuals. This bacterium is **predominantly associated with two stomach cancer types** in Europe: an estimated 89% of non-cardia gastric carcinoma cases and 73% of non-Hodgkin gastric lymphoma cases are attributed to it among the world population. In total, *Helicobacter pylori* accounts for an estimated 1.3% of the total European cancer burden⁷³.

iii. *Hepatitis B and C Viruses (HBV and HCV) and cancer causation*

Hepatitis B and C viruses (HBV and HCV) are very common viruses, each of which is estimated to be currently carried by more than 200 million people globally, predominantly transmitted through perinatal, parenteral (e.g. blood transfusion or intravenous infection) and sexual routes. Importantly, the risk of becoming chronic carrier is much higher infected as infants (90%) than those infected as adults (5%); the latter mode of transmission occurs mainly in high-income countries. **HBV and HCV are major causes of liver cancer, collectively responsible for around 75% of worldwide hepatocellular carcinomas.** Furthermore, HCV is also involved in the development of some B-cell non-Hodgkin lymphomas, accounting for an estimated 3% of global non-Hodgkin lymphomas.

Other infectious agents recognised as carcinogenic by the IARC and present in Europe include the **Epstein-Barr Virus (EBV)**, associated with a number of lymphomas and of nasopharyngeal cancer cases, and **Kaposi Sarcoma Herpesvirus (KSHV, also known as human herpesvirus 8)**, to which all cases of Kaposi sarcoma are attributed^{74,75}.

According to latest estimates, these infections account in total for an estimated **3.5-4% of the**

⁶⁸ De Martel C., Georges D., Bray F. et al., Global burden of cancers attributable to infections in 2018: a worldwide incidence analysis. *Lancet Glob Health*. 2020 Feb; 8(2): e180–90.

⁶⁹ Hartwig S., Syrjänen S., Dominiak-Felden G. et al., Estimation of the epidemiological burden of human papillomavirus-related cancers and non-malignant diseases in men in Europe: a review. *BMC Cancer* 2012 Jan 20; 12(30).

⁷⁰ International Agency for Research on Cancer (IARC)'s Monographs on the identification of carcinogenic hazards to humans. List of classified agents, Volumes 1-125: <https://monographs.iarc.fr/agents-classified-by-the-iarc/> (accessed June 2020).

⁷¹ Wild C.P., Weiderpass E., Stewart B.W., editors (2020). *World Cancer Report: Cancer Research for Cancer Prevention*. Lyon, France: International Agency for Research on Cancer.

⁷² Prevalence is defined in epidemiology as the number of individuals affected by a certain disease in a particular population at a given time.

⁷³ IARC (2018). *Les cancers attribuables au mode de vie et à l'environnement en France métropolitaine*. Lyon: International Agency for Research on Cancer. Available from: http://gco.iarc.fr/resources/paf-france_fr.php (accessed May 2020).

⁷⁴ Wild C.P., Weiderpass E., Stewart B.W., editors (2020). *World Cancer Report: Cancer Research for Cancer Prevention*. Lyon, France: International Agency for Research on Cancer.

⁷⁵ De Martel C., Georges D., Bray F. et al. Global burden of cancers attributable to infections in 2018: a worldwide incidence analysis. *Lancet Glob Health*. 2020 Feb; 8(2): e180–90.

European cancer burden^{76,77}.

Importantly, Human immunodeficiency virus (HIV) infection continues to be of major public health importance in several EU countries. Although HIV is not directly carcinogenic, HIV infection causes immunosuppression, thereby increasing the risk of developing numerous cancers caused by other infections, including Kaposi sarcomas, lymphomas, cervical cancers and anal cancers^{78,79}.

c. Environmental and occupational cancer risk factors

i. Ultraviolet radiation and cancer causation

Ultraviolet (UV) radiation is part of the electromagnetic spectrum emitted naturally from the sun or from artificial sources such as tanning devices (commonly known as sunbeds). UV radiation causes damage to the skin, including erythema (skin reddening) or sunburn, and the acquisition of a suntan triggered by UV radiation-induced DNA damage; in the long term, this damage may lead to skin cancer⁸⁰.

Exposure to UV radiation is the main cause of skin cancer, including cutaneous malignant melanoma, basal-cell carcinoma, and squamous-cell carcinoma. Importantly, **epidemiological evidence has clearly established that sunbed use increases skin cancer risk** and radiation from tanning devices is classified as carcinogenic to humans within the IARC Monographs on the identification of carcinogenic risks to humans⁸¹. Skin cancer incidence has been increasing steeply over recent decades, particularly affecting fair-skinned populations. According to estimates for 2018, about 103 000 new cases of cutaneous melanoma and about 17 000 deaths from it occurred in Europe⁸²; in total, UV radiation is thought to account for around 3-4% of the European cancer burden^{83,84}.

The main mechanisms by which UV radiation causes cancer are well understood. Exposure during childhood appears to be particularly harmful⁸⁵.

ii. Ionising radiation and cancer causation

Ionising radiation is defined as high-energy, very short-wavelength electromagnetic waves, capable of transferring sufficient energy to remove otherwise tightly bound electrons from atoms, thereby ionising molecules. Such radiation can be in the form of electromagnetic rays, such as X-rays or γ-rays,

⁷⁶ Brown K.F., Rumgay H., Dunlop C. et al., The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. *Br J Cancer*. 2018 Apr; 118(8): pp. 1130-1141.

⁷⁷ IARC (2018). Les cancers attribuables au mode de vie et à l'environnement en France métropolitaine. Lyon: International Agency for Research on Cancer. Available from: http://gco.iarc.fr/resources/paf-france_fr.php (accessed May 2020).

⁷⁸ Wild C.P., Weiderpass E., Stewart B.W., editors (2020). *World Cancer Report: Cancer Research for Cancer Prevention*. Lyon, France: International Agency for Research on Cancer.

⁷⁹ Villain P., Gonzalez P., Almonte M. et al., European Code against Cancer 4th Edition: Infections and Cancer. *Cancer Epidemiol*. 2015 Dec; 39 Suppl 1: pp. 38-5120.

⁸⁰ Association of European Cancer Leagues (ECL)'s Vision paper about the European Beating Cancer Plan: European Code Against Cancer: https://www.iccp-portal.org/sites/default/files/resources/ECL-vision-EU-Beating-Cancer-Plan_final.pdf (accessed June 2020).

⁸¹ International Agency for Research on Cancer (IARC)'s Monographs on the identification of carcinogenic hazards to humans. List of classified agents, Volumes 1-125: <https://monographs.iarc.fr/agents-classified-by-the-iarc/> (accessed June 2020).

⁸² Data on skin melanoma incidence and mortality in 2018 in the EU extracted from the IARC Global Cancer Observatory: <https://gco.iarc.fr>

⁸³ Brown K.F., Rumgay H., Dunlop C. et al., The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. *Br J Cancer*. 2018 Apr; 118(8): pp. 1130-1141.

⁸⁴ IARC (2018). Les cancers attribuables au mode de vie et à l'environnement en France métropolitaine. Lyon: International Agency for Research on Cancer. Available from: http://gco.iarc.fr/resources/paf-france_fr.php (accessed May 2020).

⁸⁵ Greinert R., De Vries E., Erdmann F. et al., European Code against Cancer 4th Edition: Ultraviolet radiation and cancer. *Cancer Epidemiol*. 2015 Dec; 39 Suppl 1: pp. 83-575.

or in the form of subatomic or related particles, such as protons or neutrons, as well as α -particles and β -particles⁸⁶.

When interacting with cells, the ionising power of this radiation can lead to chemical changes, including DNA damage and mutations. According to latest estimates, **around 2% of the European cancer burden can be attributed to ionising radiation**^{87,88}. Key evidence for the carcinogenicity of ionising radiation comes from: follow-up studies of the survivors of the atomic bombings in Japan, other epidemiological studies of groups that have been exposed to radiation from medical, occupational or environmental sources; experimental animal studies; and studies of cellular responses to radiation.

Exposure to ionising radiation can occur in a wide range of circumstances. In the occupational context, it typically affects **specific categories of workers, such as airline crew and nuclear plant workers**; furthermore, **several common medical procedures, including radiology, radiation therapy and nuclear medicine**⁸⁹, also involve the use of ionising radiation. These procedures can provide major health benefits, including in the context of cancer treatment; however, prudent practices need to be in place, with procedures and techniques providing the needed diagnostic information or therapeutic gain with the lowest possible radiation exposure^{90,91,92}.

Considering exposure to environmental ionising radiation, inhalation of naturally occurring radon is the major source of radiation in the population - in doses orders of magnitude higher than those from nuclear power production or nuclear fallout. **Indoor exposure to radon and its decay products is the second leading cause of lung cancer**, which may be approximately responsible for **one in ten lung cancers in Europe**⁹³.

iii. Other environmental and occupational cancer risk factors

People are exposed throughout life to a wide range of environmental and occupational pollutants from different sources at home, in the workplace or in the general environment - **exposures that normally cannot be directly controlled by the individual**. According to latest estimates, around **4-5% of the European cancer burden can be attributed to these exposures**, including 3.5-4% attributable to occupational cancer risk factors and 0.5-1% attributable to environmental risk factors, such as air pollution^{94,95}.

⁸⁶ World Cancer Report 2014. Geneva, Switzerland: World Health Organisation, International Agency for Research on Cancer, WHO Press, 2015.

⁸⁷ Brown K.F., Rumgay H., Dunlop C. et al., The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. *Br J Cancer*. 2018 Apr; 118(8): pp. 1130-1141.

⁸⁸ IARC (2018). Les cancers attribuables au mode de vie et à l'environnement en France métropolitaine. Lyon: International Agency for Research on Cancer. Available from: http://gco.iarc.fr/resources/paf-france_fr.php (accessed May 2020).

⁸⁹ See section 3.1.2. section for a definition of nuclear medicine.

⁹⁰ Friis S., Kesminiene A., Espina C. et al., European Code against Cancer 4th Edition: Medical exposures, including hormone therapy, and cancer. *Cancer Epidemiol*. 2015 Dec; 39 Suppl 1: pp. 19-S107.

⁹¹ Council Directive 2013/59/Euratom of 5 December 2013 laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation.

⁹² Vano E., Frijia G., Stiller W. et al., Harmonisation of Imaging Dosimetry in Clinical Practice: Practical Approaches and Guidance From the ESR EuroSafe Imaging Initiative. *Insights Imaging*. 2020 Mar 30;11(1):54.

⁹³ McColl N., Auvinen A., Kesminiene A. et al., European Code against Cancer 4th Edition: Ionising and non-ionising radiation and cancer. *Cancer Epidemiol*. 2015 Dec; 39 Suppl 1: pp. 100-593.

⁹⁴ Brown K.F., Rumgay H., Dunlop C. et al., The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. *Br J Cancer*. 2018 Apr; 118(8): pp. 1130-1141.

⁹⁵ IARC (2018). Les cancers attribuables au mode de vie et à l'environnement en France métropolitaine. Lyon: International Agency for Research on Cancer. Available from: http://gco.iarc.fr/resources/paf-france_fr.php (accessed May 2020).

Occupational cancer risk factors

Multiple **chemicals, metals, dusts, fibres, and occupations** have been established to be causally associated with an **increased risk of specific cancers**⁹⁶. Within this list, **asbestos** is the carcinogen to which the most important cancer burden has been attributed. This fibre, used for many years as a building material, is associated with an increased incidence of lung, laryngeal and ovarian cancers in exposed individuals; furthermore, it is also considered to be responsible for nearly all cases of mesothelioma. Other prominent confirmed occupational carcinogens include **silica dust**, used in construction and mining, and associated with an increased risk of lung cancer, and **benzene**, used in the chemical industry and associated with a higher risk of leukaemia. **Painters** constitute the largest occupational group with a known increased risk of (bladder and lung) cancer, but for which the agent(s) responsible for this risk have not been identified.

Importantly, the higher risk of cancer associated with these occupational agents and exposure circumstances may not be limited to those exposed to them in the workplace; affected individuals can also include relatives of exposed workers, neighbours of carcinogen-using industries. Furthermore, most of the confirmed occupational carcinogens are not exclusively found in the workplace and can also occur in the general environment, as well as, in some cases (such as asbestos), in the residential setting⁹⁷.

Environmental cancer risk factors: food, air and water pollution

More generally, environmental exposure caused by pollution, that is by chemical contamination of the air breathed, the water and food consumed, and the soil, sediments, surface waters and groundwater surrounding living space, also results in an increased risk of cancer. Many carcinogens can indeed be found in the environment and all people carry traces of these pollutants in their body⁹⁸.

Air pollution

Significant amounts of air pollutants - mainly from road transport and industry - continue to be emitted in the EU. **Outdoor air pollution, particulate matter in outdoor air pollution**, resulting from combustion of fossil fuels and biomass for power generation, cooking, and transportation, **and diesel engine emissions** are suspected to harbour a mutagenic activity to humans and associated with a higher risk of several cancers, including lung cancer and bladder cancer⁹⁹, in exposed individuals. As a result, these three agents **have been recognised as confirmed carcinogens** by the IARC Monographs on the identification of carcinogenic hazards to humans¹⁰⁰. Furthermore, an increased occurrence of lung cancer has been attributed to air pollution even in areas below the EU limits for daily air pollution.

Of note, air pollution by chlorofluorocarbons is believed to be indirectly responsible for increases in skin cancer rates around the globe in past decades. These chemicals, emitted from home air conditioners, foam cushions and many other products, are carried by winds into the stratosphere, where the action of strong solar radiation drives them to cause the elimination of ozone molecules. This depletion of the ozone layer is believed to be responsible for global increases in ultraviolet B (UVB)

⁹⁶ Espina C., Straif K., Friis S. et al., European Code against Cancer 4th Edition: Environment, occupation and cancer. *Cancer Epidemiol.* 2015 Dec; 39 Suppl 1: pp. 92-584.

⁹⁷ World Cancer Report 2014. Geneva, Switzerland: World Health Organisation, International Agency for Research on Cancer, WHO Press, 2015.

⁹⁸ World Cancer Report 2014. Geneva, Switzerland: World Health Organisation, International Agency for Research on Cancer, WHO Press, 2015.

⁹⁹ Loomis D., Grosse Y., Lauby-Secretan B. et al., The carcinogenicity of outdoor air pollution. *Lancet Oncol.* 2013 Dec;14(13):1262-3.

¹⁰⁰ International Agency for Research on Cancer (IARC)'s Monographs on the identification of carcinogenic hazards to humans. List of classified agents, Volumes 1-125: <https://monographs.iarc.fr/agents-classified-by-the-iarc/> (accessed June 2020).

radiation, themselves associated with a higher risk of developing skin cancer in exposed individuals¹⁰¹. Furthermore, although of lesser relevance in Europe as compared to developing countries, indoor air pollution, resulting from indoor burning of solid fuels (either coal or biomass) is also a confirmed carcinogen, associated with a higher risk of lung cancer¹⁰².

Food and water pollution

Additionally, a wide range of **pesticides as well as industrial and household chemicals** may lead to widespread human exposure, mainly through food and water¹⁰³.

Arsenic is the most prominent water pollutant being confirmed as a carcinogen and is associated with higher risks of lung, skin and bladder cancers; however, high-exposure to arsenic from drinking-water mainly occurs in developing countries, rather than in Europe.

Exposure to pesticides in the occupational or the environmental setting, mainly through water and food pollution, is a matter of particular concern in Europe, as many of these chemicals, used to increase agricultural production, are suspected to be carcinogenic to humans. Although some pesticides, such as inorganic arsenic compounds, are recognised as confirmed carcinogens by the IARC, conclusive scientific evidence is still missing in the case of most of these agents to their carcinogenic character in humans to be fully confirmed, so that **many pesticides are currently rather classified as only "probable" or "possible" carcinogens by the IARC**¹⁰⁴. This is for instance the case of the herbicide glyphosate, which, in the last evaluation conducted by the IARC in 2015, was identified as "probably carcinogenic to humans"¹⁰⁵.

d. Medical or reproductive cancer risk factors

Current evidence shows that hormone replacement therapy (HRT), generally prescribed as menopausal hormone therapy, is associated with an increased risk of cancers of the breast, endometrium, and ovary, with the risk pattern depending on factors such as the type of therapy (oestrogen-only or combined oestrogen-progestogen), duration of treatment, and initiation according to the time of menopause.

Carcinogenicity has also been established for anti-neoplastic agents used in cancer therapy, immunosuppressants, oestrogen-progestogen contraceptives, and tamoxifen. For pharmaceutical drugs and medical radiation exposure with convincing evidence on their carcinogenicity, health benefits have to be balanced against the risks. Potential increases in long-term cancer risk should be considered in the context of the often substantial and immediate health benefits from diagnosis and/or treatment¹⁰⁶.

A slight increase in the risk of breast cancer has been established in women taking oral contraceptives. This is also true for cervical cancer, only for women using the combined pill for more than 5 years. However, this risk falls back down again in those who stopped taking it for more than 10 years.

¹⁰¹ IARC (2012). Radiation. IARC Monogr Eval Carcinog Risks Hum, 100D:1–437.

¹⁰² World Cancer Report 2014. Geneva, Switzerland: World Health Organisation, International Agency for Research on Cancer, WHO Press, 2015.

¹⁰³ Espina C, Straif K, Friis S, et al. European Code against Cancer 4th Edition: Environment, occupation and cancer. Cancer Epidemiol. 2015 Dec; 39 Suppl 1: pp. 92-584.

¹⁰⁴ International Agency for Research on Cancer (IARC)'s Monographs on the identification of carcinogenic hazards to humans. List of classified agents, Volumes 1-125: <https://monographs.iarc.fr/agents-classified-by-the-iarc/> (accessed June 2020).

¹⁰⁵ IARC's factsheet "IARC Monographs volume 112: evaluation of five organophosphate insecticides and herbicides": <https://www.iarc.fr/wp-content/uploads/2018/07/MonographVolume112-1.pdf> (accessed June 2020).

¹⁰⁶ Friis S., Kesminiene A., Espina C. et al., European Code against Cancer 4th Edition: Medical exposures, including hormone therapy, and cancer. Cancer Epidemiol. 2015 Dec; 39 Suppl 1: pp. 19-5107.

Furthermore, the combined pill has also been described to protect against the development of ovarian and womb cancers, even decades after the pill has stopped being used.

Therefore, even if oral contraceptives are sometimes shown as a category of cancer risk factors, to which a certain share of the cancer burden can be attributed, latest evidence suggest that their protective effects outweigh the risks associated with their uptake¹⁰⁷.

Breast cancer is the most frequent cancer in women, and incidence rates have been rising in EU countries over recent decades. Some of this increase has been attributed to a decline in breastfeeding practices. Evidence for a **protective association between breastfeeding and the risk of breast cancer at all ages** is convincing, and modest protective relationships between breastfeeding and the risk of endometrial and ovarian cancers have been suggested. The reduction in breast cancer risk is estimated at 2% for an increase of 5 months of lifetime breastfeeding. **The longer women breastfeed, the more they are protected against breast cancer.** In addition, breastfeeding is associated with several health benefits for both the mother and the breastfed child¹⁰⁸.

1.1.3. Cancer risk prediction and development of risk-adapted strategies in cancer

a. Rationale and potential of cancer risk prediction

As elaborated in the sections below, knowledge of cancer causative factors can inform interventions aiming at preventing the onset of the disease, notably through mitigation of the exposure of the general population to identified modifiable risk factors¹⁰⁹. However, this knowledge also carries potential for the conduct **individualised cancer risk prediction, that is assessing each individual for his/her risk of developing cancer**, according to his/her personal situation toward known cancer causative factors, including exposure to modifiable cancer risk factors and genetic cancer predisposition. Such predictions open the way to **risk stratification in cancer management**, i.e. to classify individuals into "risk groups" according to their evaluated level of cancer risk and to **develop distinct, risk-adapted strategies** for these different groups, including specific strategies for individuals with an identified higher risk of cancer. **Such strategies can notably aim at:**

- **Better preventing the onset of cancer**, through personalised primary prevention measures for high-risk individuals.

This can include behaviour change programmes for individuals with an identified high-risk behaviour (e.g. smoking cessation programmes for heavy smokers)¹¹⁰ and risk-reducing strategies advising individuals with an identified genetic susceptibility for a certain type of cancer to give strengthened attention to the mitigation of their exposure to modifiable risk factors known to be associated with this type of cancer¹¹¹ (e.g. limiting sun exposure in individuals affected by a genetic susceptibility to skin cancer¹¹²).

¹⁰⁷ Cancer research UK's factsheet "Does the contraceptive pill increase cancer risk?": <https://www.cancerresearchuk.org/about-cancer/causes-of-cancer/hormones-and-cancer/does-the-contraceptive-pill-increase-cancer-risk> (accessed June 2020).

¹⁰⁸ Scoccianti C., Key T.J., Anderson A.S. et al, European Code against Cancer 4th Edition: Breastfeeding and cancer. *Cancer Epidemiol.* 2015 Dec; 39 Suppl 1: pp. 6-S101.

¹⁰⁹ See section 1.2. about primary prevention of cancer.

¹¹⁰ See section 1.2.1.a.ii. about individualised approaches for health promotion in cancer primary prevention.

¹¹¹ See section 1.2.2. about primary prevention of cancer targeting genetic susceptibility to cancer.

¹¹² US National Cancer Institute's factsheet about the genetics of skin cancer: <https://www.cancer.gov/types/skin/hp/skin-genetics-pdq> (accessed May 2020).

- **Facilitating the earlier detection of cancer**, through personalised secondary prevention strategies for high-risk individuals.

This can include risk-adapted cancer screening, i.e. selection of individuals for cancer screening not only on their basis of their age, but also of their assessed cancer risk¹¹³ and active surveillance programmes for earlier diagnosis of cancer¹¹⁴.

This concept of risk stratification has received increasing attention in recent years in the management of non-communicable diseases, including cancer, and is seen as a promising prospect to both reduce the burden of these diseases and improve the cost-effectiveness of their management.

b. Approaches and requirements to cancer risk prediction

A primary approach to cancer risk prediction relies on the **identification of individuals affected by single factors known to be associated with a high risk of cancer.**

i. Cancer risk prediction on the basis of modifiable cancer risk factors

Regarding modifiable cancer risk factors, this mainly involves approaches that ensure awareness of cancer risk factors among healthcare professionals, including those working outside the oncology field, notably primary healthcare providers. **Optimal coordination and flow of information between all professionals** taking care of the same patient is also crucial in this context, all the more since many cancer risk factors are also associated with a higher risk of developing a wide range of other medical conditions, such as cardio-vascular, pulmonary or digestive diseases.

ii. Cancer risk prediction on the basis of genetic cancer risk factors: genetic germline testing

In respect to genetic cancer risk factors, a positive cancer family history, the belonging to a population affected by known cancer-associated founder mutations, an early age of diagnosis for that cancer type or the occurrence of multiple primary tumours can all be used as indicators of genetic predisposition to cancer¹¹⁵. However, **accurate cancer risk prediction requires the conduct of genetic germline testing**, i.e. testing of individuals for germline mutations they are suspected to harbour.

In the presence of positive indicators, **genetic germline testing can therefore be offered to either cancer-free individuals** (when using positive cancer family history or the belonging to a population affected by known cancer-associated founder mutations as eligibility criteria), **or cancer patients** (when using early age at diagnosis for that cancer type or the occurrence of multiple primary tumours as eligibility criteria), in order to confirm a suspected hereditary cancer predisposition. Importantly, the latter approach, where testing is primarily started in cancer patients whose tumour has features suggesting a genetic germline causation, is considered as the most sensitive to detect cancer-associated germline mutations and is therefore viewed as the golden standard in genetic germline testing. By contrast, although such an approach has been proved beneficial in some settings¹¹⁶, the primary offer of genetic germline testing to healthy individuals from a population with an increased incidence of hereditary cancer predisposition (owing to either a positive cancer family history or to known cancer-associated founder mutations) is currently not performed as a routine procedure.

¹¹³ See section 2.1.3.c. about adaptation of cancer screening programmes to scientific and technological developments.

¹¹⁴ See section 2.2.1. about education of healthcare providers and of the general public to cancer warning signs.

¹¹⁵ See section 1.1.1.b.ii. about germline mutations and genetic susceptibility to cancer.

¹¹⁶ Hadar T., Mor P., Amit G. et al., Impact of germline BRCA identification on subsequent breast cancer stage and therapy: Implications for routine screening. J Clin Oncol. 2018 May 20;36(15 suppl): p.1584.

Once a germline mutation has been identified, the affected individual's healthy relatives will be offered testing. Thousands of cancer patients with hereditary cancer predisposition are diagnosed in Europe annually, with many more relatives at high genetic risk. Subsequent risk prediction and risk-adapted strategies translate into significant benefits, including earlier diagnosis and less extensive treatment in those eventually developing cancer after a positive genetic testing result.

Although above mentioned indicators for hereditary cancer predisposition are commonly used as eligibility criteria for genetic germline testing, recent studies show that **this approach may be too restrictive** to capture all individuals and families at risk. **For some tumour types, such as ovarian cancer, genetic testing has already been offered to all affected patients**, regardless of age at diagnosis and family history, and has demonstrated capacity to capture significant proportions of individuals harbouring cancer-associated germline mutations which would have been missed using the more restrictive criterions¹¹⁷, thereby opening the way for healthy relatives of these patients to benefit from testing for the same germline mutations. This approach has also been suggested for breast cancer¹¹⁸ and experts recommend that it is expanded where appropriate for other tumour types.

Furthermore, general healthy population genetic testing, such as new-born genetic testing programmes, also have the theoretical potential of early identification of potentially all individuals with genetic cancer predisposition. More research, however, is needed before prediction of risk in healthy individuals in the absence of positive family histories for the associated cancer types can reliably be performed¹¹⁹.

Genetic testing for cancer-associated germline mutations is also of increasing relevance beyond the field of risk prediction, as such mutations also constitute predictive biomarkers of potential benefit from targeted cancer treatments¹²⁰.

Nevertheless, in spite of the benefits that can be realisable for the individual's health, allied to the dropping costs of genetic testing, with accumulating demonstrating its cost-effectiveness, access to genetic testing for germline cancer-associated mutations is not yet routine across Europe. Furthermore, significant inequalities subsist across Europe in respect to the provision of adapted prevention interventions to healthy individuals tested positively for cancer-associated germline mutations^{121,122,123}.

Importantly, such genetic germline testing must **always be accompanied by access to genetic counselling**. This corresponds to an intervention provided by a trained health professional, aimed at supporting individuals before and after the genetic test, providing them with information about their cancer risk, advice on whether or not having a genetic germline test and how to minimise their cancer risk through risk-reducing strategies, as well as support to manage the many psycho-social impacts that a higher risk to develop cancer confer¹²⁴. **Ethical issues should also be closely considered** when

¹¹⁷ George A., Kaye S., Banerjee S., Delivering widespread BRCA testing and PARP inhibition to patients with ovarian cancer. *Nat Rev Clin Oncol.* 2017 May; 14(5): pp. 284-296.

¹¹⁸ Sun L., Brentnall A., Patel S. et al., A Cost-effectiveness Analysis of Multigene Testing for All Patients with Breast Cancer. *JAMA Oncol.* 2019 Oct 3; 5(12): pp. 1718-1730.

¹¹⁹ Turner H., Jackson L., Evidence for penetrance in patients without a family history of disease: a systematic review. *Eur J Hum Genet.* 2020 May; 28(5): pp. 539-550.

¹²⁰ See sub-chapter 3.1.'s section about precision oncology and companion diagnostics.

¹²¹ See section 1.2.2. about primary prevention of cancer targeting genetic susceptibility to cancer.

¹²² See section 2.1.3.c. about adaptation of cancer screening programmes to scientific and technological developments.

¹²³ See section 2.2.1. about education of healthcare providers and of the general public to cancer warning signs.

¹²⁴ US National Human Genome Research Institute's factsheet about genetic counselling: <https://www.genome.gov/genetics-glossary/Genetic-Counseling> (accessed May 2020).

recommending genetic germline testing to healthy individuals, especially in the paediatric population¹²⁵, as well as when managing cases of conflicting interests of patients and their relatives regarding the conduct of genetic germline testing or the disclosure of results¹²⁶.

Recommendation: Developing cancer risk prediction and risk stratification

As part of efforts aiming at the reduction of cancer burden, the EU should support the development of cancer risk prediction and the integration of risk stratification as a stronger component of primary and secondary cancer prevention strategies.

An EU Cancer Dashboard monitoring patient access to quality cancer care across Europe should include in its parameters access to genetic germline testing and to associated genetic counselling.

The establishment and/or endorsement of clear guidelines at the European level may also prove instrumental in guiding this development at the national level and in ensuring that healthy individuals and cancer patients benefit from the best clinical and ethical standards in respect to genetic testing.

A secondary approach to cancer risk prediction is the use of integrative cancer prediction models, tapping the potential of both translational genomics and digital tools. Such models differ by integrating genomic profiling tests, that is information not only on a few specific genes or mutations, but on the entire genome of the individual, with non-genetic factors, such as lifestyle risk factors, personal medical history or imaging results from the organ of interest, into a single comprehensive risk prediction digital tool that automatically stratifies individuals into risk levels. Such models are currently being developed or already used in the context of several prominent cancer types, such as breast cancer¹²⁷ and prostate cancer¹²⁸, and may represent a promising prospect in respect to cancer risk prediction and stratification.

Finally, the concepts of risk prediction and risk stratification are also used in the context of cancer follow-up care, in order to allow for optimal management of long-term side-effects of cancer and of cancer treatments^{129,130}.

¹²⁵ Kesserwan C., Friedman Ross L., Bradbury A.R. et al., The Advantages and Challenges of Testing Children for Heritable Predisposition to Cancer. *Am Soc Clin Oncol Educ Book*. 2016; 35: pp. 69-251.

¹²⁶ Kenny J., Burcher S., Kohut K. et al., Ethical Issues in Genetic Testing for Inherited Cancer Predisposition Syndromes: The Potentially Conflicting Interests of Patients and Their Relatives. *Curr Genet Med Rep*. 2020; 8: pp. 72-77.

¹²⁷ Gagnon J., Lévesque E., Clinical Advisory Committee on Breast Cancer Screening and Prevention, et al. Recommendations on breast cancer screening and prevention in the context of implementing risk stratification: impending changes to current policies. *Curr Oncol*. 2016 Dec; 23(6): e615-e625.

¹²⁸ Palsdottir T., Nordström T., Aly M. et al., A Unified Prostate Cancer Risk Prediction Model Combining the Stockholm3 Test and Magnetic Resonance Imaging. *Eur Urol Oncol*. 2019 Sep; 2(5): pp. 490-496.

¹²⁹ See section 3.2.2. about cancer survivorship needs and follow-up care.

¹³⁰ UK National Health Service's guide to implementation of stratified pathways of care for people living with and beyond cancer: <https://www.england.nhs.uk/wp-content/uploads/2016/04/stratified-pathways-update.pdf> (accessed May 2020).

1.2. Primary prevention of cancer

KEY FINDINGS & RECOMMENDATIONS: PRIMARY PREVENTION OF CANCER

Primary prevention interventions, aiming at minimising the incidence of the disease, i.e. at preventing its onset through action on cancer causative factors, are the most cost-effective strategy in cancer control. These interventions notably include: health promotion through population-wide campaigns, such as the European Code Against Cancer; legislative and regulatory initiatives addressing both behavioural or involuntary exposures to cancer risk factors; and fighting carcinogenic infectious agents through vaccination.

In spite of its potential, primary cancer prevention remains under-developed and under-resourced. **Common efforts by EU Member States to prevent cancer should be significantly enhanced**, including but not limited to: tobacco control measures, regulation of artificial tanning devices; and common initiatives to improve diet and healthier living, such as in respect to food labelling and regulating promotion of alcohol.

A continued long-term commitment should be made by the EU to support the promotion of the European Code Against Cancer to the general public in all countries.

Options in respect to **further tobacco control measures** include raising minimum excise duties for all tobacco products and enforcing mandatory plain/standardised packaging for all tobacco products and/or electronic cigarettes.

In respect to promoting healthier diets, potential EU policy responses include helping consumers to make informed choices about food products by **implementing "best in class" food labelling standards** and supporting Member States in **restricting the advertising of ultra-processed food products and sugary/sweetened beverages**, including on social media.

Options in respect to encouraging more responsible consumption of alcohol include **improving the labelling of alcohol beverages** to include prominent warning labels and nutritional information and **prohibition of alcohol sponsorship of sport**.

Options in respect to protecting citizens from harmful occupational and environmental exposure to carcinogens include: **ensuring that employers recognise occupational carcinogens** and comply with the established exposure limit values; **implementing an EU-level asbestos plan**, requiring EU Member States to support safe cleaning and removal of asbestos; and taking **appropriate measures to improve air quality in European urban spaces**.

Vaccination advances make it possible to envisage the elimination of some cancers caused by infectious agents, including HPV-caused cancers. In the context of the WHO Strategy for elimination of cervical cancers, the EU should become a global leader in these efforts, alongside actions on screening and treatment. This can be achieved with the **implementation of gender-neutral HPV vaccination** for boys and girls in EU Member States to bring about effective elimination of all HPV-caused cancers as a public health problem. Collaborations with EU Member States and international stakeholders should also be set up to **combat the impact of fake news on vaccination** and address vaccine hesitancy.

A strong element of the EU Cancer Mission should be devoted to prevention, including aetiological research on cancer causative factors and cancer-related inequalities, epidemiological research on the cancer burden associated with cancer risk factors and implementation research to identify and improve the implementation of successful primary prevention interventions.

Defining the three levels of disease prevention

According to the WHO, disease prevention can be defined as the set of measures aiming at minimising the burden of the disease, by limiting both the number of cases and their seriousness. **Disease prevention activities are usually categorised into three levels**^{131, 132}:

- **primary prevention**, aiming at minimising the incidence of the disease, i.e. at preventing its onset through action on cancer causative factors;
- **secondary prevention**, aiming at promptly detecting and intervening on the disease once it has occurred, in order to reduce its impact on the patient and to improve the chances of positive outcomes, thus minimising the prevalence of the disease and its mortality; and
- **tertiary prevention**, aiming at reducing and managing the long-term impacts of the disease, including morbidity (due to the disease in itself or to the treatment), disability, risk of disease recurrence and psycho-social effects, in order to restore function and to improve the quality of life of patients and survivors, as well as their participation to society¹³³.

Below sections are focused on primary prevention of cancer; secondary and tertiary prevention are addressed in subsequent chapters^{134, 135}.

Primary prevention of cancer: key components and rationale

Primary prevention measures typically aim at reducing the exposure of the population to identified or suspected modifiable risk factors. Thus, cancers associated with such risk factors are considered as preventable; according to latest studies, they represent an estimated 40% of cancer cases newly diagnosed each year in the EU^{136, 137, 138, 139}. Primary prevention measures include:

- **health promotion through population-wide campaigns, such as the European Code Against Cancer**¹⁴⁰, or **individualised approaches**, aimed at changing individual behaviours toward the adoption of healthy lifestyles;
- **legislative and regulatory initiatives** limiting exposure to cancer risk factors, including in respect to the **tobacco control** legislative framework, **food and alcohol labelling**, regulation of artificial tanning devices ("**sunbeds**") and management of occupational exposure to carcinogens, including hazardous drugs in healthcare environments; and
- **vaccination programmes** against carcinogenic infectious agents, such as **HPV** and **HBV**¹⁴¹.

¹³¹ Canadian Institute for Work and Health's factsheet about the three levels of disease prevention: <https://www.iwh.on.ca/what-researchers-mean-by/primary-secondary-and-tertiary-prevention> (accessed May 2020).

¹³² US Centers for Disease Control and prevention (CDC)'s report about disease prevention: https://www.cdc.gov/pictureofamerica/pdfs/picture_of_america_prevention.pdf (accessed May 2020).

¹³³ Philip T., Karjalainen S., De Lorenzo F. et al., What could be a cancer mission objective if we join our forces in the fight against cancer? *Tumori*. 2019 Dec; 105(6): pp. 447-455.

¹³⁴ See Chapter 2 about secondary prevention of cancer through early detection.

¹³⁵ See Chapter 3 about tertiary prevention of cancer through cancer survivors' care.

¹³⁶ See section 1.1.2. about modifiable cancer risk factors.

¹³⁷ Brown K.F., Rungay H., Dunlop C. et al., The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. *Br J Cancer*. 2018 Apr; 118(8): pp. 1130-1141.

¹³⁸ IARC (2018). Les cancers attribuables au mode de vie et à l'environnement en France métropolitaine. Lyon: International Agency for Research on Cancer. Available from: http://qco.iarc.fr/resources/paf-france_fr.php (accessed May 2020).

¹³⁹ Islami F., Goding Sauer A., Miller K.D. et al., Proportions and numbers of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. *CA Cancer J Clin*. 2018 Jan; 68(1): pp. 31-54.

¹⁴⁰ See <https://cancer-code-europe.iarc.fr/index.php/en/> (accessed May 2020).

¹⁴¹ World Cancer Report 2014. Geneva, Switzerland: World Health Organisation, International Agency for Research on Cancer, WHO Press, 2015.

Furthermore, although cancers associated with unchangeable, inherited genetic mutations are classically considered as non-preventable, **there exists ways to effectively delay or prevent their onset**. These interventions can therefore be considered as primary prevention measures; they notably include prophylactic (or risk-reducing) surgery¹⁴² and chemoprevention¹⁴³.

Owing to this important potential and to the increasing costs associated with cancer treatment and care, **primary prevention is recognised as the most cost-effective strategy in the control of cancer, and generally of non-communicable diseases**^{144,145}. Demographic changes leading to an older population in the EU and growing pressures on healthcare budgets therefore strengthen the **need for optimal primary cancer prevention strategies, which represent a crucial component of any strategy to limit increases in cancer incidence and mortality in the coming decades**¹⁴⁶.

Furthermore, it should be kept in mind that, owing to the long latency between exposure of individuals to certain cancer risk factors and subsequent cancer development, a long time period elapses between implementation of most primary prevention measures and the observation of significant effects on cancer rates¹⁴⁷; thus, **long-term primary cancer prevention policies are of particular relevance**.

Primary prevention of cancer: key cross-cutting challenges

In spite of its above explained potential and rationale, primary cancer prevention remains under-developed and under-resourced¹⁴⁸. The infrastructure for primary cancer prevention tends to be fragmented between and within different countries in the EU¹⁴⁹; this **lack of coordination** hampers the impact of primary prevention on cancer incidence in the EU and frameworks supporting the broad **implementation of key measures of proven efficacy across EU Member States need strengthening**. Stakeholders and experts in the field therefore highlight the **need for concerted action in primary prevention, through a holistic approach**. It is indeed important to acknowledge that primary prevention is not just changing individual behaviours in isolation, but requires broader changes in social, economic, political, environmental and cultural contexts. It therefore needs capacity and resources, and public adoption of the measures, as well as multi-sectoral action addressing the underlying, overlapping and interacting social determinants of non-communicable diseases^{150,151}.

Research is also crucial to further delivering better primary cancer prevention. Aetiological research is indeed required to decipher the still large "known unknowns" regarding cancer causation and gain better understanding of the observed socioeconomic differences in cancer incidence and

¹⁴² See section 1.2.2.b. about primary prevention targeting genetic susceptibility to cancer through prophylactic surgery.

¹⁴³ Chemoprevention: The use of drugs, vitamins, or other agents to try to reduce the risk of, or delay the development or recurrence of, cancer. See US National Cancer Institute's definition of chemoprevention: <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/chemoprevention> (accessed May 2020).

¹⁴⁴ Cancer control: prevention. WHO Guide for effective programmes. Geneva: World Health Organisation; 2007.

¹⁴⁵ WHO's factsheet about cancer prevention: <https://www.who.int/cancer/prevention/en/> (accessed May 2020).

¹⁴⁶ Philip T., Karjalainen S., De Lorenzo F. et al., What could be a cancer mission objective if we join our forces in the fight against cancer? *Tumori*. 2019 Dec; 105(6): pp. 447-455.

¹⁴⁷ Schüz J., Espina C., Wild C.P., Primary prevention: a need for concerted action. *Mol Oncol*. 2019 Mar; 13(3): pp. 567-578.

¹⁴⁸ Schüz J., Espina C., Wild C.P., Primary prevention: a need for concerted action. *Mol Oncol*. 2019 Mar; 13(3): pp. 567-578.

¹⁴⁹ Wild C.P., Espina C., Bauld L. et al., Cancer Prevention Europe. *Mol Oncol*. 2019 Mar; 13(3): pp. 528-534.

¹⁵⁰ Schüz J., Espina C., Wild C.P., Primary prevention: a need for concerted action. *Mol Oncol*. 2019 Mar; 13(3): pp. 567-578.

¹⁵¹ World Health Organisation (WHO). Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013–2020 In Follow-up to the Political Declaration of the High-level Meeting of the General Assembly on the Prevention and Control of Non-communicable Diseases. Sixty-Sixth World Health Assembly, 2013.

mortality across Europe, and even within countries, that cannot be explained by behavioural risk factors alone^{152,153}. In association with aetiological research, **epidemiological research** is necessary to measure the burden of cancer and the fractions of it that can be attributed to cancer causative factors, thereby providing instrumental quantitative basis for adequate primary prevention policies. Finally, **implementation research** is needed to identify novel primary cancer prevention measures and decipher the factors that hamper their implementation within health care systems and in the community¹⁵⁴. In this respect, the international multidisciplinary consortium Cancer Prevention Europe was created in 2018 to develop world-class prevention research that can be translated into effective cancer prevention guidelines and policies at the national and international level¹⁵⁵.

Recommendation: Supporting European research into primary cancer prevention

Further to policies aiming at the implementation of primary cancer prevention interventions, a strong element of the upcoming EU Cancer Mission, incorporated within the next EU research and innovation framework programme Horizon Europe, should be devoted to prevention. Research on cancer prevention should be supported following a holistic approach, including aetiological research on cancer causative factors and cancer-related inequalities, epidemiological research on the cancer burden associated with cancer risk factors and implementation research to identify and improve the implementation of successful primary prevention interventions.

1.2.1. Primary prevention of cancer targeting cancer modifiable risk factors

a. Health promotion to change individual behaviours toward healthy lifestyles

Health promotion can be defined as all of elements enabling an individual to protect one's health and quality of life by addressing and preventing the root causes of ill health¹⁵⁶. Therefore, health promotion goes well beyond awareness-raising, since, rather than solely increasing knowledge of the disease, its causative factors and the ways to prevent its onset, it aims at modifying individual behaviours toward the adoption of healthy, protective lifestyles. Owing to the importance of lifestyle-related risk factors in cancer and to the existence of well identified, but not obligatory, cancer primary prevention interventions, health promotion is of critical relevance to reduce the cancer burden. It may primarily be conducted through two means: population-wide cancer prevention campaigns and individualised approaches.

i. Health promotion through population-wide cancer prevention campaigns

Rationale and features of population-wide cancer prevention campaigns

Population-wide prevention campaigns can be an effective and efficient way to modify cancer risk¹⁵⁷. In view of the abundance of often confusing, ambiguous, or apparently contradictory messages on disease prevention overwhelming the general population in today's multiple media streams, such

¹⁵² Philip T., Karjalainen S., De Lorenzo F. et al., What could be a cancer mission objective if we join our forces in the fight against cancer? *Tumori*. 2019 Dec; 105(6): pp. 447-455.

¹⁵³ Schüz J., Espina C., Wild C.P., Primary prevention: a need for concerted action. *Mol Oncol*. 2019 Mar; 13(3): pp. 567-578.

¹⁵⁴ Philip T., Karjalainen S., De Lorenzo F. et al., What could be a cancer mission objective if we join our forces in the fight against cancer? *Tumori*. 2019 Dec; 105(6): pp. 447-455.

¹⁵⁵ Philip T., Karjalainen S., De Lorenzo F. et al., What could be a cancer mission objective if we join our forces in the fight against cancer? *Tumori*. 2019 Dec; 105(6): pp. 447-455.

¹⁵⁶ WHO's factsheet about health promotion: <https://www.who.int/news-room/q-a-detail/what-is-health-promotion> (accessed June 2020).

¹⁵⁷ World Cancer Report 2014. Geneva, Switzerland: World Health Organisation, International Agency for Research on Cancer, WHO Press, 2015.

campaigns, carrying the authority and reliability of expert scientists, are crucial in providing authoritative, clear, and evidence-based instructions on how individuals can actively contribute to the reduction of their cancer risk¹⁵⁸.

Such campaigns make use of mass media, often through carefully planned paid advertising, as well as other simultaneous communication and policy interventions¹⁵⁹. Their aim is not only to raise awareness of the general population on cancers and their associated risk factors, which is, in some cases, of questionable public health value, and can lead to inadequate behaviours^{160,161}. They are rather **meant to drive changes in defined individual cancer-related behaviours or higher adherence of individuals to primary prevention interventions**.

Given that population-wide cancer prevention campaigns are designed to reach the general population, they are better adapted to convey messages addressing widely spread cancer risk factors, while prevention measures relating to rare cancers or specific subpopulations may rather be implemented through more targeted, personal approaches. Primary cancer prevention issues tackled by such campaigns therefore include common cancer-related behaviours, such as tobacco use, overnutrition, under-exercising and alcohol consumption, and widely implemented primary prevention interventions, such as participation to HPV or HBV vaccination programmes.

Importantly, **these campaigns have been shown to be effective in driving changes in such primary cancer prevention issues**. The extent of this impact is larger on the adherence to primary prevention interventions than on the modification of cancer-related behaviours, owing to the inherent resistance of lifelong individual habits to change (as well as to the addictive nature of some cancer risk factors), as compared to actions to be taken only once or twice, such as vaccination, which intake by individuals is usually easier to prompt. Nevertheless, it is noteworthy that even incremental changes in risk factor behaviours equate to large numbers of people when a risk factor is common among the general population, and that where relative risks associated to these factors are large, the potential for reducing early death associated to cancer is substantial; this is notably the case when considering tobacco use. These challenges in modifying individual behaviours through population-wide cancer prevention campaigns highlight the need to give close attention the psychological factors opposing or facilitating such individual changes when designing messages to be conveyed by such campaigns, as well as to systematically evaluate the results obtained through those campaigns¹⁶².

A European population-wide cancer prevention campaign: the European Code Against Cancer

At the European level, a prominent initiative in the field of population-wide cancer prevention campaigns is the European Code Against Cancer, initiated by the European Commission, developed by the International Agency for Research on Cancer and whose fourth edition was published in 2015. The Code is a preventive tool aimed to reduce the cancer burden by **informing people how to avoid or reduce carcinogenic exposures, adopt behaviours to reduce the cancer risk, or to participate in organised intervention programmes, through 12 key**

¹⁵⁸ Espina C., Herrero R., Sankaranarayanan R. et al., Toward the World Code Against Cancer. *J Glob Oncol.* 2018 Sep; 4: pp. 1-8.

¹⁵⁹ World Cancer Report 2014. Geneva, Switzerland: World Health Organisation, International Agency for Research on Cancer, WHO Press, 2015.

¹⁶⁰ Chapman S., Barratt A., Stockler M. (2010). *Let Sleeping Dogs Lie? What Men Should Know before Getting Tested for Prostate Cancer.* Sydney, Australia: Sydney University Press.

¹⁶¹ Schröder F.H., Hugosson J., Roobol M.J. et al., Screening and prostate-cancer mortality in a randomised European study. *N Engl J Med.* 2009 Mar 26; 360(13): pp. 8-1320.

¹⁶² World Cancer Report 2014. Geneva, Switzerland: World Health Organisation, International Agency for Research on Cancer, WHO Press, 2015.

recommendations that most people can follow without any special skills or advice^{163, 164} (see **Annex 3**¹⁶⁵). These recommendations are based on latest scientific evidence compiled by leading cancer scientists from across Europe, working under the coordination of the IARC. Over the years, the Code has been widely promoted across Europe, thus becoming a key element of the European strategy to prevent cancer¹⁶⁶. Nevertheless, national policies aiming at addressing each of the Code's 12 messages are still unequally implemented across EU Member States, as shown by monitoring tools developed by stakeholders of the European cancer community¹⁶⁷.

Recommendation: Providing long-term support to the European Code Against Cancer

Population-wide campaigns in cancer prevention are often conceived and funded by public health authorities as time-limited operations, whereas in reality their objectives can rarely be achieved or maintained without long-term investment of time, effort, and money. Experts consider that such campaigns are better thought of as a health service for which the need is continuous than as a "project" that has a defined end.

Therefore, cancer prevention in the EU would greatly benefit from a long-term commitment by the EU to support the promotion of the European Code Against Cancer to the general public in all countries, as well as its further updates, in order to factor in latest evidence regarding cancer risk factors and most effective primary prevention interventions allowing individuals to protect themselves from them.

Source: World Cancer Report 2014. Geneva, Switzerland: World Health Organisation, International Agency for Research on Cancer, WHO Press, 2015.

Of note, as in the case of the European Code Against Cancer¹⁶⁸, population-wide prevention campaigns can also convey messages relating to secondary prevention, such as participation to cancer screening programmes. However, they are not considered to represent a major element in this case. Contacting individuals directly with invitation letters may indeed be more effective than public advertising of an early detection service alone¹⁶⁹, which could in addition generate demand for services that could meet it, or even whose harms could eventually outweigh the benefits, such as in the case of controversial cancer screening programmes^{170, 171}.

Crucially, **population-wide cancer prevention campaigns should never be undertaken as a substitute for potentially effective public health policy and regulation on cancer prevention**. Rather, they should build on good policy and generate public acceptance of the need for measures

¹⁶³ See <https://cancer-code-europe.iarc.fr/index.php/en/> (accessed May 2020).

¹⁶⁴ Schuz J, Espina C, Villain P, et al. European Code Against Cancer 4th Edition: 12 Ways to Reduce Your Cancer Risk. *Cancer Epidemiol.* 2015 Dec; 39 Suppl 1: S1-10.

¹⁶⁵ The European Code Against Cancer (4th edition); adapted from <https://cancer-code-europe.iarc.fr/index.php/en/> (accessed May 2020).

¹⁶⁶ Association of European Cancer Leagues (ECL)'s factsheet about the European Code Against Cancer: <https://www.european-cancerleagues.org/cancer-prevention-the-european-code-against-cancer/> (accessed June 2020).

¹⁶⁷ Association of European Cancer Leagues (ECL)'s interactive maps of national efforts of EU Member States against each of the 12 messages from the European Code Against Cancer: <https://www.european-cancerleagues.org/cancer-prevention-ecac-map/> (accessed June 2020).

¹⁶⁸ Schuz J, Espina C, Villain P, et al., European Code Against Cancer 4th Edition: 12 Ways to Reduce Your Cancer Risk. *Cancer Epidemiol.* 2015 Dec; 39 Suppl 1: S1-10.

¹⁶⁹ Ferroni E., Camilloni L., Jimenez B. et al., Methods to Increase Participation Working Group (2012). How to increase uptake in oncologic screening: a systematic review of studies comparing population-based screening programmes and spontaneous access. *Prev Med.* 2012 Dec; 55(6): pp. 96-587.

¹⁷⁰ Chapman S., Barratt A., Stockler M. (2010). Let Sleeping Dogs Lie? What Men Should Know before Getting Tested for Prostate Cancer. Sydney, Australia: Sydney University Press.

¹⁷¹ Schröder F.H., Hugosson J., Roobol M.J. et al., Screening and prostate-cancer mortality in a randomised European study. *N Engl J Med.* 2009 Mar 26; 360(13): pp. 8-1320.

that facilitate change in behaviours known to increase cancer risk¹⁷², as elaborated in below sections.

ii. Health promotion through individualised approaches

Beyond population-wide campaigns, health promotion in primary cancer prevention can also make use of more individualised approaches. **A number of lifestyle elements associated with a high risk of cancer are indeed linked with complex biopsychosocial mechanisms**, involving not only addiction to a carcinogenic agent or behaviour, but also habits and social conventions, which may constitute significant barriers to overcome when aiming at the adoption of healthy behaviours^{173,174,175}. **Affected individuals therefore often require long-term personal follow-up, which justifies the need for individualised approaches in health promotion**; this is particularly true when addressing smoking cessation and body weight control¹⁷⁶.

Examples of such approaches include the **use of medication** (e.g. through nicotine replacement therapy for smoking cessation) and the setup of **advice-based programmes** (in the form of self-help resources, quit lines, face-to-face individual or group meetings with medical professionals, or other automatic personalised digital advice resources, such as dedicated smartphone applications)^{177,178}. Critically, the precise modalities of such programmes should adapt to cultural and local specificities, so that their impact on individual behaviours can be maximised.

Improving uptake of such assistance by individuals with high-risk behaviours requires it to be subsidised, reimbursed or provided for free by healthcare systems. Nevertheless, sole financial incentives may be often not be sufficient for such individuals to make the decision to enter an often long and difficult process of behavioural change. It is therefore critical that these individuals are motivated to do so by a favourable environment, including through **denormalisation of risky behaviours and elimination of social benefits from these behaviours**; this goal may be attained through a combination of population-wide cancer prevention campaigns and legislative or regulatory initiatives¹⁷⁹.

b. Legislative and regulatory initiatives to limit exposure to cancer risk factors

A range of legislative measures and corresponding regulations are directed at, or relevant to, cancer primary prevention, where they play a crucial role in limiting or preventing exposure to carcinogens. Such regulatory measures adopted under legislation to tackle the risk presented by exposure to carcinogens are almost invariably specific to particular classes of agents or circumstances of exposure; these controls address occupational, environmental, pesticide, pharmaceutical, and foodborne exposures. Among these regulations, a distinction can be made between those applied to behavioural exposure to carcinogens (primarily lifestyle-related cancer risk

¹⁷² World Cancer Report 2014. Geneva, Switzerland: World Health Organisation, International Agency for Research on Cancer, WHO Press, 2015.

¹⁷³ West R, Brown J. (2013). Theory of Addiction, 2nd ed. Oxford: Wiley.

¹⁷⁴ Henningfield J.E., Benowitz N.L. (2010). Pharmacology of tobacco addiction. In: Boyle P, Gray N, Henningfield J et al., eds. Tobacco: Science, Policy, and Public Health, 2nd ed. Oxford: Oxford University Press, pp. 155–170.

¹⁷⁵ DiFranza J.R., Savageau J.A., Fletcher K et al., Measuring the loss of autonomy over nicotine use in adolescents: the DANDY (Development and Assessment of Nicotine Dependence in Youths) study. Arch Pediatr Adolesc Med. 2002 Apr; 156(4): pp. 397-403.

¹⁷⁶ World Cancer Report 2014. Geneva, Switzerland: World Health Organisation, International Agency for Research on Cancer, WHO Press, 2015.

¹⁷⁷ Cahill K, Stevens S., Perera R., Lancaster T. (2013). Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev, 5: CD009329.

¹⁷⁸ Hartmann-Boyce J., Stead L.F., Cahill K, Lancaster T. (2013). Efficacy of interventions to combat tobacco addiction: Cochrane update of 2012 reviews. Addiction. 2013 Oct; 108(10): pp. 21-1711.

¹⁷⁹ World Cancer Report 2014. Geneva, Switzerland: World Health Organisation, International Agency for Research on Cancer, WHO Press, 2015.

factors¹⁸⁰) and those applied to unavoidable situations or involuntary circumstances associated with a high cancer risk (primarily environmental and occupational cancer risk factors¹⁸¹), which follow different approaches^{182, 183}.

i. Minimising behaviour-related exposure to cancer risk factors

When addressing behaviour-related exposure to cancer risk factors, legislative and regulatory initiatives apply to products or commercial services that are responsible for an increased risk of cancer among their consumers or users; they can follow a range of approaches, including:

- increasing taxes on carcinogenic products, in order to disincentivise their consumption, internalise the societal cost of their use in their actual price and help finance primary prevention policies;
- regulating or banning consumption of carcinogenic products in public spaces (especially in the case of tobacco, to protect non-smokers from second-hand smoke);
- regulating or banning advertising, promotion and sponsorship associated with carcinogenic products and commercial services associated with a high risk of cancer, especially when directed toward children or adolescents;
- regulating naming and labelling of carcinogenic products, so that consumers can make informed choices and benefit from health warnings; and
- regulating or banning the sale of carcinogenic products or the provision of commercial services associated with a risk of cancer¹⁸⁴.

Reducing the use of tobacco

Tobacco use, and in particular cigarette smoking, is the single largest preventable cause of cancer in the EU¹⁸⁵. Both the attributable risk of smoking for lung cancer and the relative risk are so large that the effect of particular measures to discourage smoking may be readily evident in terms of case numbers – a scenario that does not apply to many cancer prevention initiatives¹⁸⁶.

To address this situation, EU institutions and Member States' governments have taken various tobacco control measures, in the form of legislation, recommendations, and information campaigns. The **EU Tobacco Products Directive** (2014/40/EU) aimed at improving the functioning of the internal market for tobacco and related products, while ensuring a high level of health protection for European citizens. The Council Directive on the structure and rates of excise duty applied to manufactured tobacco (2011/64/EU; also known as the **EU Tobacco Products Tax Directive**) introduced high taxes on tobacco products, which are effective in reducing tobacco use, notably among young people¹⁸⁷.

¹⁸⁰ See section 1.1.2.a. about lifestyle-related cancer risk factors.

¹⁸¹ See section 1.1.2.c. about environmental and occupational cancer risk factors.

¹⁸² World Cancer Report 2014. Geneva, Switzerland: World Health Organisation, International Agency for Research on Cancer, WHO Press, 2015.

¹⁸³ Stewart BW. Priorities for cancer prevention: lifestyle choices versus unavoidable exposures. *Lancet Oncol* 2012 Mar; 13(3): e126–e133.

¹⁸⁴ World Cancer Report 2014. Geneva, Switzerland: World Health Organisation, International Agency for Research on Cancer, WHO Press, 2015.

¹⁸⁵ See section 1.1.2.a.i. about the roles of tobacco and smoking in cancer causation.

¹⁸⁶ World Cancer Report 2014. Geneva, Switzerland: World Health Organisation, International Agency for Research on Cancer, WHO Press, 2015.

¹⁸⁷ Association of European Cancer Leagues (ECL)'s Vision paper about the European Beating Cancer Plan: European Code Against Cancer: https://www.iccp-portal.org/sites/default/files/resources/ECL-vision-EU-Beating-Cancer-Plan_final.pdf (accessed June 2020).

However, owing to the persistently high mortality associated to tobacco use in the EU¹⁸⁸, experts and stakeholders from the European cancer community call for **strengthening this tobacco control regulatory framework**¹⁸⁹.

Recommendation: Reducing the use of tobacco in the EU

As part of efforts to revise the EU Tobacco Products Directive and the EU Tobacco Products Tax Directive, the EU should consider the adoption of following measures:

- raising minimum excise duties for all tobacco products which should result in significant tax increases and smaller tax differences between cigarettes and handrolled tobacco;
- enforcing mandatory plain/standardised packaging with 80% front and back pictorial health warnings for all tobacco products and/or electronic cigarettes;
- banning flavouring agents in tobacco products and restricting or banning flavouring in novel nicotine products, which improve the palatability and attractiveness of such products to non-smokers, adolescents and young adults; and
- investigating a ban on plastic cigarette filters and allowing Member States to introduce such bans on health and environmental grounds.

Source: Association of European Cancer Leagues (ECL)'s Vision paper about the European Beating Cancer Plan: European Code Against Cancer: https://www.iccp-portal.org/sites/default/files/resources/ECL-vision-EU-Beating-Cancer-Plan_final.pdf (accessed June 2020).

Promoting healthy lifestyles

There is substantial evidence that an individual's cancer risk can be increased by excess body fatness and reduced by adopting a healthy diet and increased physical activity¹⁹⁰. Encouraging people to adopt healthier behaviours concerning diet and physical activity in their daily lives is not seen as sufficient to address this issue. Much of people's behaviour, including their willingness to adopt health promotion strategies, is indeed influenced by the social and economic context of the environment in which they live and work. Consequently, **actions to improve diet, nutrition and physical activity include population-wide regulatory measures addressing the social, economic and commercial determinants of health**¹⁹¹.

¹⁸⁸ See section 1.1.2.a.i. about the roles of tobacco and smoking in cancer causation.

¹⁸⁹ Association of European Cancer Leagues (ECL)'s Vision paper about the European Beating Cancer Plan: European Code Against Cancer: https://www.iccp-portal.org/sites/default/files/resources/ECL-vision-EU-Beating-Cancer-Plan_final.pdf (accessed June 2020).

¹⁹⁰ See section 1.1.2.a.ii. about the roles of obesity, diet and physical activity in cancer causation.

¹⁹¹ Association of European Cancer Leagues (ECL)'s Vision paper about the European Beating Cancer Plan: European Code Against Cancer: https://www.iccp-portal.org/sites/default/files/resources/ECL-vision-EU-Beating-Cancer-Plan_final.pdf (accessed June 2020).

Recommendation: Promoting healthy lifestyles in the EU

As part of its current work on the Europe's Beating Cancer Plan, the European Green Deal and the Farm to Fork Strategy, the EU should:

- help consumers to make informed choices about food products by implementing 'best in class' food labelling standards (e.g. Nutri-score);
- implement EU-wide nutrient profiles for nutrition and health claims following WHO recommendations;
- promote the adoption of a planetary health diet through implementing fiscal measures to make fresh local foods (especially pulses, grains, and legumes) more affordable and accessible, especially for people with low incomes;
- work with Member States to use pricing policies and marketing controls to influence demand, access and affordability of foods and drinks high in saturated fats, trans-fats, salt, and sugar; and
- support Member States in restricting the advertising of ultra-processed food products and sugary/sweetened beverages, including on social media.

Source: Association of European Cancer Leagues (ECL)'s Vision paper about the European Beating Cancer Plan: European Code Against Cancer: https://www.iccp-portal.org/sites/default/files/resources/ECL-vision-EU-Beating-Cancer-Plan_final.pdf (accessed June 2020).

Addressing Europe's alcohol problem

Alcohol drinking is contributing significantly to the overall cancer burden in Europe¹⁹². However, according to a study conducted in the United Kingdom, only 1 in 10 people know the established links between alcohol consumption and increased cancer risk^{193, 194}; this highlights the **need for action to tackle Europe's alcohol problem with regulatory measures**, notably including fostering better information about cancer risks associated with alcohol consumption through **appropriate labelling of alcohol beverages**.

¹⁹² See section 1.1.2.a.iii. about the roles of alcohol in cancer causation.

¹⁹³ Buykx P., Li J., Gavens L. et al., Public Awareness of the Link Between Alcohol and Cancer in England in 2015: A Population-Based Survey. *BMC Public Health*. 2016 Nov 30; 16(1): p.1194.

¹⁹⁴ Association of European Cancer Leagues (ECL)'s Vision paper about the European Beating Cancer Plan: European Code Against Cancer: https://www.iccp-portal.org/sites/default/files/resources/ECL-vision-EU-Beating-Cancer-Plan_final.pdf (accessed June 2020).

Recommendation: Addressing Europe's alcohol problem

Given the impact of alcohol-related harm on cancer and on other public health concerns, the EU should act to support:

- better informing consumers by improving the labelling of alcohol beverages to include prominent warning labels and nutritional information;
- adoption of comprehensive national alcohol control legislation, such as the Republic of Ireland's Alcohol Bill;
- prohibition of alcohol advertising on sports grounds for events where the majority of competitors or participants are children;
- prohibition of alcohol sponsorship of sport; and
- protection of children and young people by restricting alcohol advertising and exposure to marketing of alcohol in the digital environment, especially on social media and video-sharing platforms as well as near schools.

Source: Association of European Cancer Leagues (ECL)'s Vision paper about the European Beating Cancer Plan: European Code Against Cancer: https://www.iccp-portal.org/sites/default/files/resources/ECL-vision-EU-Beating-Cancer-Plan_final.pdf (accessed June 2020).

Decreasing Europe's skin cancer burden

Exposure to UV radiation is the main cause of skin cancer, whose incidence has been increasing steeply over recent decades¹⁹⁵. Although being usually classified as an environmental cancer risk factor, exposure to UV radiation has a strong **behavioural component, especially through the use of artificial tanning devices, commonly known as sunbeds**. This UV radiation has the same damaging effects on the skin as natural sunlight and, as it is an unnecessary exposure, it should be avoided at all times, as recommended by the European Code Against Cancer¹⁹⁶, which has a clear and definitive message against their use¹⁹⁷. Beyond these health promotion efforts and owing to the harm that these devices are causing, there is room for the EU to act through regulatory measures against the use of sunbeds.

¹⁹⁵ See section 1.1.2.c.ii. about the roles of UV radiation in cancer causation.

¹⁹⁶ See the European Code Against Cancer: <https://cancer-code-europe.iarc.fr/index.php/en/> (accessed May 2020).

¹⁹⁷ Association of European Cancer Leagues (ECL)'s Vision paper about Europe's Beating Cancer Plan: European Code Against Cancer: https://www.iccp-portal.org/sites/default/files/resources/ECL-vision-EU-Beating-Cancer-Plan_final.pdf (accessed June 2020).

Recommendation: Decreasing Europe's skin cancer burden

The EU should take steps to fight skin cancer by:

- treating the regulation of artificial tanning devices (sunbeds) as a public health concern by transferring responsibility for sunbed regulation from DG GROW to DG SANTE;
- investigating potential collaboration with Member States in order to phase out the use of sunbeds for cosmetic purposes, and implement other public health interventions suggested by the WHO;
- implementing mandatory pictorial warning labels on sunbed devices, stating 'sunbeds cause cancer: even infrequent usage will increase your risk of skin cancer';
- prohibiting references to any supposed health benefits associated with using artificial tanning devices;
- increasing market surveillance of sunbeds with strict enforcement protocols in compliance with age requirements on sunbed use and radiation limits;
- enhancing UV protection measures in EU-level occupational health and safety regulations, paying special attention to risks faced by outdoor workers; and
- fostering the use of sun protection devices and personal measures (e.g. sun creams) by promoting lower taxation of those products.

Source: Association of European Cancer Leagues (ECL)'s Vision paper about the European Beating Cancer Plan: European Code Against Cancer: https://www.iccp-portal.org/sites/default/files/resources/ECL-vision-EU-Beating-Cancer-Plan_final.pdf (accessed June 2020).

ii. Preventing involuntary exposure to cancer risk factors

People are exposed throughout life to a wide range of environmental and occupational cancer risk factors from different sources at home, in the workplace or in the general environment. This includes ionising radiation, occupational carcinogens (e.g. asbestos), air pollution, as well as food and water pollution by pesticides¹⁹⁸.

Protecting people from injury caused by such exposures, over which individuals have little or no control, is a particular responsibility of government. Within that broad scope, the prospect or proof of cancer causation has prompted a range of legislative measures, depending on the context in which relevant exposures may occur.

Prevention of occupational cancer can be seen in the broader context of avoiding adverse workplace-related health effects due to a broad spectrum of agents. Occupational cancer is wholly preventable by regulatory controls when causation is attributable to a specific chemical or chemicals, as distinct from when increased risk is identified among people engaged in a particular type of work. The **adoption of occupational exposure limits for carcinogens** is a fundamental regulatory approach in this respect¹⁹⁹.

Conversely, the regulatory approach toward environmental cancer risk factors may notably involve **regulating or banning known sources of pollutants** (e.g. applying compulsory emission standards to

¹⁹⁸ See section 1.1.2.c. about the roles of occupational and environmental cancer risk factors in cancer causation.

¹⁹⁹ World Cancer Report 2014. Geneva, Switzerland: World Health Organisation, International Agency for Research on Cancer, WHO Press, 2015.

diesel cars, limiting or banning the use of certain pesticides) and **adopting environmental exposure limits for carcinogens** (e.g. air quality standards).

Although their attributable cancer burden may be of limited extent, as compared to major cancer risk factors such as tobacco smoking, occupational and environmental cancer risk factors cause significant harms and concerns to the European population, which require to be addressed in the context of a European primary prevention policy.

Recommendation: Protecting EU citizens from harmful occupational and environmental exposure to carcinogens

Owing to the health risks posed by occupational and environmental carcinogens in the EU, the EU should develop tangible and effective guidance to reduce citizens' exposure to these agents, by:

- protecting citizens at the workplace by ensuring that employers recognise occupational carcinogens, and comply with the established exposure limit values;
- taking action on radon by ensuring Member States publish updated national radon action plans to reduce the indoor exposure to radon, and enhance guidelines on radon mitigation for new constructions;
- implementing an EU-level asbestos plan, requiring EU Member States to support safe cleaning and removal of asbestos;
- taking appropriate measures to improve air quality in European urban spaces, reflecting the latest WHO guidelines;
- ensuring the Common Agricultural Policy strives to reduce intake of pesticide residues and revise food contact materials legislation to ensure carcinogens and endocrine-disrupting chemicals associated with increased cancer risk are eliminated; and
- ensuring Europe's Beating Cancer plan is closely linked to a comprehensive EU Chemical Strategy for Sustainability and other chemical policy frameworks to rationalise and simplify the EU's chemical and pesticide regulations for substances causing cancer.

Source: Association of European Cancer Leagues (ECL)'s Vision paper about the European Beating Cancer Plan: European Code Against Cancer: https://www.iccp-portal.org/sites/default/files/resources/ECL-vision-EU-Beating-Cancer-Plan_final.pdf (accessed June 2020).

c. Primary prevention targeting carcinogenic infectious agents: vaccination and antimicrobial treatments

A notable fraction of cancer cases is caused by carcinogenic infectious agents. These cancers are largely amenable to primary prevention^{200,201}, following two approaches: vaccination and the use of antimicrobial treatments.

²⁰⁰ Wild C.P., Weiderpass E., Stewart B.W., editors (2020). World Cancer Report: Cancer Research for Cancer Prevention. Lyon, France: International Agency for Research on Cancer.

²⁰¹ See section 1.1.2.b. about the roles of carcinogenic infectious agents in cancer causation.

i. Vaccination against carcinogenic infectious agents

Vaccines are the most effective way of preventing cancer-causing infections. Highly effective vaccines have been developed against two of the most important infectious agents associated with cancers, namely Hepatitis B virus (HBV) and Human Papillomavirus (HPV).

Vaccines against HBV have been available for several decades and most countries include HBV vaccination in their childhood immunisation programmes. Their efficacy in preventing chronic HBV infection and liver cancer has been clearly demonstrated in children and adolescents. It is expected that HBV vaccination will nearly eliminate HBV-associated liver cancer in many areas when the vaccination will reach adulthood²⁰².

Highly effective vaccines have been available since 2006 to prevent infection by HPV16 and HPV18, which are the most oncogenic HPV subtypes and are responsible for most HPV-related cancers. Furthermore, a vaccine has recently been available that targets several additional oncogenic HPV subtypes, thereby further increasing the potential efficacy of HPV vaccination against HPV infection and HPV-caused cancers²⁰³. Similarly to HBV, **the elimination of HPV-caused cancers is achievable through vaccination** and is seen as a major public health goal by the WHO²⁰⁴ and by stakeholders from the European cancer community²⁰⁵.

Furthermore, vaccine development efforts are also being undertaken to *Helicobacter pylori*, as another major carcinogenic infectious agent. An effective therapeutic or prophylactic vaccine against *Helicobacter pylori* would provide a cheap and effective way to decrease gastric cancer risk. All of the vaccines currently under development against this bacterium are at an early stage and there appears to be little, if any, investment from pharmaceutical companies, without which progress is likely to be limited.

By contrast, there is currently no vaccine available against HCV, notably owing to the high genetic variability of this virus, which significantly complicates vaccine development²⁰⁶.

²⁰² WHO (2017). Global hepatitis report 2017. Geneva, Switzerland: World Health Organisation.

Available from: <https://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/> (accessed June 2020).

²⁰³ Wild C.P., Weiderpass E., Stewart B.W., editors (2020). World Cancer Report: Cancer Research for Cancer Prevention. Lyon, France: International Agency for Research on Cancer.

²⁰⁴ WHO's Global Call for Cervical Cancer Elimination: <https://www.who.int/reproductivehealth/call-to-action-elimination-cervical-cancer/en/> (accessed June 2020).

²⁰⁵ European Cancer Organisation. Eliminating HPV-caused cancers and diseases in Europe: Case for action. <https://www.european-cancer.org/resources/51:eliminating-hpv-caused-cancers-and-diseases-in-europe-case-for-action.html> (published December 2019; accessed June 2020).

²⁰⁶ Wild C.P., Weiderpass E., Stewart B.W., editors (2020). World Cancer Report: Cancer Research for Cancer Prevention. Lyon, France: International Agency for Research on Cancer.

Recommendation: Enabling population-wide access to vaccines against carcinogenic infectious agents in the EU

In order to harness the full potential of vaccination in the fight against cancer and to enable population-wide access to relevant vaccines, the EU should take measures to:

- become a global leader in the elimination of HPV-caused cancers as a public health problem, by supporting Member States in implementing gender-neutral HPV vaccination for boys and girls;
- investigate harmonisation of HBV and HPV vaccination within Member States' national vaccination programmes as well as ensuring equitable access;
- support further research into the most effective vaccination regimens against carcinogenic viruses and bacteria; and
- collaborating with Member States and international stakeholders to combat the impact of fake news on vaccination and address potential vaccine hesitancy and confidence issues that may arise from the introduction of generic HPV vaccines produced in emerging economies, through collaboration with the WHO and global stakeholders.

Source: Association of European Cancer Leagues (ECL)'s Vision paper about the European Beating Cancer Plan: European Code Against Cancer: https://www.iccp-portal.org/sites/default/files/resources/ECL-vision-EU-Beating-Cancer-Plan_final.pdf (accessed June 2020). European Cancer Organisation. Eliminating HPV-caused cancers and diseases in Europe: Case for action. <https://www.europecancer.org/resources/51:eliminating-hpv-caused-cancers-and-diseases-in-europe-case-for-action.html> (published December 2019; accessed June 2020)

ii. *Use of antimicrobial treatments to prevent chronic infection with carcinogenic infectious agents*

As elaborated above, vaccines are not currently available for several major carcinogenic infectious agents, namely *Helicobacter pylori* and HCV. **Although vaccination remains the most effective way of preventing cancer-causing infections, the latter can also be addressed through the use of direct anti-microbial treatment**, aiming at resolving the infection by eliminating the carcinogenic infectious agent of interest, thereby preventing chronic infection to establish, as well as associated cancers to appear.

There exists an effective direct treatment for *Helicobacter pylori* infection; this treatment comprises a combination of antimicrobial drugs and a proton-pump inhibitor and is used widely in symptomatic individuals. Mass treatment provides a means of primary prevention against *Helicobacter pylori*-associated cancers, although studies are bedevilled by the need for large numbers and lengthy follow-up; there may also be deleterious consequences in terms of drug resistance and the unknown impact of changes to the microbiome. However, the evidence from several published studies indicates that *Helicobacter pylori* eradication programmes can be effective^{207, 208, 209}.

Furthermore, HCV treatment has seen the introduction of direct-acting antiviral agents in 2014, resulting in cure rates of greater than 90% in treated individuals, with minimal side-effects, raising the

²⁰⁷ Franceschi S., El-Serag H.B., Forman D. et al. (2018), Infectious agents. In: Thun MJ, Linet MS, Cerhan JR, et al. Schottenfeld and Fraumeni cancer epidemiology and prevention. 4th ed. New York (NY), USA: Oxford University Press; pp. 60-433.

²⁰⁸ IARC *Helicobacter pylori* Working Group (2014). *Helicobacter pylori* eradication as a strategy for preventing gastric cancer. Lyon, France: International Agency for Research on Cancer (IARC Working Group Reports, No. 8).

²⁰⁹ Pan K.F., Zhang L., Gerhard M. et al., A large randomised controlled intervention trial to prevent gastric cancer by eradication of *Helicobacter pylori* in Linq County, China: baseline results and factors affecting the eradication. *Gut*. 2016 Jan; 65(1): pp. 9-18.

hope for HCV elimination. However, the complexity of testing for HCV and the high cost of treatment mean that treatment is currently unavailable to most of the people who would benefit, even in high-income countries^{210,211}.

1.2.2. Primary prevention of cancer targeting genetic susceptibility to cancer

Although these cancers are classically classified as non-preventable, **there exists ways to effectively delay or prevent the onset of certain cancers associated with unchangeable, inherited genetic mutations**; these interventions can therefore also be considered as primary prevention measures.

A primary approach to this is the **implementation of risk-reducing strategies**, which is possible in all individuals affected by genetic susceptibility to cancer. Such strategies correspond to providing strengthened attention to, and advice on, the application of primary prevention measures recommended for the general population to mitigate exposure to modifiable risk factors known to be associated with the type of cancer the considered individual is at risk of developing. A concrete example of such strategies is limiting sun exposure and avoiding sunbed use for individuals affected by a genetic susceptibility to skin cancer. **Additional research needs to be conducted to assess the extent of the benefits of similar approaches in the context of other tumour types.**

Furthermore, in some cases, **individuals affected by genetic susceptibility to cancer can be offered treatments to reduce their risk of developing cancer.** Two modalities of such treatments can be distinguished: chemoprevention and prophylactic (or risk-reducing) surgery.

a. Chemoprevention

Chemoprevention, i.e. the use of drugs, vitamins, or other agents to try to reduce the risk of, or delay the development or recurrence of, cancer²¹², can be offered to healthy individuals with known high risk of developing cancer. Currently used chemopreventive agents notably include:

- tamoxifen, raloxifene and anastrozole for women at high risk of developing breast cancer²¹³;
- isotretinoin and acitretin for individuals at high-risk of developing basal cell carcinoma²¹⁴; and
- aspirin for Lynch syndrome mutation carriers²¹⁵.

Importantly, owing to the frequent side-effects of these medicines, they are currently only recommended for individuals with highly suspected or confirmed genetic susceptibility (identified through positive cancer family history or results from a genetic testing for germline cancer-associated cancer mutations) or who previously had cancer, in order to lower the risk of cancer recurrence.

In view of the clear clinical evidence in favour of above mentioned chemopreventive interventions, their recommendation should be broadly promoted to ensure that all patients to

²¹⁰ Kanwal F., El-Serag H.B., Hepatitis C., virus treatment: the unyielding chasm between efficacy and effectiveness. *Clin Gastroenterol Hepatol* 2014 Aug; 12(8): pp. 3-1381.

²¹¹ Wild C.P., Weiderpass E., Stewart B.W., editors (2020). World Cancer Report: Cancer Research for Cancer Prevention. Lyon, France: International Agency for Research on Cancer.

²¹² US National Cancer Institute's definition of chemoprevention: <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/chemoprevention> (accessed May 2020).

²¹³ UK National Health Service's factsheet about breast cancer prevention: <https://www.nhs.uk/conditions/breast-cancer/prevention/> (accessed May 2020).

²¹⁴ US National Cancer Institute's factsheet about the genetics of skin cancer: <https://www.cancer.gov/types/skin/hp/skin-genetics-pdq> (accessed May 2020).

²¹⁵ UK National Institute for Health and Care Excellence's guidelines in colorectal cancer: <https://www.nice.org.uk/guidance/ng151/chapter/Recommendations#prevention-of-colorectal-cancer-in-people-with-lynch-syndrome> (accessed May 2020).

whom they can benefit have access to them across the EU. Furthermore, given the significant prevalence of genetic susceptibility to cancer in the EU and the paucity of interventions allowing to prevent the onset of cancer in many cases, further research toward identification and clinical confirmation of new chemopreventive agents should be supported.

b. Prophylactic surgery

A second possible treatment for primary prevention of cancer in individuals affected by genetic susceptibility to cancer is prophylactic surgery. This corresponds to the **removal of an organ or a gland that shows no signs of cancer, in an attempt to prevent development of cancer in individuals with high-risk of cancer in that organ or gland**²¹⁶. The indication to prophylactic surgery is a syndrome-dependent evidence-based approach for monogenetic hereditary disposition, i.e. individuals harbouring single germline mutations associated with a known high risk of cancer. Currently recommended prophylactic surgery interventions include:

- **Prophylactic mastectomy**, that is surgery to reduce the risk of developing breast cancer by removing one or both breasts before disease develops²¹⁷; and
- **Prophylactic salpingo-oophorectomy**, that is surgery intended to reduce the risk of ovarian and Fallopian tube cancers by removing the ovaries and the Fallopian tubes before disease develops²¹⁸.

Both interventions are notably offered to patients harbouring BRCA mutations, which are associated with an increased risk of both breast and ovarian/Fallopian tube cancer. Importantly, although the surgeon attempts to remove the entire breast or ovarian/Fallopian tube tissue where cancer could develop, morphology prevents total ablation, so that there exists a residual risk of cancer after prophylactic surgery. For this reason, **prophylactic surgery can also be referred as risk-reducing surgery** in the literature. Research nevertheless shows that the extent of this risk is limited; for instance, prophylactic mastectomy was indeed proven to allow for a 90% reduction of the probability to develop breast cancer²¹⁹.

Given the invasive and irreversible nature of prophylactic surgery, close attention has to be given to **providing patients eligible for these interventions with information and advice** regarding the consequences of whether or not having them. Furthermore, patients undergoing prophylactic surgery also need **specific support to deal with the biological, psychological and social impacts of this intervention**. In this regard, experts of the field call for **accessibility to harmonised and constantly updated guidance in addition to educational platforms for physicians and the public** to be ensured.

²¹⁶ US National Cancer Institute's definition of prophylactic surgery: <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/prophylactic-surgery> (accessed May 2020).

²¹⁷ US National Cancer Institute's definition of prophylactic mastectomy: <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/prophylactic-mastectomy> (accessed May 2020).

²¹⁸ US National Cancer Institute's definition of prophylactic oophorectomy: <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/prophylactic-oophorectomy> (accessed May 2020).

²¹⁹ Domchek S.M., Friebel T.M., Singer C.F. et al., Association of Risk-Reducing Surgery in BRCA1 or BRCA2 Mutation Carriers With Cancer Risk and Mortality. *JAMA*. 2010 Sep 1; 304(9): pp. 75-967.

2. EARLY DETECTION OF CANCER: SCREENING AND EARLY DIAGNOSIS

KEY FINDINGS & RECOMMENDATIONS: EARLY DETECTION OF CANCER

Primary prevention is the most cost-effective intervention in the control of cancer; however, **secondary prevention through screening and early diagnosis of cancer is also vital** to improve outcomes of affected patients.

In order to achieve European cooperation in cancer screening, the **Council of the European Union issued in 2003 a set of recommendations on the establishment of organised breast, cervical and colorectal cancer screening programmes** in EU Member States. Although a number of initiatives have been performed at the European, national and local levels, **implementation of the recommendations is still far from complete and there remain significant inequalities in access to quality-assured cancer screening** across the EU, as shown by wide variations in coverage and participation rates, as well as in other performance indicators.

Beyond screening, significant challenges remain in respect to early diagnosis of cancer. **To achieve improved levels of early diagnosis of cancer, the public must be assisted in gaining sufficient awareness of potential cancer symptoms**, overcoming fear or stigma associated with cancer and accessing appropriate healthcare advice. This requires primary **healthcare professionals to possess the clinical skills and knowledge to identify potential symptoms** described or presented by patients and ensure timely referral to specialist cancer services. Another critical element of early diagnosis is **accurate clinical evaluation, diagnosis and staging**, which again requires appropriate expertise. **The European Council Recommendations of 2003 on Cancer Screening should be updated** to take account of developments in science, practice and evidence in cancer screening.

Within Europe's Beating Cancer Plan and EU Cancer Mission significant attention should be provided to screening and early diagnosis matters, including:

- **supporting the construction of an EU Cancer Dashboard to monitor access and performance of screening programmes** (and by so doing encourage spread of best practice);
- **improving the harmonisation of cancer screening data collection;**
- **promoting improved quality assurance of screening programmes;**
- **helping to address workforce shortage and education/training needs** to assist earlier detection and diagnosis of cancer, including via monitoring instruments and utilisation of EU qualification recognition tools;
- **supporting initiatives that will improve public awareness of potential cancer symptoms**, taking inspiration from the success of the European Code Against Cancer; and
- **ensuring continued investment in research into relevant areas** such as the application of artificial intelligence and deep learning for the purposes of improving cancer detection.

As previously discussed, primary prevention is known to be the most cost-effective strategy in the control of cancer, and generally of non-communicable diseases^{220,221}. However, other approaches are also needed to factor in the multifactorial and incompletely understood causation of many cancers, as well as the long latency for primary prevention strategies to have significant impacts on cancer rates^{222,223} and the difficulties for them to reach entire populations²²⁴.

Secondary prevention through early detection²²⁵ is an instrumental component of the fight against cancer. Cancer, when identified early, is more likely to respond to effective treatment, resulting in a **greater probability of survival**, reduced morbidity and less expensive treatment²²⁶. An estimated **one third of cancer cases** worldwide can be positively impacted by this approach, including some of the current biggest cancer killers in Europe, such as breast cancer and colorectal cancer²²⁷.

Early detection aims at detecting tumours at an early stage, when they are still localised to their organ of origin, before invading surrounding tissues and distant organs, or even at a pre-cancerous stage. It is comprised of **two distinct strategies**²²⁸:

- **screening**, which aims to identify unrecognised cancer or its precursor lesions in apparently healthy, asymptomatic individuals, by means of examinations, tests, imaging or other procedures that can be applied rapidly and accessed widely by a defined target population²²⁹; and
- **early diagnosis**, which, by contrast, focuses on detecting symptomatic patients as early as possible²³⁰, often involving the patient's awareness of early signs and symptoms, leading to a consultation with a health provider – who then promptly refers the patient for confirmation of diagnosis and treatment by a cancer specialist²³¹.

2.1. Cancer screening

2.1.1. Rationale of cancer screening and associated requirements

Screening has the unique potential of decreasing both cancer incidence, through detection and treatment of precursor lesions before they develop to invasive cancer²³², and **cancer stage at diagnosis**. Screening indeed allows for the identification of cases before the onset of symptoms and for subsequent referral to a cancer specialist, therefore **reducing both mortality²³³ and economic costs implied by cancer**, as already observed in several EU Member States^{234,235}.

²²⁰ Cancer control: prevention. WHO Guide for effective programmes. Geneva: World Health Organisation; 2007.

²²¹ WHO's factsheet about cancer prevention: <https://www.who.int/cancer/prevention/en/> (accessed May 2020).

²²² See Chapter 1.2. section about primary prevention.

²²³ Schüz J., Espina C., Wild C.P., Primary prevention: a need for concerted action. Mol Oncol. 2019 Mar; 13(3): pp. 567-578.

²²⁴ Guide to cancer early diagnosis. Geneva: World Health Organisation; 2017.

²²⁵ See Chapter 1.2 definition of the three levels of cancer prevention.

²²⁶ Guide to cancer early diagnosis. Geneva: World Health Organisation; 2017.

²²⁷ Cancer control: early detection. WHO Guide for effective programmes. Geneva: World Health Organisation; 2007.

²²⁸ Cancer control: early detection. WHO Guide for effective programmes. Geneva: World Health Organisation; 2007.

²²⁹ Guide to cancer early diagnosis. Geneva: World Health Organisation; 2017.

²³⁰ WHO/Europe's factsheet about screening and early detection: www.euro.who.int/en/health-topics/non-communicable-diseases/cancer/policy/screening-and-early-detection (accessed February 2020).

²³¹ Cancer control: early detection. WHO Guide for effective programmes. Geneva: World Health Organisation; 2007.

²³² Cancer control: early detection. WHO Guide for effective programmes. Geneva: World Health Organisation; 2007.

²³³ Guide to cancer early diagnosis. Geneva: World Health Organisation; 2017.

²³⁴ Cancer screening in the European Union: Report on the implementation of the Council recommendation on cancer screening (2nd edition). International Agency for Research on Cancer; 2017.

²³⁵ Digestive Cancers Europe: White Paper on Colorectal Cancer Screening in Europe, February 2019.

However, as opposed to early diagnosis programmes or to any other medical intervention in the cancer field, screening differs by targeting entire, asymptomatic, mostly cancer-free populations. This has crucial impacts on **financial costs and human resource needs** associated to screening programmes, as well as on their **possible harm** both **for patients**, notably in case of overdiagnosis and overtreatment, **and healthcare systems**²³⁶.

Therefore, **screening is recommended only for those cancers where a demonstrated life-saving effect substantially outweighs potential disadvantages** of potentially population-wide examinations²³⁷. Implementation of cancer screening therefore depends on a number of factors, including the burden associated to that corresponding cancer type, the quality of the available screening tests, the health system's capacity to act on the results of the screening test, the available infrastructure and competing priorities in the cancer field²³⁸.

Cancer screening can be performed through **two strategies**:

- **organised population-based screening programmes**, where invitations to screening are systematically issued by public authorities to a defined target population, within the framework of a documented public policy specifying key modalities for screening examinations; and
- **opportunistic non-population-based screening**, where screening is made available depending on requests from individuals or their health advisor^{239, 240}.

Organised screening programmes ensure that every individual has an equal opportunity to participate in screening and that patients receive relevant support and treatment if their test result is abnormal²⁴¹. Such programmes are considered to be more cost-effective than opportunistic screening and to cause less harm, by avoiding over-screening and over-treatment²⁴².

2.1.2. Overview of current European framework on cancer screening

a. The 2003 Council recommendations

The implementation of screening programmes to reduce the burden of common cancers was established by the European Council as a priority for Member States²⁴³, and the **Council of Health Ministers issued in 2003 a set of recommendations** for cancer screening. The recommendations importantly include a shared commitment by the Member States to **implement systematic population-based** national (or regional) **screening programmes** for three cancer types: **breast** cancer, **colorectal** cancer (respectively the third and second leading cause of death due to cancer in

²³⁶ Guide to cancer early diagnosis. Geneva: World Health Organisation; 2017.

²³⁷ Amaroli P., Villain P., Suonio E. et al., European Code against Cancer, 4th Edition: Cancer screening. Cancer Epidemiol. 2015 Dec; 39 Suppl 1: pp. S2-S139.

²³⁸ Guide to cancer early diagnosis. Geneva: World Health Organisation; 2017.

²³⁹ Cancer screening in the European Union: Report on the implementation of the Council recommendation on cancer screening (2nd edition). International Agency for Research on Cancer; 2017.

²⁴⁰ Glossary and definitions in cancer screening from the IARC Cancer Screening in Five Continents (CanScreen5) project's website: <https://canscreen5.iarc.fr/?page=help> (accessed March 2020).

²⁴¹ European Code Against Cancer's factsheet about organised cancer screening programmes: <https://cancer-code-europe.iarc.fr/index.php/en/ecac-12-ways/screening-recommandation/key-points-about-cancer-screening/213-what-is-an-organized-screening-programme> (accessed March 2020).

²⁴² Cancer control: early detection. WHO Guide for effective programmes. Geneva: World Health Organisation; 2007.

²⁴³ Cancer screening in the European Union: Report on the implementation of the Council recommendation on cancer screening (2nd edition). International Agency for Research on Cancer; 2017.

the EU²⁴⁴) and **cervical cancer**²⁴⁵, collectively responsible for an estimated 286 157 deaths in the EU in 2018²⁴⁶.

In detail, the following tests were recommended:

- pap smear screening for cervical cancer precursors starting not before the age of 20 and not later than the age of 30;
- mammography screening for breast cancer in women aged 50 to 69; and
- faecal occult blood screening for colorectal cancer in men and women aged 50 to 74²⁴⁷.

Furthermore, the recommendation affirms the importance of quality assurance at all appropriate levels of screening programmes, notably on the basis of already established or future European evidence-based guidelines on best practice, as well as to ensure availability of human and financial resources for appropriate organisation of these programmes and of monitoring their implementation, through data collection in Member States and reports from the European Commission to the European Council²⁴⁸.

b. Initiatives arising from the 2003 recommendations

In accordance with these recommendations, several initiatives were developed since 2003 at the European level to accompany the deployment of the recommended cancer screening programmes:

- further updates of the **European guidelines for quality assurance in breast**²⁴⁹, **cervical**²⁵⁰ **and colorectal**²⁵¹ **cancer screening**, published by European Commission Directorate General for Health and Food Safety (DG SANTE), whose successive editions reported new evidence and best practices in order to optimise all aspects of screening, including new screening tests, information and invitation messages, administration of tests, interpretation of results and referral of patients to further testing or treatment;
- **European Commission Initiatives on Breast Cancer (ECIBC)** and on **Colorectal Cancer (ECICC)**, launched as multidisciplinary platforms, bringing together health care professionals, researchers and patient advocates and aimed at reviewing, developing and facilitating the implementation of European guidelines addressing the entire care pathway for these cancer types, including screening programmes^{252,253};
- **Reports on the implementation of the Council recommendation on cancer screening**, prepared by the **International Agency for Research on Cancer (IARC)** for the European Commission, aimed at monitoring the implementation of recommended cancer screening programmes in Member States, as well as their performance in terms of population coverage

²⁴⁴ Data retrieved from IARC Global Cancer Observatory <https://gco.iarc.fr/> (accessed March 2020).

²⁴⁵ Council Recommendation of 2 December 2003 on Cancer Screening (2003/878/EC). OJ L 327: 34-38.

²⁴⁶ Data retrieved from IARC Global Cancer Observatory <https://gco.iarc.fr/> (accessed March 2020).

²⁴⁷ Council Recommendation of 2 December 2003 on Cancer Screening (2003/878/EC). OJ L 327: 34-38.

²⁴⁸ Council Recommendation of 2 December 2003 on Cancer Screening (2003/878/EC). OJ L 327: 34-38.

²⁴⁹ European guidelines for quality assurance in breast cancer screening and diagnosis: 4th edition, supplements. Directorate-General for Health and Food Safety (European Commission); 2013.

²⁵⁰ European guidelines for quality assurance in cervical cancer screening: 2nd edition, supplements. Directorate-General for Health and Food Safety (European Commission); 2015.

²⁵¹ European guidelines for quality assurance in colorectal cancer screening and diagnosis. Directorate-General for Health and Food Safety (European Commission); 2011.

²⁵² European Commission's factsheet about ECIBC, <https://healthcare-quality.jrc.ec.europa.eu/discover-ecibc> (accessed March 2020).

²⁵³ European Commission's factsheet about ECICC: <https://ec.europa.eu/jrc/en/publication/ecicc-european-commission-initiative-colorectal-cancer> (accessed March 2020).

and detection rates, and providing justification for further initiatives at the European and the national level in relation to cancer screening²⁵⁴; and

- **The European Code Against Cancer's recommendation on cancer screening²⁵⁵**, encouraging European citizens to take part in organised cancer screening programmes for breast, colorectal and cervical cancer²⁵⁶.

c. Status of implementation of recommended cancer screening programmes

Despite substantial progress over the last years, the status of **implementation of recommended cancer screening programmes is still heterogeneous across the EU**, with only 18 EU Member States (and the United Kingdom) being reported to have national or regional population-based screening programmes for breast, cervical and colorectal cancers as of 2016²⁵⁷ (see Annex 4²⁵⁸). Furthermore, **advancement in the development and implementation of these programmes differs** between countries, with some programmes still being at a planning phase owing to recent legislation, at a pilot phase only in a limited geographical area or having their rollout ongoing or complete^{259,260} (see Table 1 and Annex 5²⁶¹).

In most current organised screening programmes, the chosen target populations and screening intervals are compliant with European recommendations and guidelines, with some variations due to national epidemiological evidence and prioritisation²⁶² (see Annex 6²⁶³).

Thus, still not all recommended screening programmes are currently running in every EU Member State; therefore, the European cancer community unanimously calls for **continuing efforts towards exhaustive implementation of population-based screening programmes for breast, cervical and colorectal cancers in the EU**.

²⁵⁴ Cancer screening in the European Union: Report on the implementation of the Council recommendation on cancer screening (2nd edition). International Agency for Research on Cancer; 2017.

²⁵⁵ See Chapter 1.2 section on primary prevention for a presentation of the European Code Against Cancer.

²⁵⁶ European Code Against Cancer's 12th recommendation <https://cancer-code-europe.iarc.fr/index.php/en/> (accessed March 2020).

²⁵⁷ Cancer screening in the European Union: Report on the implementation of the Council recommendation on cancer screening (2nd edition). International Agency for Research on Cancer; 2017.

²⁵⁸ European Cancer Leagues' interactive map of national efforts regarding implementation of cancer screening programmes, within the frame of policies addressing European Code Against Cancer's recommendations to reduce cancer risk. Available at: <https://www.european-cancer-leagues.org/cancer-prevention-ecac-map/#12> (accessed March 2020).

²⁵⁹ See definitions of population-based screening programmes' stages of implementation within the Glossary and definitions in cancer screening from the IARC Cancer Screening in Five Continents (CanScreen5) project's website: <https://canscreen5.iarc.fr/?page=help> (accessed March 2020).

²⁶⁰ Cancer screening in the European Union: Report on the implementation of the Council recommendation on cancer screening (2nd edition). International Agency for Research on Cancer; 2017.

²⁶¹ Distribution of cancer screening programmes in the EU in 2016. Extracted from Cancer screening in the European Union: Report on the implementation of the Council recommendation on cancer screening (2nd edition). International Agency for Research on Cancer; 2017.

²⁶² Cancer screening in the European Union: Report on the implementation of the Council recommendation on cancer screening (2nd edition). International Agency for Research on Cancer; 2017.

²⁶³ Adoption of recommended target populations and screening intervals by organised screening programmes in the EU in 2016. Extracted from: Cancer screening in the European Union: Report on the implementation of the Council recommendation on cancer screening (2nd edition). International Agency for Research on Cancer; 2017.

Table 1: Implementation of recommended breast, cervical and colorectal cancer screening programmes in EU Member States and the UK in 2016

	Breast cancer screening	Cervical cancer screening	Colorectal cancer screening
Population-based screening program	25 (95%)	22 (72%)	23 (72%)
Rollout complete	21 (88%)	9 (28%)	9 (27%)
Rollout ongoing	3 (3%)	10 (27%)	8 (26%)
Piloting	1 (4%)	1 (<1%)	4 (3%)
Planning	0	2 (17%)	2 (18%)
Non-population-based screening program	3 (5%)	4 (25%)	2 (4%)
No screening program	0	2 (2%)	3 (24%)

Source: Cancer screening in the European Union: Report on the implementation of the Council recommendation on cancer screening (2nd edition). International Agency for Research on Cancer; 2017.

Note: Displayed numbers correspond to the number of EU Member States (and the UK) reporting the respective situation regarding the respective cancer screening program; percentages displayed in brackets correspond to the proportion of EU populations targeted by the respective screening program²⁶⁴ living in the corresponding countries.

2.1.3. Optimising cancer screening programmes

a. Performance of cancer screening programmes

i. Screening rates and target population coverage

Performance of a population-based screening programme can primarily be described through its **examination coverage rate**, defined as the proportion of individuals from the recommended target population who received the screening test of interest within the scheduled screening interval, in the framework of this screening program.

This rate depends itself on:

- the **invitation coverage rate**, defined as the proportion of individuals from the recommended target population who received a personal invitation to screening within the scheduled screening interval, in the framework of the screening program; and
- the **participation rate**, defined as the proportion of personally invited individuals who responded and subsequently received the screening test of interest²⁶⁵.

Average values of examination coverage rates, invitation coverage rates and participation rates for recommended breast, cervical and colorectal cancer screening programmes as of 2013 in the EU are shown in Table 2.

²⁶⁴ Target populations considered were: women aged 50 to 69 for breast cancer screening; men and women aged 50 to 74 for colorectal cancer screening (as in the 2003 Council recommendation); women aged 30 to 59 for cervical cancer screening.

²⁶⁵ Cancer screening in the European Union: Report on the implementation of the Council recommendation on cancer screening (2nd edition). International Agency for Research on Cancer; 2017.

Table 2: Average screening rates within recommended (or common) target populations for breast, cervical and colorectal cancer screening programmes in the EU in 2013

	Breast cancer screening	Cervical cancer screening	Colorectal cancer screening
Examination coverage rate	49.2%	29.8%	14.0%
Invitation coverage rate	78.9%	59.2%	32.6%
Participation rate	60.2%	50.7%	38.2%

Source: Cancer screening in the European Union: Report on the implementation of the Council recommendation on cancer screening (2nd edition). International Agency for Research on Cancer; 2017. (Data provided by Member States mostly concerning year 2013).

Several limitations should be considered when analysing these average rates. Their accuracy is hindered by discrepancies in data provision by Member States (data lacking or reported concerning a different year than 2013; see Annex 7²⁶⁶) and by their calculation over a single year rather than the full corresponding screening intervals, requiring corrections²⁶⁷ but still exposing them to inter-annual variability.

Furthermore, these rates do not factor in the impact of pre-invitation exclusion criteria, adopted by some Member States to identify individuals ineligible to screening. Opportunistic screening, which still exists, besides or instead of organised screening, in numerous European countries, may also result in apparent lower coverage and participation rates in the framework of organised screening programmes as compared with actual screening rates in the target population. The latter is especially true for cervical cancer screening: opportunistic activity accounts for a significant share of examinations performed in several Member States with a population-based screening programme rolling out (up to more than 90%), increasing total examination coverage rate of the target population to more than 80% in some cases²⁶⁸.

Nevertheless, these rates show that **target population coverage by recommended population-based screening programmes is still far from reaching sufficient levels to achieve maximum clinical efficacy throughout the EU**²⁶⁹.

Importantly, all screening rates show **wide variability between European countries** and, in some cases, between regions of a single European country. When considering only Member States where recommended population-based cancer screening programmes were actively implemented at the time of data collection, examination coverage rates indeed ranged between 17% and 84% for breast

²⁶⁶ Screening rates for the three recommended cancer screening programmes within target (or common) populations in EU Member States in 2013. Data extracted from Cancer screening in the European Union: Report on the implementation of the Council recommendation on cancer screening (2nd edition). International Agency for Research on Cancer; 2017.

²⁶⁷ Complete rollout of a screening programme is expected to happen over its full corresponding screening interval. Due to the reporting of data on a single year, invitation and examination coverage rates were calculated using as a reference the "annual target population", computed as the target population according to EUROSTAT figures, divided by the screening interval applied to the relevant individuals, or, in the case of a screening test offered once in a lifetime, by the number of years in the target age range.

²⁶⁸ Cancer screening in the European Union: Report on the implementation of the Council recommendation on cancer screening (2nd edition). International Agency for Research on Cancer; 2017.

²⁶⁹ Cancer screening in the European Union: Report on the implementation of the Council recommendation on cancer screening (2nd edition). International Agency for Research on Cancer; 2017.

cancer screening, 4% and 71% for cervical cancer screening and 1% and 53% for colorectal cancer screening (see Annex 7²⁷⁰ & Annex 8²⁷¹).

These rates also demonstrate a **low or very low coverage and participation of the target population in recommended cancer screening programmes in many European countries**. Coverage of over 70% of the target population by organised screening, considered by the World Health Organisation (WHO) as a threshold to define an efficient cancer screening program²⁷² was only achieved by five EU Member States and the UK in breast cancer screening, one in cervical cancer screening and by no EU Member State in colorectal cancer screening. Additionally, a participation rate of over 65%, defined as a desirable target by the European Council²⁷³, is only achieved by nine EU Member States and the UK in breast cancer screening, three in cervical cancer screening and two in colorectal cancer screening (see Annex 7²⁷⁴).

While some improvements is expected as a result of the currently planned, piloting or ongoing rollout of recommended cancer screening programmes in numerous EU Member States, and in general of further progress towards implementation of these programmes on the entire recommended target population, these figures and the associated health inequities are also linked with **inadequate adherence by the policy-makers and medical professionals to the quality assurance requirements**. This is reflected by additional performance indicators²⁷⁵ as well as by various **issues related to the organisation of screening programmes**, hampering access and participation of patients to efficient screening.

ii. *Additional performance indicators and quality assurance*

As affirmed by the 2003 Council recommendations on cancer screening²⁷⁶ and by European guidelines produced for all three recommended programmes^{277,278,279}, all steps of the screening process need to be considered when assessing the performance and ensuring the quality of a screening program, including:

- information and invitation of the target population;
- performing the screening test;

²⁷⁰ Screening rates for the three recommended cancer screening programmes within target (or common) populations in EU Member States in 2013. Data extracted from: Cancer screening in the European Union: Report on the implementation of the Council recommendation on cancer screening (2nd edition). International Agency for Research on Cancer; 2017.

²⁷¹ Target population examination coverage rates for the three recommended cancer screening programmes in EU Member States in 2013. Extracted from: Cancer screening in the European Union: Report on the implementation of the Council recommendation on cancer screening (2nd edition). International Agency for Research on Cancer; 2017.

²⁷² WHO's factsheet about cancer screening: <https://www.who.int/cancer/prevention/diagnosis-screening/screening/en/> (accessed March 2020).

²⁷³ Digestive Cancers Europe: White Paper on Colorectal Cancer Screening in Europe, February 2019.

²⁷⁴ Screening rates for the three recommended cancer screening programmes within target (or common) populations in EU Member States in 2013. Data extracted from: Cancer screening in the European Union: Report on the implementation of the Council recommendation on cancer screening (2nd edition). International Agency for Research on Cancer; 2017.

²⁷⁵ Cancer screening in the European Union: Report on the implementation of the Council recommendation on cancer screening (2nd edition). International Agency for Research on Cancer; 2017.

²⁷⁶ Council Recommendation of 2 December 2003 on Cancer Screening (2003/878/EC). OJ L 327: 34-38.

²⁷⁷ European guidelines for quality assurance in breast cancer screening and diagnosis: 4th edition, supplements. Directorate-General for Health and Food Safety (European Commission); 2013.

²⁷⁸ European guidelines for quality assurance in cervical cancer screening: 2nd edition, supplements. Directorate-General for Health and Food Safety (European Commission); 2015.

²⁷⁹ European guidelines for quality assurance in colorectal cancer screening and diagnosis. Directorate-General for Health and Food Safety (European Commission); 2011.

- assessment or follow-up of abnormalities detected;
- referral for diagnostic confirmation and treatment; and
- treatment, if applicable²⁸⁰.

While the above displayed participation and coverage rates are well suited to describe the first steps, additional performance indicators are needed to assess the performance and the quality of the screening test in itself, as well as of all subsequent steps during the screening process:

- detection rates of cancer and other clinical outcomes specific to the three types of screening programmes;
- rates of referral to and compliance with further assessment; and
- treatment referral rates, when applicable²⁸¹.

When analysing these rates in EU Member States, wide variations between and within screening programmes are observed, underlining needed progress to ensure access to high-quality screening across the EU²⁸².

b. Organisation of cancer screening programmes

In addition to performance standards to ensure sufficient quality of screening provided to patients, organised cancer screening programmes also come with a number of organisational prerequisites, including:

- an explicit screening policy, either as a law or an official notification specifying the target population, screening tests and screening intervals;
- public funding of the screening programme and provision of screening tests free of charge;
- well-defined plan for inviting the eligible men and women (through letters or through primary healthcare providers);
- a management team responsible for programme implementation and quality assurance; and
- existence of screening registries and linkage with cancer registries.

When collecting and analysing data in these regards, it first appears that the vast majority of the countries in the EU have public funded screening programmes, thus ensuring access to free screening and diagnostic tests. Almost all the countries with population-based screening programmes have teams responsible for implementation and quality assurance. **However, many screening programmes still do not have screening registries linked to the cancer and cause-of death registries that is a necessary condition to identify the cancer occurrence and deaths in the targeted population.** The invitations to participate in the screening programmes are sent by specified organisations, by primary health care or by the general practitioners. A majority of the countries

²⁸⁰ Cancer screening in the European Union: Report on the implementation of the Council recommendation on cancer screening (2nd edition). International Agency for Research on Cancer; 2017.

²⁸¹ Cancer screening in the European Union: Report on the implementation of the Council recommendation on cancer screening (2nd edition). International Agency for Research on Cancer; 2017.

²⁸² Cancer screening in the European Union: Report on the implementation of the Council recommendation on cancer screening (2nd edition). International Agency for Research on Cancer; 2017.

practice sending invitation letters with pre-fixed appointments or with faecal occult blood test kits for colorectal screening²⁸³.

c. Adaptation to scientific and technological developments

Since the 2003 Council recommendations on cancer screening, a number of scientific of technological developments have emerged in the fields of breast, cervical and colorectal cancer screening. This notably includes new screening tests, such as full field digital mammography, digital breast tomography or supplemental magnetic resonance imaging (MRI) in women with extremely dense breast tissue²⁸⁴, for breast cancer screening, HPV test for cervical cancer screening, faecal immunological test or endoscopy for colorectal screening, which are progressively being implemented within screening programmes across the EU.

Of note, beyond the implementation of new screening tests, cancer screening programmes may also benefit from scientific progress in the field of cancer risk prediction²⁸⁵ allowing for the **development of risk-adapted screening**. In risk-stratified screening, the specific screening policy regarding screening ages, intervals, tests and follow-up is based on the risk profile of a group of individuals in the population. This may include no screening for those at lowest risk and an unfavourable expected benefit-harm ratio. Risk-stratified approaches have a theoretical potential to improve overall cost-effectiveness as well as benefit-harm ratios of population-based screening programmes²⁸⁶ and are therefore seen in the European cancer community as an important prospect in order to optimise cancer screening programmes and accelerate cancer diagnosis. Of note, selection of high-risk individuals for implementation of this approach of risk-adapted screening is also central in the below elaborated ongoing discussions regarding the possible rollout of additional cancer screening programmes, including lung cancer screening and prostate cancer screening.

2.1.4. Possible broadening of cancer screening programmes

The 2003 Council recommendations on cancer screening recommended the implementation of screening programmes for only three cancer types: breast, cervical and colorectal cancer screening.

The WHO's current position on cancer screening is aligned with current recommendations at the European level. It supports the implementation of screening programmes for breast, cervical and colorectal cancers, but not for other cancer types, considering the latter as not yet proved to be cost-effective, nor to allow for significant reduction of overall mortality²⁸⁷. This is also in line with the conclusions of the recent EU co-funded Cancer Control Joint Action (CanCon), according to which further evidence was sought before being able to recommend such additional cancer screening programmes²⁸⁸. However, the possibility of screening programmes for additional cancer types is

²⁸³ Cancer screening in the European Union: Report on the implementation of the Council recommendation on cancer screening (2nd edition). International Agency for Research on Cancer; 2017.

²⁸⁴ Bakker M.F., De Lange S.V., Pijnappel R.M. et al., Supplemental MRI Screening for Women with Extremely Dense Breast Tissue. *N Engl J Med*. 2019 Nov 28; 381(22): pp. 2091-2102.

²⁸⁵ See section 1.1.3. about cancer risk prediction and risk stratification.

²⁸⁶ Lönnberg S., Šekerija M., Malila N. et al., Cancer screening: policy recommendations on governance, organisation and evaluation of cancer screening IN Albrecht T., Kiasuwa R., Van den Bulcke M., European Guide on Quality Improvement in Comprehensive Cancer Control. Cancer Control Joint Action (Chapter 4); 2017.

²⁸⁷ WHO European Technical Consultation on Screening, February 2019.

²⁸⁸ Lönnberg S., Šekerija M., Malila N. et al., Cancer screening: policy recommendations on governance, organisation and evaluation of cancer screening IN Albrecht T., Kiasuwa R., Van den Bulcke M., European Guide on Quality Improvement in Comprehensive Cancer Control. Cancer Control Joint Action (Chapter 4); 2017.

intensely discussed in the European cancer community and such screening programmes are already in place or being launched in some EU Member States, such as lung cancer screening in Croatia.

Following disease indications are being investigated:

- Prostate-Specific Antigen (PSA) test for prostate cancer^{289,290}; and
- Low-dose computed tomography (CT) screening for lung cancer^{291,292}.

Other prospects for additional cancer screening tests include gastric cancer screening, through endoscopy/fluoroscopy, pepsinogen testing or *Helicobacter pylori* testing, and CA125-based ovarian cancer screening²⁹³.

These developments address some of the most deadly cancer types in the EU, notably with lung and prostate cancers being the first and fifth leading cause of death due to cancer in the EU, responsible for an estimated 296 140 and 81 542 deaths in 2018, respectively²⁹⁴.

Nevertheless, as already mentioned in above sections, it should be kept in mind that, as opposed to most medical interventions in the cancer field, screening programmes differ by targeting entire, asymptomatic, mostly cancer-free populations, therefore causing a significant burden for healthcare systems, as well as unavoidable harm for patients²⁹⁵. Therefore, the implementation of such additional screening programmes must be based on evidence, with quantitative estimates of their benefits, harms and cost-effectiveness. Specific attention needs to be given to addressing concerns in terms of overdiagnosis (and overtreatment) for prostate and ovarian cancer screening, lack of cost-effectiveness for lung cancer screening, long-term adverse effects for gastric cancer screening. In order to generate such evidence, the funding of randomised trials for these potential new screening tests at the European level will be instrumental²⁹⁶.

²⁸⁹ European Association of Urology: Position Paper on PSA screening for prostate cancer, 2019.

²⁹⁰ Gandaglia G., Albers P., Abrahamsson P.A. et al., Structured Population-based Prostate-specific Antigen Screening for Prostate Cancer: The European Association of Urology Position in 2019. *Eur Urol.* 2019 Aug; 76(2): pp. 142-150.

²⁹¹ European Society of Radiology-European Respiratory Society fact sheet on lung cancer screening, December 2019.

²⁹² De Koning H.J., Van der Aalst C.M., De Jong P.A. et al., Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomised Trial. *N Engl J Med.* 2020 Feb 6; 382(6): pp. 503-513.

²⁹³ Gandaglia G., Albers P., Abrahamsson P.A. et al., Structured Population-based Prostate-specific Antigen Screening for Prostate Cancer: The European Association of Urology Position in 2019. *Eur Urol.* 2019 Aug; 76(2): pp. 142-150.

²⁹⁴ Data retrieved from IARC Global Cancer Observatory <https://gco.iarc.fr/> (accessed March 2020).

²⁹⁵ Guide to cancer early diagnosis. Geneva: World Health Organisation; 2017.

²⁹⁶ Lönnberg S., Šekerija M., Malila N. et al., Cancer screening: policy recommendations on governance, organisation and evaluation of cancer screening IN Albrecht T, Kiasuwa R, Van den Bulcke M. European Guide on Quality Improvement in Comprehensive Cancer Control. Cancer Control Joint Action (Chapter 4); 2017.

 Recommendation: Harnessing the full potential of cancer screening in the EU

In order to harness the full potential of cancer screening, the EU should consider an update of the 2003 Council recommendations on cancer screening and of their implementation. Such an effort could allow to:

- take into account new screening tests and most recent data on best screening protocols;
- address heterogeneity between Member States and inequalities within Member States regarding screening, possibly by making the criteria of cancer screening as to the legal frameworks, governance and quality assurance structures more stringent; and
- look into the possible inclusion of new cancer screening programmes and of comprehensive strategies with primary prevention within the recommendations.

Further policy recommendations aiming at increasing coverage and quality of recommended cancer screening programmes include:

- improving and harmonising cancer screening data collection to allow for regular monitoring of current screening programmes at the EU level;
- adopting performance reference standards at the EU level to foster performance improvements of national screening programmes;
- ensuring robust implementation of recommendations arising from European guidelines;
- developing best practices exchanges between EU Member States and education on cancer screening; and
- further involving a wide range of health professionals, such as cancer nurses, and patient organisations in promoting access and acceptability of screening programmes.

Source: Cancer screening in the European Union: Report on the implementation of the Council recommendation on cancer screening (2nd edition). International Agency for Research on Cancer; 2017. Innovative Partnership for Action Against Cancer (iPAAC) – Work Package 5 Cancer Prevention.

2.2. Early diagnosis of cancer

Detecting cancer early can effectively reduce the mortality associated with cancer. In resource-poor settings, cancer is often diagnosed at a late-stage of the disease resulting in lower survival and potentially greater morbidity and higher costs of treatment. Even in countries with strong health systems and services, many cancer cases are diagnosed at a late stage. Addressing delays in cancer diagnosis and inaccessible treatment is therefore critical in all settings for optimal cancer control²⁹⁷.

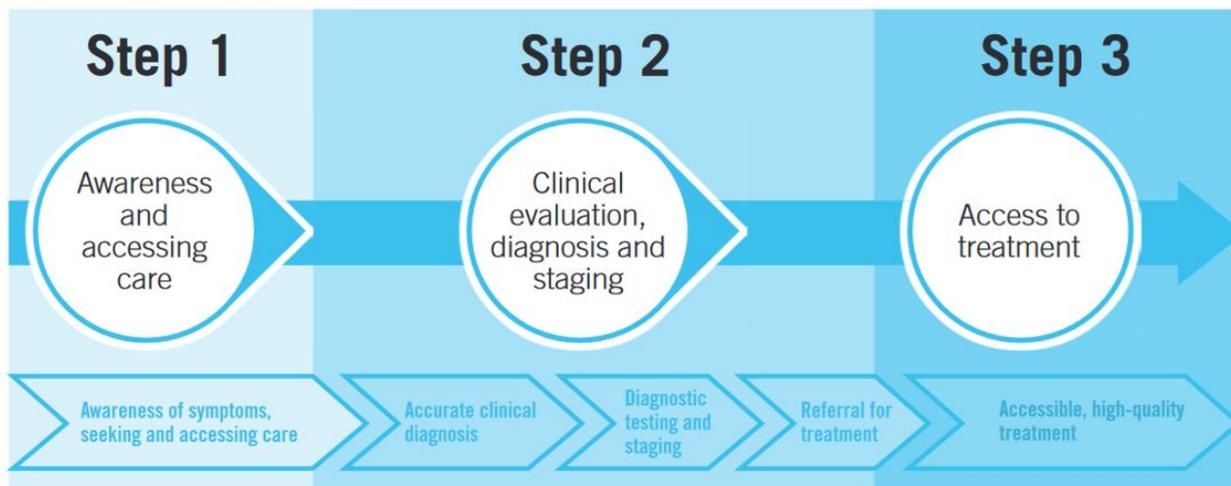
While improving early diagnosis generally improves outcomes, it should be noted that not all cancer types benefit equally. Cancers that are common, that can be diagnosed at early stages from signs and symptoms and for which early treatment is known to improve the outcome are generally those that benefit most from early diagnosis. Examples in this regard include breast, cervical, colorectal and oral cancers²⁹⁸.

²⁹⁷ WHO Guide to cancer early diagnosis: https://www.who.int/cancer/publications/cancer_early_diagnosis/en/.

²⁹⁸ Cancer control: early detection. WHO Guide for effective programmes. Geneva: World Health Organisation; 2007.

The WHO advises 3 key steps to achieving optimal systems for early diagnosis of cancer: awareness; clinical evaluation, diagnosis and staging; and, access to treatment. The first and second of these stages will be dealt with within this chapter, with access to treatment described more thoroughly in the succeeding chapter.

Figure 3: The 3 Essential elements to cancer early diagnosis



Source: Guide to cancer early diagnosis. Geneva: World Health Organisation; 2017.

Amongst other elements, improving early diagnosis of cancer requires health system investment in public awareness and education, health workforce education and training, access to priority diagnostic technologies and robust and interoperative health information systems.

2.2.1. Educating health care providers and the general public about cancer warning signs

a. Education of the general public about cancer warning signs

To achieve improved levels of early diagnosis of cancer, the public should be assisted in achieving a reasonable level of awareness of specific cancer symptoms, understanding the urgency of these symptoms, overcoming fear or stigma associated with cancer and be able to easily access appropriate healthcare referral and advice. Examples of such warning signs for a subset of common cancers are shown in Table 3.

Table 3: Common symptoms and warning signs associated to main cancer types

Site of cancer	Common symptoms
Breast	Lump in the breast, asymmetry, skin retraction, recent nipple retraction, blood stained nipple discharge, eczematous changes in areola
Cervix	Post-coital bleeding, excessive vaginal discharge
Colon and rectum	Change in bowel habits, unexplained weight loss, anaemia, blood in the stool (rectal cancer)
Oral cavity	White lesions (leukoplakia) or red lesions (erythroplakia), growth or ulceration in mouth
Naso-pharynx	Nosebleed, permanent blocked nose, deafness, nodes in upper part of the neck
Larynx	Persistent hoarseness of voice
Stomach	Upper abdominal pain, recent onset of indigestion, weight loss
Skin melanoma	Brown lesion that is growing with irregular borders or areas of patchy colouration that may itch or bleed
Other skin cancers	Lesion or sore on skin that does not heal
Urinary bladder	Pain, frequent and uneasy urination, blood in urine
Prostate	Difficulty (long time) in urination, frequent nocturnal urination
Retinoblastoma	White spot in the pupil, convergent strabismus (in a child)
Testis	Swelling of one testicle (asymmetry)

Source: Guide to cancer early diagnosis. Geneva: World Health Organisation; 2017.

Note: These common symptoms may be due to cancer or due to a different medical condition. People with these symptoms should seek medical attention without delay.

To make greater progress in Europe in respect to patient awareness of early warning signs of cancer requires improving population-level health literacy. Indeed, a recent survey of European cancer experts, published in 2019 and conducted by the EU co-funded Joint Action iPAAC (innovative Partnership for Action Against Cancer) found lack of awareness of these signs in the general public to be one of the most cited barriers to achieving earlier diagnosis of cancer²⁹⁹.

In its recent response to the Roadmap Consultation on Europe's Beating Cancer Plan the European Cancer Organisation suggested that an EU-level project to improve health literacy vis-à-vis citizens' ability to recognise potential early warning signs of cancer could be of enormous value in improving early detection, and may be achieved at comparatively modest cost³⁰⁰. The example of the EU-supported European Code Against Cancer in respect to helping European citizens to understand how to reduce their cancer risk, was suggested as an example to learn from and potentially emulate in this respect.

b. Healthcare providers and early signs of cancer

Another critical element of early diagnosis of cancer is accurate clinical evaluation, diagnosis and staging by healthcare providers. Accurate clinical diagnosis requires the clinical skills and knowledge

²⁹⁹ Lack of awareness is a major barrier to early cancer detection: <https://www.ipaac.eu/news-detail/en/24-lack-of-awareness-is-a-major-barrier-to-early-cancer-detection/>.

³⁰⁰ Public consultation on Europe's Beating Cancer Plan: <https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12154-Europe-s-Beating-Cancer-Plan/F507755>.

of healthcare professionals within a health system to be of requisite levels to identify potential symptoms described or presented by patients and refer to appropriate specialist expertise in a timely fashion. The regulation of the skills and competences of healthcare professionals is primarily undertaken at national levels, with some EU-level role where the specific clinical profession is subject to harmonisation of training requirements under the Professional Qualifications Directive (Directive 2005/36/EC, as amended by Directive 2013/55/EU). The work of European-level healthcare professional associations in delivering high quality continuing professional education also supports the achievement of continuous upskilling of healthcare professions with roles in early diagnosis.

Beyond knowledge of cancer-associated symptoms, it is also important to increase awareness of cancer risk factors and risk indicators in the context of cancer early diagnosis. Individuals with a higher risk of cancer, owing to either indicators of hereditary cancer predisposition³⁰¹ or exposure to known modifiable cancer risk factors, should benefit from active surveillance programmes allowing for earlier diagnosis of the cancer they may develop. The presence of cancer risk-factors and indicators may put the patients symptoms in different perspective and call for different courses of action; for instance, rectal blood loss rarely is a sign of colorectal cancer in young adults, but should be seen as an important warning sign in those with a strong positive cancer family history. Moreover, primary healthcare providers are well placed to provide these patients with information and advice, as well as to direct them to genetic testing and genetic counselling³⁰².

The European Cancer Organisation has recently emphasised the particular roles that healthcare professionals in the primary care sector should conduct in achieving earlier diagnosis of cancer via a new consensus publication entitled "Essential Requirements for Quality Cancer Care: Primary Care"³⁰³.

Amongst its key recommendations include the need for all General Practitioners/Community Doctors in Europe to have access to clear and useable guidelines and risk assessment tools for detecting and preventing cancer. These tools must be integrated into electronic medical records for optimal use and must help to avoid increasing rates of overdiagnosis and overtreatment.

2.2.2. Efficiency and timeliness of patient referral

All healthcare systems in Europe wrestle with the challenge of efficiency in respect to achieving early and accurate diagnosis and timely referral. Indeed, a 2019 pan-European survey by the All.Can collaboration found that of almost 4,000 cancer patients and caregivers surveyed, 26% cited diagnosis as the area of cancer care where they identified the most inefficiency in their experience, more than any other area of cancer care³⁰⁴.

a. Addressing shortages in the pathology workforce

Pathologic diagnosis is made by assessing cells and tissues for the presence of cancerous changes; accurate microscopic and molecular interpretation of these changes by pathologists is essential for establishing the diagnosis and prognosis of cancer, as well as for predicting its response to therapy. Procedures performed to obtain cells for pathology studies include collection of body fluids, fine-needle aspiration, core-needle biopsy, endoscopic biopsy, radiology-directed biopsy, surgical biopsy

³⁰¹ See section 1.1.1.b.i. about the roles of germline mutations in cancer causation and the indicators of hereditary cancer predisposition.

³⁰² See section 1.1.3.b. about access to genetic testing and genetic counselling.

³⁰³ Banks I, Weller D., Ungan M. et al., ECCO Essential Requirements for Quality Cancer Care: Primary Care. Crit Rev Oncol Hematol. 2019 Oct; 142: pp. 187-199.

³⁰⁴ All.Can patient survey: <https://www.all-can.org/what-we-do/research/patient-survey/>.

and surgical resection. The quality of pathology studies is critical, since an inaccurate diagnosis of cancer may result in harmful, inappropriate and unnecessary treatment³⁰⁵.

Unfortunately, health care systems in Europe and the rest of the world are suffering from a significant shortage of trained pathologists³⁰⁶. As a result, inefficient bottlenecks preventing early diagnosis of cancer are a common occurrence. Organisations such as Cancer Research UK and the Royal College of Pathologists consider such workforce shortages are contributing to real life delays in cancer diagnosis and treatment³⁰⁷.

b. Continuing investments in new diagnosis technologies

New technologies such as Artificial Intelligence (AI) and Deep Learning are offering promise of improvement in the quality of cancer diagnosis³⁰⁸. **Publicly funded research in the possible uses of these tools for improving the fight against cancer, including for detection and diagnosis, should be continued, including as part of the EU Cancer Mission.** In this context, the advance of Artificial Intelligence and Deep Learning in cancer diagnosis is closely linked to the full development of digital pathology, which greatly facilitates expert consultation, educational activities, and uniformity of diagnostic criteria across different European countries.

c. Quality indicators as a route for improving timeliness of referral

The EU co-funded Cancer Control Joint Action (CanCon) convened representative cancer stakeholders and experts from across Europe to examine and make joint conclusions on overcoming key challenges to improving cancer care and control. Amongst the areas considered was early diagnosis and improved referral. The final output of the Joint Action was the landmark "European Guide on Quality Improvement in Comprehensive Cancer Control"³⁰⁹. Amongst the many recommendations within the Guide are suggestions that health systems have in place core indicators to measure:

- interval of time between symptom suspicion/referral by a physician, detection and confirmation of the diagnosis; and
- delays in the delivery of treatments (surgery, chemotherapy and radiation therapy), due to diagnostic delays.

Recommendation: Improving early diagnosis of cancer in Europe

Opportunities for EU to make use of the Europe's Beating Cancer Plan and the EU Cancer Mission to improve the current European framework in respect to early diagnosis of cancer include:

- **helping to address workforce shortage and education/training needs** to assist earlier detection and diagnosis of cancer, including via monitoring instruments and utilisation of EU qualification recognition tools;
- **supporting initiatives that will improve public awareness of potential cancer symptoms**, taking inspiration from the success of the European Code Against Cancer; and
- **ensuring continued investment in research into relevant areas** such as the application of artificial intelligence and deep learning for the purposes of improving cancer detection.

³⁰⁵ Guide to cancer early diagnosis. Geneva: World Health Organisation; 2017.

³⁰⁶ Horton S., Sullivan R., Flanagan J. et al., Delivering Modern, High-Quality, Affordable Pathology and Laboratory Medicine to Low-Income and Middle-Income Countries: A Call to Action. Lancet. 2018 May 12; 391(10133): pp. 1953-1964.

³⁰⁷ Pathologists shortage "delaying cancer diagnosis": <https://www.bbc.com/news/health-45497014>.

³⁰⁸ AI - A vision for future cancer care: <https://www.theparliamentmagazine.eu/articles/event-coverage/ai-vision-future-cancer-care>.

³⁰⁹ European Guide for Quality National Cancer Control Programmes: https://cancercontrol.eu/archived/uploads/images/European_Guide_for_Quality_National_Cancer_Control_Programmes_web.pdf.

3. ACCESS TO CANCER TREATMENT, CARE AND RESEARCH

According to latest estimates from the IARC Global Cancer Observatory, nearly 3 million new people are diagnosed with cancer in the EU27 each year³¹⁰. Each newly diagnosed individual requires access to relevant treatment and care. Increasing knowledge of the biology of cancer and molecular characterisation of tumours are demonstrating that cancer is a heterogeneous disease, with hundreds of specific cancer types, defined on the basis of the anatomic site of the tumour and the cell type involved in abnormal proliferation³¹¹. Furthermore, each individual cancer differs according to the genetic changes underlying carcinogenesis and the individual characteristics of the affected patient. **Cancer treatment and care must therefore reflect the individuality of the patient and of their cancer.**

Furthermore, despite major progress in the treatment and management of cancer, cancer mortality remains high and is the second leading cause of death globally. According to latest estimates from the IARC Global Cancer Observatory, around 1.2 million cancer patients die from cancer every year³¹², which shows the need for access to end-of-life cancer care.

Therefore, **cancer treatment and care involve a very wide range of treatment modalities, spanning a large number of medical disciplines.** These notably include:

- cancer surgery, radiation therapy, interventional oncology;
- chemotherapy, nuclear therapy, immunotherapy, hormonal therapy, targeted therapy;
- primary care, specialist oncology nursing, oncology pharmacy; and
- psycho-oncology, supportive care and palliative care.

Furthermore, the **management of cancer cases by multidisciplinary teams, involving integration of all relevant medical professions, is known to be critical for the patient's outcome.** Cancer treatment and care can be seen as a complex machine of many constituent parts, all reliant upon each other to achieve the best results. Each medical profession brings unique skillsets and insights to the clinical decision-making process on individualised patient treatment and care. It is this **multidisciplinarity and multiprofessionalism** that ensures that cancer patients receive optimal treatment and care.

Key requirements to deliver the best treatment and care to cancer patients include:

- ensuring sustainable access to the best available treatment and to high-quality multidisciplinary care;
- enhancing possibilities of new technologies;
- improving opportunities for advanced education and specialty oncology training for healthcare professions;
- addressing known workforce shortages; and

³¹⁰ Incidence of cancer in 2018 in the EU27, retrieved from the IARC Global Cancer Observatory: <https://gco.iarc.fr/today/home> (accessed May 2020).

³¹¹ See section 1.1.1.d. about the heterogeneity of cancer.

³¹² Mortality of cancer in 2018 in the EU27, retrieved from the IARC Global Cancer Observatory: <https://gco.iarc.fr/today/home> (accessed May 2020).

- stimulating research for the improvement of cancer treatments and the elevation of the standards of cancer care.

3.1. Access to cancer treatment

KEY FINDINGS & RECOMMENDATIONS: ACCESS TO CANCER TREATMENT

Cancer treatment must be understood to be multimodal. Key modalities of cancer treatment include non-systemic treatments, such as radiation therapy and surgery, and systemic treatments through pharmaceutical agents. **There is a need to address inequalities in access to all forms of cancer treatment.**

Surgery is a key component of cancer treatment and contributes significantly to improved cancer survival in Europe. Surgery has the potential to cure most solid tumours and therefore remains the primary treatment option in cancer. In the EU, variations in the quality of surgery delivered and unequal access to appropriate surgical interventions leads to significant differences in cancer outcomes between groups of people within countries and between countries. **Recognising surgical oncology as a specialist discipline and facilitating patients' access to 'high volume' centres for cancer surgery could go a long way to addressing these differences.**

Radiation therapy is a safe and highly effective cancer treatment, using ionising radiation, predominantly high-energy X-rays. Radiation therapy is a key pillar of cancer treatment and is essential in more than half of all cases of cancer, to cure localised disease, palliate symptoms and control disease in incurable cancers. Radiation therapy is recommended as part of treatment for more than 50% of cancer patients. However, studies suggest that at least one in four people needing radiation therapy does not receive it. Despite its curative impacts, radiation therapy is a comparatively low cost investment too often neglected. **Promotion and recognition of harmonised education and training standards across Europe, and stronger investment of EU and national research and innovation funds to support radiation therapy research are amongst the chief requests to advance this field of treatment in all countries.**

The area of **cancer medicine** is undergoing rapid development and change, not least as a result of advances in personalised therapy and precision oncology. The advent of CAR-T therapy has been a prominent example in this regard. This, in turn, has been driving demands for change in terms of both regulatory approval mechanisms and in respect to pricing and reimbursement strategies for such new treatments. In this respect, **the new EU Pharmaceutical Strategy should be bold and ambitious in achieving a timely update of both regulatory and incentive models**, and taking full account of new developments in science, practice and evidence collection. The Strategy should also serve to achieve a lasting upgrade of the modes of cooperation between EU Member States in ensuring equitable and timely access for patients to medicines.

The delay in passing into legislation the European Commission's legislative proposal for improving Member State cooperation on Health Technology Assessment must end. Continued delay represents a serious frustration of a common will for its implementation.

To achieve longer term resolution of the persisting problem of **cancer medicines shortages**, the EU Pharmaceutical Strategy should: strengthen EU pharmaceutical legislation in respect to notification of shortage; provide clearer guidance to member states on the operation of parallel trade; bring better information sharing between countries in respect to shortage management and prevention; and, encourage improved procurement procedures for generic medicine.

As mentioned in the above introduction, **cancer treatment must be understood to be multimodal**. Key modalities of cancer treatment include:

- non-systemic treatments, such as cancer surgery, radiation therapy and interventional oncology; and
- systemic treatments through cancer medicines, used in chemotherapy, nuclear therapy, immunotherapy, hormonal therapy or targeted therapy.

Importantly, the treatment of individual cancer patients often requires the **combination of several of these treatment modalities**; two prominent categories of such combinations can be distinguished:

- neo-adjuvant therapies, which correspond to interventions (either medicines or radiation therapy) provided to the patient to shrink a tumour before the main treatment, which is usually surgery^{313,314}; and
- adjuvant therapies, in which cancer medicines are administered to the patient as an additional treatment after surgery or radiation therapy to lower the risk of cancer recurrence or eliminate remaining cancer cells³¹⁵.

There are known challenges and inequalities in respect to the access to all of these treatment modalities; all steps have to be addressed, from the development of new treatments to the requirements for their effective provision to the patients.

3.1.1. Access to non-systemic cancer treatments

As opposed to medical oncology treatments, non-systemic cancer treatments do not involve the spreading of substances through the patient's bloodstream to reach and affect cancer cells; they encompass three main modalities: cancer surgery, radiation therapy and interventional oncology.

a. Access to cancer surgery

Surgery is a key component of cancer treatment and contributes significantly to improved cancer survival in Europe. Surgery has the potential to cure most solid tumours³¹⁶ and therefore remains the primary treatment option in cancer. It is indeed estimated that 80% of all new cases of cancer require surgery, some several times³¹⁷. Therefore, surgeons have a central role in cancer prevention, diagnosis, treatment and research, leading the diagnostic and treatment pathways for most cancers. Surgeons are most often the first specialist that the patient meets and are involved in the whole patient pathway, from counselling patients about their diagnosis to surgery and aftercare³¹⁸.

As opposed to many other cancer treatment modalities, surgery is a local treatment, affecting only the anatomic site of the tumour. It can be used to physically remove either the entire tumour, or only a part of it ("debulking"), in cases where entire removal would result in organ (or body) damage, often in

³¹³ US National Cancer Institute's definition of neo-adjuvant therapies: <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/neoadjuvant-therapy> (accessed May 2020).

³¹⁴ See section 3.1.1.a. about the critical importance of cancer surgery in cancer treatment.

³¹⁵ US National Cancer Institute's definition of adjuvant therapies: <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/adjuvant-therapy> (accessed May 2020).

³¹⁶ Solid tumors are defined as opposed to "liquid", or haematological, tumours, which involve abnormal proliferation of cells in the blood or in the blood marrow, such as leukaemias.

³¹⁷ Sullivan R., Alatisse O.I., Anderson B.O. et al., Global cancer surgery: delivering safe, affordable, and timely cancer surgery. *Lancet Oncol.* 2015; 16(11): pp. 224-1193.

³¹⁸ See the European Society of Surgical Oncology (ESSO) White Paper "The value of surgical oncology in the management of cancer patients": <https://www.essoweb.org/media/documents/value-of-surgical-oncology.pdf> (published April 2020; accessed June 2020).

combination with other treatment modalities to successfully treat patients. Selected patients with metastatic disease can also benefit from surgery³¹⁹. In the palliative setting, surgery can also ease cancer symptoms by removing tumours causing pain or pressure³²⁰. Furthermore, surgery can also, in some specific cases, be used as a prophylactic approach for primary prevention of cancer³²¹.

Importantly, cancer surgery greatly benefits from scientific developments allowing to gain an increased understanding of tumour biology at the molecular level; this indeed allows to define the best timing for cancer surgery to be performed, as well as to what extent nearby tissues surrounding the tumour should also be removed. Furthermore, recent years have also seen **the emergence of a number of technological advances in cancer surgery, including robotic assisted surgery, image-guided minimally-invasive cancer surgery and organ sparing surgery**. These innovations offer opportunities to improve the precision of surgical procedures, as well as to decrease immediate and long-term side-effects faced by cancer patients after surgery³²². Nevertheless, it is crucial to fully evaluate these innovations, as well as to provide related training and implement quality assurance systems, so that patient safety can be ensured³²³.

Despite the increasing incidence of cancer and the need for surgery as a viable treatment, **only 25% of the patients worldwide will receive safe, timely, affordable, and high-quality surgical care**. In the EU, **variations in the quality of surgery delivered and unequal access to appropriate surgical interventions leads to significant differences in cancer outcomes** between patients, within countries and between countries³²⁴. These variations in surgical performance can be related to surgeon activity and workload, including how many specific cancer patients they operate a year (volume), as well as to subspecialty certification and to the hospital setting. Multiple studies have indeed evidenced that "high volume" cancer centres and surgical specialists have better outcomes for treating complex or advanced cancers. Furthermore, it has been shown that specialised surgeons have better outcomes for cancer surgery than their non-specialised colleagues³²⁵.

³¹⁹ See the European Society of Surgical Oncology (ESSO) White Paper "The value of surgical oncology in the management of cancer patients": <https://www.essoweb.org/media/documents/value-of-surgical-oncology.pdf> (published April 2020; accessed June 2020).

³²⁰ US National Cancer Institute's factsheet about cancer surgery: <https://www.cancer.gov/about-cancer/treatment/types/surgery> (accessed May 2020).

³²¹ See section 1.2.2.b. about prophylactic surgery in cancer.

³²² US National Cancer Institute's factsheet about cancer surgery: <https://www.cancer.gov/about-cancer/treatment/types/surgery> (accessed May 2020).

³²³ See the European Society of Surgical Oncology (ESSO) White Paper "The value of surgical oncology in the management of cancer patients": <https://www.essoweb.org/media/documents/value-of-surgical-oncology.pdf> (published April 2020; accessed June 2020).

³²⁴ See the European Society of Surgical Oncology (ESSO) White Paper "The value of surgical oncology in the management of cancer patients": <https://www.essoweb.org/media/documents/value-of-surgical-oncology.pdf> (published April 2020; accessed June 2020).

³²⁵ Bilimoria K.Y., Phillips J.D., Rock C.E. et al., Effect of surgeon training, specialisation, and experience on outcomes for cancer surgery: a systematic review of the literature. *Ann Surg Oncol*. 2009; 16(7): pp. 808-1799.

Recommendation: Strengthening surgical systems in the EU

Disparities in the quality of cancer surgery, as well as the increased complexity of this field, show the need for strengthening surgical systems in the EU. This can be achieved by:

- recognising surgical oncology as a specialist discipline and establishing pan-European quality standards in cancer surgery;
- facilitating patients' access to 'high volume' centres for cancer surgery;
- investing in public sector infrastructure, as well as in education and training of oncology surgeons; and
- implementing access to innovative surgical procedures, provided that innovation is sustainable and brings sufficient added value to cancer patients.

Owing to the crucial importance of surgery in cancer treatment, measurements aiming at monitoring these efforts should be part of a newly established European Cancer Dashboard.

Source: Kovacs T., Rubio I.T., Markopoulos C. et al., BRESO Structure Working Group. Theoretical and practical knowledge curriculum for European Breast surgeons. *Eur J Surg Oncol.* 2020 Apr; 46(4 Pt B): p. 717. The European Guide on Quality Improvement in Comprehensive Cancer Control 2017. Policy Paper 4, "Tackling Social Inequalities in Cancer Prevention and Control".

b. Access to radiation therapy

Radiation therapy is a safe and highly effective cancer treatment, using ionising radiation, predominantly high-energy X-rays. Radiation therapy allows cancer specialists to precisely target and destroy tumour cells by delivering the most effective dose possible.

Radiation therapy is a key pillar of cancer treatment and is essential in more than half of all cases of cancer, to cure localised disease, palliate symptoms and control disease in incurable cancers.

Indeed, radiation therapy cures many cancers. There is evidence that 40% of all cancers cured are eliminated by radiation therapy, either alone or acting in combination with other types of treatment^{326, 327}. It can be used on its own or to complement or enhance the effects of other treatments, for example to shrink or control a cancer before and after surgery or in combination with chemotherapy, targeted therapy or immunotherapy.

Radiation therapy is evolving and innovating quickly, not only due to the development of higher performance radiotherapy machines, but also thanks to the better integration of imaging before and during treatment, and because of stronger capabilities brought about as a result of stronger IT computation algorithms. This has led to newer techniques with growing accuracy in delivering the dose to the target, while optimally sparing the surrounding critical organs. As a consequence, local control is improving, and acute and late toxicity is decreasing, paving the way for shorter treatment schedules, better integration with systemic cancer treatments and the addressing of new indications and patient populations³²⁸.

³²⁶ Hanna T.P., Shafiq J., Delaney G.P. et al., The population benefit of evidence-based radiotherapy: 5-Year local control and overall survival benefits. *Radiother Oncol.* 2018 Feb; 126(2): pp. 97-191.

³²⁷ Department of Health Cancer Policy Team. 2012 Radiotherapy Services in England 2012. London: Department of Health.

³²⁸ Thompson M.K., Poortmans P., Chalmers A.J. et al., Practice-changing radiation therapy trials for the treatment of cancer: where are we 150 years after the birth of Marie Curie? *Br J Cancer.* 2018 Aug; 119(4): pp. 389-407.

Radiation therapy is recommended as part of treatment for more than 50% of cancer patients. **However, studies suggest that at least one in four people needing radiation therapy does not receive it**^{329, 330}.

With rising cancer incidence, it is forecast that demand for radiation therapy will increase by 16% by 2025, with current capacity insufficient to meet this demand³³¹. The case for increased investment in radiation therapy capacity is supported by projections that if, by 2035, every cancer patient requiring radiation therapy could gain access to it, almost one million more lives would be saved every year worldwide³³².

Across Europe, there is a 6 to 7 - fold variation in the access to radiation therapy equipment and a 3 to 5 - fold variation in available personnel and workload. The courses delivered annually per resource item - be it equipment or staff - increase with decreasing gross national income per capita^{333, 334}.

Despite its curative impacts, radiation therapy is a comparatively low-cost investment too often neglected. Even if radiation therapy is a major component of cancer care, it only accounts for a small proportion of the cancer budget; in Sweden and England, for example, this figure is just 5%^{335, 336}.

Recommendation: Addressing radiation therapy challenges in the EU

Practical means by which access to high quality radiation therapy for cancer patients could be improved by action at the European level include:

- recognition of medical physics and radiation therapy as dedicated disciplines;
- promotion and recognition of harmonised education and training standards across Europe; and
- stronger investment of EU and national research and innovation funds to support radiation therapy research.

Owing to the crucial importance of radiation therapy in cancer treatment, measurements aiming at monitoring these efforts, including access to innovative radiotherapy technology and techniques³³², should be part of a newly established European Cancer Dashboard.

c. Access to interventional oncology

Interventional radiology is a medical subspecialty that performs minimally-invasive procedures for disease diagnosis and treatment under image guidance. These targeted techniques apply to a broad field of medical conditions, and over the past couple of decades they have made inroads into the field of cancer therapeutics.

³²⁹ Borrás J.M., Barton M., Grau C. et al., The impact of cancer incidence and stage on optimal utilisation of radiotherapy: Methodology of a population based analysis by the ESTRO-HERO project. *Radiother Oncol.* 2015 Jul; 116(1): pp. 45-50.

³³⁰ Borrás J.M., Lievens Y., Dunscombe P. et al., The optimal utilisation proportion of external beam radiotherapy in European countries: An ESTRO-HERO analysis. *Radiother Oncol.* 2015 Jul; 116(1): pp. 38-44.

³³¹ Borrás J.M., Lievens Y., Barton M. et al., How many new cancer patients in Europe will require radiotherapy by 2025? An ESTRO-HERO analysis. *Radiother Oncol.* 2016 Apr; 119(1): pp. 5-11.

³³² Atun R., Jaffray D.A., Barton M.B. et al., Expanding global access to radiotherapy. *Lancet Oncol.* 2015 Sep; 16(10): pp. 86-1153.

³³³ Lievens Y., Defourny N., Coffey M. et al., Radiotherapy staffing in the European countries: final results from the ESTRO-HERO survey. *Radiother Oncol.* 2014; 112: pp. 86-178.

³³⁴ Grau C., Defourny N., Malicki J. et al., Radiotherapy equipment and departments in the European countries: final results from the ESTRO-HERO survey. *Radiother Oncol.* 2014; 112: pp. 64-155.

³³⁵ Department of Health Cancer Policy Team. 2012 Radiotherapy Services in England 2012. London: Department of Health.

³³⁶ Norlund A., Costs of radiotherapy. *Acta Oncol.* 2003; 42(5-6): pp. 5-411.

Interventional oncology, the branch of interventional radiology dedicated to the diagnosis and treatment of cancer and cancer-related problems, has expanded rapidly over the past two decades to a **separate pillar of modern, personalised, multidisciplinary oncologic treatment**, alongside medical, surgical and radiation oncology. Interventional oncology allows for **direct delivery of treatments to the tumour site**; patients benefit greatly from these interventions, which are also often well suited to be combined with systemic or surgical treatments, further increasing the chance of cure. Given the numerous side effects often associated with cancer treatment, the **minimally-invasive nature of interventional oncology treatments means they usually cause less pain, fewer side effects and shorter recovery times**. Furthermore, many interventional oncology treatments can be performed on an outpatient basis, freeing up hospital beds and reducing costs.

In practice, interventional oncology employs various imaging modalities, including X-ray, ultrasound, computed tomography or magnetic resonance imaging (MRI), to help guide miniaturised instruments (e.g. biopsy needles, ablation devices, intravascular catheters) to allow targeted and precise treatment of solid tumours located in various organs of the human body, including but not limited to the liver, kidneys, lungs, and bones. Performed interventions mainly fall into two categories:

- percutaneous tumour ablation, in which a needle is placed through the skin on the tumour site thanks to image guidance and thereafter used to kill tumour cells through local delivery of either chemicals, or electric, electromagnetic or thermal energy; and
- tumour embolisation, in which catheters are used to kill tumour cells by occluding the tumour's blood supply and/or delivering chemotherapy agents or radiopharmaceuticals into blood vessels feeding the tumour^{337,338}.

In addition, a third category in the next future would be to locally deliver immune therapies or to enhance immune treatments with thermal and embolic effects.

Furthermore, interventional oncology also plays an important role in cancer diagnosis, through image-guided tissue biopsies, and in symptom palliation, such as for instance through regional anaesthesia from neurolysis³³⁹, cementoplasty³⁴⁰, gastrostomy³⁴¹, stenting of gastrointestinal stenosis³⁴² or treatment of vascular compression.

As compared to other approaches to cancer treatment, interventional oncology is a relatively young discipline, requiring a unique skillset, and the access to this treatment option is still limited.

³³⁷ Kim H.S., Chapiro J., Geschwind J.H., From the guest editor: Interventional oncology: the fourth pillar of oncology. *Cancer J.* 2016 Nov/Dec; 22(6): pp. 363-364.

³³⁸ Schoenberg S.O., Attenberger U.I., Solomon S.B. et al., Developing a roadmap for interventional oncology. *Oncologist.* 2018 Oct; 23(10): pp. 1162-1170.

³³⁹ Neurolysis is the deliberate destruction of a nerve or a network of interlacing nerves (plexus) with the aim of providing permanent relief from pain by interrupting the transmission of pain signals in the nerves. See CIRSE's factsheet about neurolysis for pain palliation: <https://www.cirse.org/patients/ir-procedures/neurolysis-and-plexus-infiltrations/> (accessed May 2020).

³⁴⁰ Cementoplasty means using a special cement to strengthen and support bone for pain palliation and prevention of bone breaks in patients affected by bone metastasis. See Cancer Research UK's factsheet about strengthening painful bones: <https://www.cancerresearchuk.org/about-cancer/coping/physically/cancer-and-pain-control/treating-pain/strengthening-painful-bones> (accessed May 2020).

³⁴¹ Gastrostomy is a procedure in which a tube is placed into the patient's stomach for nutritional support. See CIRSE's factsheet about gastrostomy: <https://www.cirse.org/patients/ir-procedures/gastrostomy/> (accessed May 2020).

³⁴² Stenting of gastrointestinal stenosis refers to a temporary measure for gastrointestinal tract decompression, practiced in cancer patients with obstructed colon. See Bonin EA, Verschoor B, Silva FH. Stents in Gastrointestinal Diseases. See: <https://www.intechopen.com/books/advanced-endoscopy/stents-in-gastrointestinal-diseases> (accessed May 2020).

Priorities identified by experts in the field focus on establishing interventional oncology as a mainstream oncological discipline and enhancing patient safety, through:

- **standardised education and training** of interventional oncologists³⁴³;
- the **development of guidelines** ensuring provision of high-quality interventional oncology³⁴⁴; and
- **setting up an accreditation system** for interventional oncology services demonstrating compliance with the published guidelines³⁴⁵.

3.1.2. Access to cancer medicines

Overview of the main medicines-based modalities of cancer treatment

Treatment of cancer through administration of cancer medicines includes five main modalities:

- **chemotherapy**, involving cytotoxic drugs aimed at killing cells undergoing active proliferation, including cancer cells³⁴⁶; and
- **nuclear therapy**; involving radioactive pharmaceuticals (radiopharmaceuticals), consisting of a drug targeted to the patient's tumour linked to a radionuclide, primarily applied to the treatment of thyroid cancer, but whose principle is currently expanding to other tumour types, such as neuroendocrine tumours³⁴⁷ and prostate cancer³⁴⁸.

In detail, the same drug is first used in combination with a gamma-emitting radionuclide for molecular imaging of the tumour through Positron Emission Tomography (PET) and then with an alpha- or beta-emitting radionuclide for local destruction of cancer cells. This approach, relying on the distinct physical properties of alpha, beta and gamma radiations to integrate diagnosis and treatment within a single procedure, therefore allows the nuclear medicine radiologists to "see what they treat" and "treat what they see" and is referred to as the "theragnostics" concept³⁴⁹.

- **immunotherapy**³⁵⁰; involving medicines aimed at stimulating the patient's immune response against its tumour, including:
 - **molecular agents**, such as:
 - **monoclonal antibodies** targeting molecules specifically present on the surface of cancer cells to mark these cells and facilitate their destruction by the patient's immune cells;

³⁴³ See the European curriculum and syllabus for interventional oncology published by the Cardiovascular and Interventional Radiological Society of Europe (CIRSE): https://www.cirse.org/wp-content/uploads/2019/03/cirse_IOcurriculum_syllabus_2018_web.pdf (accessed May 2020).

³⁴⁴ See the standards for quality assurance in interventional oncology published by the Cardiovascular and Interventional Radiological Society of Europe (CIRSE): https://www.cirse.org/wp-content/uploads/2020/01/IASIOS_quality_standards_in_IO_2019_V2_web.pdf (accessed May 2020).

³⁴⁵ See the International Accreditation System for Interventional Oncology Services currently developed by the Cardiovascular and Interventional Radiological Society of Europe (CIRSE): <https://www.iasios.org/> (accessed May 2020).

³⁴⁶ US National Cancer Institute's factsheet about chemotherapy: <https://www.cancer.gov/about-cancer/treatment/types/chemotherapy> (accessed May 2020).

³⁴⁷ Strosberg J., El-Haddad G., Wolin E. et al., Phase 3 Trial of Lu-177-Dotatate for Midgut Neuroendocrine Tumors. *N Engl J Med.* 2017; 12: pp. 125-135.

³⁴⁸ Rahbar K., Ahmadzadehfar H., Kratochwil C. et al., German Multicenter Study Investigating 177Lu-PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients. *J Nucl Med.* 2017; 58: pp. 85-90.

³⁴⁹ European Association of Nuclear Medicine's (EANM) factsheet about nuclear therapy: <https://www.eanm.org/publicpress/patient-info/patient-info-nuclear-medicine/> (accessed May 2020).

³⁵⁰ US National Cancer Institute's factsheet about immunotherapy: <https://www.cancer.gov/about-cancer/treatment/types/immunotherapy> (accessed May 2020).

- **immune checkpoint inhibitors**, directed against molecules involved in inhibitory mechanisms (immune checkpoints), which affect the activation state of the patient's immune cells: blocking these mechanisms and allowing these cells to mount a stronger immune reaction to the cancer; and
- **immune system modulators**, aimed at activating specific pathways and components of the patient's immune system involved in the response against cancer.
- o **cellular agents**, used for:
 - **T-cell transfer therapies**, in which T cells (which are among the immune cell repertoire the cells having the specific ability to specifically recognise and kill cancer cells) are collected from the patient and either selected and grown in the laboratory (in the case of Tumour-Infiltrating Lymphocytes (TIL) therapy) or also modified to improve their affinity for cancer cells (in the case of Chimeric Antigen Receptor (CAR) T-cell therapy), before being given back to the patient; and
 - **cancer treatment vaccines**, in which tumour cells or other immune cell types from the patient are also collected, treated in the laboratory and adoptively transferred again into the patient to boost their specific immune response against the tumour³⁵¹.
- **hormonal therapy**, targeting hormones used by cancer cells to grow in certain cancer types (notably breast and prostate cancers), by using drugs either to block the body's ability to produce such hormones or to interfere with their behaviour in the body³⁵²; and
- **targeted therapy**, using pharmaceutical agents or monoclonal antibodies to target molecules regulating the growth, the division and/or the metastatic spread of cancer cells³⁵³.

The emerging concept of personalised medicine and its impacts in the field of cancer medicines

As our understanding of the biology of cancer has expanded, particularly through the use of molecular biology techniques, this has informed a more precise, personalised approach to cancer treatment. This has given rise to the era of precision oncology³⁵⁴, where knowledge of the molecular abnormality implicated in the development of cancer³⁵⁵, for example the presence of the BCR-ABL leukaemia specific protein in Chronic Myeloid Leukaemia, the over production of the erbB2 protein in breast cancer, has allowed the development of a new class of medicines (Imatinib Mesylate for CML, Herceptin for breast cancer) which specifically target the abnormal cancer causing protein. These precision oncology medicines have been practice changing, providing a more targeted "personalised" approach

³⁵¹ Similarly to "classical" vaccines, "cancer treatment vaccines" are designed to elicit an immune response specifically directed against cancer; crucially however, they aim at treating cancer, not at preventing its onset. Of note, alongside cell adoptive transfer modalities, they also include the direct administration of tumour antigens to immunise cancer patients and the use of oncolytic viruses, i.e. modified viruses that will target, infect and kill cancer cells. See US National Cancer Institute's factsheet about "cancer treatment vaccines": <https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/cancer-treatment-vaccines> (accessed May 2020).

³⁵² US National Cancer Institute's factsheet about hormonal therapy: <https://www.cancer.gov/about-cancer/treatment/types/hormone-therapy> (accessed May 2020).

³⁵³ US National Cancer Institute's factsheet about targeted therapy: <https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies> (accessed May 2020).

³⁵⁴ Lawler M., Hanna G.G., Prue G. et al., Report: Evidence-enabled outcomes research to inform precision oncology innovation adoption by health systems. (2017).

³⁵⁵ Lawler M., Selby P., Personalised cancer medicine: are we there yet? *Oncologist*. 2013; 18: pp. 50-649.

to healthcare³⁵⁶. However, while these two medicines have changed the way in which we treat these diseases, precision oncology has had variable success and more research is required to ensure the best outcomes for patients. Precision oncology medicines can also be expensive and challenge health systems budgets so a balance must be found between treatment efficacy and cost effectiveness³⁵⁷.

Companion diagnostic tests allow these innovative precision oncology medicines to be targeted to particular molecular subtypes in different cancers (e.g. breast, lung, colorectal, blood cancers), thus maximising their therapeutic potential. Diagnostic tests in Europe (including diagnostic tests for cancer) have been regulated by the In Vitro Diagnostic Directive (Directive 98/79/EC – IVDD) from 27 October of 1998. However, this will change when the In Vitro Diagnostic Regulation (Regulation (EU) 2017/746 – IVDR) becomes applicable on 26th May 2022 after a five-year transition period. A number of potential problems have been highlighted in to how the regulation will be interpreted and how this may adversely impact on diagnostic testing in Europe, particularly in relation to Laboratory Developed Tests (LDTs) for a range of clinical conditions including cancer. Most immediate issues could include lack of availability of tests, which will affect patients' treatment decisions and outcomes, and which is an unintended consequence of the regulation. The new IVD Regulation must not make it more difficult to perform innovative tests for cancer diagnosis and treatment allocation, particularly in relation to precision oncology. In addition, it is important to ensure equal access to molecular diagnostics to ensure that all European cancer patients can receive effective innovative precision oncology medicines³⁵⁸.

Overview of the main challenges in respect to access to cancer medicines

Both essential³⁵⁹ and innovative medicines play a very important role in improving the quality and the length of life of cancer patients. Access challenges are many, but often relate to high costs, reimbursement decision-making and physical availability (e.g. shortage).

a. Cancer medicines approval

i. Cancer medicines approval procedures

All medicines must be authorised before they can be marketed and made available to patients. In the EU, there are two main routes for authorising medicines: a centralised route and a national route. Central authorisation is administered by the European Medicines Agency (EMA). Cancer medicines are significant beneficiaries of this procedure, which applies to both new active drugs and biosimilar³⁶⁰ cancer medicines. In 2018 almost half of all EMA extensions of indication related to centrally authorised medicines were for cancer medicines.

ii. Cancer medicines approval challenges

Cancer medicines accelerated market access pathways

It is necessary to balance the evaluation of safety and efficacy of new medicines, simultaneously with fast market access of treatments, particularly in the areas of high unmet medical need. The assessment

³⁵⁶ Horgan D., Paradiso A., McVie G. et al., Is precision medicine the route to a healthy world? *Lancet*. 2015 Jul 25; 386(9991): pp. 7-336.

³⁵⁷ Lawler M., French D., Henderson R. et al., Shooting for the Moon or Flying Too Near the Sun? Crossing the Value Rubicon in Precision Cancer Care. *Public Health Genomics*. 2016; 19: pp. 6-132.

³⁵⁸ Plun-Favreau J., Immonen-Charalambous K., Steuten L. et al., Enabling Equal Access to Molecular Diagnostics: What Are the Implications for Policy and Health Technology Assessment? *Public Health Genomics*. 2016; 19: pp. 52-144.

³⁵⁹ WHO model lists of essential medicines: <https://www.who.int/medicines/publications/essentialmedicines/en/>.

³⁶⁰ A biosimilar is a biological medicine highly similar to another already approved biological medicine (called "reference medicine" or "originator"). Biosimilars are approved according to the same standards of pharmaceutical quality, safety and efficacy that apply to all biological medicines by the EMA.

of a marketing authorisation application for a new medicine takes up to 210 "active" days. This active evaluation time is the time spent by EMA experts to critically appraise the evidence provided by the applicant. This time is interrupted by one or two "clock-stops" during which the applicant prepares the answers to any questions raised by the Committee for Medicinal Products for Human Use (CHMP)³⁶¹. Overall, the assessment of a new medicine takes approximately around a year, depending on the amount of outstanding issues and the length of the time period in which the applicant answers them³⁶².

To ensure access to new promising therapies to patients in a timely manner, the EMA initiated several accelerated approval programmes, these include:

- **the PRIME scheme**, which offers accelerated approval and increased cooperation with a sponsor and the EMA for medicines offering major therapeutic advantage over existing treatments or benefit to patients without treatment options (for instance, the 2018 approval of CAR-T cell therapies benefited from this scheme);
- **conditional marketing authorisation**, which is awarded for medicines where the benefit of the immediate availability of the medicine outweighs the risk of less comprehensive data, for example in the case of serious, debilitating or life-threatening disease; and
- **adaptive pathways** aimed at medicines addressing unmet medical needs in specific groups of patient populations.

In 2019, out of the seven new active medicines approved in oncology and haemato-oncology, four received a conditional marketing authorisation³⁶³. However, introduction of these fast-track processes has not been without criticism. Some published studies have raised questions about the quality of data on which approved decisions are being made, as well as ethical implications if patients access such therapies without a fuller understanding of their particular risk-benefit profile^{364, 365}.

Personalised treatments driving changes in regulatory approach

Treatments such as Imatinib Mesylate (for Chronic Myeloid Leukaemia) and Herceptin (for erb-B2 positive breast cancer) highlighted the potential for precision oncology and underpinned a personal healthcare revolution. Multi-stage, multi-arm clinical trials which recruit patients based on the molecular make-up of their tumour³⁶⁶, are increasingly being used to deliver innovative medicines to patients. But these new approaches require more flexible and nimbler regulatory framework to ensure delivery of optimal therapies for patients.

The 2019 EMA approval of Kymriah® and Yescarta® as the first two "CAR-T cell therapies" for use in the EU³⁶⁷ was a significant moment in respect to an emerging era in which regulatory approvals for these new forms of medicines are expected to be an increasing part of the Agency's workload.

Both Kymriah and Yescarta are indicated for use for patients with blood cancers. They belong to a new generation of personalised cancer immunotherapies that are based on collecting and modifying the

³⁶¹ Committee for Medicinal Products for Human Use; the committee responsible for preparing the Agency's opinions on questions concerning human medicines.

³⁶² The evaluation of medicines, EMA step-by-step:

<https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/evaluation-medicines-step-step>.

³⁶³ EMA Human medicines highlights 2019: https://www.ema.europa.eu/en/documents/report/human-medicines-highlights-2019_en.pdf.

³⁶⁴ Hoekman, J., Boon W.P., Bouvy J.C. et al., Use of the conditional marketing authorisation pathway for oncology medicines in Europe. *Clin Pharmacol Ther.* 2015 Nov; 98(5): pp. 41-534.

³⁶⁵ Banzi R., Gerardi C., Bertele' V. et al., Conditional approval of medicines by the EMA. *BMJ.* 2017 May 2; 357: j2062.

³⁶⁶ Lawler M., Kaplan R., Wilson R.H. et al., Changing the Paradigm-Multistage Multiarm Randomised Trials and Stratified Cancer Medicine. *Oncologist.* 2015; 20: pp. 51-849.

³⁶⁷ First two CAR-T cell medicines recommended for approval in the European Union:

<https://www.ema.europa.eu/en/news/first-two-car-t-cell-medicines-recommended-approval-european-union>.

patients' own immune cells to treat their cancer.

However, these emerging treatments pose numerous new challenges for the regulatory agency in respect to the lack of available evidence on the medicines' efficacy and safety at the time of approval and the need for a robust system of real-world data collection in the post-authorisation phase.

Improving our understanding of the clinical impact of approved cancer medicines

The increasing trend of personalisation in medicine and new treatment options for diseases with small patient populations is now being accompanied with scrutiny on the available evidence in respect to the treatment and efficacy of such treatments. The small trial populations, some numbering 100 or less, can make extrapolation to "real world" impact problematic. For example, it is known that trial samples often under-represent the generally older population and large number of co-morbidities among the overall patient population³⁶⁸.

Aligned with this, a challenge to the existing medicines approval landscape is being posed by evidence of lower than expected clinical value from some approved cancer medicines. As an example, in 2017 a study was published in the British Medical Journal that analysed the efficacy of 48 new treatments approved for 68 indications by the EMA between 2009 and 2013. The study highlighted that only 35% (24 indications) resulted in prolonged survival ranging from 1 to 5.8 months (with a median of 2.7 months). Moreover, out of the treatments associated with the prolonged survival, only 48% (11 indications) were deemed to be clinically meaningful according to the standards developed by the **European Society of Medical Oncology (ESMO)**^{369, 370}.

To address these issues, in the newly published EMA "Regulatory science to 2025" Strategy, the Agency has placed a strong emphasis on data quality, evidence generation and post-marketing follow up, including enhanced involvement of patient and other stakeholders in the monitoring of performance of new products and in the generation and assessment of real-world evidence post (conditional/full) marketing authorisation³⁷¹. Furthermore, the EMA aims to cooperate more closely with Health Technology Assessment bodies and payers in order to ensure their data requirements fit both the purpose of market approval as well as the cost-effectiveness analysis used by HTA and payers for the purpose of product reimbursement.

b. Cancer medicines pricing and reimbursement

Europe, alongside the rest of the developed world, is experiencing an increasing incidence of cancer, partly in consequence of an ageing population. Meanwhile, new science and technology is bringing forward an increasing amount of treatment options in respect to radiation oncology, surgery, and in pharmaceutical treatment. Such positive developments are also accompanied by rising cost pressures on health systems, with equity of access to new medicines proving difficult to achieve. High prices are often cited as a main contributory factor³⁷². New scrutiny therefore falls on the current approaches towards medicines pricing and reimbursement in Europe and the available opportunities for

³⁶⁸ Prasad V., De Jesús K., Mailankody S., The high price of anticancer drugs: origins, implications, barriers, solutions. *Nat Rev Clin Oncol*. 2017 Jun; 14(6): pp. 381-390.

³⁶⁹ Davis C., Naci H., Gurpinar E. et al., Availability of Evidence of Benefits on Overall Survival and Quality of Life of Cancer Drugs Approved by European Medicines Agency: Retrospective Cohort Study of Drug Approvals 2009-13. *BMJ*. 2017 Oct 4;359: j4530.

³⁷⁰ ESMO Magnitude of Clinical Benefit (MCB) scale; see section 3.1.2.b.ii.

³⁷¹ EMA's "Regulatory Science to 2025" strategy: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf.

³⁷² Cherny N., Sullivan R., Torode J. et al., ESMO European Consortium Study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in Europe. *Ann Oncol*. 2016 Aug; 27(8): pp. 43-1423.

improvement, especially in the context of a forthcoming new EU Pharmaceutical Strategy to be published by the end of 2020.

Recommendation: An ambitious EU Pharmaceutical Strategy

The new EU Pharmaceutical Strategy should be bold and ambitious in achieving a timely update of regulatory and incentive models that takes account of new developments in science and practice.

The Strategy should also serve to achieve a lasting upgrade of the modes of cooperation between EU Member States in ensuring equitable and timely access for patients to cancer medicines.

i. Cancer medicines pricing

Medicines pricing models and the challenge of establishing value

"Cost-based pricing" is the primary model for establishing price of new medicines. In this model prices should reflect costs, including research and development (R&D), marketing, production costs, profit mark up, and R&D investment risk. This model is now often critiqued for the crude nature of its incentive structure, and also receives criticisms for transparency in respect to how the cost of development is accounted for and demonstrated.

As a shift away from cost-based pricing approaches, value-based pricing attempts to capture a patient- and payer relevant (incremental) value of the medicine e.g., a health gain compared to the current treatment. Any increase in price is justified by an increase in "units of health" compared to the current treatment available.

Contention can then arise in respect to demonstration of value. In recent years, a number of published studies have served to cast doubt on the level of meaningful benefit many new medicines are achieving over that of standard of care. For example, according to a recent German study reviewing new medicines brought to market between 2011 and 2017, only 54 (25%) of the 216 assessed by the study were judged to have a considerable or major added benefit³⁷³.

In the context of a forthcoming EU Pharmaceutical Strategy, the value of fostering stronger EU co-operation on issues such as measuring added therapeutic value of new medicines, as promoted in a recently published European Commission "Roadmap" consultation document, is well recognised^{374,375}.

Use of biosimilars as a perspective to address the increasing financial burden of cancer medicines

Due to patent expiry of many cancer treatments in the past years, the use of biosimilars in cancer has become increasingly important. Growing competition, particularly related to increased availability of biosimilars, significantly contributes to savings in medicine's budget, allowing for both greater availability of off-patent medicines, but also greater investments in innovative treatment options. Several studies showed the potential benefit of biosimilars on medicines spending. A 2016 study by IMS Health, a US-based health data service, concluded that an optimal uptake of biosimilars could lead

³⁷³ Wieseler B, McGauran N, Kaiser T., New drugs: when did we go wrong and can what we do better? *BMJ*. 2019 Jul 10; 366: 14340.

³⁷⁴ Pharmaceuticals – safe and affordable medicines (new EU strategy): <https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12421-Pharmaceutical-Strategy-Timely-patient-access-to-affordable-medicines>.

³⁷⁵ See section 3.1.2.b.ii. about regulatory approaches toward cancer medicines pricing and reimbursement, including Health Technology Assessment.

to cost savings up to €100 billion by 2020 in the US and the 5 biggest markets in the EU³⁷⁶. However, prices of generic medicines highly depend on the number of manufacturers. Another study showed that, for medicines with only one generic manufacturer, the price of the generic often did not differ from the price of the brand-name drug. With two competing manufacturers, the price drop was estimated between 10% and 50%, and with three or more manufacturers the price further continued to decrease³⁷⁷. **Nevertheless, the uptake of biosimilars after the patent expiry has been rather slow, and more education related to the product safety and trust building among healthcare professionals and payers is required**³⁷⁸.

European Commission responds to growing pressures with new Pharmaceutical Strategy

Due to emerging challenges in the European pharmaceutical system, both the European Medicines Agency³⁷⁹ and the European Commission are conducting a continuous evaluation of ways to optimise pharmaceutical development and patient access pathways. In this respect, the European Commission aims to publish a new EU Pharmaceutical Strategy by the end of 2020.

In her written reply to a parliamentary question concerning shortages of medicinal products in the EU, the EU Commissioner for Health and Food Safety indicated that this Strategy would "*aim to deliver a future-proof pharmaceutical policy to address all levels of the value chain, from research and development to authorisation and access of patients to medicines*" and would also raise "*the issue of dependency of the pharmaceutical industry on the manufacturing capacities of, and the supply of starting materials and active pharmaceutical ingredients from third countries*"³⁸⁰. The recently published Commission communication on the new industrial strategy also refers to the upcoming pharmaceutical strategy, and promises to put the availability, affordability, sustainability and security of supply of pharmaceuticals into strong focus³⁸¹.

Recommendation: Remodelling the incentive structure for pharmaceutical research and innovation in the EU

The advent of a new EU Pharmaceutical Strategy is an opportunity to look afresh at the ways in which the existing pharmaceutical regulatory structure in Europe supports meaningful innovation, and where new approaches could be brought forward to achieve improvement.

ii. Regulatory approaches toward cancer medicines pricing and reimbursement decisions

Health Technology Assessment

As mentioned, with increasing number of treatment options and rising prices of new medicines, it is increasingly crucial for public authorities to evaluate the added-value and cost-effectiveness of new treatments in order to enable reasonable decisions in respect to reimbursement.

³⁷⁶ IMS Institute for Healthcare Informatics, "Delivering on the Potential of Biosimilar Medicines: Role of Functioning Competitive Markets." <http://www.medicinesforeurope.com/wp-content/uploads/2016/03/IMS-Institute-Biosimilar-Report-March-2016-FINAL.pdf>.

³⁷⁷ Dave C.V., Hartzema A., Kesselheim A.S., Prices of Generic Drugs Associated with Numbers of Manufacturers. *N Engl J Med*. 2017 Dec 28; 377(26): pp. 2597-2598.

³⁷⁸ Dylst P., Vulto A., Simoens S., Barriers to the uptake of biosimilars and possible solutions: a Belgian case study. *Pharmacoeconomics*. 2014 Jul; 32(7): pp. 91-681.

³⁷⁹ EMA's "Regulatory Science to 2025" strategy: <https://www.ema.europa.eu/en/about-us/how-we-work/regulatory-science-strategy>.

³⁸⁰ Answer given by Commissioner Kyriakides on behalf of the European Commission to parliamentary question E-004370/2019, 21/02/2020: https://www.europarl.europa.eu/doceo/document/E-9-2019-004370-ASW_EN.html (accessed April 2020).

³⁸¹ Communication from the Commission on a new industrial strategy for Europe, COM(2020)120, https://ec.europa.eu/info/sites/info/files/communication-eu-industrial-strategy-march-2020_en.pdf.

Health Technology Assessment (HTA) is a now well-established process by which health systems are seeking to make the best-informed determinations on access decisions. Health Technology Assessment is defined by the World Health Organisation as *"the systematic evaluation of the properties and effects of a health technology, addressing the direct and intended effects of this technology, as well as its indirect and unintended consequences, and aimed mainly at informing decision making regarding health technologies"*³⁸². In countries where health technology assessment is in place, payers and pricing and reimbursement agencies rely on the assessment by HTA bodies to:

- provide information on the clinical, economical and ethical benefits and harms of new treatments compared to available treatment options;
- support the price negotiation process; and
- determine reimbursement status.

Interestingly, and of relevance for achieving a more balanced form of decision-making on access decisions, in many but not all European countries, the national HTA body also conducts evaluations of non-pharmacological interventions such as devices, surgical procedures, and (in some cases) public health interventions.

European cooperation in HTA

Recognising that there is a potential inherent inefficiency in countries across Europe in terms of assessment duplication and divergent approaches to HTA, efforts have been made for many years to enhance cooperation between national HTA bodies across Europe. Prominent among these efforts has been the EU-supported European Network for Health Technology Assessment (EUnetHTA)³⁸³. In existence since 2005, EUnetHTA has been supported by three EU Health Programme "Joint Action" collaborations between 2010 and 2020.

EUNetHTA clearly identified the need for more sustainable HTA collaboration between countries to help reduce duplication and improve access. As a response, and following consultation, in 2018 the European Commission issued a legislative proposal envisaging a unified approach towards the clinical part of HTA³⁸⁴, including:

- **joint clinical assessments** focusing on the most innovative health technologies with the most potential impact for patients;
- **joint scientific consultations** whereby developers can seek advice from HTA authorities; and
- **joint identification of emerging health technologies** to identify promising technologies early.

Under the proposal, clinical aspects of HTA would be assessed centrally, while non-clinical domains, including economic, ethical and organisational aspects would stay under national or regional jurisdiction.

The proposal, seen as a way to achieve better quality assessment and ultimately enable faster access to effective treatments, has received a wide support from the European Parliament and a wide range of stakeholders including patient, consumer and payer organisations, health NGOs, academia and

³⁸² WHO Definition (EB 134/30) of health technology assessment: <https://www.who.int/health-technology-assessment/about/Defining/en/>.

³⁸³ European Network for Health Technology Assessment: <https://eunetha.eu/>.

³⁸⁴ Proposal for a regulation on health technology assessment, COM(2018)51: <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52018PC0051&from=EN>.

industry^{385,386}. The European Parliament adopted its position on the proposal³⁸⁷, including key amendments such as the establishment of a coordination group; reinforced transparency measures; ensuring dialogue through a stakeholder network with patient and consumer organisations, experts and health professionals; better use of the joint clinical assessment reports by Member States in order to ensure harmonised procedures and avoid duplication; and provisions on stable and permanent public funding through the Union's Multiannual Financial Framework.

However, progress on the legislative proposal has been stalled as a result of Member States' disagreement on the desirable levels of cooperation to be achieved in this area. Though Member States favour enhanced cooperation on HTA at EU level, there are substantial differences in their view on the balance between voluntary and mandatory elements. The main dividing line is to clarify how the new law would influence national decisions on the reimbursement by national health insurance schemes, and whether Member States should have the possibility to perform national clinical assessments when necessary^{388,389}.

Recommendation: Resolving the EU HTA cooperation impasse

Renewed emphasis must be given to breaking the political logjam that prevents the proposal for greater EU cooperation on Health Technology Assessment from becoming legislation. Continued delay in its passage into legislation represents a serious frustration of a common will for its implementation.

Regional cooperation initiatives

In response to the budgetary challenges associated with new medicines coming to the market and while the future of the European Commission's legislative proposal on HTA is uncertain, some Member States have started pooling resources in regional cooperation initiatives outside of the formalised EU structures. They cooperate in areas such as horizon scanning³⁹⁰, health technology assessment and information sharing about pricing and reimbursement practices. The scope of activities of these initiatives range from identification of emerging technologies to joint pricing negotiation and joint procurement. While the idea of joint procurement for medicines is relatively new in Europe, similar collaborations already occurred in the late 70s among low- and middle-income countries³⁹¹.

There are currently 11 joint procurement initiatives being formed among the European Economic Area (EEA) countries³⁹², with the below elaborated BeneluxA and Valletta Declaration being the most advanced.

³⁸⁵ Position paper of the Association of European Cancer Leagues on the Commission's HTA legislative proposal: https://www.europeanancerleagues.org/wp-content/uploads/ECL-Position-HTA_June18.pdf.

³⁸⁶ Position on the European Cancer Patient Coalition on the Commission's HTA legislative proposal: <https://ecpc.org/news-events/ecpc-response-to-hta-proposal/>.

³⁸⁷ Resolution of the European Parliament in first reading on the Commission's HTA legislative proposal, P8_TA(2019)0120: <https://oeil.secure.europarl.europa.eu/oeil/popups/summary.do?id=1573866&t=e&l=en>.

³⁸⁸ State of play in the Council concerning the HTA legislative proposal: <https://www.consilium.europa.eu/en/policies/health-technology-assessment-post-2020/>.

³⁸⁹ Note from the Presidency of the Council to the delegations concerning the HTA legislative proposal: <https://data.consilium.europa.eu/doc/document/ST-9770-2019-INIT/en/pdf>.

³⁹⁰ Horizon scanning is to "highlight important pharmaceutical innovations before they reach the market" through continuous data gathering and the analysis of research and literature. This improves the insight of BeneluxA participants of expected costs, and enables timely decision making and (joint) price negotiations. <https://beneluxa.org/horizonscanning>.

³⁹¹ Such as the Pan American Health Organisation Drug Revolving Fund, the Gulf Cooperation Council and the Organisation of Eastern Caribbean States Pharmaceutical Procurement Service.

³⁹² Espín J., Rovira J., Calleja A. et al., How can voluntary cross-border collaboration in public procurement improve access to health technologies in Europe? Copenhagen (Denmark): European Observatory on Health Systems and Policies; 2016.

The BeneluxA Initiative on Pharmaceutical Policy³⁹³ is an initiative involving health services in Belgium, the Netherlands, Luxembourg, Austria and Ireland to deliver sustainable access to innovative medications to people in these smaller countries. It was established in April 2015 by Belgium and the Netherlands. Luxemburg joined in September 2015, Austria in June 2016 and Ireland in June 2018. This covers a population of about 43 million people, and other countries may join in the future.

BeneluxA's stated goal is to ensure "timely access and affordability of medicines". It aims to achieve this through five principal activities: joint horizon scanning; mutual recognition of HTAs; sharing policy expertise and best practice; enhanced bargaining power through joint price negotiation; and, improved price transparency³⁹⁴.

In a similar vein, "**the Valetta Declaration**" is bringing a coalition of interested and willing countries together with the aim of advancing strategies to jointly negotiate reimbursement with the pharmaceutical industry.

The Valetta Declaration was signed in Malta in a meeting held on 8 and 9 May 2017 during Malta's Presidency of the EU. Initially, the declaration was signed by the Ministers for Health of Cyprus, Greece, Ireland, Italy, Malta, Portugal, Romania and Spain. Subsequently it was also signed by Slovenia and Croatia. The cooperation remains open to Ministers of Health of other EU Member States to join.

Prioritised areas include medicinal products with high expenditure, active ingredients which are about to lose their exclusivity and biosimilars, all of which have strong relevance for cancer treatment. For example, one area under particular attention by the Valetta group is CAR-T cell therapy. As described in earlier sections, during this treatment the patient's own T cells, a type of immune system cell, are altered in the laboratory so that they will attack cancer cells. However, the high cost associated to the treatment, as well as the need for further data in many cancer types, continue to limit its availability. Strategic approaches such as BeneluxA and the Valetta Declaration may be able to address this through strengthened collaboration.

Emerging scientific tools for consistent assessment of medicines' clinical efficiency

In view of the need for many countries to prioritise public health spending in a context of budgetary constraints, the European Society of Medical Oncology (ESMO) has developed the Magnitude of Clinical Benefit (MCB) scale. This scale is a standardised, generic and validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies, which can be used as a tool by public health authorities when defining which of these therapies should be made available to all cancer patients. Therefore, the MCB scale is an opportunity for all such decisions across Europe to be made on the basis of consistent, high-quality and regularly updated clinical information, thus representing a key step towards the access of all European cancer patients to the most beneficial anti-cancer treatments currently approved for their condition³⁹⁵.

The use of such tools as the MCB scale, that help to ensure rational decision-making in respect to *medicines access*, is also now attracting interest in respect to the evaluation of the value for other cancer treatment modalities such as radiation therapy and surgery³⁹⁶.

³⁹³ Beneluxa Initiative on Pharmaceutical Policy: <https://beneluxa.org/>.

³⁹⁴ Beneluxa: What are the Prospects for Collective Bargaining on Pharmaceutical Prices Given Diverse Health Technology Assessment Processes? <https://link.springer.com/article/10.1007/s40273-019-00781-w>.

³⁹⁵ Presentation of the Magnitude of Clinical Benefit Scale on the ESMO website: <https://www.esmo.org/guidelines/esmo-mcbs>.

³⁹⁶ Towards an evidence-informed value scale for surgical and radiation oncology: a multi-stakeholder perspective: [https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(18\)30917-3/fulltext](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(18)30917-3/fulltext).

c. Availability of cancer medicines and security of supply

Though there is no legal definition of medicine shortage, in the context of preparing a recent guidance document on shortage notification, EMA and the Heads of Medicine Agencies, in consultation with stakeholders, agreed on a common definition, describing that "shortage of a medicinal product for human or veterinary use occurs when supply does not meet demand at a national level"³⁹⁷.

Ensuring the availability of medicines is the primary responsibility of the marketing authorisation holder. Directive 2001/83 on the Community code related to medicines for human use³⁹⁸ requires the marketing authorisation holder and the distributor of a given medicinal product to ensure, within the limits of their responsibilities, appropriate and continued supply to pharmacies and other persons authorised to supply medicines to ensure patients' needs are met (Article 81, subparagraph 2 of the Directive). Marketing authorisation holders are also obliged to notify the competent authority of the given Member State in good time in case of shortages, when the medicine "either temporarily or permanently, ceases to be placed on the market" of the given Member State (Article 23a, subparagraph 2 of the Directive). If the shortage concerns a centrally authorised medicine, EMA should also be notified.

There is a growing experience of medicines shortage across Europe and the world, which is adversely impacting care across all therapeutic areas including in cancer³⁹⁹. Recent investigations of the topic by the European Society of Medical Oncology (ESMO), in collaboration with the Economist Intelligence Unit, evidence that countries large and small, highly resourced and low resourced, are experiencing the real-life daily impacts of the medicines shortage crisis⁴⁰⁰.

In respect to cancer care, delays and interruptions to chemotherapy caused by medicine shortage can be highly distressing for patients, families, carers and healthcare professionals in view of the vital nature of treatment, which in the curative setting is often highly dependent on keeping its dose-intensity stable. Furthermore, cancer medicines affected by shortages often have few or no proven effective alternatives.

Common and well-established cancer medicines being reported as in periodic shortage in Europe include essential drugs, like carboplatin and tamoxifen⁴⁰¹, and other drugs, such as methotrexate and 5-fluorouracil⁴⁰². These are widely used in the treatment of cervical cancer, head and neck cancer, lung cancer, colorectal cancer and breast cancer.

The causes of medicines shortages are multi-factorial, and include:

- **Manufacturing issues**

This may include problems with the sourcing of raw materials, intermediates, active pharmaceutical ingredients (APIs) and finished medicines; problems occurring at manufacturing sites; or impacts of external events such as man-made or natural disasters. Though for innovative medicines many APIs are produced in Europe, "even when APIs are

³⁹⁷ EMA guidance on shortage detection and notification: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidancedetection-notification-shortages-medicinal-products-marketing-authorisation-holders-mahs_en.pdf.

³⁹⁸ Directive 2001/83/EC on the Community code related to medicines for human use. Latest consolidated version: <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02001L0083-20190726&from=EN>.

³⁹⁹ EAHp's 2018 Survey on Medicines Shortages to improve patient outcomes: <https://www.eahp.eu/practice-and-policy/medicines-shortages/2018-medicines-shortage-survey>.

⁴⁰⁰ Shortages of inexpensive, essential care medicines: <https://www.esmo.org/policy/shortages-of-inexpensive-essential-cancer-medicines>.

⁴⁰¹ Cancer medicine shortages in Europe: <https://www.eiu.com/graphics/marketing/pdf/ESMO-Cancer-medicines-shortages.pdf>.

⁴⁰² Country profile of Germany: Cancer medicine shortages: <https://www.esmo.org/content/download/197312/3552896/1>.

produced in the EU, most of the raw materials, for both generics and innovative medicines, are sourced from China⁴⁰³.

- **Commercial decisions of the market authorisation holder**

This may include a withdrawal from a national market or a complete stop of the production of a particular product.

- **Production capacity problems**

This can include unexpected surges in demand or inaccurate estimation of needs which cannot be resolved by moving production lines or making use of buffer capacity.

- **Supply issues**

Examples of supply-related medicine shortages include those that may be the result of parallel trade, where the medicine stock in one country is depleted by export of the medicine to another country for economic benefit.

Marketing authorisation holders should be particularly vigilant for medicines for which the manufacturing process or part of it is dependent on a single facility; as well as for those medicines for which no or only limited alternatives are available thus, the shortage would lead to a potential risk for public health (e.g., amongst others, critical or essential medicines). In those cases, competent authorities may require marketing authorisation holders to develop a shortage prevention plan, as part of their obligation to ensure continuous supply. Wholesale distributors also have a responsibility as they should ensure continuous supply to pharmacists and the person entitled to supply to the public, to cover the needs of the patients on the territory where the distributor is established. Most medicine shortages are dealt with at national level, by the national competent authorities; EMA can be involved e.g. when the shortage affects several Member States or when it is linked to a safety concern.

Healthcare professionals on the frontline of care often cite lack of information about the reason for the shortage, and the expected length of its duration as one of the many frustrations they experience, making it harder to provide accurate information to patients and make robust and timely contingency plans. This comes alongside the lost valuable clinician time that must be redirected to making alternative treatment plans to manage the shortage situation.

Although it holds limited legal mandate in this area, the EMA has sought to provide forms of assistance, such as a central EMA shortages catalogue where the Agency publishes information on specific medicine shortages that affect or are likely to affect more than one Member State⁴⁰⁴. It also promotes collaboration between national medicines agencies⁴⁰⁵, which has included the construction of a special Task Force of the EMA and the Heads of Medicines Agencies (HMA) on the Availability of Authorised Medicines for Human and Veterinary Use. The Task Force established, as a pilot, a single point of contact (SPOC) network, improving information sharing between Member States, EMA and the Commission on important medicine shortages, and coordinating actions to help to prevent and manage shortages.

Against this backdrop, policy recommendations to better prevent and manage medicines shortages in the EU, also expressed by stakeholders at European level, include:

⁴⁰³ Note by the European Commission, DG SANTE to the Pharmaceutical Committee:
https://ec.europa.eu/health/sites/health/files/files/committee/ev_20200312_795_en.pdf.

⁴⁰⁴ EMA medicine shortages catalogue:
<https://www.ema.europa.eu/en/human-regulatory/post-authorisation/availability-medicines/shortages-catalogue>.

⁴⁰⁵ The regulatory aspects of availability of medicines in the EU:
<https://www.ema.europa.eu/en/human-regulatory/post-authorisation/availability-medicines/shortages-catalogue>.

- strengthening of EU pharmaceutical legislation in respect to early notification of forthcoming supply issues;
- improved requirements for marketing authorisation holders to have strong plans in place for the prevention of shortages;
- clearer legal guidance for EU Member States in respect to the situations when parallel trade of medicines may be restricted to prevent or manage shortage;
- better arrangements for the sharing of information between countries on medicines in shortage, including publicly; and
- stronger onus in ensuring prevention of generic medicine shortage by encouraging all EU health systems to tender for generic medicine supply in forms that enable more than one supplier to enter the market.

Recommendation: Addressing medicines shortages

To achieve longer term resolution of the persisting problem of medicines shortages, the EU Pharmaceutical Strategy should: strengthen EU pharmaceutical legislation in respect to notification of shortage; provide clearer guidance to member states on the operation of parallel trade; bring better information sharing between countries in respect to shortage management and prevention; and, encourage improved procurement procedures for generic medicines and biosimilars.

3.2. Access to quality cancer care

KEY FINDINGS & RECOMMENDATIONS: ACCESS TO QUALITY CANCER CARE

Just as doctors are advised to 'treat the patient' rather than solely the disease, so too should EU cancer policy give attention to the full needs of cancer patients. This means taking account of care and quality of life issues with as much vigour as treatment per se.

To provide patients with **quality cancer** care means ensuring a balanced and comprehensive approach that enables them to access not only the core modalities of cancer treatment, but also the many other essential components that make up the foundation of high quality cancer care, including robust primary care, pathology, specialist cancer nursing, oncology pharmacy, palliative care, supportive care and psycho-oncology.

While this section seeks to address these matters in turn, over-arching recommendations that apply to **improving the elements of cancer care** include:

- Better use of EU legal and funding mechanisms to pro-actively support specialties within the cancer workforce, including assisting the harmonisation and development of education and training requirements at the European level;
- Official EU-level monitoring and reporting on patient access to critical elements of cancer care across Europe. This will help to best direct improvement requirements and heighten accountability for system performance. It is suggested this might be conducted via a European Cancer Dashboard or similar tool, potentially supported through the new EU4Health funding programme; and
- Encouraging all national cancer plans in Europe to address issues of access to care, quality of life and survivorship matters via specific and measurable actions.

The vision of European cancer care delivery through Comprehensive Cancer Care Networks (CCCNs), as established by the EU co-funded Cancer Control Joint Action (CanCon) should be advanced. **It is recommended that Europe's Beating Cancer Plan support the goal of at least one comprehensive cancer centre in each Member State, and one for every 5 million inhabitants in countries with a larger population.**

On survivorship and quality of life more specifically, this section indicates particular needs in ensuring improved access of patients to high quality palliative, supportive care and psycho-oncology. Stronger embedding of **Survivorship Care Planning** should be encouraged in all health systems. **Survivorship and quality of life issues should be core elements of the EU Cancer Mission and other EU research funding mechanisms.**

Legal and other tools should be leveraged to protect cancer patients and survivors from discrimination. This includes introducing '**the right to be forgotten**' (in respect to cancer survivors' access to financial services) in all countries and boosting the role of the European Agency for Health and Safety at Work (OSHA) in protecting cancer patients and survivors from discrimination in the workplace.

The possibilities of Artificial Intelligence and digital technology to enhance cancer care should be embraced and be firmly supported via EU initiatives focused on the digital economy.

Differences in cancer survival rates across EU Member States exceed 25% (see Annex 9⁴⁰⁶). Beyond above elaborated access to cancer treatment, **the quality of care provided to cancer patients is a known critical determinant of these inequalities⁴⁰⁷ and therefore deserves close attention from a public policy perspective⁴⁰⁸.**

To provide patients with quality cancer care means ensuring a balanced and comprehensive approach that enables them to access not only the core modalities of cancer treatment, but also the many other essential components that make up the foundation of high quality cancer care, including robust primary care, pathology, specialist cancer nursing, oncology pharmacy, palliative care, supportive care and psycho-oncology⁴⁰⁹.

An assessment conducted as part of the first EU Joint Action on Cancer, the European Partnership for Action Against Cancer (EPAAC) reported in 2014 important variations in service delivery between and within countries, with repercussions in quality of care and in patients outcomes. Factors such as waiting times and provision of optimal treatment can explain about a third of the differences in cancer survival, while lack of cancer plans, for example a national cancer plan that promotes clinical guidelines, professional training and quality control measures, may be responsible for a quarter of the survival differences⁴¹⁰. Furthermore, the EU Cancer Control Joint Action (CanCon), which replaced EPAAC from 2014, also focused on quality of cancer care and in 2017 published the European Guide on Quality Improvement in Comprehensive Cancer Control⁴¹¹.

3.2.1. Access to multidisciplinary integrated cancer care

a. Access to robust primary care

There is a growing recognition of the depth and value of the roles primary care healthcare professions can provide in respect to advancing the quality of cancer care and outcomes, including in areas such as prevention, early diagnosis, management of co-morbidities and long-term follow up care. This comes in part as health systems seek ways to deliver more healthcare in the community setting, a preference often shared by patients themselves, and being supported by increased use of oral chemotherapy and other home-based treatment and care options.

⁴⁰⁶ Epidemiology of cancer across EU Member States. Incidence, mortality and survival estimates extracted from the European Cancer Information System (ECIS): <https://ecis.jrc.ec.europa.eu/index.php> (accessed June 2020).

⁴⁰⁷ Lawler M, Selby P, Banks I. et al., The European Cancer Patient's Bill of Rights, update and implementation 2016. ESMO Open. 2017; 1: e000127.

⁴⁰⁸ Philip T., Karjalainen S., De Lorenzo F. et al., What could be a cancer mission objective if we join our forces in the fight against cancer? Tumori. 2019 Dec; 105(6): pp. 447-455.

⁴⁰⁹ See the Essential Requirements for Quality Cancer Care published by the European Cancer Organisation for fuller descriptions of all such elements: <https://www.european-cancer.org/2-content/8-ergcc> (accessed May 2020).

⁴¹⁰ Martin-Moreno J.M., Albrecht T., Radoš Krnel S., Boosting Innovation and Cooperation in European Cancer Control. European Partnership for Action Against Cancer; 2014.

⁴¹¹ Albrecht T., Kiasuwa R., Van den Bulcke M., European Guide on Quality Improvement in Comprehensive Cancer Control. Cancer Control Joint Action; 2017.

Recommendation: Strengthening primary care's role in cancer care in the EU

Ways in which Europe's Beating Cancer Plan could elevate primary care's role in cancer care include by:

- Encouraging all national cancer plans in Europe to contain ambitious measurable goals and actions to improve the integration of primary care healthcare professionals and informal carers within multidisciplinary care to patient;
- Reporting on the extent to which primary care is integrated in the delivery of cancer care in European health systems within health system monitoring exercises such as the 'State of Health in the EU', 'Health at a Glance' and the European Cancer Information System (ECIS); and
- Publishing best practice guidelines to EU Member States on the means by which better integration of cancer care can be achieved. This can be informed by, among other sources, existing European Commission best practice collections on integration of healthcare, the findings and recommendations of the State of Health in the EU exercise, and the work of several EU Health Programme funded Joint Actions on Cancer Control.

Source: European Cancer Organisation 2018 resolution on integrated cancer care: <https://www.europecancer.org/resources/114:resolution-integration-of-cancer-care.html> (accessed May 2020). Essential Requirements for Quality Cancer Care: Primary Care, published by the European Cancer Organisation: <https://www.europecancer.org/resources/47:essential-requirements-for-quality-cancer-care-primary-care.html> (accessed May 2020).

b. Access to pathology services

Accurate and timely diagnoses are critical components for developing treatment plans for patients with cancer and also for informing prognosis and assessment of responses. Pathologists are therefore an essential part of the multidisciplinary teams caring for these patients. Selection, performance and interpretation of diagnostic tests are dependent on their specialised knowledge. Nevertheless, **access to pathology services is quite unequal across Europe** and this disparity is being made worse by the increasing shortage of pathologists and budgetary restrictions⁴¹².

Initiatives contributing to the harmonisation of pathology practice in Europe include diagnostic quality assurance programmes, physical and virtual educational activities, funding of fellowships and bursaries, progress tests for residents and young pathologists, and close interaction with the national pathology societies, amongst others⁴¹³.

c. Access to specialist cancer nursing

Cancer nurses play a significant and growing role in meeting a wide variety of needs throughout the cancer care pathway. They are highly valued members of the multidisciplinary team conducting such roles as:

- public health education and information in respect to **primary prevention**, for example, supporting people in lifestyle changes and self-management;
- reducing inequalities, improving access and acceptability of **cancer screening programmes**;

⁴¹² Horton S., Sullivan R., Flanigan J. et al., Delivering Modern, High-Quality, Affordable Pathology and Laboratory Medicine to Low-Income and Middle-Income Countries: A Call to Action. *Lancet*. 2018 May 12; 391(10133): pp. 1953-1964.

⁴¹³ See section 2.2.2.a. about addressing shortages in the pathology workforce.

- **administration of treatment**, including conveying information to patients; and
- **follow-up care**, with many nurses now conducting supportive care roles in respect to such matters as counselling and in palliative care.

Cancer nurses are also effective advocates for cancer survivor rights within health systems and support patient capacity to make their own decisions about their healthcare. These roles across the care continuum often lead to nurses being considered an important "glue" holding the patient's care pathway together.

Accordingly, the roles of cancer nurses are strongly recognised⁴¹⁴. However, progress remains to be made in achieving the full status of cancer nursing in the pathways of care in all countries. Indeed, it has been evidenced that training and educational disparities of the cancer nursing workforce across Europe contribute to inequalities in cancer outcomes between countries⁴¹⁵. Further to this, there is a known international challenge in addressing shortages of nurses across all health systems. The WHO has forecast a shortfall of 7.6 million nurses globally by 2030. The persistence of such shortages further contributes to inequalities in the quality of cancer treatment and care, as well as adversely affecting working conditions with negative impacts on patient safety and other quality outcomes.

In response to such evidenced disparity in access across Europe to specialist cancer nursing, the European Oncology Nursing Society (EONS), supported by the European Cancer Organisation, has established a pan-European research network to further evidence to health systems the value of investing in this key profession for high functioning multidisciplinary cancer care teams⁴¹⁶.

Among more recently highlighted evidence include the positive impact that specialist cancer nursing has for improving management of chronic problems suffered by cancer patients. This includes improving patient knowledge and self-management, reducing rates of emergency admissions, length of hospital stays and fewer follow-up appointments^{417,418}. Through the better supportive care of the patient, specialist cancer nursing has also been associated with improved Health Related Quality of Life outcomes⁴¹⁹. Patient experience surveys have consistently identified the presence of clinical nurse specialists the factor most likely to be associated with a good experience of cancer care.

A number of other European-level initiatives to promote awareness of, assess evidence about, and encourage education in, specialist cancer nursing, include the European Cancer Nursing Day, the EONS Cancer Nursing Index and the EONS Cancer Nursing Education Framework.

⁴¹⁴ See the Essential Requirements for Quality Cancer Care published by the European Cancer Organisation: <https://www.european-cancer.org/2-content/8-ergcc> (accessed May 2020).

⁴¹⁵ Sharp L., Rannus K., Olofsson A. et al., Patient safety culture among European cancer nurses - an exploratory, cross-sectional survey comparing data from Estonia, Germany, Netherlands, and United Kingdom. *J Adv Nurs*. 2019 Dec; 75(12): pp. 3535-3543.

⁴¹⁶ RECAN project: Recognising European cancer nursing: <https://www.cancernurse.eu/research/recan.html>.

⁴¹⁷ Charalambous A., Wells M., Campbell P. et al., A Scoping Review of Trials of Interventions Led or Delivered by Cancer Nurses. *Int J Nurs Stud*. 2018 Oct; 86: pp. 36-43.

⁴¹⁸ Sharp L., Rannus K., Olofsson A. et al., Patient safety culture among European cancer nurses - an exploratory, cross-sectional survey comparing data from Estonia, Germany, Netherlands, and United Kingdom. *J Adv Nurs*. 2019 Dec; 75(12): pp. 3535-3543.

⁴¹⁹ Sussman J., Howell D., Bainbridge D., Brazil K., Pyette N., Abbasi S., Whelan T., The impact of specialised oncology nursing on patient supportive care outcomes. *J Psychosoc Oncol*. 2011; 29(3): pp. 286-307.

Recommendation: Improving access to specialist cancer nursing in the EU

To elevate the status and contribution of cancer nursing across Europe, EU regulatory tools for professional qualification recognition should be deployed to assist in the standardisation and harmonisation of cancer nursing education. The Education Framework of the European Oncology Nursing Society (EONS), a European level post-graduate Masters degree curriculum, is readily available to serve as the basis of a Common Training Framework in this respect.

To help overcome ongoing challenges with workforce shortage, EU-level health workforce planning initiatives should continue, alongside monitoring of access to cancer nursing, potentially as part of a European Cancer Dashboard, drawing on the established work of the EONS Cancer Nursing Index.

3.2.2. Survivorship needs and end-of-life cancer care: life with and beyond cancer

Whilst sections above mainly address the modalities of cancer treatment, specific attention must be given to the needs of cancer survivors. This includes not only disease-free patients, having completed their treatment, but also those experiencing cancer recurrence or second primary cancer, those with intermittent periods of active disease (chronic cancers) and those living with advanced cancer for many years, in some cases even after the expected death^{420,421}.

As a result of the ageing population, progress in early diagnosis and effectiveness of therapies, **cancer survival rates have increased substantially** over past decades in Europe, where there are now more than 10 million cancer survivors⁴²². **Whether being cured (disease-free) or not, cancer survivors face a wide range of common issues**, including:

- late and long-term effects of treatment and of cancer itself (comorbidities) on health, potential tumour recurrence;
- emotional distress, strains on personal relationships, social stigma; and
- financial toxicity, loss of independence and employment difficulties^{423,424}.

These effects represent a challenge for health care systems and social systems as a whole, which have to **ensure that cancer survivors benefit from appropriate follow-up care and more generally from rehabilitation services**, which correspond to all interventions allowing them to remain as independent as possible and to participate in education, work and meaningful life roles, therefore representing a key component of tertiary prevention of cancer^{425,426}. Of note, the case of survivorship needs in the paediatric population is addressed in a dedicated section of this study⁴²⁷.

⁴²⁰ Albrecht T., Borrás Andrés J.M., Dalmas M. et al., Survivorship and rehabilitation: policy recommendations for quality improvement in cancer survivorship and rehabilitation in EU Member States IN Albrecht T., Kiasuwa R., Van den Bulcke M., European Guide on Quality Improvement in Comprehensive Cancer Control. Cancer Control Joint Action (Chapter 7); 2017.

⁴²¹ Welch-McCaffrey D. et al., Surviving adult cancers. Part 2: Psychosocial implications. *Annals of Internal Medicine*, 1989; 111(6): pp. 517-524.

⁴²² Survivorship – the next frontier of cancer care improvement, on the European Organisation for Research and Treatment of Cancer website (2018): <https://www.eortc.org/blog/2018/09/04/survivorship-the-next-frontier-of-cancer-care-improvement/> (accessed April 2020).

⁴²³ Albrecht T., Borrás Andrés J.M., Dalmas M. et al., Survivorship and rehabilitation: policy recommendations for quality improvement in cancer survivorship and rehabilitation in EU Member States IN Albrecht T., Kiasuwa R., Van den Bulcke M., European Guide on Quality Improvement in Comprehensive Cancer Control. Cancer Control Joint Action (Chapter 7); 2017.

⁴²⁴ Factsheet about cancer survivorship issues on the US National Cancer Survivors Day website: <https://www.ncsd.org/cancer-survivorship-issues> (accessed April 2020).

⁴²⁵ Albrecht T., Borrás Andrés J.M., Dalmas M. et al., Survivorship and rehabilitation: policy recommendations for quality improvement in cancer survivorship and rehabilitation in EU Member States IN Albrecht T., Kiasuwa R., Van den Bulcke M., European Guide on Quality Improvement in Comprehensive Cancer Control. Cancer Control Joint Action (Chapter 7); 2017.

⁴²⁶ WHO's factsheet about rehabilitation: https://www.who.int/health-topics/rehabilitation#tab=tab_1 (accessed April 2020).

⁴²⁷ See section 4.2.3.d.

Furthermore, specific attention must also be given the needs of cancer patients regarding **end-of-life care**. Despite major progress in the treatment and management of cancer, cancer mortality indeed remains high and is the second leading cause of death globally⁴²⁸, accounting for 1.2 million deaths every year in the EU⁴²⁹; **caring for people with advanced and incurable cancer therefore remains a large part of the work of oncologists**⁴³⁰.

a. Organising follow-up cancer care through survivorship care plans

In its conclusions on reducing the burden of cancer, the Council of the EU invited Member States in 2008 to "take into account the psycho-social needs of patients and improve the quality of life for cancer patients through support, rehabilitation and palliative care"⁴³¹. However, **there still exist a number of hurdles impeding the access of cancer survivors to the care they need**, including poor coordination of care and occurrence of many psychosocial unmet needs. According to accumulating reviews, surveys and recommendations from the cancer community, **a robust approach to address these issues is survivorship care planning**. Even though evidence shows the important added-value for patients, healthcare providers and healthcare systems from such plans, only few cancer patients have access to one, owing to two main barriers: the feasibility of integrating them into practice and the human and financial resources required to develop and manage them^{432,433,434,435,436,437}.

The EU co-funded Cancer Control Joint Action (CanCon) recently produced a set of recommendations concerning the content and management of these plans in EU Member States. Such plans are meant to be delivered to each cancer patient after completion of the acute treatment phase, following an integrated and patient-centred approach. **They should contain information regarding both medical and non-medical aspects**, notably including:

- the possible **medical effects of the treatment and of the disease**, as well as the corresponding follow-up care that will be provided;
- **tertiary prevention of cancer**, that is information on how survivors can, through healthy lifestyle and self-management, increase their quality of life and decrease their risk of tumour recurrence;

⁴²⁸ World Health Organisation (2020) <https://www.who.int/news-room/fact-sheets/detail/cancer> (accessed May 2020).

⁴²⁹ Mortality of cancer in 2018 in the EU27, retrieved from the IARC Global Cancer Observatory: <https://qco.iarc.fr/today/home> (accessed May 2020).

⁴³⁰ Cherny N. & Catane R., Attitudes of medical oncologists toward palliative care for patients with advanced and incurable cancer: Report on a Survey by the European Society of Medical Oncology Taskforce on Palliative and Supportive Care. *Cancer*. 2003 Dec 1; 98(11): pp. 10-2502.

⁴³¹ Council of the European Union. 2876th Employment, Social Policy, Health and Consumer Affairs, Council meeting: conclusions on reducing the burden of cancer. Luxembourg, Employment, Social Policy, Health and Consumer Affairs Council; 2008: <https://register.consilium.europa.eu/doc/srv?l=EN&f=ST%209636%202008%20INIT> (accessed April 2020).

⁴³² Albrecht T., Borrás Andrés J.M., Dalmás M. et al., Survivorship and rehabilitation: policy recommendations for quality improvement in cancer survivorship and rehabilitation in EU Member States IN Albrecht T, Kiasuwa R, Van den Bulcke M. European Guide on Quality Improvement in Comprehensive Cancer Control. Cancer Control Joint Action (Chapter 7); 2017.

⁴³³ Hewitt M., Greenfield S., Stovall E., From cancer patient to cancer survivor: lost in transition. Washington, DC, US National Academy of Sciences; 2006.

⁴³⁴ Wolff SN. The burden of cancer survivorship. a pandemic of treatment success. In Feuerstein M, ed. Handbook of cancer survivorship. New York, Springer; 2006: pp. 7–18.

⁴³⁵ Earle CC. Quality of care. In Feuerstein M, ed. Handbook of cancer survivorship. New York, Springer; 2006: pp. 19–42.

⁴³⁶ American Society of Clinical Oncology. ASCO cancer treatment and survivorship care plans. Alexandria, VA, American Society of Clinical Oncology; 2016: (<http://www.cancer.net/survivorship/follow-care-after-cancer-treatment/asco-cancer-treatment-and-survivorship-care-plans>, accessed April 2020).

⁴³⁷ Keesing S., McNamara, Rosenwax L. Cancer survivors' experience of using survivorship care plans: a systematic review of qualitative studies. *Journal of Cancer Survivorship*, 2015; 9: pp. 260–268.

- access to **psycho-oncology services** to address fear of recurrence and other sources of emotional distress;
- access to **social support and return-to-work interventions**, aimed at helping patients dealing with economic implications of cancer survivorship and at facilitating their professional reintegration; and
- access to **supportive and palliative care**, especially in the case of patients with advanced cancer⁴³⁸.

Importantly, the Joint Action's conclusions underline the necessity of conducting early assessment and anticipation of the patients' needs in respect to the above-mentioned interventions, in order to ensure their timely provision. In terms of management of these plans, coordination of primary healthcare and community care providers with oncology specialists around a specialist nurse or a social worker acting as a single case manager is seen as instrumental, while education and empowerment of survivors as well as of their relatives hold the potential of increasing their active participation in rehabilitation. Of note, the Joint Action's conclusions also include an elaborate set of precise policy recommendations designed to convert these priorities into practice and to address the current barriers towards the implementation of these survivorship care plans in national health systems^{439,440}.

Finally, further support to research in the survivorship field is also necessary in order to better understand the clinical basis of the issues faced by cancer survivors, assess the benefit they take from interventions they receive and identify the determinants of inequalities linked to cancer survivorship⁴⁴¹.

b. Ensuring access to the core components of follow-up cancer care

As the number of cancer patients and survivors is growing, new challenges have arisen for both health and social protection systems in order to meet patients' needs during and after diagnosis and treatment, with a focus shifting beyond patient's survival, towards patients' quality of life throughout their cancer journey. Timely systemic integration of the assessment of patients' health-related quality of life (including physical, mental and social health) and the management of the multi-dimensional impact of cancer diagnosis and treatment as a vital part of long-term follow up care is often neglected. Comprehensive cancer care must include all actions that help patients to cope with the disease and ensure the best quality of life possible during and after treatment. Ensuring patients' access to supportive care, psycho-oncology and palliative care services is instrumental in this respect.

i. Access to supportive care

Supportive care in cancer is defined as the prevention and management of the adverse effects of cancer and its treatment. This includes management of both physical and psychological symptoms and side effects across the continuum of the cancer experience from diagnosis,

⁴³⁸ Albreht T., Borrás Andrés J.M., Dalmas M. et al., Survivorship and rehabilitation: policy recommendations for quality improvement in cancer survivorship and rehabilitation in EU Member States IN Albreht T., Kiasuwa R, Van den Bulcke M. European Guide on Quality Improvement in Comprehensive Cancer Control. Cancer Control Joint Action (Chapter 7); 2017.

⁴³⁹ Albreht T., Borrás Andrés J.M., Dalmas M. et al., Survivorship and rehabilitation: policy recommendations for quality improvement in cancer survivorship and rehabilitation in EU Member States IN Albreht T., Kiasuwa R, Van den Bulcke M. European Guide on Quality Improvement in Comprehensive Cancer Control. Cancer Control Joint Action (Chapter 7); 2017.

⁴⁴⁰ EU Cancer Control Joint Action. Peiró Pérez R., Molina Barceló A., De Lorenzo F. et al., Policy Paper: Tackling Social Inequalities in Cancer Prevention and Control for the European Population.

⁴⁴¹ Albreht T., Borrás Andrés J.M., Dalmas M. et al., Survivorship and rehabilitation: policy recommendations for quality improvement in cancer survivorship and rehabilitation in EU Member States IN Albreht T., Kiasuwa R., Van den Bulcke M., European Guide on Quality Improvement in Comprehensive Cancer Control. Cancer Control Joint Action (Chapter 7); 2017.

through anticancer treatment, to post-treatment care. The concept of supportive care can therefore be seen as an "umbrella", covering all of the needs of cancer patients in addition to their anticancer therapy and maximising their quality of life. Enhancing rehabilitation, secondary cancer prevention, survivorship, and end-of-life care are integral to supportive care⁴⁴².

Supportive care is often delivered by medical oncologists but any organ-related specialist, geriatrician, palliative care clinician, pain specialist, nutritionist, psycho-oncologist, social worker, physiotherapist, nurse or allied health worker who is required to relieve a patient's symptoms or side effects may be involved in a multidisciplinary way. Among essential components of supportive care are the adoption of a patient-centred approach, giving also close attention to the needs of the family and the carers and the provision of care across the cancer timeline, from diagnosis to survival or end-of-life, in a multidimensional and holistic manner, attending to physical and functional, psychological, social and spiritual well-being of patients⁴⁴³.

A prominent and persisting focus of supportive care is the management of the multiple side-effects experienced by cancer patients as a result from their cancer treatment. In this respect, immunosuppressive effects of chemotherapy and neuropathic effects of cancer surgery have long been known and well-characterised; however, the development of new medical agents comes brings new toxicities, about which very little is still known in the long-term⁴⁴⁴. This notably includes immune-related adverse effects⁴⁴⁵, which are autoimmune or autoinflammatory disorders arising from the use of immunotherapies⁴⁴⁶, more specifically of immune checkpoint inhibitors⁴⁴⁷, and have been reported to occur in almost every organ^{448,449,450}.

The heavy cost of curing cancer in terms of lifelong physical and mental legacy for the patient is often under-recognised. As a striking illustration of the extent of these side-effects, study conducted in 2013 has estimated that, in the UK alone, 500,000 people are facing poor health and disability after treatment for cancer - approximately one in four (25%) of those who have been diagnosed with cancer at some point in their lives. This includes for instance 350,000 people experiencing chronic fatigue or sexual difficulties, 240,000 people living with mental health problems and 200,000 people facing chronic pain after curative treatment⁴⁵¹. These long-term consequences of cancer treatment therefore affect the lives of millions of cancer patients across Europe and deserve close attention from a public health policy perspective.

⁴⁴² Multinational Association of Supportive Care in Cancer (MASCC)'s definition of supportive care: <https://www.mascc.org/mascc-strategic-plan> (accessed July 2020).

⁴⁴³ Olver I., Keefe D., Herrstedt J. et al., Supportive Care in Cancer-A MASCC Perspective. Support Care Cancer. 2020 Apr 27.

⁴⁴⁴ Olver I., Keefe D., Herrstedt J. et al., Supportive Care in Cancer-A MASCC Perspective. Support Care Cancer. 2020 Apr 27.

⁴⁴⁵ Brahmer J.R., Lacchetti C., Schneider B.J. et al., Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018 Jun 10; 36(17): pp. 1714-1768.

⁴⁴⁶ Rapoport B.L., van Eden R., Sibud V., et al. Supportive care for patients undergoing immunotherapy. Support Care Cancer 2017 Oct; 25(10): pp. 3017-3030.

⁴⁴⁷ See section 3.1.2. for a definition of immune checkpoint inhibitors.

⁴⁴⁸ Postow M.A., Sidlow R., Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N. Engl. J. Med. Jan 11; 378(2): pp. 158-168.

⁴⁴⁹ Weber J.S., Hodi F.S., Wolchok J.D. et al., Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients with Advanced Melanoma. J Clin Oncol. 2017 Mar; 35(7): pp. 785-792.

⁴⁵⁰ Calabrese L.H., Calabrese C., Cappelli L.C., Rheumatic Immune-Related Adverse Events from Cancer Immunotherapy. Nat Rev Rheumatol. 2018 Oct; 14(10): pp. 569-579.

⁴⁵¹ MacMillan Cancer Support. "Cured but at what cost?" (2013): https://www.macmillan.org.uk/images/cured-but-at-what-cost-report_tcm9-295213.pdf (accessed June 2020).

Recommendation: Improving cancer patients' quality of life through supportive care in the EU

In view of the extent of long-term side-effects experienced by cancer patients after their treatment, the focus of EU cancer policies should be truly moved from achieving survival only to improving patients' quality of life. The provision of supportive care should be seen as a relatively cheap, effective and instrumental component of such efforts. Options to allow for further development of supportive care services in Europe include:

- improving the education of all healthcare professionals to the management of long-term side-effects arising from cancer and cancer treatment;
- setting up systems to broadly monitor long-term outcomes of cancer patients, as a means to allow for holistic assessment of the benefits and harms arising from each cancer treatment; and
- increasing investment dedicated to research into, and provision of, supportive care in the EU.

ii. Access to psycho-oncology

Psychological distress is commonly experienced by cancer patients before, during and after their treatment, notably owing to the fear of cancer recurrence. It is a major factor in poor quality-of-life, reflected in challenges such as self-esteem, changing roles of couples in relationships, social isolation, or even psychiatric disorders^{452, 453, 454}. These issues can be further reinforced in the case of cancer types associated with important stigma, such as lung cancer⁴⁵⁵. Importantly, beyond its impact on cancer patients' quality of life, psychological distress has been found to be related to delayed or denied treatment, reluctance to disclose cancer status, difficulties in attending support groups and lower survival which further underlines its high importance^{456, 457, 458}. **Healthcare services should therefore consider the provision of psychological services not only as a crucial part of supportive care offered to cancer patients and survivors, but more generally as an integral component of the care provided to cancer patients throughout the cancer continuum.** This includes ensuring that all cancer patients and survivors have **access to early, systematic and regularly updated psychosocial screening** and monitoring in all phases of the cancer disease trajectory^{459, 460, 461, 462},

⁴⁵² Mehnert A., Hartung T.J., Friedrich M. et al., One in Two Cancer Patients Is Significantly Distressed: Prevalence and Indicators of Distress. *Psychooncology*. 2018 Jan; 27(1): pp. 75-82.

⁴⁵³ Harju E., Michel G., Roser K., A systematic review on the use of the emotion thermometer in individuals diagnosed with cancer. *Psychooncology*. 2019 Sep; 28(9): pp. 1803-1818.

⁴⁵⁴ Mehnert A., Herschbach P., Berg P. et al., Fear of progression in breast cancer patients - Validation of the short form of the Fear of Progression Questionnaire (FoP-Q-SF). *Z Psychosom Med Psychother*. 2006; 52(3): pp. 88-274.

⁴⁵⁵ Lehto R.H., Psychosocial challenges for patients with advanced lung cancer: interventions to improve well-being. *Lung Cancer (Auckl)*. 2017 Jul 28; 8: pp. 79-90.

⁴⁵⁶ Chambers S.K., Dunn J., Occhipinti S. et al., A systematic review of the impact of stigma and nihilism on lung cancer outcomes. *BMC Cancer*. 2012 May 20; 12: p. 184.

⁴⁵⁷ Henningfield M.F., Adjei A.A., Lung Cancer Awareness Month - A Lot of Progress, But More Work Needs to Be Done. *J Thorac Oncol*. 2017 Nov; 12(11): pp. 1603-1605.

⁴⁵⁸ Vordermaier A., Lucas S., Linden W. et al., Anxiety after diagnosis predicts lung cancer-specific and overall survival in patients with stage III non-small cell lung cancer: a population-based cohort study. *J Pain Symptom Manage*. 2017 Jun; 53(6):1057-1065.

⁴⁵⁹ Albrecht T., Kiasuwa R., Van den Bulcke M., European Guide on Quality Improvement in Comprehensive Cancer Control. *Cancer Control Joint Action (Chapter 4)*; 2017.

⁴⁶⁰ Gysels M., Higginson I.J., Rajasekaran M. et al., Improving supportive and palliative care for adults with cancer: research evidence. London: National Institute for Health and Clinical Excellence; 2004.

⁴⁶¹ Loscalzo M., Clark K.L., Holland J., Successful strategies for implementing biopsychosocial screening. *Psychooncology*. 2011 May; 20(5): pp. 455-462.

⁴⁶² Sussman J., Baldwin L.M., The Interface of Primary and Oncology Specialty Care: From Diagnosis Through Primary Treatment. *J Natl Cancer Inst Monogr*. 2010; 2010(40): pp. 18-24.

especially around critical or challenging points throughout the patient experience, such as at the initial visit and during changes in disease status^{463,464}. Cancer distress screening with standardised instruments is considered as an absolute minimum for providing whole patient-centered care^{465, 466, 467, 468, 469} and allows cancer patients to receive adapted psychosocial support at the right time. Identified distressed cancer patients and survivors subsequently need to be provided with a **comprehensive and stepped psychosocial assessment**, taking into account physical, emotional, practical, family and spiritual/religious concerns^{470, 471, 472}. **Psycho-oncology support can then take the form of various interventions, such as psychoeducation, relaxation training, individual and group psychotherapies**. Cancer patients can also greatly benefit from prehabilitation interventions, which correspond to the provision of specific support ahead of them undergoing cancer surgery and aim at helping them withstand the physiological and psychological stress caused by surgery, as well as at reducing postoperative complications^{473, 474}.

Importantly, **psychosocial interventions have been demonstrated to be effective in improving psychosocial outcomes in cancer patients**, including emotional distress/well-being, anxiety, depression and quality of life^{475, 476, 477, 478, 479, 480, 481} and **also to be cost-effective at different, potentially acceptable, willingness-to-pay thresholds**⁴⁸².

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- ⁴⁶³ Hewitt M., Greenfield S., Stovall E., From cancer patient to cancer survivor: lost in transition. Committee on cancer survivorship: improving care and quality of life, institute of medicine and national research council. Washington, DC: The National Academies Press; 2006.
- ⁴⁶⁴ Page A.E., Adler N.E., Cancer care for the whole patient: Meeting psychosocial health needs. National Academies Press; 2008.
- ⁴⁶⁵ Albrecht T., Kiasuwa R., Van den Bulcke M., European Guide on Quality Improvement in Comprehensive Cancer Control. Cancer Control Joint Action (Chapter 4); 2017.
- ⁴⁶⁶ Andritsch E., Beischon M., Bielack S. et al., ECCO Essential Requirements for Quality Cancer Care: Soft Tissue Sarcoma in Adults and Bone Sarcoma. A critical review. Crit Rev Oncol Hematol. 2017 Feb; 110: pp. 94-105.
- ⁴⁶⁷ Beets G., Sebag-Montefiore D., Andritsch E et al., ECCO Essential Requirements for Quality Cancer Care: Colorectal Cancer. A critical review. Crit Rev Oncol Hematol. 2017 Feb; 110: pp. 81-93.
- ⁴⁶⁸ Loscalzo M., Clark K.L., Holland J. Successful strategies for implementing biopsychosocial screening. Psychooncology. 2011 May; 20(5): pp. 455-462.
- ⁴⁶⁹ Page A.E., Adler N.E.. Cancer care for the whole patient: Meeting psychosocial health needs. National Academies Press; 2008.
- ⁴⁷⁰ CPAC, Bultz B., Canadian Partnership Against Cancer - Guide to Implementing Screening for Distress, the 6th Vital Sign Moving Towards Person-Centered Care; 2009. Retrieved from Toronto: http://www.virtualhospice.ca/Assets/Distress-%20CPAC_20150713161546.p.pdf (accessed July 2020).
- ⁴⁷¹ Gysels M., Higginson I.J., Rajasekaran M. et al., Improving supportive and palliative care for adults with cancer: research evidence. London: National Institute for Health and Clinical Excellence; 2004.
- ⁴⁷² Nekhlyudov L., O'Malley D.M., Hudson, S.V., Integrating Primary Care Providers in the Care of Cancer Survivors: Gaps in Evidence and Future Opportunities. Lancet Oncol. 2017 Jan; 18(1): e30-e38.
- ⁴⁷³ Jensen B.T., Lauridsen S.V., Jensen J.B., Prehabilitation for Major Abdominal Urologic Oncology Surgery. Curr Opin Urol. 2018 May; 28(3): pp. 243-250.
- ⁴⁷⁴ Vahr Lauridsen S., Thomsen T., Kaldan G. et al., Smoking and Alcohol Cessation Intervention in Relation to Radical Cystectomy: A Qualitative Study of Cancer Patients' Experiences. BMC Cancer. 2017 Nov 25; 17(1):793.
- ⁴⁷⁵ Carlson L., Bultz B., Efficacy vs. cost of psychosocial interventions: an evidence-based call for action. Oncol Exchange. 2002; 1(2): pp. 24-29.
- ⁴⁷⁶ Carlson L., Bultz B.D., Efficacy and medical cost offset of psychosocial interventions in cancer care: making the case for economic analyses. Psychooncology. 2004; 13(12): pp. 837-849.
- ⁴⁷⁷ European Cancer Organisation. Position Statement - Integrated Cancer Care: Bringing Primary Care and Secondary Care Together: <https://www.european-cancer.org/resources/57:integrated-cancer-care-bringing-primary-care-and-secondary-care-together.html> (accessed July 2020).
- ⁴⁷⁸ Gysels M., Higginson I.J., Rajasekaran M. et al. Improving supportive and palliative care for adults with cancer: research evidence. London: National Institute for Health and Clinical Excellence; 2004.
- ⁴⁷⁹ Jacobsen P.B., Shibata D., Siegel E.M., Evaluating the quality of psychosocial care in outpatient medical oncology settings using performance indicators. Psychooncology. 2011 Nov; 20(11): pp. 1221-1227.
- ⁴⁸⁰ Raingruber B., The Effectiveness of Psychosocial Interventions with Cancer Patients: An Integrative Review of the Literature (2006–2011). ISRN Nursing, 2011, 638218.
- ⁴⁸¹ Faller H., Schuler M., Richard M. et al., Effects of Psycho-Oncologic Interventions on Emotional Distress and Quality of Life in Adult Patients With Cancer: Systematic Review and Meta-Analysis. J Clin Oncol. 2013 Feb 20; 31(6): pp. 782-93.
- ⁴⁸² Jansen F., Van Zwieten V., Coupé V.M.H. et al., A Review on Cost-Effectiveness and Cost-Utility of Psychosocial Care in Cancer Patients. Asia-Pacific Journal of Oncology Nursing 2016; 3(2): pp. 125-136.

All cancer patients and survivors should therefore have access to psychosocial workers and consultants appropriate to their needs^{483,484,485} and to basic formal sources of psychosocial support (e.g. compassionate and non-judgmental communication)^{486,487}. The provision of psycho-oncology involves a wide range of professionals, including social workers, nurses and various other healthcare professionals, which can make it challenging to precisely assess the human and financial resources dedicated to it. **Psycho-oncology is, however, clearly identified as an area of constantly unmet needs for cancer patients, even when compared to pain-related needs in oncology settings⁴⁸⁸.** A 2015 study conducted as part of the European Partnership for Action Against Cancer (EPAAC) indeed found only ten European health systems reporting as having specific budgetary arrangements for the provision of psychosocial oncology care, only eight having nationally recommended psychosocial oncology clinical guidelines and only six having an official certification for psychosocial oncology education. Furthermore, research in psycho-oncology is also significantly under-funded, with for instance only 1% of research in lung cancer aimed at understanding and improving supportive care and quality of life issues in patients, despite known high levels of psychosocial needs for this cancer type⁴⁸⁹.

Identified requirements to advance psycho-oncological care in Europe include:

- integrating and embedding structural financial resources for psychosocial rehabilitation, reintegration and survivorship within national cancer control plans⁴⁹⁰;
- ensuring that all primary care and oncology providers are primed to cancer survivorship educational programs, expanding their areas of psychosocial competencies^{491,492,493,494};
- developing a certification in a subspecialty of cancer survivorship, including a psycho-oncology core⁴⁹⁵;
- providing sustained investment in appropriate psycho-oncology and cancer survivorship

⁴⁸³ Borras J.M., Albrecht T., Audisio R. et al., Policy statement on multidisciplinary cancer care. *Eur J Cancer*. 2014 Feb; 50(3): pp. 80-475.

⁴⁸⁴ CPAC, Bultz B., Canadian Partnership Against Cancer - Guide to Implementing Screening for Distress, the 6th Vital Sign Moving Towards Person-Centered Care; 2009. Retrieved from Toronto: http://www.virtualhospice.ca/Assets/Distress-%20CPAC_20150713161546.p df (accessed July 2020).

⁴⁸⁵ Page AE, Adler NE. Cancer care for the whole patient: Meeting psychosocial health needs. National Academies Press; 2008.

⁴⁸⁶ Gysels M., Higginson I.J., Rajasekaran M. et al., Improving supportive and palliative care for adults with cancer: research evidence. London: National Institute for Health and Clinical Excellence; 2004.

⁴⁸⁷ Pascoe S.W., Neal R.D., Allgar V.L. et al., Psychosocial care for cancer patients in primary care? Recognition of opportunities for cancer care. *Fam Pract*. 2004 Aug; 21(4): pp. 437-42.

⁴⁸⁸ Jacobsen P.B., Shibata D., Siegel E.M., Evaluating the quality of psychosocial care in outpatient medical oncology settings using performance indicators. *Psychooncology*. 2011 Nov; 20(11): pp. 1221-1227.

⁴⁸⁹ Henningfield M.F., Adjei A.A., Lung Cancer Awareness Month - A Lot of Progress, But More Work Needs to Be Done. *J Thorac Oncol*. 2017 Nov; 12(11): pp. 1603-1605.

⁴⁹⁰ Albrecht T., Kiasuwa R., Van den Bulcke M., European Guide on Quality Improvement in Comprehensive Cancer Control. Cancer Control Joint Action (Chapter 4); 2017.

⁴⁹¹ Cohen E.E., LaMonte S.J., Erb N.L. et al., American Cancer Society head and neck cancer survivorship care guideline. *CA Cancer J Clin*. 2016 May; 66(3): pp. 39-203.

⁴⁹² O'Malley D.M., Davis S.N., Crabtree B.F. et al., Primary care physicians experiences of caring for cancer survivors: Toward developing a primary care-responsive cancer survivorship research agenda. *J Clin Oncol*. 2017; 35(5_suppl): p. 97.

⁴⁹³ Resnick M.J., Lacchetti C., Penson D.F., Prostate cancer survivorship care guidelines: American Society of Clinical Oncology practice guideline endorsement. *J Oncol Pract*. 2015 May; 11(3): e445-9.

⁴⁹⁴ Runowicz C.D., Leach C.R., Henry N.L. et al., American cancer society/American society of clinical oncology breast cancer survivorship care guideline. *CA Cancer J Clin*. 2016 Jan-Feb; 66(1): pp. 43-73.

⁴⁹⁵ Rubinstein E.B., Miller W.L., Hudson S.V. et al., Cancer survivorship care in advanced primary care practices: A qualitative study of challenges and opportunities. *JAMA Intern Med*. 2017 Dec 1; 177(12): pp. 1726-1732.

trainings^{496,497,498,499,500,501}, and

- harnessing the potential of new technologies to enhance data collection and tracking, and to strengthen communication and interaction between oncological specialised care providers, primary care providers and psychosocial professionals, with the aim of achieving a dynamic and coordinated management of care needs and psychosocial conditions in cancer patients^{502,503}.

iii. *Access to palliative care*

The important role of palliative care within multidisciplinary cancer care

Palliative care focuses on patients with a life-threatening or life-limiting condition through a holistic approach addressing physical, psychosocial and spiritual problems. The goal of palliative care is to improve patients' quality of life and that of their families, and to uphold their dignity, by alleviating health-related suffering in all its forms.

The importance of palliative care has been recognised with the acknowledgement, by leading oncology societies, that the provision of palliative care is part of high-quality cancer treatment⁵⁰⁴. The Lancet Commission on Palliative Care and Pain Relief Study Group also suggests that **palliative care is an essential component of comprehensive care that should be practised by all health and social care providers and by palliative care specialists**, in any healthcare setting, including patients' own homes⁵⁰⁵. In 2014, a specific resolution of the World Health Assembly called for all countries to incorporate palliative care provision into their health care systems⁵⁰⁶. Viewing palliative care as a human right, the World Health Assembly 67.19 stressed the importance of palliative care within a public health agenda and advocated for the development, strengthening and implementation of palliative care policies, funding for human resources in palliative care, multi-sectorial partnerships and increased access to the essential medicines routinely used in palliative care.

The benefits of integrating palliative care within the cancer patient pathway

Whilst recent advances in the cancer treatment effectiveness and tolerability have resulted in a chronic

⁴⁹⁶ Albrecht T., Kiasuwa R., Van den Bulcke M., European Guide on Quality Improvement in Comprehensive Cancer Control. Cancer Control Joint Action (Chapter 4); 2017.

⁴⁹⁷ Gysels M., Higginson I.J., Rajasekaran M. et al., Improving supportive and palliative care for adults with cancer: research evidence. London: National Institute for Health and Clinical Excellence; 2004.

⁴⁹⁸ Holland J.C., Bultz B.D., The NCCN guideline for distress management: a case for making distress the sixth vital sign. J Natl Compr Canc Netw. 2007 Jan; 5(1): pp. 3-7.

⁴⁹⁹ Jacobsen P., Ransom S., Implementation of NCCN distress management guidelines by member institutions. J Natl Compr Canc Netw. 2007 Jan; 5(1): pp. 99-103.

⁵⁰⁰ Kim H.L., Puymon M.R., Qin M. et al., NCCN clinical practice guidelines in oncology™; 2013.

⁵⁰¹ Sussman J., Baldwin L.M., The Interface of Primary and Oncology Specialty Care: From Diagnosis Through Primary Treatment. J Natl Cancer Inst Monogr. 2010;2010(40): pp. 18-24.

⁵⁰² Jacobsen P.B., Shibata D., Siegel E.M., Evaluating the quality of psychosocial care in outpatient medical oncology settings using performance indicators. Psychooncology. 2011 Nov; 20(11): pp. 1221-1227.

⁵⁰³ Banks I., Weller D., Ungan M. et al., ECCO Essential Requirements for Quality Cancer Care: Primary Care. Crit Rev Oncol Hematol. 2019 Oct; 142: pp. 187-199.

⁵⁰⁴ American Society of Clinical Oncology (ASCO) - European Society of Medical Oncology (ESMO) consensus statement on quality cancer care. J Clin Oncol. 2006 Jul 20; 24(21): pp. 3498-9.

⁵⁰⁵ Knaut F.M., Farmer P.E., Krakauer E.L. et al., Lancet Commission on Palliative Care and Pain Relief Study Group. Alleviating the access abyss in palliative care and pain relief - an imperative of universal health coverage: the Lancet Commission report. Lancet. 2018 Apr 7; 391(10128): pp. 1391-454.

⁵⁰⁶ World Health Assembly resolution on Strengthening of palliative care as a component of comprehensive care throughout the life course (2014): https://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R19-en.pdf (accessed May 2020).

disease trajectory for some tumours, in parallel, **there is growing evidence of the benefits of the introduction of early palliative care** for both non-haematological^{507,508} and haematological malignancies^{509,510}. Palliative care aims to provide improved quality of life and evidence suggests that the introduction of palliative care early in the disease trajectory can lead to **improved survival in patients with cancer**^{511,512,513,514}. Furthermore, **the benefits of early palliative care intervention have also been reported in terms of symptom control, emotional status and quality of life**. This early intervention, without abandoning the care for those at the end-of-life, has fostered changes in the provision of palliative care, particularly in hospitals, where **there are calls for closer integration of palliative care and oncology**⁵¹⁵ where palliative care should extend beyond a simple palliative care consultation⁵¹⁶. Palliative care teams working closely with colleagues from oncology and haematology, ensures that different and complimentary knowledge and skills are utilised to benefit the care of patients and their families.

Importantly, there is also evidence suggesting that **the integration of palliative care into the care of people with cancer can be cheaper and more cost-effective** when compared to standard cancer treatments^{517,518,519,520,521}. Early referral to palliative care has also been shown to decrease readmission rates to hospital and can decrease the duration of hospital stays⁵²² thus contributing to substantial reductions in cost. Integrating palliative care into a health system and expanding coverage of cancer care in ways that do not prevent patients from accessing curative care also allows for flexibility and fluid integration of disease management and palliative care from the point of diagnosis. Indeed, for patients and families to accept palliative care early in the disease trajectory, they must be assured and reassured that acceptance does not mean foregoing disease-modifying treatment.

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- ⁵⁰⁷ Tassinari D., Drudi F., Monterubbianesi M.C. et al., Early palliative care in advanced oncologic and nononcologic chronic diseases: a systematic review of literature. *Rev Recent Clin Trials*. 2016; 11(1): pp. 63-71.
- ⁵⁰⁸ Haun M.W., Estel S., R cker G. et al. (2017), Early palliative care for adults with advanced cancer. *Cochrane Database Syst Rev*. 2017 Jun 12; 6: CD011129.
- ⁵⁰⁹ Loggers E.T., LeBlanc T.W., El-Jawahri A. et al., Pre-transplantation Supportive and Palliative Care Consultation for High-Risk Hematopoietic Cell Transplantation Patients. *Biol Blood Marrow Transplant*. 2016 Jul; 22(7): pp. 1299-1305.
- ⁵¹⁰ Porta-Sales J., Guerrero-Torrelles M., Moreno-Alonso D. et al., Is Early Palliative Care Feasible in Patients With Multiple Myeloma? *J Pain Symptom Manage*. 2017 Nov; 54(5): pp. 692-700.
- ⁵¹¹ Hui D., Kim Y.J., Park J.C. et al., Integration of oncology and palliative care: a systematic review. *Oncologist*. 2015 Jan; 20(1): pp. 77-83.
- ⁵¹² Holmenlund K., Sj gren P., Nordly M., Specialised palliative care in advanced cancer: what is the efficacy? A systematic review. *Palliat Support Care*. 2017 Dec; 15(6): pp. 724-740.
- ⁵¹³ Haun M.W., Estel S., R cker G. et al. (2017), Early palliative care for adults with advanced cancer. *Cochrane Database Syst Rev*. 2017 Jun 12; 6: CD011129.
- ⁵¹⁴ Temel J.S., Greer J.A., Muzikansky A. et al., Early Palliative Care for Patients With Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med*. 2010 Aug 19; 363(8): pp. 733-42.
- ⁵¹⁵ Kaasa S., Loge J.H., Aapro M. et al., Integration of oncology and palliative care: a Lancet Oncology Commission. *Lancet Oncol*. 2018 Nov; 19(11): e588-e653.
- ⁵¹⁶ Slama O., Pochop L., Sedo J. et al., Effects of Early and Systematic Integration of Specialist Palliative Care in Patients with Advanced Cancer: Randomised Controlled Trial PALINT. *J Palliat Med*. 2020 May 8.
- ⁵¹⁷ Kavalieratos D., Corbelli J., Zhang D. et al. Association Between Palliative Care and Patient and Caregiver Outcomes: A Systematic Review and Meta-analysis. *JAMA*. 2016 Nov 22; 316(20): pp. 2104-2114.
- ⁵¹⁸ Gaertner J, Siemens W, Meerpohl JJ, et al. Effect of Specialist Palliative Care Services on Quality of Life in Adults With Advanced Incurable Illness in Hospital, Hospice, or Community Settings: Systematic Review and Meta-Analysis. *BMJ*. 2017 Jul 4; 357: j2925.
- ⁵¹⁹ Brick A., Smith S., Normand C. et al., Costs of Formal and Informal Care in the Last Year of Life for Patients in Receipt of Specialist Palliative Care. *Palliat Med*. 2017 Apr; 31(4): pp. 356-368.
- ⁵²⁰ Chalkidou K, Marquez P, Dhillon P.K. et al., Evidence-informed frameworks for cost-effective cancer care and prevention in low, middle, and high-income countries. *Lancet Oncol*. 2014 Mar; 15(3): e119-e131.
- ⁵²¹ May P., Garrido M.M., Cassel J.B. et al., Cost analysis of a prospective multi-site cohort study of palliative care consultation teams for adults with advanced cancer: Where do cost-savings come from? *Palliat Med*. 2017 Apr; 31(4): pp. 378-386.
- ⁵²² Cassel J.B., Kerr K., Pantilat S. et al., Palliative care consultation and hospital length of stay. *J Palliat Med*. 2010 Jun; 13(6): pp. 7-761.

Identified challenges in ensuring provision of quality palliative care across the EU

The most recent edition of the European Association of Palliative (EAPC)'s Atlas of Palliative Care in Europe, reports much progress being made to better integrate the provision of palliative care within national health systems in Europe⁵²³. However **increasingly attention is being focused on access and availability challenges in respect to pain relief, such as cultural differences between health systems, regulatory barriers to access, and lack of understanding by some healthcare professionals**. To achieve early and full integration of palliative care in cancer care, there is a need to evaluate and enhance physicians' basic palliative care education and training. There is evidence that suggests that those working in oncology are still insufficiently prepared to provide the palliative care their patients require^{524,525,526, 527, 528, 529}. **Addressing this issue will inevitably lead to better care for patients with cancer and their families.**

c. Protecting cancer survivors from discriminations through regulatory initiatives

Beyond the provision of appropriate care and support, cancer survivors can also benefit from adapted regulations protecting them from the socio-economic consequences of their disease.

These include regulations aimed at **safeguarding cancer survivors' working lives**, by granting them the right to switch between full-time and part-time positions⁵³⁰, by protecting them from discrimination at work arising from their disability or by requiring their employers to make reasonable adjustments to the employee's tasks, working hours and environment according to their condition^{531, 532}. The identification of such best practices across EU Member States and the work towards their broader implementation is seen as a promising prospect within the European cancer community, which could be fostered by a strengthened role of the European Agency for Health and Safety at Work (OSHA)⁵³³.

Cancer treatment poses an increasingly high financial burden on patients and their families. It is, therefore, critical to identify high-risk patients and provide them with the necessary support to overcome financial hardship during and after treatment. Crucially, the key issue of **financial discrimination against cancer survivors**, which is characterised by obstacles to their access to financial services, such as health insurance or bank loan contracts, owing to their past diagnosis of cancer, and has a wide range of dramatic implications on their daily life, can be addressed through

⁵²³ EAPC Atlas of Palliative Care in Europe 2019: https://www.eapcnet.eu/Portals/0/PDFs/Atlas%20Europa%202019_DEF.pdf (accessed May 2020).

⁵²⁴ Prazak K.A., Lester P.E., Fazzari M., Evaluation of physician assistant student knowledge and perception of competence in palliative symptom management. *J Allied Health*. Winter 2014; 43(4): e69–e74.

⁵²⁵ Chen E., McCann J.J., Lateef O.B., Attitudes toward and experiences in end-of-life care education in the intensive care unit: A survey of resident physicians. *Am J Hosp Palliat Care*. 2015 Nov; 32(7): pp. 44-738.

⁵²⁶ Lesnock J.L., Arnold R.M., Meyn L.A. et al., Palliative care education in gynecologic oncology: A survey of the fellows. *Gynecol Oncol*. 2013 Sep; 130(3): pp. 5-431.

⁵²⁷ Buss M.K., Lessen D.S., Sullivan A.M. et al., Hematology/oncology fellows' training in palliative care: Results of a national survey. *Cancer*. 2011 Sep 15; 117(18): pp. 11-4304.

⁵²⁸ Thomas R.A., Curley B., Wen S. et al., Palliative Care Training During Fellowship: A National Survey of U.S. Hematology and Oncology Fellows. *J Palliat Med*. 2015 Sep; 18(9): pp. 747-51.

⁵²⁹ Al-Kindi S.G., Zeinah G.F., Hassan A.A., Palliative care knowledge and attitudes among oncology nurses in Qatar. *Am J Hosp Palliat Care*. 2014 Aug; 31(5): pp. 469-74.

⁵³⁰ Italian decree-law n° 276/2003, article 46, as amendment of decree-law n° 61/2000, article 12 bis.

⁵³¹ UK Equality Act 2010.

⁵³² Albrecht T., Borrás Andrés J.M., Dalmás M. et al., Survivorship and rehabilitation: policy recommendations for quality improvement in cancer survivorship and rehabilitation in EU Member States IN Albrecht T, Kiasuwa R, Van den Bulcke M. *European Guide on Quality Improvement in Comprehensive Cancer Control. Cancer Control Joint Action (Chapter 7)*; 2017.

⁵³³ ECL position paper on the "Europe's Beating Cancer Plan": https://www.europeanleague.org/wp-content/uploads/ECL-Vision-EU-Beating-Cancer-Plan_Final.pdf.

"right to be forgotten" regulations⁵³⁴. Such regulations are already in place in France, Belgium and Luxembourg, where they grant the right to cancer survivors not to declare their cancer 10 years after the end of the active treatment and 5 years if they had cancer under 18⁵³⁵. The broader implementation of this "right to be forgotten" across European countries is considered a priority by the European cancer community. This is reflected by a number of stakeholder initiatives, including the European Cancer Organisation's 2018 Summit resolution on addressing financial discrimination against cancer survivors. This resolution was agreed on, following public consultation, by 400 leading representatives of healthcare professional, patient, research and other stakeholder communities, which set 2025 as a target for delivery⁵³⁶.

Recommendation: Addressing pressing cancer survivorship needs in the EU

Europe's Beating Cancer Plan should include the aspiration that every patient in Europe receives a Survivorship Care Plan when completing treatment.

The EU Cancer Mission should support research into survivorship matters, to better understand the clinical basis of the issues faced by cancer survivors, assess the benefit they take from interventions they receive and identify the determinants of inequalities linked to cancer survivorship.

Europe's Beating Cancer Plan should also include a target to establish the right of cancer survivors to no longer declare their cancer when seeking to access financial services such as mortgages, loans and insurance. This 'right to be forgotten' is already in place in several EU countries.

The European Agency for Health and Safety at Work (OSHA) should be mandated to play a stronger role in promoting good practices to EU Member States with respect to the integration of cancer patients and survivors in the workplace and their protection from workplace discrimination.

3.2.3. Cross-cutting requirements for provision of quality cancer care

Beyond above elaborated discipline-specific challenges, provision of cancer care also relies on a range of cross-cutting requirements in terms of human resources, organisation of care, adaptation to innovation, fight against inequalities and empowerment of cancer patients.

a. Ensuring provision of quality cancer care by quality workforce within quality health infrastructures

i. *The central role of multidisciplinary teams in cancer care*

Provision of cancer care by a multidisciplinary team, made up of all medical professionals required to deal with the case of the individual patient, is recognised as one of the essential requirements for the organisation of quality cancer care. Evidence clearly indicates that care provided by

⁵³⁴ Davenport L., "Economic Discrimination of Cancer Survivors Hampers Recovery", Medscape, 6 Mar. 2018: <https://www.medscape.com/viewarticle/893456> (accessed April 2020).

⁵³⁵ Factsheet about the "right to be forgotten" on the European Cancer Patient Coalition (ECPC) website: <https://ecpc.org/policy/the-right-to-be-forgotten-a-new-research-project/> (accessed April 2020).

⁵³⁶ ECCO 2018 European Cancer Summit resolution on Survivorship and Financial Discrimination: <https://www.european-cancer.org/resources/115:resolution-survivorship-financial-discrimination.html> (accessed June 2020).

multidisciplinary teams result in better outcomes for patients^{537,538,539,540}.

In detail, treatment strategies for all patients should be decided on, planned and delivered as a result of consensus among a core multidisciplinary team that comprises the most appropriate dedicated health professionals for the particular diagnosis and stage of cancer, patient characteristics and preferences, and with input from the extended community of professionals. The heart of this decision-making process is normally a weekly or more frequent meeting of the multidisciplinary team, where patients are discussed with the objective of balancing the recommendations of clinical guidelines with the "reality" of the individual patient^{541, 542}.

Members of core multidisciplinary teams typically include specialists in a wide range of cancer treatment options (**surgical oncologists, radiation oncologists, medical oncologists, interventional radiologists**), but also **radiologists, pathologists** and **cancer nurses**^{543,544}. Depending on the cancer type and on the patient pathway, core multidisciplinary teams may also involve a number of additional professionals, such as urologists (in the case of prostate cancer⁵⁴⁵), dermatologists (in the case of melanoma⁵⁴⁶), ophthalmologists (in the case of uveal melanoma⁵⁴⁷), gastroenterologists/endoscopists (in the case of colorectal cancer⁵⁴⁸) or nutrition specialists (in the case of oesophageal and gastric cancer⁵⁴⁹).

This core multidisciplinary team notably discusses the case of:

- all new patients after diagnosis and staging to decide on optimal treatment;
- patients after major treatment to decide on further treatment and follow-up; and
- patients with a recurrence during follow-up to decide on optimal treatment^{550,551}.

Extended multidisciplinary teams, whose members do not need to attend every meeting but have essential roles for aspects of patient care and whose expertise need to be included when necessary, comprise health professionals from a wide range of disciplines, such as nuclear medicine, anaesthesia/intensive care, oncology pharmacy, geriatric oncology, psycho-oncology, psychotherapy,

⁵³⁷ Selby P., Popescu R., Lawler M. et al., The Value and Future Developments of Multidisciplinary Team Cancer Care. Am Soc Clin Oncol Educ Book. 2019; 39: pp. 332-340.

⁵³⁸ See the Essential Requirements for Quality Cancer Care published by the European Cancer Organisation: <https://www.european-cancer.org/2-content/8-ergcc> (accessed May 2020).

⁵³⁹ Biganzoli L., Cardoso F., Beishon M. et al., The Requirements of a Specialist Breast Centre. Breast. 2020 Jun; 51: pp. 65-84.

⁵⁴⁰ Prades J., Remue E., Van Hoof E. et al., Is it worth re-organising cancer services on the basis of multidisciplinary teams (MDTs)? A systematic review of the objectives and organisation of MDTs and their impact on patient outcomes. Health Pol 2015; 119(4): 464e74.

⁵⁴¹ See the Essential Requirements for Quality Cancer Care published by the European Cancer Organisation for fuller descriptions of all such elements: <https://www.european-cancer.org/2-content/8-ergcc>.

⁵⁴² Biganzoli L., Cardoso F., Beishon M. et al., The Requirements of a Specialist Breast Centre. Breast. 2020 Jun; 51: pp. 65-84.

⁵⁴³ See the Essential Requirements for Quality Cancer Care published by the European Cancer Organisation: <https://www.european-cancer.org/2-content/8-ergcc> (accessed May 2020).

⁵⁴⁴ Biganzoli L., Cardoso F., Beishon M. et al., The Requirements of a Specialist Breast Centre. Breast. 2020 Jun; 51: pp. 65-84.

⁵⁴⁵ Brausi M., Hoskin P., Andritsch E. et al., ECCO essential requirements for quality cancer care: Prostate cancer. Crit Rev Oncol Hematol. 2020 Apr; 148: 102861.

⁵⁴⁶ Wouters M.W., Michielin O., Bastiaannet E. et al., ECCO essential requirements for quality cancer care: Melanoma. Crit Rev Oncol Hematol. 2018 Feb; 122: pp. 164-178.

⁵⁴⁷ Wouters M.W., Michielin O., Bastiaannet E. et al., ECCO essential requirements for quality cancer care: Melanoma. Crit Rev Oncol Hematol. 2018 Feb; 122: pp. 164-178.

⁵⁴⁸ Beets G., Sebag-Montefiore D., Andritsch E. et al., ECCO Essential Requirements for Quality Cancer Care: Colorectal Cancer. A critical review. Crit Rev Oncol Hematol. 2017 Feb; 110: pp. 81-93.

⁵⁴⁹ Allum W., Lordick F., Alsina M. et al., ECCO essential requirements for quality cancer care: Oesophageal and gastric cancer. Crit Rev Oncol Hematol. 2018 Feb; 122: pp. 179-193.

⁵⁵⁰ See the Essential Requirements for Quality Cancer Care published by the European Cancer Organisation: <https://www.european-cancer.org/2-content/8-ergcc> (accessed May 2020).

⁵⁵¹ Biganzoli L., Cardoso F., Beishon M. et al., The Requirements of a Specialist Breast Centre. Breast. 2020 Jun; 51: pp. 65-84.

palliative care, sexual rehabilitation, neuro-oncology, plastic surgery, self-image support, clinical genetics and prevention^{552,553}.

ii. Comprehensive cancer centres: key features and rationale

Beyond the provision of care by multidisciplinary teams, the **crucial role of institutions specialised in cancer management** has been recognised, prominently including those known as **comprehensive cancer centres, which are based on the integration of patient care with education and research activity**^{554,555}. Importantly, the **superiority of comprehensive cancer centres in terms of treatment outcomes** has been well documented^{556,557,558}. Furthermore, recent research demonstrates that institutions active in research achieve better outcomes, not only for the patients involved in the research project(s), but for the entire patient group treated in the institution^{559,560,561}. These centres are therefore seen as instrumental to ensure provision of high quality multidisciplinary cancer care to cancer patients across the EU and thereby eliminate geographical inequalities in cancer survival rates⁵⁶².

Although a consistent and broadly applicable definition of a comprehensive cancer centre does not exist, known typical features of these centres include:

- a concentration in one location of qualified oncology-dedicated staff;
- volumes of patients sufficiently large to produce economies of scale;
- adequate numbers of patients with less common tumours that require special expertise;
- ongoing opportunities for keeping all personnel up to date;
- ability to design and to run clinical trials;
- expertise in epidemiology, oncology and cancer research in various areas; and

⁵⁵² See the Essential Requirements for Quality Cancer Care published by the European Cancer Organisation: <https://www.european-cancer.org/2-content/8-ergcc> (accessed May 2020).

⁵⁵³ Biganzoli L., Cardoso F., Beishon M. et al., The Requirements of a Specialist Breast Centre. *Breast*. 2020 Jun; 51: pp. 65-84.

⁵⁵⁴ Albrecht T., Amati C., Angelastro A. et al., Integrated cancer control: the case for comprehensive cancer care networks (CCCN) IN Albrecht T., Kiasuwa R., Van den Bulcke M., European Guide on Quality Improvement in Comprehensive Cancer Control. Cancer Control Joint Action (Chapter 5); 2017.

⁵⁵⁵ See US National Cancer Institute's definition of a comprehensive cancer centre, featuring cancer research activity as a key criterion: <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/comprehensive-cancer-center> (accessed May 2020).

⁵⁵⁶ Albrecht T., Amati C., Angelastro A. et al., Integrated cancer control: the case for comprehensive cancer care networks (CCCN) IN Albrecht T., Kiasuwa R., Van den Bulcke M., European Guide on Quality Improvement in Comprehensive Cancer Control. Cancer Control Joint Action (Chapter 5); 2017.

⁵⁵⁷ Selby P., Gillis C., Haward R., Benefits from specialised cancer care. *Lancet*. 1996 Aug 3; 348(9023): pp. 8-313.

⁵⁵⁸ Stead M., Cameron D., Lester N. et al., Strengthening clinical cancer research in the United Kingdom. *Br J Cancer*. 2011 May 10; 104(10): pp. 34-1529.

⁵⁵⁹ Selby P., Liu L., Downing A. et al., How can clinical research improve European health outcomes in cancer? *J Cancer Policy* 2019; 20: 100182, pp. 1-6.

⁵⁶⁰ Beets G., Sebag-Montefiore D., Andritsch E., ECCO Essential Requirements for Quality Cancer Care: Colorectal Cancer. A Critical Review. *Crit Rev Oncol Hematol*. 2017 Feb; 110: pp. 81-93.

⁵⁶¹ Downing A., Morris E.J., Corrigan N. et al., 2016. High hospital research participation and improved colorectal cancer survival outcomes: a population-based study. *Gut*. 2017 Jan; 66(1): pp. 89-96.

⁵⁶² Philip T., Karjalainen S., De Lorenzo F. et al., What could be a cancer mission objective if we join our forces in the fight against cancer? *Tumori*. 2019 Dec; 105(6): pp. 447-455.

- facilities in data management^{563,564,565}.

iii. *Beyond comprehensive cancer centres: the development of specialist cancer centres/units*

Owing to the rising burden of cancer in the EU as well as to the increasingly understood, wide variety of cancer types affecting patients, each coming with distinct clinical implications and requiring healthcare professionals comprising multidisciplinary teams to possess expert knowledge to allow for optimal treatment and care, there has been growing emphasis on the **need for further specialisation of institutions managing cancer cases**.

Countries have been concentrating expertise for certain tumour types in dedicated centres or units, such as for childhood and rare cancers, and all comprehensive cancer centres have teams for the main cancer types. For common adult tumours, however, at the European level there has been widespread effort to establish universal, dedicated units only for breast cancer, following several European declarations that set a target of the year 2016 for care of all women and men with breast cancer to be delivered in **specialist multidisciplinary centres**^{566,567}. While this target was not met⁵⁶⁸, **experts call for healthcare systems to adopt the principles of such dedicated care for all types of cancer**^{569,570}.

iv. *Standardised quality of cancer care through guidelines, quality standards and certification systems*

Given the absence of regulatory measures setting a compulsory definition for comprehensive and specialist cancer centres, **standards and certification systems are of critical relevance to allow for their appropriate badging, quality assurance and continuous quality improvement**. Several European-level programmes have been developed in this regard by expert groups, including:

- the Accreditation & Designation Programme operated by the Organisation of European Cancer Institutes (OECI) on the basis of the OECI standards for high qualitative cancer care⁵⁷¹; and
- the Breast Centres certification scheme operated⁵⁷² on the basis of the guidelines on the requirements of a specialist breast centre developed by the European Society of Breast Cancer Specialists (EUSOMA)⁵⁷³.

Beyond the identification of comprehensive and specialist cancer centres, **ensuring equal access of cancer patients to high-quality cancer care across the EU also requires the standardisation and the assessment of specialist services provided in such centres**. Examples of additional international or European-level standards and certification systems developed in this regard include:

⁵⁶³ Albrecht T., Amati C., Angelastro A. et al., Integrated cancer control: the case for comprehensive cancer care networks (CCCN) IN Albrecht T., Kiasuwa R., Van den Bulcke M., European Guide on Quality Improvement in Comprehensive Cancer Control. Cancer Control Joint Action (Chapter 5); 2017.

⁵⁶⁴ Selby P., Gillis C., Haward R., Benefits from specialised cancer care. Lancet. 1996 Aug 3; 348(9023): pp. 8-313.

⁵⁶⁵ Stead M., Cameron D., Lester N. et al., Strengthening clinical cancer research in the United Kingdom. Br J Cancer. 2011 May 10; 104(10): pp. 34-1529.

⁵⁶⁶ European Parliament. Resolution on breast cancer in the enlarged European Union. 18 October 2006, <http://bit.ly/1XTOWTu>; 2006.

⁵⁶⁷ European Parliament. Written declaration submitted on the fight against breast cancer in the European Union. 27 April 2015, <http://bit.ly/1zS6aHB>.

⁵⁶⁸ Cardoso F., Cataliotti L., Costa A. et al., European Breast Cancer Conference manifesto on breast centres/units. Eur J Cancer. 2017 Feb; 72: pp. 244-250.

⁵⁶⁹ See the Essential Requirements for Quality Cancer Care published by the European Cancer Organisation: <https://www.european-cancer.org/2-content/8-erqcc> (accessed May 2020).

⁵⁷⁰ Biganzoli L., Cardoso F., Beishon M. et al., The Requirements of a Specialist Breast Centre. Breast. 2020 Jun; 51: pp. 65-84.

⁵⁷¹ See the OECI's website's section about the Accreditation & Designation Programme: <https://oeci.eu/Accreditation/> (accessed May 2020).

⁵⁷² See the Breast Centres Certification scheme's website: <https://www.breastcentrescertification.com/> (accessed May 2020).

⁵⁷³ Biganzoli L., Cardoso F., Beishon M. et al., The Requirements of a Specialist Breast Centre. Breast. 2020 Jun; 51: pp. 65-84.

- the Multinational Association of Supportive Care in Cancer (MASCC)-designated centres of excellence in supportive care in cancer⁵⁷⁴;
- the International Accreditation System for Interventional Oncology Services currently developed by the Cardiovascular and Interventional Radiological Society of Europe (CIRSE)⁵⁷⁵ on the basis of the CIRSE standards for quality assurance in interventional oncology⁵⁷⁶;
- the European Association of Nuclear Medicine (EANM) procedure guidelines for tumour Positron Emission Tomography (PET) imaging⁵⁷⁷;
- the International Psycho-Oncology Society (IPOS) International Standard of Quality Cancer Care⁵⁷⁸; and
- international standards developed by the International Organisation for Standardisation (ISO) with a wide range of applications in ensuring high-quality cancer care, such as in respect to digital imaging or medical devices⁵⁷⁹.

Furthermore, the provision of high-quality care to cancer patients also requires the **organisation of care as a whole to be standardised according to the most recent available evidence**. European-level organisational guidelines have therefore also been developed by expert groups, defining key features of the care pathway, such as the composition of the multidisciplinary team and the roles of its members, in the case of distinct tumour types and/or patient groups. These guidelines include:

- the Essential Requirements for Quality Cancer Care (ERQCC)⁵⁸⁰ published by the European Cancer Organisation for sarcoma⁵⁸¹, colorectal cancer⁵⁸², oesophageal-gastric cancer⁵⁸³, melanoma⁵⁸⁴, breast cancer⁵⁸⁵ and prostate cancer⁵⁸⁶ and being currently developed for lung cancer, pancreatic cancer and glioma;
- the European Association of Urology (EAU) guidelines for the management of cancers of the urinary tract⁵⁸⁷;

⁵⁷⁴ See the MASCC's website's section about the Centers of Excellence in Supportive Care in Cancer: <https://www.mascc.org/centers-of-excellence-in-supportive-care-in-cancer-policy> (accessed May 2020).

⁵⁷⁵ See the standards for quality assurance in interventional oncology published by CIRSE: https://www.cirse.org/wp-content/uploads/2020/01/IASIOS_quality_standards_in_IO_2019_V2_web.pdf (accessed May 2020).

⁵⁷⁶ See the International Accreditation System for Interventional Oncology Services' website: <https://www.iasios.org/> (accessed May 2020).

⁵⁷⁷ Boellard R, Delgado-Bolton R, Oyen W. et al, FDG PET/CT: EANM Procedure Guidelines for Tumour Imaging: Version 2.0. Eur J Nucl Med Mol Imaging. 2015 Feb; 42(2): pp. 54-328.

⁵⁷⁸ See the IPOS's website's section about the International Standard of Quality Cancer Care: <https://www.ipos-society.org/about/quality> (accessed May 2020).

⁵⁷⁹ See the "ISO and Health" report from the International Organisation for Standardisation: <https://www.iso.org/files/live/sites/iso.org/files/store/en/PUB100343.pdf> (accessed June 2020).

⁵⁸⁰ See the Essential Requirements for Quality Cancer Care published by the European Cancer Organisation: <https://www.european-cancer.org/2-content/8-ergcc> (accessed May 2020).

⁵⁸¹ Andritsch E., Beischon M., Bielack S. et al., ECCO Essential Requirements for Quality Cancer Care: Soft Tissue Sarcoma in Adults and Bone Sarcoma. A critical review. Crit Rev Oncol Hematol. 2017 Feb; 110: pp. 94-105.

⁵⁸² Beets G., Sebag-Montefiore D., Andritsch E. et al., ECCO Essential Requirements for Quality Cancer Care: Colorectal Cancer. A critical review. Crit Rev Oncol Hematol. 2017 Feb; 110: pp. 81-93.

⁵⁸³ Allum W., Lordick F., Alsina M. et al., ECCO essential requirements for quality cancer care: Oesophageal and gastric cancer. Crit Rev Oncol Hematol. 2018 Feb; 122: pp. 179-193.

⁵⁸⁴ Wouters M.W., Michielin O., Bastiaannet E. et al., ECCO essential requirements for quality cancer care: Melanoma. Crit Rev Oncol Hematol. 2018 Feb; 122: pp. 164-178.

⁵⁸⁵ See the MASCC's website's section about the Centers of Excellence in Supportive Care in Cancer: <https://www.mascc.org/centers-of-excellence-in-supportive-care-in-cancer-policy> (accessed May 2020).

⁵⁸⁶ Brausi M., Hoskin P., Andritsch E. et al., ECCO essential requirements for quality cancer care: Prostate cancer. Crit Rev Oncol Hematol. 2020 Apr; 148: 102861.

⁵⁸⁷ See guidelines published by EAU: <https://uroweb.org/individual-guidelines/oncology-guidelines/> (accessed May 2020).

- the European Hereditary Tumour Group (EHTG) guidelines for the management of hereditary cancer syndromes⁵⁸⁸;
- the European Society of Gynaecological Oncology (ESGO) guidelines and quality indicators for the management of gynaecological cancers⁵⁸⁹;
- the European Society for Paediatric Oncology (SIOP Europe) Standards of Care for Children with Cancer⁵⁹⁰; and
- the International Society of Geriatric Oncology (SIOG) guidelines for provision of cancer care to older patients⁵⁹¹.

v. *Bridging the gap between expertise and patients: the role of cancer networking*

In spite of the above elaborated accumulating evidence and initiatives in favour of provision of care within institutions specialised in cancer care, such as comprehensive cancer centres and specialist cancer centres/units, **many cancer patients are treated in general hospitals** rather than in such centres today in the EU. This often relates to **territorial inequalities in access to high-quality cancer care**. Studies have found that travel distance is a significant factor in not being able to attend a comprehensive cancer centre.

In this context, the opportunities offered by **cancer networking in bringing together physically distant multidisciplinary cancer care expertise, as well as education and research activities** has received increased attention in the recent years. A survey conducted as part of the recent EU co-funded Cancer Control Joint Action (CanCon) indicated that **cancer networks do exist in many EU countries**, as institutions share expertise and facilities for cancer services, and that networks can adopt various configurations that may fit the context of individual countries. Despite this variety of approaches across regions and countries, a common aim of networks is seeking to improve and to integrate cancer services, as well as clinical research^{592,593}.

In order to formalise these efforts and to provide guidance for further implementation of such networks, CanCon defined a model of "**comprehensive cancer care networks**". Such networks would be more likely to **achieve equity in access to good-quality care nearer home** and could thereby **reconcile the expertise of high-volume specialised referral centres with the greater accessibility of general hospitals, other health care institutions** (e.g. imaging centres, community care centres) **and primary care professionals** in existing healthcare systems^{594,595,596}.

⁵⁸⁸ See guidelines published by EHTG: <https://ehtg.org/guidelines/> (accessed May 2020).

⁵⁸⁹ See guidelines published by ESGO: <https://guidelines.esgo.org/> (accessed May 2020).

⁵⁹⁰ See Standards of Care for Children with Cancer published by SIOP Europe: <https://siop.eu/european-research-and-standards/standards-of-care-in-paediatric-oncology/> (accessed May 2020).

⁵⁹¹ See guidelines published by SIOG: <https://www.sioq.org/content/siog-guidelines-0> (accessed May 2020).

⁵⁹² Albreht T., Amati C., Angelastro A. et al., Integrated cancer control: the case for comprehensive cancer care networks (CCCN) IN Albreht T, Kiasuwa R, Van den Bulcke M. European Guide on Quality Improvement in Comprehensive Cancer Control. Cancer Control Joint Action (Chapter 5); 2017.

⁵⁹³ Stead M., Cameron D., Lester N. et al., Strengthening clinical cancer research in the United Kingdom. Br J Cancer. 2011 May 10; 104(10): pp. 34-1529.

⁵⁹⁴ Albreht T., Amati C., Angelastro A. et al., Integrated cancer control: the case for comprehensive cancer care networks (CCCN) IN Albreht T, Kiasuwa R, Van den Bulcke M. European Guide on Quality Improvement in Comprehensive Cancer Control. Cancer Control Joint Action (Chapter 5); 2017.

⁵⁹⁵ See the Essential Requirements for Quality Cancer Care published by the European Cancer Organisation: <https://www.european-cancer.org/2-content/8-erqcc> (accessed May 2020).

⁵⁹⁶ Biganzoli L., Cardoso F., Beishon M. et al., The Requirements of a Specialist Breast Centre. *Breast*. 2020 Jun; 51: pp. 65-84.

Comprehensive cancer care networks (CCCNs) are defined as multi-centred structures characterised by deliberate and comprehensive integration of activities, working under a common governance and dealing with the management of all aspects of cancer care. CCCNs consist of multiple units belonging to different institutions dedicated to research, prevention, diagnosis, treatment, follow-up, supportive and palliative care and rehabilitation, interacting and having a formal agreement to work together in a programmatic and structured way with uniform systems for quality assurance and exchange of information. Within the CCCN model, the care of patients is the responsibility of multidisciplinary and tumour-specific interprofessional teams encompassing specialised hospitals and community care, working together following a patient-centred approach, with the objective to **provide comprehensive cancer care to all the people living in a certain geographic area**. Additional identified advantages of establishing such networks include:

- better cost-effectiveness of cancer care through pooled resources, shared facilities and elimination of unnecessary duplication;
- easier liaison/integration with complementary expertise from individual professionals and with primary care;
- provision of a seamless care pathway, even for patients needing to move to more than one place to receive unique or complex treatment procedures; and
- optimal conditions to conduct basic and translational research, as well as clinical trials and population-based research programmes.

In view of these benefits, the Cancer Control Joint Action issued a set of recommendations for broader implementation of comprehensive cancer networks across the EU. Importantly, these recommendations include the definition of performance indicators and evaluation models, as well as the conduct quality measurements and continuous quality improvement processes⁵⁹⁷. Therefore, **given the role of cancer networks in response to the needs of contemporary oncology, standards and accreditation systems will have to be defined to allow for their quality assurance**, following a similar approach to the one that is already in place for comprehensive cancer centres and specialist cancer centres, as elaborated above.

Recommendation: Fostering equal access to multidisciplinary quality cancer care in the EU

Organisation of cancer care by multidisciplinary teams within established cancer centres and associated networks is key to the provision of high-quality cancer care to patients and the elimination of inequalities in cancer survival and cancer patients' quality of life across Europe. The EU should therefore support the setup of at least one comprehensive cancer centre in each Member State (one for every 5 million inhabitants in countries with a larger population), as well as of recommended specialist cancer centres and cancer networks around these centres.

Usage of best organisational and clinical practices will be crucial to guide such efforts. In this regard, the EU should make best use of latest standards and certification systems developed by expert groups in the European cancer community, by endorsing them as measurements of progress toward equal access to multidisciplinary quality cancer care as part of a newly established Cancer Dashboard.

⁵⁹⁷ Albrecht T., Amati C., Angelastro A. et al. Integrated cancer control: the case for comprehensive cancer care networks (CCCN) IN Albrecht T., Kiasuwa R., Van den Bulcke M., European Guide on Quality Improvement in Comprehensive Cancer Control. Cancer Control Joint Action (Chapter 5); 2017.

Of note, the current status of the organisation of comprehensive cancer care in the EU suggests that significant policy interventions and investment will be required in Central, Eastern, and many Southern Member States to make these recommendations a reality.

b. **Enhancing possibilities from new technologies in cancer care: Artificial intelligence and health "big data"**

One of the major disease areas that will benefit from Artificial Intelligence (AI) and innovative technologies is cancer. AI and deep learning algorithms can **support cancer specialists in accurately diagnosing cancer** and the disease extent, for example by timely detecting breast, colorectal, lung and brain cancer. Furthermore, AI could **result in a better understanding of the disease and contribute to clinical decision-making** by monitoring disease progression. Data analytics would enable to rapidly analyse data and achieve a personalised diagnosis that considers information from lifestyle patterns, genetic and tissue data, pathological data and medical images. The analytical capabilities of AI-powered solutions would also **reduce time to diagnosis, and consequently, accelerate the delivery of treatment.**

Despite the widely recognised potential of AI in cancer care, it faces undeniably barriers in terms of interoperability, legal and ethical standards, governance, cybersecurity, and technical requirements. In addition to launching the Europe's Beating Cancer Plan, Health Commissioner Stella Kyriakides was mandated to "make the most of the potential of e-health and to work on the creation of a European Health Data Space to promote health data exchange and support research on new preventive strategies, as well as treatments, medicines, medical devices and outcomes"⁵⁹⁸. In February 2020, the European Commission unveiled its plans and actions for the development of Artificial Intelligence and a data economy, including blueprints for a regulatory framework on AI and the creation of a European Health Data Space⁵⁹⁹.

These policy actions should **create legally sound conditions to safely collect, storage, exchange and use data, in full compliance with privacy and ethical standards, in cancer research and care.** The Europe's Beating Cancer Plan could better support the transformation of cancer care to include targeted use of AI by defining actions to improve data access, infrastructure and quality with the aim of improving the precision of early diagnosis and treatment optimisation. In respect to cancer research, the EU Cancer Mission and the forthcoming Horizon Europe research and innovation programme are critical components to advance EU-wide research and leverage investments with regards to the use of AI, algorithms, and data in cancer care.

Recommendation: Leveraging AI in the EU's battle against cancer

Europe's Beating Cancer Plan should better support the transformation of cancer care to include targeted use of AI by defining actions to improve data access, infrastructure and quality with the aim of improving the precision of early diagnosis and treatment optimisation.

The EU Cancer Mission and the forthcoming Horizon Europe research and innovation programme should be considered as critical components in advance EU-wide research and leveraging investments with regards to the use of AI, algorithms, and data in cancer care.

⁵⁹⁸ Mission letter of Commissioner-designate Kyriakides: https://ec.europa.eu/commission/sites/beta-political/files/mission-letter-stella-kyriakides_en.pdf.

⁵⁹⁹ Commission presents strategies for data and Artificial Intelligence: https://ec.europa.eu/commission/presscorner/detail/en/ip_20_273.

c. Addressing inequalities and needs of specific populations in cancer care

Whilst sections above address geographic inequalities in cancer care, treatment and outcomes, due attention must be given to the known other forms of inequality and discrimination that can occur.

Particular considerations should be made in respect to age and cancer⁶⁰⁰. In the years to come, with an ageing society, the incidence of older adults diagnosed with cancer in Europe and throughout the world will rapidly increase. About 50% of all cancers are diagnosed in persons beyond the age of 65 years. Evidence suggests that older cancer patients can receive a form of age discrimination in respect to receiving less investigation and less effective treatment. Policy recommendations developed to tackle these challenges include:

- integrating geriatric oncology in the curricula for medical and nursing education, both during studies and post-graduate education;
- integrating geriatric evaluation (including comorbidities) into oncology decision-making and guidelines (all oncologists need to become "geriatric oncologists");
- stimulating research that is relevant for older adults. Current research, and for instance new drug development, mainly focus on younger populations;
- addressing the shortage of specialist oncologists/geriatricians & allied health staff in geriatric oncology; and
- developing interdisciplinary geriatric oncology clinics, especially in academic institutions and comprehensive cancer centres.

Of note, the state of place and policy needs in respect to paediatric oncology are dealt with at length in a dedicated section of this study.

In respect to migrant populations, studies have found that migrant populations have greater difficulty navigating unfamiliar healthcare systems, are less likely to participate in screening programmes and may also experience denied cancer treatment.

On cultural elements of cancer care, work by the European Cancer Organisation in developing its campaign for the elimination of HPV-caused cancers as a public health problem in Europe has indicated the particular considerations that may be required in respect to ensuring appropriate communication about HPV vaccination with some religious communities in which open discussion of sexuality with juveniles and adolescents can require sensitive attention. Furthermore, policies to vaccinate girls but not boys in respect to HPV could be a form of gender discrimination in view of the fact that a number of HPV cancers can develop in men, such as cancers of the penis, anus and oropharynx. Men who have sex with other men have an elevated risk of such cancers, indicative of the need for sensitivity to particular communication and cancer policy needs in respect of the lesbian, gay, bisexual, and transgender (LGBT) community.

⁶⁰⁰ Lawler M., Selby P.J., Aapro M.S., Ageism in Cancer care. *BMJ*. 2014; 348: g1 614.

3.3. Cancer research: developing new cancer treatments and elevating the standards of cancer care

KEY FINDINGS & RECOMMENDATIONS: CANCER RESEARCH

Cancer research, and its translation into everyday clinical practice, is fundamental to ensuring continual improvements in cancer prevention, diagnosis, treatment and follow-up care for survivors.

The EU Cancer Mission, and the next Horizon Europe research and innovation programme, therefore present an unrivalled opportunity to position cancer research at the heart of the EU's renewed emphasis of making beating cancer one of its top priorities. However, it is also an opportunity that must not be squandered. **The EU Cancer Mission should be therefore accompanied by a strong sense of long-term vision for cancer research in Europe.**

Within this cancer research vision should be an articulation of: how the EU can accelerate the translation of cancer research into real-life practice improvement; how research disparity across Europe can be addressed; and how the power of stronger data collaboration across Europe can enhance and accelerate cancer research. Within such a vision too, the role to be played by initiatives such as the European Health Data Space, European Cancer Information System, the European Network of Cancer Registries, European Reference Networks and the suggested European Cancer Dashboard in bringing to life a new era for European cancer research should be clarified and stated.

An underlying concept for developing Europe's translational research strength, and relating to matters raised in Section 3.2 of the study on organisation of cancer care, is the potential for wider application of the Comprehensive Cancer Care Network (CCCN) vision to not only improve delivery of cancer care, but also to advance Europe's network for practical cancer research.

Opportunities abound for improving the conduct of clinical cancer research, especially in the context of a new EU Pharmaceutical Strategy, Europe's Beating Cancer Plan, the EU Cancer Mission and the EU4Health funding stream. Amongst those highlighted in this section include:

- recommended approaches to achieve a greater degree of **treatment optimisation** research;
- stronger promotion of opportunities for **drug repurposing** research; and
- additional support for **research in respect of non-systemic/loco-regional cancer treatment**, such as surgery, radiation therapy and interventional oncology.

As Europe enters a new era in how treatment research is conducted, the continued development of the regulatory structure to embrace the use of **patient reported outcome measures** is encouraged.

Common complaints from the cancer research community about the impact of the General Data Protection Regulation (GDPR) on the conduct of research need to be taken seriously, with both study of impact and open consideration of recommendations for amendment of the Regulation.

Work via the European Commission's Joint Research Centre to help cancer registries in Europe harmonise and raise standards should continue and accelerate.

Alongside other proposals, clear consideration should be given to amendment of the Cross Border Healthcare Directive to help ensure the environment for patients to gain access to clinical trials across borders is improved. An underlining principle in this respect should be of the trial travelling to the patient, rather than the patient to the trial, wherever possible.

3.3.1. State of play and cross-cutting challenges in cancer research

Cancer research, and its translation into everyday clinical practice, is fundamental to ensuring continual improvements in cancer prevention, diagnosis, treatment and follow-up care for survivors.

The EU Cancer Mission, and the next Horizon Europe research and innovation programme, therefore present an unrivalled opportunity to position cancer research at the heart of the EU's renewed emphasis of making beating cancer one of its top priorities. However, it is also an opportunity that must not be squandered.

The EU Cancer Mission and the Europe's Beating Cancer Plan to some degree echo the USA's Cancer Moonshot⁶⁰¹. This is a collaborative effort to deliver a biomedical research vision that results in better outcome for cancer patients. **In Europe, there are significant disparities in cancer research and innovation, which in turn lead to significant inequalities in outcomes, both between and within European countries**^{602, 603}. A striking aspect of this disparity includes the unequal distribution of cancer research strength across Europe⁶⁰⁴, particularly with respect to Central and Eastern Europe⁶⁰⁵.

This has prompted European researchers to propose a European Cancer Groundshot⁶⁰⁶, to generate the empirical evidence that will precisely define both the significant inequalities that exist and the research gaps that are relevant to Europe. In so doing it can help to deliver a research and innovation roadmap for a patient-centred European cancer research and control agenda. The Groundshot will notably address the challenges that are experienced in Central and Eastern European countries.

Recommendation: An EU vision for cancer research

The EU Cancer Mission should be accompanied by a strong sense of long-term vision for cancer research in Europe.

Within this cancer research vision should be an articulation of: how the EU can accelerate the translation of cancer research into real-life practice improvement; how research disparity across Europe can be addressed; and how the power of stronger data collaboration across Europe can enhance and accelerate cancer research.

Within such a vision, the role to be played by initiatives such as the European Health Data Space, European Cancer Information System, the European Network of Cancer Registries, European Reference Networks and the suggested European Cancer Dashboard in bringing to life a new era for European cancer research should be clarified and stated.

⁶⁰¹ Lowy D.R., Singer D.S., Implementing the Cancer Moonshot and beyond. *Lancet Oncol.* 2017; 18: e622-e623.

⁶⁰² Lawler M., Le Chevalier T., Banks I. et al., European Cancer Concord (ECC). A Bill of Rights for patients with cancer in Europe. *Lancet Oncol.* 2014; 15: pp. 60-258.

⁶⁰³ Aapro M., Astier A., Audisio R. et al., Identifying critical steps towards improved access to innovation in cancer care: a European CanCer Organisation position paper. *Eur J Cancer.* 2017; 82: pp. 193-202.

⁶⁰⁴ Begum M., Lewison G., Lawler M. et al., Mapping the European cancer research landscape: An evidence base for national and Pan-European research and funding. *Eur J Cancer.* 2018; 100: pp. 75-84.

⁶⁰⁵ Begum M., Lewison G., Jassem J. et al., Mapping cancer research across Central and Eastern Europe, the Russian Federation and Central Asia: Implications for future national cancer control planning. *Eur J Cancer.* 2018; 104: pp. 127-136.

⁶⁰⁶ Lawler M., Naredi P., Cufer T. et al., Lancet Oncology European Groundshot Commission. Moonshot or groundshot: addressing Europe's cancer challenge through a patient-focused, data-enabled lens. *Lancet Oncol.* 2019; 20: pp. 1482-1485.

3.3.2. Cancer research components: specific opportunities and challenges

It must be understood that cancer research encompasses a wide range of activities of very different nature. These activities can be classified into three categories: basic, translational and clinical research.

a. Cancer basic research

Basic cancer research (also described as "fundamental cancer research") aims at improving the understanding of cellular, molecular, genetic, biochemical and immunological mechanisms affecting the progression, diagnosis and treatment of cancer⁶⁰⁷. This type of research is primarily conducted through laboratory studies by public research institutions. **Owing to the complex and diverse nature of cancers, basic science is critically relevant in the oncology field.**

Basic cancer research offers the opportunity, among others, to decipher the processes underlying the acquisition by a normal cell (or by a group of normal cells) of all the features of a malignant tumour, from genomic instability and chronic proliferation capacity to disruption of the immune response, ability to attract nutrients through blood vessels and to invade new organs of the body through metastasis⁶⁰⁸. It can also look into mechanisms of resistance, how the immune system naturally reacts and how it fights cancerous cells before it gets out of body's control.

Recent decades have seen spectacular developments in basic cancer science, due in great part to technologies such as DNA sequencing, which in turn has opened up the new possibilities emerging from precision oncology⁶⁰⁹.

Recommendation: High-profile EU support for basic cancer research

The needs of basic cancer research must achieve a high profile with the EU Cancer Mission and Horizon Europe research and innovation programme in order to maintain Europe's position at the forefront of discovery and breakthrough in understanding cancer.

b. Cancer translational research

It is recognised that there is great scope to improve Europe's record of success in respect to translating high quality fundamental cancer research into translational practice change. For this, significant improvement in the translational research ecosphere is required.

Translational research – a term often used interchangeably with translational medicine or translational science or bench to bedside – is an effort to build on basic scientific research to create new therapies, medical procedures, or diagnostics. Translational research is fundamental to the progress of precision oncology as it enables the discovery of specific features that are present only in some patients or their tumours and, thereafter, the creation of a specific therapy beneficial for them.

⁶⁰⁷ Presentation of the US Center for Cancer Research's Basic Research Laboratory: <https://ccr.cancer.gov/basic-research-laboratory> (accessed June 2020).

⁶⁰⁸ See section 1.1.1.a. about "drivers of cancer", including a definition of a malignant tumour and a description of the "hallmarks of cancer" 127.

⁶⁰⁹ See section 3.2.1. paragraph about precision oncology.

 Recommendation: Improving the infrastructure for translational cancer research in Europe

Building on recommendations from the European Academy of Cancer Sciences (EACS), Europe's Beating Cancer Plan and the EU Cancer Mission should coordinate to support the building of the comprehensive cancer centre structure across Europe, with, among other aims, the purpose of strengthening the linkage between cancer research and healthcare delivery.

Translational cancer research should be central components of the EU Cancer Mission and Horizon Research Programme.

c. Cancer clinical research

Clinical cancer research can be defined as research in which people, or data or samples of tissue from people, are studied to understand health and disease, in the aim of finding new and better ways to detect, diagnose, treat, and prevent disease.

In cancer, this includes not only all projects devoted to the development of new treatments, but also, much more generally, all studies aiming at improving the standards of care provided to patients.

Examples of clinical cancer research therefore include:

- prevention studies;
- screening studies; and
- treatment studies

Treatment studies can be focused on: systemic treatment (i.e. medicine); non-systemic/loco-regional treatment, such as surgery and radiotherapy; or, combinations of different modalities. Studies can aim at developing new treatments, as well as improving ways to deliver existing treatments such as through de-escalation, shorter treatment periods, improved patient safety and other approaches⁶¹⁰.

Clinical research can also be conducted in respect to all other areas of cancer care including follow-up and end of life care, and survivorship needs.

It should be more commonly understood that clinical cancer research is not only focused on assisting a product to come to market (e.g. a medicine or device). Any progress in cancer care (as in healthcare in general) needs to be based on strong evidence and clinical research provides methodologies to gather that level of evidence.

Recommendation: Broadening the landscape for European clinical cancer research

In the context of the EU Cancer Mission, Europe's Beating Cancer Plan and the EU Pharmaceutical Strategy, there is a need to build in review of the regulatory and incentive landscape for clinical cancer research in Europe. This includes identification and leverage of opportunities to rebalance clinical cancer research activities towards the full spectrum of cancer control, including all treatment modalities, and providing much needed support to academic, independent cancer clinical research activities.

⁶¹⁰ See section 3.3.3.a. about treatment optimisation.

3.3.3. Proposals for reform of the cancer clinical research environment in Europe

a. Treatment optimisation

Due to the particular development challenges associated with precision oncology, including the more limited number of potential users, a number of new personalised medicine therapies have been authorised. However, some concern is raised about the more limited knowledge about dosage, sequencing, combination and duration of such treatments. This in turn is raising concern about potential sub-optimal administration, prospective generation of unnecessary toxicity for patients, and negative impact on healthcare budgets. Taken together, this has served to highlight a growing need for clinical, post-market authorisation research that more thoroughly investigate the optimal way to use medicines, or other treatments, after they are authorised for use.

To help lead reform in this respect, the European Organisation for Research and Treatment of Cancer (EORTC) has developed a "Treatment Optimisation Manifesto" addressing these challenges, and which commands broad support from the European cancer community⁶¹¹. The manifesto calls for such changes as:

- the generation of treatment optimisation evidence at an earlier stage of a prospective treatment's development, i.e. as soon as the safety and efficacy profiles are known;
- establishing treatment optimisation research as an official and mandatory step in the treatment access path to market; and
- public funding for treatment optimisation research, to ensure it is free of commercial consideration, including via the EU Cancer Mission and Horizon Europe research and innovation programme.

Recommendation: Treatment optimisation as a part of the EU Pharmaceutical Strategy

The creation and implementation of a new EU Pharmaceutical Strategy should be utilised as a crucial opportunity for securing a new era for treatment optimisation in cancer care in the decades ahead.

b. Drug repurposing

Drug repurposing, also known as drug repositioning, corresponds to a development strategy predicated on the reuse of existing licensed medicines for new indications. Despite being affordable and safe, it is a largely untapped approach for improving clinical treatment options⁶¹². For example, the Repurposing Drugs in Oncology (ReDO) project, launched by the Anticancer Fund, cites over 300 non-cancer drugs as having shown some evidence of anticancer effects; of these, 50% are supported by relevant human data and 16% are supported by data from at least one positive clinical trial⁶¹³. Example of initiatives in this regard include ongoing investigations into aspirin for recurrence and survival in colon cancer, and repurposing of an angina pectoris medication as a lung cancer treatment.

However, two main policy barriers are identified in respect to achieving more active investigations of repurposing opportunities:

⁶¹¹ In support of the manifesto, the European Cancer Organisation has created a dedicated Network of its members, patient organisations and others to help support the achievement of these ambitions for change.

⁶¹² Factsheet about drug repurposing on the Anticancer Fund's website: <https://www.anticancerfund.org/en/drug-repurposing> (accessed July 2020).

⁶¹³ Repurposing Drugs in Oncology (ReDO) project's website: <http://www.redo-project.org/> (accessed July 2020).

- **Lack of clear regulatory pathways for repurposing of medicines**

Current pharmaceutical regulations principally focus on the development of new medicines, not new indications for existing medicines, and there is a clear lack of EU and national pathways to facilitate drug repurposing; and

- **Lack of financial incentives and research funding for repurposing of medicines**

Expert suggestions to address this issue include removal of restrictions on the entities eligible to apply for market authorisation (label) extensions to facilitate repurposing and EU funded research calls specifically including drug repurposing for cancer on a non-commercial, public health-driven basis⁶¹⁴.

Recommendation: Developing repurposing of medicines for cancer treatment in the EU

The EU Cancer Mission, Europe's Beating Cancer Plan and forthcoming EU Pharmaceutical Strategy should clearly cohere in creating a more positive environment for the conduct of research into repurposing of medicines for cancer treatment.

c. Non-systemic treatment trials

As is clearly described in Section 3.2, cancer treatment is multi-modal, involving not only cancer medicines, but also other major, non-systemic modalities, such as surgery, radiation therapy and interventional oncology. However, clinical research in these latter treatment modalities is of a much more limited scale. This is, in large part, attributed to differing financial incentives at stake for such research.

Yet non-systemic/loco-regional treatment also stand to benefit from scientific and technological developments, which if translated to the clinic and tested through clinical trials, could yield significant patient benefit. Such studies are therefore crucial to the improvement of patient outcomes. However, awareness of their existence and support for the conduct of such research is currently lacking. Indeed, many cancers, specifically in early stage, are treated only with surgery and/or radiotherapy. Research and studies in respect of non-systemic/loco-regional cancer treatment is therefore highly important to the improvement of patient outcomes. However, awareness of their existence and support for the conduct of such research is currently lacking.

Broader system-wide responses to improve incentives for research in these areas that could be advanced include movement to more "value-based" healthcare systems, in which innovations in treatment that offer measurable and defined improvement in agreed areas⁶¹⁵, are incentivised, regardless of treatment modality. To assist this, evidence-informed value scales for surgical and radiation oncology have been suggested.

⁶¹⁴ Repurposing drugs for cancer treatment: Unlocking the potential: https://www.anticancerfund.org/sites/default/files/attachments/policy_paper_on_repurposing.pdf.

⁶¹⁵ Towards an evidence-informed value scale for surgical and radiation oncology: a multi-stakeholder perspective: [https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(18\)30917-3/fulltext](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(18)30917-3/fulltext).

Recommendation: Encouraging European research for all treatment modalities

Without fundamental reform to the predominating financial incentive structures governing the direction of private investment in treatment research, sustained public funding for research in areas of cancer treatment such as surgery, radiation therapy and interventional oncology is required. EU research programmes, such as the EU Cancer Mission, should therefore see it as firmly within its remit to provide such support.

d. Regulatory reforms required to take account of scientific and technological developments in cancer research

i. *Supporting the continued development of patient-reported outcomes within the EU regulatory landscape*

From a patient perspective, the integration of quality of life measurements as endpoints for clinical trials, involving both psychological and medical aspects, is an increasingly relevant need. **The success of cancer treatment is not only related to increasing survival, but also achieving meaningful improvements to a patient's quality of life.**

To meet this need, in the past decade there has been sustained development of the regulatory concept of patient-reported outcome measures (PROMs) as a normalising part of the trial landscape.

A patient-reported outcome (PRO) is defined as any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else.

Patient-reported outcomes usually include information about health-related quality of life, symptoms, function, satisfaction with care or symptoms, adherence to prescribed medications or other therapy, and perceived value of treatment⁶¹⁶.

Patient-reported outcome measures are helping to collect new forms of data that can be used to guide changes in clinical and health policy decisions, to improve treatments, reduce secondary effects, increase workflow efficiency, and enhance patient-physician communication.

Recommendation: Supporting the continued development of patient-reported outcomes within the EU regulatory landscape

In the context of a new emerging EU Pharmaceutical Strategy, any adaptation of the regulatory landscape for the assessment and approval of medicines should seek to support the greater use of patient-reported outcome measures in clinical research.

ii. *Investigating fully the impact of the EU General Data Protection Regulation on cancer research*

Significant concerns have been expressed by some members of the European cancer research community concerning the burdens and restrictions on research imposed by the EU's General Data Protection Regulation (GDPR), which came into legal force in 2018. Criticisms include:

- additional hurdles presented in respect to European participation in global cancer research projects; and

⁶¹⁶ Donovan J.L., Hamdy F.C., Lane J.A. et al., Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. *N Engl J Med.* 2016 Oct 13; 375(15): pp. 1425-1437.

- barriers imposed on the conduct of secondary analysis due to the interpretation of the regulation's patient consent requirements.

Recommendation: Investigating fully the impact of GDPR on European cancer research

Concerns expressed by the cancer research community about the operation of the General Data Protection Regulation upon their work should be treated with the utmost seriousness. The European Commission should carry out ex-post evaluation on the Regulation's impact on cancer research following two years after the Regulation became applicable, and act on identified opportunities for easing regulatory burden. An example of action to be taken would be a defined process for achieving a better harmonisation of the currently divergent national GDPR requirements affecting cancer research.

iii. Leveraging the power of cancer registries

An area of strong supportive activity by the European Union over the past 30 years has been in aiding the better use of data in the battle against cancer. For example, the Joint Research Centre (JRC), acting in its scientific role to the European Commission and in close collaboration with the Commission's Directorate-General for Health and Food Safety (DG SANTE) as well as with major European stakeholders in the field, has been developing and is maintaining the European Cancer Information System (ECIS). This is a comprehensive health and research infrastructure harmonising cancer registries' data and producing meaningful information to facilitate the interpretation of the dynamics of cancer in Europe.

Data needed to quantify the cancer burden in a geographically defined population are systematically collected by population-based cancer registries (CR), which are the information source for all reportable cancer cases in the specific area. Since 2012, in response to the call from the European Council to the Commission to act further in harmonising EU cancer registration, the JRC has taken an active role in supporting the activities and exploiting the data of the CR affiliated to the European Network of Cancer Registries (ENCR), currently including 178 individual registries across Europe (comprising non-EU countries⁶¹⁷).

Recommendation: Leveraging the power of cancer registries in the EU

The mandate, funding and political support for the Joint Research Centre to continue and accelerate its coordinating work with cancer registries across Europe should be refreshed and expanded in the context of the EU Cancer Mission and Europe's Beating Cancer Plan.

iv. Cross-border access to clinical trials

Access to clinical trials is of particular importance in cancer care. Besides their role in allowing the development of new treatments, clinical trials can indeed be, especially in the case of rare malignancies, the only way for patients to access potential life-saving medicines.

In this regard, a recent study was carried out by researchers from the European Forum for Good Clinical Practice (EFGCP), the European Organisation for Research and Treatment of Cancer (EORTC), KU Leuven and Patvocates, with the support of the European Federation of Pharmaceutical Industries and

⁶¹⁷ Measuring the cancer burden in Europe: The European Cancer Information System: <https://www.emjreviews.com/oncology/abstract/measuring-the-cancer-burden-in-europe-the-european-cancer-information-system-ecis/>.

Associations (EFPIA)⁶¹⁸. A number of caveats were identified, hindering patients to benefit from the information and support they need to access innovative treatment across borders.

Further efforts should be conducted at European and national levels to reduce the barriers that prevent cancer patients from accessing innovative treatment across borders, including via clinical trials⁶¹⁹.

In the absence of EU legislation or guidelines to facilitate patients' participation in trials in locations outside their particular country, patients who travel to another country for clinical trials face issues such as the lack of clarity on protocols for follow-up after their return home, and how national insurance covers costs associated with their participation in the trial. These obstacles could be addressed through a possible revision of the EU directive on patients' rights in cross-border healthcare.

Access to innovative therapies in early clinical trials is not currently considered as part of the S2 program, under Regulation EC No 883/2004 on the coordination of social security systems. At a time when numerous examples show that access to innovative medicines under development can provide significant benefit for individual patients, it is of concern that they cannot go across borders to have access to novel therapies and be reimbursed⁶²⁰.

Existing initiatives in certain countries have identified viable interim solutions, which could serve as guidance, and provide possible models for future legislation. These include:

- the Nordic network for sharing new trial results and information on access to new therapies;
- Slovakia's legislation specifying that citizens participating in trials in other countries will be covered by national insurance at home if they have informed medical authorities beforehand; and
- the Dutch-German cooperation in the border regions, where university hospitals collaborate on research, exchange data and work together to facilitate and simplify the access for trial patients.

The purpose of cross-border trials is not to encourage mass movements of patients between countries. That would be unlikely to happen in any case, as patients prefer treatment near home in a familiar environment. Cross-border trials add value to treatment in specific cases, such as rare diseases, where there are no local options left. At this point, the possibility to easily access new therapies in another country brings life-changing potential.

Importantly, in considering cross-border access to clinical trials, an underlying motif should be the concept of the trial travelling to the patient, rather than the patient travelling to the trial. In an era of ever more available means of digital communication this should be made a straightforward endeavour to achieve.

Of note, the conduct of clinical trials for non-systematic treatment options, such as surgery, radiation oncology and interventional oncology, is associated with specific methodological and organisational challenges. This is reflected, for instance, by the fact that only 1% of cancer patients are recruited into surgical oncology trials in Europe. Given the relevance of such trials to foster better outcomes and higher quality of cancer care for patients, clinical research in these fields should therefore be promoted through collaboration between specialists and public funding.

⁶¹⁸ ECCO 2019 Summit Report, section on clinical trials across borders: <https://www.ecco-org.eu/component/attachments/?task=download&id=171> (accessed June 2020).

⁶¹⁹ European Cancer Summit 2019, session report on clinical trials across borders: <https://www.european-cancer.org/component/attachments/?task=download&id=154:Crossborder-access-to-clinical-trials-2> (accessed May 2020).

⁶²⁰ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 3).

Furthermore, the integration of quality of life measurements as endpoints for clinical trials, involving both psychological and medical aspects, is seen as a promising prospect by cancer patients; it also represents an opportunity for the development of psycho-oncology services across Europe.

Recommendation: Cross-border access to clinical trials in the EU

The operation and content of the Cross-Border Healthcare Directive should be reviewed with the intent of identifying and securing opportunities to increase citizen rights and access to participate in clinical trials across borders.

4. RARE CANCERS AND CANCER IN CHILDREN

Despite their individual rarity, rare cancers represent a major public health concern in Europe, affecting an estimated 5.1 million of patients across Europe⁶²¹. Their **uncommon nature** is associated with a wide range of specific challenges regarding clinical research, healthcare organisation and clinical decision-making⁶²², therefore requiring a **dedicated policy approach**.

Of note, all **paediatric cancers** are rare^{623, 624}. Nevertheless, they have age-related, biological, clinical and organisational specificities that require them to be addressed through further **tailored approaches, strategies and measures beyond simple extrapolation of adult services**⁶²⁵. In addition to overarching concerns shared with the adult rare cancer sector, considerations specific to paediatric cancers are therefore detailed in a dedicated section.

Given the lack of straightforward epidemiological or biological criterion, setting a definition of rare cancers represents in itself a challenge. In the EU, rare diseases are considered as those currently affecting less than 5 in 10,000 persons⁶²⁶. While this threshold is used by the EMA as a basis for regulatory decisions, the impact of mortality on prevalence creates possible biases, since rare, but good prognosis, malignancies can be mistaken as common cancers and vice versa⁶²⁷. Furthermore, many steps of the patient pathway occur only "once" in rare cancers; thus, incidence is considered to better reflect their actual burden on healthcare systems⁶²⁸. The EU-funded Surveillance of Rare Cancers in Europe (RARECARE) project (2007-2010), gathering European experts to generate consensus epidemiological data on rare cancers, therefore proposed a **definition based on incidence (less than 6 out of 100,000 people per year in the European population**⁶²⁹), which is now considered as conventional in the European oncology community⁶³⁰ and even used in some studies beyond Europe⁶³¹.

Rare and paediatric cancers have been a quite active field of European cancer policy in recent years. **Latest initiatives supported by EU funding programmes include:**

- the Information Network on Rare Cancers (**RARECAREnet**) project (2012-2016): Europe-wide epidemiological study conducted as a follow-up to the RARECARE project, aimed at producing updated data about rare cancers in the EU and at studying the degree of centralisation of treatment of these conditions⁶³²;

⁶²¹ RARECAREnet website's online analysis tool. <http://www.rarecarenet.eu/analysis.php> (accessed February 2020).

⁶²² Joint Action on Rare Cancer (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 1).

⁶²³ Steliarova-Foucher E., Fidler M.M., Colombet M. et al. Changing geographical patterns and trends in cancer incidence in children and adolescents in Europe, 1991–2010 (Automated Childhood Cancer Information System): a population-based study. *Lancet Oncol* 2018 Sep; 19(9): pp. 1159-1169.

⁶²⁴ Joint Action on Rare Cancer (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 1).

⁶²⁵ Joint Action on Rare Cancer (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers.

⁶²⁶ EU Orphan Medicines Regulation.

⁶²⁷ Joint Action on Rare Cancer (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 1).

⁶²⁸ Joint Action on Rare Cancer (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 1).

⁶²⁹ Gatta G., Van der Zwan J.M., Casali P.G. et al., Rare cancers are not so rare: the rare cancer burden in Europe. *Eur J Cancer* 2011 Nov; 47(17): pp. 2493-2511.

⁶³⁰ Joint Action on Rare Cancer (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 1).

⁶³¹ Gaddipati H., Liu K., Pariser A. et al., Rare cancer trial design: lessons for FDA approvals. *Clin Cancer Res* 2012; 18(19): pp. 8-5172.

⁶³² Gatta G., Capocaccia R., Botta L. et al., Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet-a population-based study. *Lancet Oncol* 2017 Aug; 18(8): pp. 1022-1039.

- the EU Joint Action on Rare Cancers (**JARC**; 2016-2019): Member-State driven, multi-stakeholder initiative, which produced the Rare Cancer Agenda 2030 (10 key policy recommendations on rare cancers, to be implemented at national and EU level⁶³³); and
- European Reference Networks (**ERNs**): virtual networks, launched in 2017, involving healthcare providers across Europe, aimed at tackling complex or rare diseases and conditions that require highly specialised treatment and a concentration of knowledge and resource⁶³⁴, four of which are specifically devoted to rare cancers (EURACAN, EuroBloodNet, PaedCan and GENTURIS).

⁶³³ Joint Action on Rare Cancer (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers.

⁶³⁴ European Commission's factsheet about European Reference Networks:
https://ec.europa.eu/health/sites/health/files/ern/docs/2017_brochure_en.pdf (accessed February 2020).

4.1. Rare cancers

KEY FINDINGS & RECOMMENDATIONS: RARE CANCERS

Despite their individual rarity, rare cancers represent a major public health concern in Europe, affecting an estimated 5.1 million of patients across Europe. Estimated **5-year relative survival is significantly lower** on average for rare cancers than for their common cancer counterparts. Their **uncommon nature** is associated with a wide range of specific challenges regarding clinical research, healthcare organisation and clinical decision-making.

Noting ongoing dramatic variations in survival across Europe, even for individually highly curable rare cancer types, sustained attention to rare cancer policy is required within the context for the forthcoming Europe's Beating Cancer Plan, EU Cancer Mission and new EU Pharmaceutical Strategy.

One of the most intuitive and prominent issues in rare cancer management is the scarcity of clinical expertise, which is directly linked to the small number of rare cancer cases encountered by healthcare providers and has strong impacts on the provision of diagnosis and care to affected patients.

To address these conditions in terms of health system organisation, three complementary approaches have been developed and recommended by the rare cancer community: **centralised referral, networking and national planning**. Each is addressed further within the section.

In respect to networking, the European Union is now playing a central role in improving collaboration across countries in respect to rare cancers via the construction and operation of **'European Reference Networks'**. These were launched in 2017 in connection to the EU's Cross-Border Healthcare Directive. Four of the newly established networks are specifically devoted to rare cancers: EURACAN (ERN on rare adult solid cancer), EuroBloodNet (ERN on Rare Haematological Diseases), ERN PaedCan (ERN on paediatric cancers) and ERN GENTURIS (ERN on genetic tumour risk syndromes).

The ERNs are opening new possibilities for improving rare cancer treatment and care including via: sharing of clinical cases; rationalisation of patient referral; and, improved rare cancer management in small countries. The Joint Action on Rare Cancers (JARC) has envisaged many further potential roles to be developed within the ERNs, including with respect to production of clinical practice guidelines for rare cancers, facilitating biobanking, achieving efficiencies of scale in clinical trials, and improving access to potentially practice-improving data.

Thus, the establishment of European Reference Networks in the field of rare cancer has helped to identify a great range of additional opportunities for meaningful pan-European collaboration, making use of their infrastructure for connecting centres across Europe. **However, to achieve this, ERNs must be supported by long-term sustained funding.**

Despite EU regulatory initiatives such as the Orphan Medicines Regulation, numerous challenges still remain in respect to the research environment for rare cancers. Therefore, the recommendations of the EU co-funded Joint Action on Rare Cancers (JARC) for improving the research environment for rare cancers should be integrated within the context of Europe's Beating Cancer Plan and a new EU Pharmaceutical Strategy. This includes encouraging the development and use of innovative methodologies for clinical trial designs, improving cross-border access to clinical trials, and series of recommendations for combatting the burden imposed on research as a result of GDPR regulation.

4.1.1. Classifications and scope of rare cancers

Based on data collected from 94 European population-based cancer registries, covering 46% of the EU population⁶³⁵, RARECAREnet produced a comprehensive **European list of cancers**⁶³⁶. This list constitutes an update of the one previously devised by RARECARE⁶³⁷ and was recently re-examined within JARC⁶³⁸; it is based on the third edition of the International Classification of Diseases for Oncology (ICD-O-3), developed by the WHO⁶³⁹, and sets up a classification system organised in three tiers:

- tier 3: individual tumour entities, identified through ICD-O-3 topography (i.e. anatomical site) and morphology (i.e. cell type and biological behaviour⁶⁴⁰) codes;
- tier 2: categories of cancers considered similar for clinical management and research, among which rare cancers are identified through their estimated incidence; and
- tier 1: general categories of tumours, considered to involve the same clinical expertise and patient referral structure⁶⁴¹.

On the basis of the consensus definition of rare cancers, this system allows to define the **scope of rare cancers in Europe**: according to latest available data, **198 distinct rare cancers can be defined**, found within 62 general tumour categories (tier 1) and comprising 521 individual tumour entities (tier 3). As a matter of comparison, the entire RARECAREnet classification of cancers is divided into 218 cancers (tier 2)⁶⁴²; rare cancers therefore represent **84% of the total tumour diversity**.

Furthermore, RARECARE and RARECAREnet also grouped cancer types into a list of **12 major "families"**, each of them comprised of several general tumour categories (tier 1) managed by the same disease-based communities of physicians and clinical researchers⁶⁴³, which was recently re-examined within JARC⁶⁴⁴: **head of neck cancers, digestive cancers*, thoracic cancers*, female genital cancers*, male genital and urogenital cancers*, neuroendocrine tumours, cancers of the endocrine organs, sarcomas, cancers of the Central Nervous System (CNS), skin cancers and non-cutaneous melanoma*, "paediatric" cancers⁶⁴⁵ and haematological malignancies***.

⁶³⁵ Gatta G, Capocaccia R, Botta L. et al, Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet-a population-based study. *Lancet Oncol* 2017 Aug; 18(8): pp. 1022-1039.

⁶³⁶ RARECAREnet list of rare cancers (downloaded from RARECAREnet website: http://www.rarecaren.net/images/Resources/RARECAREnet_list_of_rare_cancers_Dec15.xlsx; accessed February 2020).

⁶³⁷ RARECARE list of rare cancers (downloaded from RARECARE website: http://www.rarecare.eu/rarecancers/Rare_Cancers_list_March2011.xls; accessed February 2020).

⁶³⁸ Joint Action on Rare Cancer (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 1).

⁶³⁹ Fritz A., Percy C., Jack A., Kanagaratnam S, Sobin L, Parkin MD. International classification of diseases for oncology (ICD-O). 3rd ed. Geneva; World Health Organisation; 2000.

⁶⁴⁰ Definitions on topography and morphology ICD-O-3 codes found on DIMDI (German Institute of Medical Documentation and Information) website. <https://www.dimdi.de/dynamic/en/classifications/icd/icd-o-3/> (accessed March 2020).

⁶⁴¹ RARECAREnet website. <http://www.rarecaren.net/> (accessed February 2020).

⁶⁴² RARECAREnet list of cancers (downloaded from RARECAREnet website: http://www.rarecaren.net/images/Resources/RARECAREnet_list_of_rare_cancers_Dec15.xlsx; accessed February 2020).

⁶⁴³ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 1).

⁶⁴⁴ JARC list of rare cancer families – extracted from Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 1).

⁶⁴⁵ This family does not encompass the entire burden of paediatric cancers; it indeed comprises a number of blastomas known to occur in the paediatric population, however the latter are also affected by rare tumour entities included under other labels (see Annex 2³¹), or even by tumour entities classified as common within the total population, but affecting children with a rare incidence. The International Childhood Cancer Classification (ICCC3) is most often referred to in the paediatric cancer sector (see Section 4.2).

* This cancer family includes both common and rare cancers.

While some of these cancer families include some common cancers, as indicated*, **all of them comprise rare cancers**. Therefore, these families are known as the "12 'families' of rare cancers" and may serve as a basis to study and address rare cancers in Europe.

Of note, for paediatric cancers, the International Childhood Cancer Classification (ICCC3) is most often referred to reflect the diagnostic spectrum of childhood cancers⁶⁴⁶.

4.1.2. Epidemiology of rare cancers

On the basis of this refined list of rare cancers, the RARECAREnet project also calculated estimates of rare cancer incidence, prevalence and survival indicators in Europe.

Of note, these figures do not reflect data for all childhood malignancies, as the underlying study excluded specific paediatric cancer registries. Statistics for paediatric cancers are provided in a dedicated section⁶⁴⁷.

Table 4: Incidence, prevalence and survival estimates for rare cancers in the EU

	INCIDENCE		PREVALENCE	SURVIVAL
	Crude incidence rate per 100 000 people in 2000-2007	Estimated new cases in 2013 in the EU	Estimated prevalent cases in 2008 in the EU	Estimated 5 year relative survival in 2000-2007
All rare tumours	114.99	636,753	5,085,137	48.5%

Source: Gatta G, Capocaccia R, Botta L, et al. Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet-a population-based study. *Lancet Oncol* 2017 Aug; 18(8):1022-1039. RARECAREnet website's online analysis tool. <http://www.rarecarenet.eu/analysis.php> (accessed February 2020).

According to this data, rare cancers account for **24% of all cancers diagnosed each year** in the EU⁶⁴⁸, however, "extremely rare" cancers, which can be defined as those whose incidence falls below 0.2 out of 100,000 people⁶⁴⁹, make up 61% of rare tumour entities but only 1% of all annual new cancer cases⁶⁵⁰. Amongst rare cancer families, haematological malignancies, female genital cancers and digestive cancers are the most frequent, with more than 100,000 annual new cases each, whereas rare skin cancers represent only around 7,000 annual new cases (see Annex 10⁶⁵¹).

When analysing incidence trends overtime, an overall increase of 0.5% per year is identified⁶⁵²; furthermore, incidence rates also show significant variability across countries, even after age

⁶⁴⁶ See Section 4.2.1. about families of paediatric cancers.

⁶⁴⁷ See Section 4.2.2. about epidemiology of paediatric cancers.

⁶⁴⁸ Gatta G, Capocaccia R, Botta L. et al., Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet-a population-based study. *Lancet Oncol* 2017 Aug; 18(8): pp. 1022-1039.

⁶⁴⁹ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 1).

⁶⁵⁰ Calculation performed on the basis of data extracted from Gatta G, Capocaccia R, Botta L, et al. Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet-a population-based study. *Lancet Oncol* 2017 Aug; 18(8): pp. 1022-1039.

⁶⁵¹ Incidence, prevalence and survival estimates for individual rare cancer families; extracted from Gatta G, Capocaccia R, Botta L, et al. Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet-a population-based study. *Lancet Oncol* 2017 Aug; 18(8):1022-1039 & from RARECAREnet website's online analysis tool. <http://www.rarecarenet.eu/analysis.php> (accessed February 2020).

⁶⁵² Gatta G, Capocaccia R, Botta L. et al., Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet-a population-based study. *Lancet Oncol* 2017 Aug; 18(8): pp. 1022-1039 (Data on 1999-2007).

adjustment^{653,654}. While these differences may be to some extent explained by variations in pathological diagnosis accuracy or in rare cancers classification and registration, they can also reflect disparities in exposure to some cancer risk factors, such as Human Papillomavirus (HPV) or obesity⁶⁵⁵, thus exemplifying needed efforts in terms of primary prevention.

Estimated **5-year relative survival is significantly lower** on average for these rare (mostly adult) cancers than for their common counterparts (63.4%). This is also true for most individual cancer families (see Annex 10⁶⁵⁶), even after excluding common tumours with known good prognosis⁶⁵⁷. Moreover, while overall relative survival for common adult cancers improved by 5.5% between 1999 and 2007, this increase was limited to 3% for rare adult cancers⁶⁵⁸. Although they might, to some extent, reflect the distinct biology of some rare cancers, these differences constitute further **strong indications of the need for policies dedicated to rare cancers**, aimed at fostering improvement in outcomes for affected patients⁶⁵⁹.

Furthermore, age- and case-mix-adjusted survival rates⁶⁶⁰, which can be considered as one of the most succinct indicators of the performance of healthcare systems to control cancer⁶⁶¹, also show large geographical disparities, with **lower survival values in Eastern European countries**⁶⁶² (falling all below 45%, down to less than 35% in Bulgaria) than in all others (all above 45%), especially in Northern⁶⁶³ and Central⁶⁶⁴ European countries (up to more than 55% in Iceland)⁶⁶⁵. Importantly, dramatic variations in survival following a similar pattern are still found when considering individual highly curable rare cancer types⁶⁶⁶, strongly suggesting the **substantial relevance of clinical expertise to the outcome for rare cancers patients**⁶⁶⁷.

⁶⁵³ Calculation performed to allow inter-country comparisons of incidence rates by eliminating variations due to different age distributions, with age being known to affect the risk of developing cancer.

⁶⁵⁴ Gatta G, Trama A, Capocaccia R, Epidemiology of rare cancers and inequalities in oncologic outcomes. *Eur J Surg Oncol*. 2019 Jan;45(1): pp. 3-11.

⁶⁵⁵ Gatta G, Capocaccia R, Botta L, et al., Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet-a population-based study. *Lancet Oncol* 2017 Aug; 18(8): pp. 1022-1039.

⁶⁵⁶ Incidence, prevalence and survival estimates for individual rare cancer families; extracted from Gatta G, Capocaccia R, Botta L, et al. Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet-a population-based study. *Lancet Oncol* 2017 Aug; 18(8): pp. 1022-1039 and from RARECAREnet website's online analysis tool. <http://www.rarecaren.net/analysis.php> (accessed February 2020).

⁶⁵⁷ Gatta G, Capocaccia R, Botta L, et al., Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet-a population-based study. *Lancet Oncol* 2017 Aug; 18(8): pp. 1022-1039.

⁶⁵⁸ Gatta G, Capocaccia R, Botta L, et al. Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet-a population-based study. *Lancet Oncol* 2017 Aug; 18(8): pp. 1022-1039.

⁶⁵⁹ Gatta G, Capocaccia R, Botta L, et al., Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet-a population-based study. *Lancet Oncol* 2017 Aug; 18(8): pp. 1022-1039.

⁶⁶⁰ Calculation performed to allow inter-country comparisons of survival rates by eliminating variations due to different distributions of age and cancer types, associated to different prognosis.

⁶⁶¹ Gatta G, Trama A, Capocaccia R, Epidemiology of rare cancers and inequalities in oncologic outcomes. *Eur J Surg Oncol*. 2019 Jan;45(1): pp. 3-11.

⁶⁶² RARECAREnet Eastern Europe region: Eastern Europe: Bulgaria, Czech Republic, Estonia, Latvia, Lithuania, Poland, Slovakia (found on RARECAREnet website <http://www.rarecaren.net/>, accessed February 2020).

⁶⁶³ RARECAREnet Northern Europe region: Finland, Iceland, Norway. (found on RARECAREnet website <http://www.rarecaren.net/>, accessed February 2020).

⁶⁶⁴ RARECAREnet Central Europe region: Austria, Belgium, France, Germany, Switzerland, The Netherlands. (found on RARECAREnet website <http://www.rarecaren.net/>, accessed February 2020).

⁶⁶⁵ Gatta G, Trama A, Capocaccia R, Epidemiology of rare cancers and inequalities in oncologic outcomes. *Eur J Surg Oncol*. 2019 Jan; 45(1): pp. 3-11.

⁶⁶⁶ Gatta G, Trama A, Capocaccia R, Epidemiology of rare cancers and inequalities in oncologic outcomes. *Eur J Surg Oncol*. 2019 Jan; 45(1): pp. 3-11.

⁶⁶⁷ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 1).

Recommendation: Maintaining focus on rare cancer policy in the EU

Noting ongoing dramatic variations in survival across Europe, even for individually highly curable rare cancer types, sustained attention to rare cancer policy is required within the context for the forthcoming Europe's Beating Cancer Plan, EU Cancer Mission and new EU Pharmaceutical Strategy.

4.1.3. Challenges in rare cancers

Rare cancers make up a highly heterogeneous group of cancer types, both in terms of anatomical location⁶⁶⁸ and of causation. Known causative factors of adult rare tumours include, among others, HPV infection, exposure to occupational risk factors⁶⁶⁹ and hereditary cancer syndromes⁶⁷⁰. The causative mechanisms of paediatric cancers are presented in a dedicated section⁶⁷¹.

However, **owing to their uncommon nature, rare cancers share similar problems** regarding provision of relevant therapies and care to affected patients, including:

- difficulty for patients to access timely and accurate **diagnosis**, as well as highly specialised **care** and adequate **treatments**, feeling of **isolation** for them and their families; and
- poor **research** opportunities, difficulties in **clinical trials** and lack of **therapies**^{672,673}.

From a health policy perspective, rare cancers can therefore be addressed through instruments of rare disease policies, such as European Reference Networks (ERNs) and the EU Orphan Medicines Regulation. They should nevertheless also fully benefit from general cancer policies' mechanisms, such as cancer registries and national cancer control plans (NCCPs)⁶⁷⁴ and the consequences of their management alongside common cancer cases on provision of care should be factored in⁶⁷⁵.

a. Access to clinical expertise and high-quality diagnosis and care

One of the most intuitive and prominent issues in rare cancer management is the **scarcity of clinical expertise**, which is directly linked to the small number of rare cancer cases encountered by healthcare providers and has strong impacts on the provision of diagnosis and care to affected patients. Furthermore, diagnosis for some rare cancers may be hindered by the presence of only negligible symptoms, the lack of associated risk factors and the fact that patients developing them are not from the population seen as "at risk of cancer".

To address these conditions in terms of health system organisation, **three complementary approaches** have been developed and recommended by the rare cancer community: centralised referral, networking and national planning⁶⁷⁶.

⁶⁶⁸ RARECAREnet list of cancers (downloaded from RARECAREnet website:

http://www.rarecarenet.eu/rarecarenet/images/Resources/RARECAREnet_list_of_rare_cancers_Dec15.xlsx; accessed February 2020).

⁶⁶⁹ Charbotel B., Fervers B., Droz J.P., Occupational exposures in rare cancers: A critical review of the literature. *Crit Rev Oncol Hematol.* 2014 May; 90(2): pp. 99-134.

⁶⁷⁰ Joint Action on Rare Cancers (2019). *Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers* (Ch. 1).

⁶⁷¹ See section 4.2.3.a. about causes of paediatric cancers.

⁶⁷² Gatta G., Trama A., Capocaccia R, Epidemiology of rare cancers and inequalities in oncologic outcomes. *Eur J Surg Oncol.* 2019 Jan; 45(1): pp. 3-11.

⁶⁷³ EURORDIS Table: "Mapping out the similarities and differences between rare cancers and rare diseases", 2015-2016.

⁶⁷⁴ Joint Action on Rare Cancers (2019). *Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers* (Ch. 9).

⁶⁷⁵ Joint Action on Rare Cancers (2019). *Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers* (Ch. 1).

⁶⁷⁶ Joint Action on Rare Cancers (2019). *Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers* (Ch. 3&9).

i. Centralised referral of rare cancer patients

Centralised referral happens when rare cancer patients have their case dealt with by **centres of expertise**, i.e. by institutions with a high degree of multidisciplinary clinical expertise, high-tech facilities and open clinical studies⁶⁷⁷. This approach has been strongly recommended by the rare cancer community^{678,679,680}. It is indeed instrumental for **the timeliness of diagnosis and appropriate treatment provision** to affected patients, as well as for their **outcomes**, which are known to correlate with volumes of cases per healthcare centre and provider^{681,682}.

Requirements for implementation of centralised referral in rare cancers include:

- awareness regarding the existence and localisation of centres of expertise;
- collaboration among clinicians and institutions, starting from general practitioners, ensuring continuity of care for patients and proper referral throughout their clinical history; and
- definition and appropriate badging of centres of expertise.

Regarding the latter, EU Member States were encouraged by a Council Recommendation in 2009 to identify or create such centres for rare diseases⁶⁸³. The European Parliament, in its resolution of 2019, reiterated "the importance of EU-wide cooperation in ensuring the efficient pooling of knowledge, information and resources to tackle rare and chronic diseases, including rare cancers, effectively across the EU", and encouraged the Commission "to support the setting up of specialised centres for rare diseases in the EU, which should be fully integrated into the ERNs". The EP also proposed that "the Commission should open a fresh call for the development of new ERNs and continue to support the development and scaling up of the ERN model, in order to overcome geographical differences and gaps in expertise"; but warned that "any extension of ERNs must not undermine the operation of existing ERNs during their initial phase"⁶⁸⁴.

Even though an important progress has been made in several Member States to **map out national expertise** for rare conditions, there remain significant differences in the way rare cancer patients are referred and managed, as illustrated by the great variability observed by the RARECAREnet when estimating the degree of centralisation of rare cancer treatment through hospital admission volume data in seven European countries⁶⁸⁵. The rare cancer community therefore call for further efforts in selecting centres of expertise for rare cancers using consistent criteria across the EU.

However, several limiting factors to centralised referral have to be considered.

⁶⁷⁷ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 3).

⁶⁷⁸ Institut National du Cancer. Organisation de la prise en charge des patients adultes atteints de cancers rares – Bilan de l'activité 2011. In: INCa, editor. Collection: Bilans d'activités et évaluations, Boulogne-Billancourt, 2012.

⁶⁷⁹ National Health Service Commissioning Board. Prescribed specialised services: commissioning intentions for 2013/14. 2012.

⁶⁸⁰ Stordeur S., Vrijens F., Leroy R., Reference centres for adults with rare and complex cancers – Policy recommendations to improve organisation of care in Belgium. *Rev Epidemiol Sante Publique* 2016; 64(1): pp. 1-6.

⁶⁸¹ Gatta G., Trama A., Capocaccia R., Epidemiology of rare cancers and inequalities in oncologic outcomes. *Eur J Surg Oncol*. 2019 Jan; 45(1): pp. 3-11.

⁶⁸² Hillner B.E., Smith T.J., Desch C.E., Hospital and physician volumes or specialisation and outcomes in cancer treatment: importance of quality of cancer care. *J Clin Oncol* 2000; 18(11): pp. 2327-2340.

⁶⁸³ Council of the European Union. Council recommendation of 8 June 2009 on an action in the field of rare diseases. OJ n°C 151/7 of 3.7.2009.

⁶⁸⁴ European Parliament's resolution of 12 February 2019 on the implementation of the Cross-Border Health Care directive, P8_TA(2019)0083 https://www.europarl.europa.eu/doceo/document/TA-8-2019-0083_EN.html.

⁶⁸⁵ Gatta G., Capocaccia R., Botta L. et al., Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet-a population-based study. *Lancet Oncol* 2017 Aug; 18(8): pp. 1022-1039 (Data on 1999-2007).

Owing to the low number of cases and the time needed to develop professional expertise in the rare cancer field, the **number of centres of reference is inevitably limited**. Given the variegated clinical expertise required today in oncology and in the aim of harmonising care provided to patients, these **centres also need to collaborate** with each other⁶⁸⁶.

Furthermore, in order to maximise the exploitation of clinical expertise and to avoid expert resources to be overwhelmed, it is recommended that the role of centres of expertise in rare cancers **focuses on multidisciplinary strategic clinical decision-making**, pathological diagnosis and complex treatments, instead of necessarily taking charge of the entire clinical journey of all affected patients. Health migration generated by centralised referral should be limited, as it implies an adverse impact on quality of life of patients, as well as costs for them, their family and society⁶⁸⁷.

Finally, one should keep in mind that, as opposed to other, highly specific rare diseases, rare cancer cases are **often treated alongside their common counterparts**, thus falling within the scope of cancer centres with no specialisation in rare tumours⁶⁸⁸.

Therefore, **health networking is of particular relevance to complement centralised referral in rare cancers**⁶⁸⁹.

ii. *Networking of healthcare providers and centres*

The concept of ERNs and linked national networks

Health networks are defined as collaborations in the health field among healthcare providers sharing explicit goals and rules⁶⁹⁰. In the EU, European Reference Networks (ERNs) were launched in 2017, in application of the 2011 Cross-Border Healthcare Directive⁶⁹¹. This followed strong advocacy efforts of the entire rare disease and rare cancer community, as networks of healthcare providers tackling a common category of rare diseases. Four of the newly established networks are specifically devoted to rare cancers: EURACAN (ERN on rare adult solid cancer), EuroBloodNet (ERN on Rare Haematological Diseases), ERN PaedCan (ERN on paediatric cancers; *see section 4.2.*) and ERN GENTURIS (ERN on genetic tumour risk syndromes).

They are defined as "peer-to-peer" networks⁶⁹², comprising centres of expertise endorsed by their respective national healthcare authorities, and also include European Patient Advocacy Groups (ePAGs), established by EURORDIS to support the involvement of patients in their development⁶⁹³. ERNs on rare cancers are recommended to liaise with national (or regional) "hub-and-spoke"

⁶⁸⁶ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 3).

⁶⁸⁷ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 3).

⁶⁸⁸ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 1).

⁶⁸⁹ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 1&3).

⁶⁹⁰ Provan K.G., Fish A., Sydow J., Interorganisational networks at the network level: a review of the empirical literature on whole networks. *Journal of Management* 2007; 33: p. 479.

⁶⁹¹ Directive 2011/24/EU of the European Parliament and the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare. OJ n° L 88/45 of 4.4.2011.

⁶⁹² Health networks only made up of highly specialised centres of reference, well adapted to produce clinical practice guidelines, drive medical and patient education or conduct clinical and translational research. (Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 3)).

⁶⁹³ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 10).

networks⁶⁹⁴, linking centres of expertise to more generalist centres taking charge in part or in whole the management of some rare cancer cases, thus becoming networks of networks⁶⁹⁵.

Contribution of ERNs to quality rare cancer care

Sharing of clinical cases

ERNs directly contribute to the management of rare cancers through sharing of clinical cases, using a secure web-based platform connecting expert clinicians. This allows for faster diagnosis and treatment of affected patients, ensuring their access to a multidisciplinary expert assessment at any strategic clinical decision⁶⁹⁶. This shows the potential of ERNs to transfer highly specialised knowledge on rare cancer diagnosis and treatments quickly, without the need for the patient to travel.

Rationalisation of patient referral

Rationalisation of patient referral is also an important goal of ERNs⁶⁹⁷. In this respect, the necessary national endorsement of centres belonging to these networks has further fostered the mapping out of rare cancer expertise in EU Member States, although progress remains to be made, especially in Eastern European countries⁶⁹⁸. Furthermore, ERNs represent an opportunity to deal with the problems posed by rare cancer management in small countries, in which no institution, by definition, will see enough patients with certain rare cancers to meet the case volumes thresholds generally used to define highly specialised centres of expertise. ERNs aim to identify "affiliated centres" in such countries, which then will liaise with their "full members"⁶⁹⁹.

Production of clinical practice guidelines

Owing to the high degree of uncertainty inherent to the rare cancer field, production of "state of the art" instruments, such as clinical practice guidelines is challenging. It is nonetheless crucial for affected patients to also be approached along diagnostic and therapeutic lines agreed upon by the medical community. A number of such clinical practice guidelines already exist in rare cancers, however important variations have been observed when assessing their quality within a study conducted by the Joint Action on Rare Cancers (JARC). Therefore, the rare cancer community calls for production of high-quality, regularly updated, disease-based guidelines, i.e. covering each the entire spectrum of a disease and conveying recommendations on all corresponding clinical presentations, factoring in the difficulties in the generation of evidence in the rare cancer field⁷⁰⁰, leaving room for patient/physician shared clinical decision-making in conditions of uncertainty⁷⁰¹ and involving patient representatives⁷⁰².

By definition, ERNs represent an ideal setting to build multidisciplinary consensus of representative experts and make use of the whole available evidence of efficacy on clinical practices. ERNs may therefore improve the possibilities to produce clinical practice guidelines in rare cancers, as well as to

⁶⁹⁴ "Hub-and-spoke" networks are health networks linking centres behaving as "providers" of clinical expertise or expert services (hubs) and others behaving as "users" (spokes); suitable for providing healthcare services to patients, maximising their chances to access high-quality clinical expertise and minimising health migration or implicit rationing of resources. (Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 3)).

⁶⁹⁵ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 3).

⁶⁹⁶ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 3).

⁶⁹⁷ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 3).

⁶⁹⁸ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 10).

⁶⁹⁹ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 3).

⁷⁰⁰ See section 4.1.3.b.i.

⁷⁰¹ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 6).

⁷⁰² Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 7).

monitor compliance of clinical practice with them. This will in turn help engage a wide range of centres within these networks and shape their management of individual cases⁷⁰³.

Recommendation: Building on the ERN foundations

The establishment of European Reference Networks in the field of rare cancer has helped to identify a great range of additional opportunities for meaningful pan-European collaboration involving all stakeholders, making use of their infrastructure for connecting centres across Europe as well as connecting these expert centres to more generalist centres, thus becoming network of networks. However, to achieve this, ERNs must be supported by long-term sustained funding.

Medical education and training

Medical education and training also face specific challenges in rare cancers. Healthcare professionals working in centres of expertise for rare cancers represent a scarce target. Educational events devoted to them may therefore struggle to obtain private sponsorship and need adequate public support⁷⁰⁴. Furthermore, owing to the involvement of "spoke" centres⁷⁰⁵ in rare cancer care, healthcare professionals working in such generalist centres are recommended to be primarily targeted by rare cancer medical education programmes. Yet, as opposed to common cancers, healthcare professionals experience a lack of reinforcement of information conveyed to them, i.e. after attending an educational event on a rare cancer, they are likely to encounter patients with that cancer neither soon, nor often, which has a critical impact on the benefit derived from the education. This is even more the case with general practitioners, whose awareness of the challenges in rare cancer management is instrumental for the timeliness of diagnosis and of proper referral of new rare cancer cases⁷⁰⁶.

To address these issues, JARC recommends rare cancer medical education to be shaped around networking. ERNs are well-placed to provide adapted educational contents on rare cancers, shape remote training modalities, as well as facilitate fellowships for young oncologists from "spoke" centres in "hubs". ERNs could also contribute to guaranteeing medical careers on rare cancers, in the aim of encouraging professionals to dedicate themselves to these conditions.

Recommendation: Unleashing the ERNs' potential for education

The role that European Reference Networks can play in improving medical education and training opportunities in the field of rare cancer should be unleashed with reference to the recommendations of the Joint Action on Rare Cancers. To achieve this, long-term secured funding of ERNs is required to ensure their sustainability and capacity.

Finally, the involvement of ERN European Patient Advocacy Groups (ePAGs) is recognised as crucial for provision of necessary information tools to the patients and their carers. Patient organisations are also involved in the design of courses intended for patients and carers. Patients can provide their own training and can participate as well in the shaping of courses for patient advocates provided by EUPATI (European Patients' Academy), the European School of Oncology (ESO), the European Organisation for Research and Treatment of Cancer (EORTC), as well as in the development of Patient Advocacy Track in

⁷⁰³ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 7).

⁷⁰⁴ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 4).

⁷⁰⁵ See footnote 694 for a definition of "spoke" centres within "hub-and-spoke" networks.

⁷⁰⁶ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 4).

annual congresses of major European professional societies such as the European Society of Medical Oncology (ESMO) and the European Haematology Association (EHA)⁷⁰⁷.

Requirements for further development of ERNs

Networking is considered as the best option to address rare cancers⁷⁰⁸. ERNs are unanimously recognised in the rare cancer community as an opportunity for step change in the management of rare cancers in Europe. Therefore, JARC calls for all policy strategies for rare cancers to be based on this approach⁷⁰⁹.

From a health system perspective, this primarily implies ERNs to continue expanding in EU countries, each of which should have at least one "full" or "affiliated" member in each ERN. Moreover, EU Member States are recommended to fully integrate ERNs into national healthcare systems⁷¹⁰, notably by establishing and maintaining national networks for all "families" of rare cancers, liaising with ERNs and ensuring access to the available expertise, as well as by promoting greater awareness of the existence and role of ERNs⁷¹¹.

From the perspective of individual patient journey, given that ERNs partly rely on movement of some patients between several healthcare centres belonging to the networks, close attention should be given to addressing identified shortcomings of the implementation of the Cross-Border Healthcare Directive^{712,713} and for efficient collaboration of national contact points with ERNs to facilitate the transfer of rare cancer patients across EU borders⁷¹⁴.

Furthermore, since ERNs are still young networks, the rare cancer community unanimously advocates their financial sustainability to be ensured, through proper, long-term funding at both the EU and the national level⁷¹⁵. Such funding should include coverage of the costs directly implied by the functioning of these networks, including services centres to manage networking routines, appropriate IT systems for sharing of cases and the medical workload entailed by teleconsultations provided by expert centres. The European Parliament also advocates for the further sustainable development and financing of the ERNs and the patient networks supporting them⁷¹⁶. Furthermore, JARC also recommends exploring possibilities for involvement of the pharmaceutical industry in ERNs and national networks linked thereto, through a robust framework ensuring effective management of conflicts of interests and preserving these networks' independence⁷¹⁷.

Finally, although it does not appear necessary to formally assess the cost-effectiveness of networking in the rare cancer field, JARC underlines the necessity for ERNs and national networks linked thereto to regularly provide data on their performance, in terms of outcomes and costs, and impact within a

⁷⁰⁷ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 4).

⁷⁰⁸ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 4).

⁷⁰⁹ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 9).

⁷¹⁰ EURORDIS Recommendations on the Integration of European Reference Networks (ERNs) into National Health Systems, 2018.

⁷¹¹ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch.9&10).

⁷¹² Directive 2011/24/EU of the European Parliament and the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare. OJ n° L 88/45 of 4.4.2011.

⁷¹³ European Parliament's resolution of 12 February 2019 on the implementation of the Cross-Border Health Care directive, P8_TA(2019)0083 https://www.europarl.europa.eu/doceo/document/TA-8-2019-0083_EN.html (accessed May 2020).

⁷¹⁴ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 10).

⁷¹⁵ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch.9&10).

⁷¹⁶ European Parliament's resolution of 12 February 2019 on the implementation of the Cross-Border Health Care directive, P8_TA(2019)0083 https://www.europarl.europa.eu/doceo/document/TA-8-2019-0083_EN.html (accessed May 2020).

⁷¹⁷ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 9).

healthcare system, in terms of the number of patients benefiting within a population⁷¹⁸. This should be achieved in the context of the implementation of quality assurance systems at the level of the network, of healthcare providers, using distinct standards for "hubs"/centres of references and for "spoke" centres, and of single patients, allowing to protect and enhance quality of diagnosis and care, improve survival and patient quality of life, educate network professionals and provide a secure basis of clinical research in rare cancers⁷¹⁹.

Recommendation: ERNs at the heart of EU rare cancer policies

The further development of EU policy for rare cancer should place the role of European Reference Networks at its heart, unlocking the many potential roles of this new infrastructure for collaboration, including via secure long-term funding of their operation.

iii. National rare cancer planning

National planning through national cancer control plans (NCCPs) is one of the most prominent instrument of cancer policy at the national level and of cancer policy coordination at the European level⁷²⁰, from which rare cancers can fully benefit. These plans have the **potential to foster a holistic approach when addressing rare cancers**, from epidemiology to survivorship, from clinical research to access of patients to care. Furthermore, given the importance of national networking alongside and within ERNs, **linking the national with the EU level when shaping strategy policies on rare cancers** is especially instrumental⁷²¹.

However, rare cancers are currently poorly considered, or even completely absent, in NCCPs, as observed in a survey conducted within JARC by the Catalan Institute of Oncology⁷²². JARC therefore calls for national cancer control plans to always involve a **dedicated section on rare cancers in adults**, as well as a **dedicated section on childhood cancers**, and to develop **synergies with national plans for rare diseases**⁷²³.

Recommendation: Rare cancer policies to be included in National Cancer Control Plans

Member States' national cancer policies should support a dedicated and tailored approach to rare cancers in adults and paediatric cancers, tacking stock of EU initiatives and fully integrate European Reference Networks into their national healthcare system, notably by establishing and maintaining national networks for all "families" of rare cancers.

⁷¹⁸ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 9).

⁷¹⁹ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 3).

⁷²⁰ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 1).

⁷²¹ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 9).

⁷²² Prades J., Weinman A., Le Cam Y. et al., Priorities on rare cancers' policy in National Cancer Control Plans (NCCPs): A review conducted within the framework of EU-JARC Joint-Action. *Journal of Cancer Policy* 2020; 24.

⁷²³ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 9&10).

b. Availability of rare cancer treatments and therapies

i. Research and development of innovative therapies

Research in, and development of innovative therapies for, rare cancers are **structurally hindered** by a number of issues, for which solutions have been suggested by JARC⁷²⁴.

Difficult generation of evidence

This affects all steps of the research process, from basic to translational to clinical, owing to:

- shortage of biological samples from patients (to be stored in biobanks);
- **challenging organisation of clinical trials** and limited "statistical precision"; and
- lack of clinical expertise and suboptimal quality of care, impairing obtained results⁷²⁵.

In this regard, JARC advocates **fully exploiting the potential of networking**. ERNs, as well as their associated networks and clinical databases, could contribute to:

- **facilitate biobanking** in centralised or virtual repositories, notably through common practices on specimen collection and storage;
- **increase referral of patients** to clinical trials and **decrease** their **costs**, through to economies of scale, access to clinical data and optimised quality of care; and
- **limit administrative requirements** implied by collaboration on clinical trials and biorepositories, through assistance to speed up agreements between partners⁷²⁶.

Additional suggested solutions include:

- covering the burden implied by centralised biobanking when it appears necessary;
- **removing legal constraints hampering collection of biosamples, with special reference to data protection rules;**
- **encouraging innovative methodologies for clinical trial designs** (including non-randomised studies, Bayesian statistics, use of surrogate endpoints⁷²⁷), maximising the chances for new treatments to display their maximum efficacy without widening eligibility criteria inappropriately, as well as **adaptive mechanisms**, allowing to modulate ongoing clinical trials depending on newly obtained data;
- concluding agreements with contract-research organisations, managing the organisation of clinical trials, to further decrease their costs;
- involving patient organisations to orient priorities and designs of clinical trials, as well as to promote and possibly fund them;

⁷²⁴ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 5).

⁷²⁵ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 5).

⁷²⁶ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 5).

⁷²⁷ Clinical endpoints (or outcomes) are measures of the effect of a treatment on patients, used for benefit-risk assessment in CTs; they may be substituted by surrogate endpoints, i.e. intermediate indicators aimed at predicting, rather than observing, this effect (e.g. shrinking tumour size instead of patient long-term survival), thereby allowing to generate quicker results; Schuster Bruce C., Brhlikova P., Heath J, McGettigan P., The use of validated and nonvalidated surrogate endpoints in two European Medicines Agency expedited approval pathways: A cross-sectional study of products authorised 2011-2018. PLoS Med. 2019 Sep 10; 16(9): e1002873.

- fostering wide opening of, and cross-border access to, clinical trials⁷²⁸; and
- exploiting the potential of artificial intelligence (AI) using big data to complement clinical trials in the generation of evidence⁷²⁹.

Recommendation: Improving the research environment on rare cancers

The recommendations of the Joint Action on Rare Cancers (JARC) for improving the research environment for rare cancers should be integrated within the context of Europe's Beating Cancer Plan and a new EU Pharmaceutical Strategy. This would include encouraging the development and use of innovative methodologies for clinical trial designs and improving cross-border access to clinical trials.

Lack of available quality epidemiological and clinical data

Alongside every other cancer type, rare cancers benefit from data collection in cancer registries, which were notably used by RARECAREnet and are of crucial importance for research. However, **epidemiological data available in cancer registries for rare cancers is of suboptimal quality**, due to high sampling variability inherent to low patient numbers, display of imprecise information, only by topography and not morphology⁷³⁰, thus impairing identification of data relating to individual rare cancer entities⁷³¹, and wrong registration of cases, as a result of misdiagnosis, or misclassification by registrars⁷³². JARC suggests addressing these issues by developing new statistical methods, adapted to rare cancers, double data reporting (by topography and morphology), as well as **specific quality checks and recommendations about rare cancer registration in cancer registries**⁷³³.

Furthermore, **clinically relevant data on rare cancers, e.g. on detection, staging and treatment, is often lacking**, because of rare collection of such data in cancer registries⁷³⁴ and of insufficient links between cancer registries and clinical registries⁷³⁵. In this regard, JARC underlines the potential of **ERNS' Rare Disease Registries**, i.e. clinical registries established within ERNs⁷³⁶, following a prior recommendation by the Council of the EU on the implementation of registries and databases for rare diseases⁷³⁷, which could indeed be linked with cancer registries, but also contributing hospitals, national networks on rare cancers, administrative and research databases, etc. to foster broad interoperability of data⁷³⁸.

Finally, there is still significant uncertainty on the **consequences of the new EU General Data Protection Regulation** on these registries; JARC therefore advocates granting **waivers to cancer registries**, so that they can function without the need of individual patient consent, developing a **right**

⁷²⁸ See Chapter 3 sub-section on access to clinical trials.

⁷²⁹ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Chs 5 & 8).

⁷³⁰ See information within 4.1.1. section on topography and morphology codes for tumours.

⁷³¹ RARECAREnet list of rare cancers (downloaded from RARECAREnet, website: http://www.rarecarenet.eu/rarecarenet/images/Resources/RARECAREnet_list_of_rare_cancers_Dec15.xlsx; accessed February 2020): each rare tumour entity is defined through a combination of ICD-O-3 topography and morphology codes.

⁷³² Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 2).

⁷³³ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 2).

⁷³⁴ Siesling S, Louwman WJ, Kwast A, et al. Uses of cancer registries for public health and clinical research in Europe: Results of the European Network of Cancer Registries survey among 161 population-based cancer registries during 2010-2012. Eur J Cancer 2015; 51(9): pp. 1039-49.

⁷³⁵ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 2).

⁷³⁶ European Parliament and the Council of the European Union. Directive 2011/24/EU of the European Parliament and the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare. OJ n° L 88/45 of 4.4.2011.

⁷³⁷ Council Recommendation of 8 June 2009 on an action in the field of rare diseases. OJ n° C 151/7 of 3.7.2009.

⁷³⁸ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 2).

for EU citizens to give "one-time consent" for their health data to be used in future research, to avoid the extra-burden of "re-consent" requirements on clinical registries, and fostering **simple procedures for data transfer** across institutions and borders in the EU⁷³⁹.

Shortage of dedicated public funding

Rare cancer research benefits from initiatives supporting research on rare diseases⁷⁴⁰, such as the European Joint Programme on Rare Diseases (EJPRD), started in 2019 and funded by EU's Horizon 2020 program⁷⁴¹, or the International Rare Disease Consortium (IRDiRC), but **insufficiently from cancer research funding instruments**. Thus, JARC recommends that rare cancers, if eligible, are clearly identified as such in public calls for research projects and that mechanisms **make sure at the EU level that a reasonable amount of funds allocated to cancer is granted to rare cancers**⁷⁴².

Such funding could especially support academic, investigator-driven clinical studies in fields of special relevance for rare cancers but in which private investment is less likely, including repurposing of drugs, natural history of rare cancers⁷⁴³, off-label⁷⁴⁴ and compassionate⁷⁴⁵ use of drugs, healthcare service research on optimisation of rare cancer management, and multimodal, including surgical and radiation, treatment strategies⁷⁴⁶.

Low attractiveness for private research investments

Limited marketing opportunities, due to small patient populations, affect the motivation of pharmaceutical and other companies to develop new drugs for rare cancers⁷⁴⁷. The mechanisms foreseen by the **EU Orphan Medicines Regulation**, consisting of a centralised procedure for the designation of orphan medicinal products, through epidemiological demonstration of the rarity of the disease, and of incentives granted to pharmaceutical companies for their research, development and marketing, under the responsibility of the EMA⁷⁴⁸, are recognised as having been instrumental in this regard in recent years⁷⁴⁹. Of note, this was however not true in the case of paediatric cancers, for which this regulation has been considered ineffective⁷⁵⁰ (see Section 4.2.).

Nonetheless, possible improvements of this regulatory framework have been suggested by some, in the aim of optimising orphan designation in oncology by using, either an incidence- rather than

⁷³⁹ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 2).

⁷⁴⁰ European Commission's factsheet about World Rare Disease Day: https://ec.europa.eu/info/research-and-innovation/events/special-features/world-rare-diseases-day_en (accessed February 2020).

⁷⁴¹ EJPRD website <https://www.ejprardiseases.org/index.php/about/> (accessed February 2020).

⁷⁴² Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 5).

⁷⁴³ Natural history of a disease progression of the disease from causes to clinical manifestations, in the absence of treatment (definition by the US Centers for Disease Control and Prevention (CDC): <https://www.cdc.gov/csels/dsepd/ss1978/lesson1/section9.html> (accessed February 2020).

⁷⁴⁴ According to the EMA, off-label use of drugs is defined as "the use of a medicine for an unapproved indication or in an unapproved age group, dosage, or route of administration". Source: <https://www.ema.europa.eu/en/about-us/about-website/glossary> (accessed April 2020).

⁷⁴⁵ According to the EMA, compassionate use of drugs is defined as "the use of an unauthorised medicine outside a clinical study in individual patients under strictly controlled conditions", thus helping "to make medicines that are still under development available to patients". Source: <https://www.ema.europa.eu/en/about-us/about-website/glossary> (accessed April 2020).

⁷⁴⁶ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 5).

⁷⁴⁷ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 5).

⁷⁴⁸ European Commission's factsheet about orphan medicinal products: <https://ec.europa.eu/health/human-use/orphan-medicines> (accessed February 2020).

⁷⁴⁹ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 5 & 8).

⁷⁵⁰ Vassal G, Kearns P, Blanc P. et al., Orphan Drug Regulation: A missed opportunity for children and adolescents with cancer. *Eur J Cancer* 2017; 84: pp. 149-158.

prevalence-based criterion⁷⁵¹, or directly the rare cancer list produced by RARECAREnet⁷⁵², or of improving patient access to drugs by reducing the period of market exclusivity for profitable orphan drugs and stating the level of clinical evidence needed to authorise orphan drugs⁷⁵³.

ii. Approval, pricing, reimbursement and provision of therapies

Owing to small patient populations and scarce expertise, **higher degree of uncertainty** is a hallmark of any evidence generated on treatments in the rare cancer field, which JARC calls to **factor in throughout all regulatory processes** undergone by rare cancer therapies⁷⁵⁴.

Regarding approval and provision of therapies to patients, various settings are of particular relevance, by combining availability of potentially promising therapies with generation of further, real-world data. JARC therefore recommends:

- encouraging accelerated approval mechanisms (e.g. **adaptive licensing**);
- addressing **off-label or compassionate use of drugs**; and
- opening the possibility for **patient/physician shared, reasonably risk-prone clinical decision-making** on provision of treatments in presence of uncertain evidence, such as shown benefit on non-validated surrogate endpoints⁷⁵⁵, but paucity of therapeutic options, to highly selected patient subgroups⁷⁵⁶.

From the perspective of value-based medicine tools governing pricing and reimbursement mechanisms, JARC advocates:

- seeing **the concept of "joint clinical assessment"**⁷⁵⁷ **as of particular relevance**, given the possible use of higher uncertainty as a reason for implicit denials of resources at the national level;
- tolerating possible deterioration in outcomes between trial and clinical settings, owing to the difficulties in the transfer of innovative therapies, when using real-world data to review approval or reimbursement decisions; and
- considering involvement of pharmaceutical companies in risk-sharing mechanisms for drug reimbursement, as a way to avoid discouraging investments in drug development⁷⁵⁸.

In these regards, JARC underlines the need for **tapping all the clinical expertise available within disease-based communities** to guide regulatory decisions or provide companies with scientific advice on drug development, as well as **the full potential of ERNs** in managing non-classical regulatory settings for provision of therapies to patients⁷⁵⁹.

⁷⁵¹ See Chapter 4's Introduction; Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 1).

⁷⁵² See section 4.1.1; Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 8).

⁷⁵³ Picavet E., Cassiman D., Simoens S., Evaluating and improving orphan drug regulations in Europe: a Delphi policy study. Health Policy. 2012 Nov; 108(1): pp. 1-9.

⁷⁵⁴ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 8).

⁷⁵⁵ Whose statistical correlation with clinical endpoints is not supported by evidence in the literature; Schuster Bruce C., Brhlikova P., Heath J., McGettigan P., The use of validated and nonvalidated surrogate endpoints in two European Medicines Agency expedited approval pathways: A cross-sectional study of products authorised 2011-2018. PLoS Med. 2019 Sep 10; 16(9): e1002873.

⁷⁵⁶ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 8).

⁷⁵⁷ See Chapter 3 section on medicines pricing and reimbursement mechanisms.

⁷⁵⁸ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 8).

⁷⁵⁹ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 8).

4.1.4. The role of patient organisations in rare cancers

Patient organisations have acquired a very solid knowledge on the rare cancer, or group of rare cancers they represent, on research in their field and on the whole spectrum of the patient's journey, from accurate diagnosis to accessing adequate treatment and follow up care, survivorship as well as end of life management. Of note, the specificities of the paediatric cancer patient community – which has been part of the long-term organised European multi-stakeholder community in this disease area – are addressed in Section 4.2.

As recommended by the JARC, rare cancer patients and patient organisations should be engaged in all crucial areas relating to these diseases, such as awareness and education, healthcare organisation, state-of-the-art treatments and devices, regulatory mechanisms, HTA and clinical and translational research. Patient organisations have the capacity to act as a bridge between the patient community they represent and healthcare professionals as well as decision-making bodies and industry and, in this way, they can raise awareness of patients' needs and expectations.

Many of the patient organisations dealing with rare cancers and rare diseases that may give rise to tumours are actively involved in research projects, including EU Horizon 2020 and Innovative Medicines Initiative (IMI) research projects. Due to their intimate knowledge of the disease, they bring strong added value to the conduct of research projects as well as to the design of clinical trials to optimise their success. Additionally, they are involved in public health projects and in EU Joint Actions on cancer/rare cancer. Moreover, they also play an active role in educating patients and their families to help them make informed choices about their health and treatment. This is particularly relevant in the field of adult rare cancers where more and more patient-physician shared clinical decision-making should be especially valued for the right treatment approach⁷⁶⁰. Furthermore, patient organisations play a significant role in promoting and informing about patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs) and they are involved in producing good practice guidelines.

Lastly, given their extensive expertise, rare cancer patient organisations must be able to meaningfully engage in the design, drafting, implementation and evaluation of all national and European initiatives concerning them, including National Cancer Control Plans and the EU Beating Cancer Plan. These can be based on the model of National Rare Disease Plans in Europe⁷⁶¹ and the European Cancer Plan for Children and Adolescents with Cancer developed by the European Society for Paediatric Oncology (SIOP Europe)⁷⁶².

Recommendation: Supporting the role of patient organisations in rare cancers

The role of patient organisations in the field of rare cancers is crucial in terms of support to patients, their families, carers, in education, research and improving policies. Their action of general interest should be better recognised and supported by EU and national institutions.

⁷⁶⁰ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 6).

⁷⁶¹ Prades J., Weinman A., Le Cam Y. et al., Priorities on rare cancers' policy in National Cancer Control Plans (NCCPs): A review conducted within the framework of EU-JARC Joint-Action. *Journal of Cancer Policy* 2020; p. 24.

⁷⁶² Vassal G., Schrappe M., Pritchard-Jones K. et al., The SIOPE strategic plan: A European cancer plan for children and adolescents. *J Cancer Policy* 2016; 8: pp. 17–32.

4.2. Paediatric cancers

KEY FINDINGS & RECOMMENDATIONS: PAEDIATRIC CANCERS

All paediatric cancers are rare. Nevertheless, they have age-related, biological, clinical and organisational specificities that require them to be addressed through further tailored approaches, strategies and measures beyond simple extrapolation of adult services.

While individual paediatric cancer types are all rare, cancer in children and adolescents overall represents a leading burden in Europe. **Paediatric cancers are jointly the first cause of death by disease in children older than 1 year in Europe - more than 35,000 cases are diagnosed annually and over than 6,000 young patients die each year.** There are furthermore substantial inequalities in access to the best available care and expertise across Europe, causing **up to 20% differences in children's survival rates among European countries.**

Among very clear policy requirements is further attention to paediatric cancer research needs. Amongst these needs is research into genetic predisposition in paediatric cancers as a key pillar of a broader paediatric cancer research agenda. More generally, to redress unequal allocation of investment to paediatric cancer, a clear and specific EU funding stream should be dedicated to paediatric cancer research and budget allocations earmarked across all relevant EU programmes.

Education of the new generation of paediatric cancer specialists is a clear priority in ensuring continuous access to state-of-the-art expertise. **A comprehensive training programme for paediatric oncology accessible to all Member States is required across Europe and necessitates adequate investment.**

The professional figure of the paediatric oncologist should be recognised in all Member States, and mutual recognition of qualifications across the EU should be considered. Appropriate training of specialised professionals who regularly work with children with cancer should be foreseen, based on existing European guidelines.

Also supportive to raising education and knowledge is the concept of twinning programmes. These allow healthcare personnel exchange across paediatric cancer centres in different countries to share specialist knowledge. **Non-competitive EU funding should be allocated to support twinning of paediatric haematology and oncology healthcare providers within the ERN PaedCan to foster mutual learning and improve standards of care across Europe.**

From a regulatory perspective, the EU Orphan Medicines Regulation has been ineffective for paediatric cancer medicine development. The EU regulatory environment should be revisited in this respect, to address the unmet needs of children and adolescents with cancer and make medicine development for this group faster, more efficient, and in line with the rate of innovation observed in the adult cancer sector.

While there are nearly half a million childhood cancer survivors in Europe, the majority are experiencing adverse long-term effects hindering their health, daily life and participation. Beyond five years from diagnosis, disease-free survivors also have higher mortality rates than their non-affected peers. Long-term follow-up of childhood cancer survivors is key to address this issue. In this regard, the EU co-funded **Joint Action on Rare Cancers has recommended the roll-out of a European Unique Patient Identifier, in order to ensure monitoring of long-term outcomes in childhood cancer survivors in a cross-border setting.** It is also recommended that EU programmes support the implementation of **the Survivorship Passport model** across the EU.

Individual paediatric cancer types are all rare yet cancer in children and adolescents overall represents a leading burden in Europe. **Thus, paediatric cancers are jointly the first cause of death by disease in children older than 1 year in Europe - more than 35,000 cases are diagnosed annually and over than 6,000 young patients die each year**⁷⁶³.

Despite research progress that has enabled to achieve 80% survival at five years, there has been very little advancement for some types of malignancies affecting the paediatric and adolescent population^{764,765}.

There are furthermore substantial inequalities in access to the best available care and expertise across Europe, causing **up to 20% differences in children's survival rates among European countries**^{766,767}.

Among those who have beaten the disease – the nearly half a million childhood cancer survivors in Europe – the majority are experiencing adverse long-term effects hindering their health, daily life and participation^{768,769}.

Whereas a range of issues are shared with the adult cancer, age-related and biological specificities in the paediatric and adolescent population call for tailored approaches for this age group across the patient pathway and in relation to enabling policies.

4.2.1. Overview of childhood cancer families

As discussed in above sections, rare cancers can be defined as those malignancies whose incidence is <6/100,000/year⁷⁷⁰. According to this definition, all malignancies in children and adolescents are rare, including leukaemias and lymphomas⁷⁷¹.

The RARECAREnet project has produced a classification of rare cancers, identifying 12 "families". This list includes some malignancies affecting children and adolescents under the "family" of paediatric cancers, but several tumours which mainly, or also, occur during childhood are included under other "families", namely haematological tumours, sarcomas, central nervous system tumours, head and neck cancers, digestive cancers, thoracic cancers, endocrine tumours⁷⁷². Furthermore, it is important to note that the genetic profile of these common cancer entities in the very young age groups may have a distinct biological makeup and a different clinical behaviour and prognosis⁷⁷³.

The scope of paediatric cancer entities is well reflected through the International Childhood Cancer Classification (ICCC-3), which provides a full list of cancers occurring in children⁷⁷⁴. The list is also based on the third edition of the International Classification of Diseases for Oncology (ICD-O-3), developed

⁷⁶³ International Agency for Research on Cancer. (2018). Cancer Today. Retrieved from Cancer Today website: <https://gco.iarc.fr/today/home>.

⁷⁶⁴ Vassal G., Schrappe M., Pritchard-Jones K. et al. The SIOPE strategic plan: A European cancer plan for children and adolescents. *J Cancer Policy* 2016; 8: pp. 17–32.

⁷⁶⁵ Joint Action on Rare Cancer (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 1).

⁷⁶⁶ Gatta G., Botta L., Rossi S. et al., Childhood cancer survival in Europe 1999-2007: results of EURO-CARE-5—a population-based study. *Lancet Oncol* 2014; 15(1): pp. 35-47.

⁷⁶⁷ Kowalczyk J.R., Samardakiewicz M., Fitzgerald E. et al., Towards reducing inequalities: European Standards of Care for Children with Cancer. *Eur J Cancer* 2014; 50(3): pp. 481–485.

⁷⁶⁸ Hjorth L., Haupt R., Skinner R. et al., Survivorship after childhood cancer: PanCare: A European Network to promote optimal long-term care. *Eur J Cancer* 2015; 51(10): pp. 1203–1211.

⁷⁶⁹ Joint Action on Rare Cancer (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 1).

⁷⁷⁰ Gatta G., Botta L., Rossi S. et al., Childhood cancer survival in Europe 1999-2007: results of EURO-CARE-5—a population-based study. *Lancet Oncol* 2014; 15(1): pp. 35-47.

⁷⁷¹ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 1).

⁷⁷² See section 4.1.1.

⁷⁷³ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 1).

⁷⁷⁴ Steliarova-Foucher E., Stiller C., Lacour B. et al., International Classification of Childhood Cancer, third edition. *Cancer* 2005; 103: pp. 1457-1467.

by the World Health Organisation (WHO)⁷⁷⁵ and identifies 12 main groups of paediatric cancers⁷⁷⁶. Among these groups, a distinction can be made between:

- haematological malignancies;
- brain tumours; and
- solid cancers⁷⁷⁷.

As previously mentioned, cancers with an incidence of less than 0.2 cases/100,000/year are classified as extremely rare (see Section 4.1.1.). In the case of the paediatric population, two subgroups can be identified: tumour types typical of childhood (i.e. hepatoblastoma, pleuropulmonary blastoma, pancreatoblastoma) and those typical of adult age occurring extremely rarely in the young population (i.e. carcinomas, melanoma)⁷⁷⁸.

4.2.2. Epidemiology of paediatric cancers

Table 5: Incidence and mortality estimates for paediatric cancers

	Age group	INCIDENCE		MORTALITY	
		Estimated new cases in 2018		Estimated deaths in 2018	
		WHO Europe region	EU27	WHO Europe region	EU27
All types of cancer	0 – 24	38,370	24,075	6,337	3,367
	0 – 19	25,094	15,350	4,482	2,325
	0 – 14	17,455	10,256	3,256	1,606

Source: International Agency for Research on Cancer. (2018). Cancer Today. Retrieved from Cancer Today website: <https://gco.iarc.fr/today/home>.

According to latest available data for 2018, extracted from the Cancer Today section of the IARC Global Cancer Observatory⁷⁷⁹, there are **each year more than 35,000 new cases of cancer in children and adolescents in Europe (15,000 in children below the age of 15 years and 20,000 in those aged 15-24)**. 1 out of 300 newborns will develop cancer before turning 20.

Absolute mortality exceeds 6,000 deaths per year, which makes **cancer the first cause of death by disease in children and young people above the age of one in Europe**.

When looking at paediatric cancer types, leukaemias appear to be the most frequent, especially in children below the age of 15 years, where they account for more than 30% of annual new cases and of deaths. Tumours affecting the brain and the nervous system are also associated with particularly high

⁷⁷⁵ Fritz A., Percy C., Jack A., Kanagaratnam S., Sobin L., Parkin M.D., International classification of diseases for oncology (ICD-O). 3rd ed. Geneva; World Health Organisation; 2000.

⁷⁷⁶ ICC-3 list of paediatric cancers. Extracted from Steliarova-Foucher E, Stiller C, Lacour B et al. International Classification of Childhood Cancer, third edition. Cancer 2005; 103: pp. 1457-1467.

⁷⁷⁷ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 1).

⁷⁷⁸ Ferrari A, Brecht IB, Gatta G, et al. Defining and listing very rare cancers of pediatric age: consensus of the Joint Action on Rare Cancers (JARC) in cooperation with the European Cooperative Study Group for Pediatric Rare Tumors (EXPERT). Eur J Cancer 2019; 110: pp. 120-126.

⁷⁷⁹ International Agency for Research on Cancer. (2018). Cancer Today. Retrieved from Cancer Today website: <https://gco.iarc.fr/today/home>.

death rates, since they are responsible for more than a quarter of the total mortality due to paediatric cancers (see Annex 11⁷⁸⁰ & 12⁷⁸¹).

In respect to survival and prognosis, three main groups of paediatric cancers can be identified:

- **those with a good prognosis** (with a higher than 85% chance of survival after five years) under current standard multidisciplinary treatments, using cytotoxic drugs in often an intensive mode (acute lymphoblastic leukaemia, lymphomas, retinoblastoma and renal tumours);
- **those with a poor prognosis** (~50% or less reach the 5-year survival mark) such as acute myeloid leukaemia, several Central Nervous System (CNS) tumours, neuroblastoma, bone and soft tissue sarcomas (among these diseases, some have a very poor prognosis such as diffuse intrinsic pontine glioma, high-risk neuroblastoma and metastatic sarcomas); and
- **the extremely rare tumours**, for which there is insufficient information on their real incidence and survival⁷⁸².

The number of survivors in Europe is estimated at 500,000 in 2020 and is expected to further increase over time. The majority of this population is affected by long-term morbidity due to their disease and treatment side effects^{783,784}. Beyond five years from diagnosis, disease-free survivors have higher mortality rates than their non-affected peers.

4.2.3. Challenges in paediatric cancers

a. Causes of paediatric cancers and early detection

"Why does my child have cancer?" is a crucial question for parents, which most of the time receives no answer. Whereas cancers in adults are often influenced by carcinogen exposures acting over time, paediatric cancers develop early in life and over a much shorter period. Except for high dose ionising radiation and prior chemotherapy, there are no known alterable risk factors for most childhood cancers. This is in contrast to the substantial proportion of adult malignancies that are potentially preventable through modifiable exposures⁷⁸⁵.

On the other hand, genetic predisposition is the major known cause of childhood cancer which remains under-explored. It is estimated that **up to 10% of paediatric cancers occur within a known genetic predisposition**. More than 100 genetic syndromes with a risk of cancer in childhood are known. The proportion may increase as more and more rare cancer gene mutations are discovered through ongoing analyses in areas such as genomics.

Some studies already suggest that up to one in four children and adolescents with a history of cancer may have a genetic predisposition condition. The identification of the genetic basis of rare inherited cancers in children has revealed key pathways that are shared with sporadic tumours (even in adults). **Sequencing of the whole genome will generate new information that can be used to improve**

⁷⁸⁰ Childhood cancer incidence and mortality estimates in the EU in 2018. Retrieved from Cancer Today website: <https://gco.iarc.fr/today/home>.

⁷⁸¹ Cause of death in the paediatric population by different cancers. Courtesy of Eva Steliarova-Foucher IN Vassal G., Schrappe M., Pritchard-Jones K. et al, The SIOPE strategic plan: A European cancer plan for children and adolescents J Cancer Policy 2016; 8: pp. 17–32.

⁷⁸² Vassal G., Schrappe M., Pritchard-Jones K. et al., The SIOPE strategic plan: A European cancer plan for children and adolescents. J Cancer Policy 2016; 8: pp. 17–32.

⁷⁸³ Hjorth L., Haupt R., Skinner R. et al., Survivorship after childhood cancer: PanCare: A European Network to promote optimal long-term care. Eur J Cancer 2015; 51(10): pp. 1203–1211.

⁷⁸⁴ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 1).

⁷⁸⁵ See section 1.2. about primary prevention of cancer.

care and to identify new genetic hallmarks of cancer, which can be turned into targets for new therapies⁷⁸⁶.

There is a critical need for more research into genetic predisposition in paediatric cancers, including systematic whole genome sequencing and exploiting big data integration and artificial intelligence (AI). Related priorities are investment into clinical infrastructure for comprehensive cancer surveillance programmes as well as genetic counselling for early family guidance and psychological support for these under-served patients. A comprehensive public research programme on childhood cancer holds the potential to unlock such new horizons and enable preventive strategies and programmes, which have been almost non-existent in the paediatric cancer field to date.

Recommendation: Developing research on causes of paediatric cancers

Critical needs for more research into genetic predisposition in paediatric cancers as a key pillar of a broader paediatric cancer research agenda should be addressed within the context of the EU Cancer Mission, Europe's Beating Cancer Plan, EU4Health programme and other relevant initiatives.

b. Access to clinical expertise for diagnosis and treatment of paediatric cancers

i. Challenges

Developing new strategies for prevention and monitoring, including through early diagnosis and screening, is an important goal. Diagnosis of paediatric cancers pose special requirements beyond those in the adult cancer field.

The rarity of individual childhood cancers may preclude early symptom recognition in primary care, leading to delayed diagnosis and poorer outcomes. These issues are documented for instance for paediatric brain tumours and bone tumours. The child or adolescent needs to be diagnosed as quickly as possible in order to provide the greatest chance for cure and full recovery. This requires both the public and family general practitioners to be highly aware of the potential for children and young people to develop cancer. The symptoms and signs associated with cancer need to be recognised both by general practitioners and paediatricians so that there is the shortest symptom interval and no delays in diagnosis and initiation of treatment.

Analysing the specific biology (molecular profiling) of both the patient and tumour at the point of diagnosis and throughout treatment may improve risk stratification for adapted individual treatments. Whereas improving early diagnosis through professional education and public awareness is important, investment in accessibility to relevant diagnostics is crucial.

There are substantial inequalities in access to the best standard treatment, care, and research, particularly in central and Eastern Europe but also in other European countries, as highlighted most recently by findings of the Joint Action on Rare Cancers (JARC)^{787,788}.

⁷⁸⁶ Vassal G., Schrappe M., Pritchard-Jones K. et al., The SIOPE strategic plan: A European cancer plan for children and adolescents. J Cancer Policy 2016; 8: pp. 17–32.

⁷⁸⁷ Joint Action Against Rare Cancers (2019). Report summarising the result of the survey on accessibility of standard treatment and recommendations to Member States and Europe to overcome bottlenecks. (Deliverable 9.1.)

⁷⁸⁸ Joint Action Against Rare Cancers (2019). Report summarising recommendations to facilitate referral of children to trial centers offering innovative medicines. (Deliverable 9.2.)

ii. *Importance of specialisation, networking and education*

Specialisation: multidisciplinary care units and centres

It is acknowledged that optimal care for paediatric cancer is delivered in specialised multidisciplinary care units, also known as reference or principal treatment centres, which provide the full range of diagnostic, therapeutic and supportive care options to optimise survival and minimise toxicity⁷⁸⁹.

Multidisciplinary is the hallmark of paediatric haematology and oncology. Treatment and care for children and adolescents with cancer in Europe are delivered in about 330 paediatric haemato-oncology centres. The vast majority are public hospitals. For up to 90% of newly diagnosed paediatric cancer patients in Europe there are standard protocols established through prospective clinical research, and up to 40% of all patients are treated within clinical studies. The latter are organised through the European Clinical Trial Group networks, established by SIOP Europe. In addition to clinical specialists and nurses, other professionals such as psycho-oncologists, play therapists and educators, are required⁷⁹⁰. Specialised paediatric haemato-oncology professionals provide their services across the entire continuum of care⁷⁹¹. It is crucial that these specialist cancer services are accessible to all paediatric and adolescent cancer patients, as this population is not catered for by simple extrapolation of adult services.

Inequalities in the access to the best available multidisciplinary treatment across Europe are currently responsible for up to 20% differences in survival across Europe^{792, 793, 794}. Small patient numbers with age-specific requirements pose limitations to national investment capacity to deliver the best standards. European coordinated research and health policies and programmes are ideally placed to make a transformative change given the rarity and specificity of individual paediatric cancers and their important burden across countries. **EU health policy in particular must focus on delivering equal access to best specialist diagnostics and multi-disciplinary treatment for children and adolescents with cancer to improve outcomes in all Member States.** Concurrently, national cancer control plans (NCCPs) should include a clearly designated section on paediatric cancers and integrate specific provisions across the whole patient pathway, as recommended by stakeholders⁷⁹⁵.

Networking: role of the ERN PaedCan

The European Reference Network for Paediatric Oncology (ERN PaedCan) involves healthcare providers across Europe to deliver high quality, accessible and cost-effective cross-border healthcare to children and adolescents with cancer in the EU with the mission to eradicate existing inequalities in access and survival.

⁷⁸⁹ SIOP Europe. European Standards of Care for Children with Cancer. 2009: <https://siope.eu/european-research-and-standards/standards-of-care-in-paediatric-oncology/> (Accessed March 2020).

⁷⁹⁰ SIOP Europe. European Standards of Care for Children with Cancer. 2009: <https://siope.eu/european-research-and-standards/standards-of-care-in-paediatric-oncology/> (Accessed March 2020).

⁷⁹¹ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 3).

⁷⁹² Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 1).

⁷⁹³ Gatta G, Botta L., Rossi S. et al., Childhood cancer survival in Europe 1999-2007: results of EURO-CARE-5—a population-based study. *Lancet Oncol* 2014; 15(1): pp. 35-47.

⁷⁹⁴ Kowalczyk J.R., Samardakiewicz M., Fitzgerald E. et al., Towards reducing inequalities: European Standards of Care for Children with Cancer. *Eur J Cancer* 2014; 50(3): pp. 481-485.

⁷⁹⁵ Vassal G., Schrappe M., Pritchard-Jones K. et al., The SIOPE strategic plan: A European cancer plan for children and adolescents. *J Cancer Policy* 2016; 8: pp. 17-32.

The ERN PaedCan is an integral part of the long-term established European community of paediatric cancer researchers, physicians, and parent/patient groups working together across the borders, through dedicated network structures with mutual membership, official partnerships, and joint projects.

A principal means by which ERN PaedCan fulfils its mission is linking pre-existing reference centres inherent to the already established European Clinical Trial Groups through European Virtual Tumour Boards. These can play a major role in ensuring that all patients with a new diagnosis or in relapse are discussed and have access to the recommended standard treatment options. Given the burden of health-related travel on families, ERN PaedCan prioritises movement of information, clinical practice guidelines, and knowledge rather than patients whenever possible.

To ensure that children and adolescents can benefit from networking, appropriate reimbursement of cross-border care and virtual advice is necessary. The S2 program, formerly E112, under Regulation EC No 883/2004 on the coordination of social security systems, is in place for EU citizens seeking healthcare abroad but a series of shortcomings to its implementation have become evident. Modifying the current S2 programme to compensate for virtual care time provided by experts through teleconsultations is an important orientation. Solutions are also needed to ensure seamless access to, and reimbursement of, cross-border care when patients do need to travel. This should encompass innovative therapies under development – a second chance for young patients in treatment failure and relapse and provisions for accompanying families.

Another important aspect is **twinning programmes. These allow healthcare personnel exchange across paediatric cancer centres in different countries to share specialist knowledge.** Non-competitive EU funding should be allocated to support twinning of paediatric haematology and oncology healthcare providers within the ERN PaedCan to foster mutual learning and improve standards of care across Europe.

Recommendation: Ensuring equal access of children and adolescents with cancer to the best possible care

In order to ensure the delivery of the best available care to all children and adolescents with cancer in the EU, the EU should:

- allocate non-competitive funding to ERN PaedCan and pre-existing associated structures to fulfil the objectives of the Cross-Border healthcare legislation; and
- streamline rules governing cross-border healthcare to reduce the uncertainty burden for families and provide compensation for cross-border virtual healthcare consultations.

Education and training in paediatric oncology

Education of the new generation of paediatric cancer specialists is a clear priority in ensuring continuous access to state-of-the-art expertise. **A comprehensive training programme for paediatric oncology accessible to all Member States is required across Europe and necessitates adequate investment.**

Specialised paediatric haemato-oncology professionals provide their services across the entire continuum of care. While there are well established, full medical careers in paediatric oncology, a comprehensive training pathway is lacking in many Member States. Paediatric oncologists are overall either paediatricians or medical oncologists. Some radiation oncologists and surgeons may specialise in treating some or all childhood cancers, in both cases without dedicated training pathways.

The professional figure of the paediatric oncologist should be recognised in all Member States, and mutual recognition of qualifications across the EU should be considered. Appropriate training of specialised professionals who regularly work with children with cancer should be foreseen, based on existing European guidelines^{796,797}.

c. *Development of, and access to, essential medicines for paediatric cancers*

i. *Access to essential medicines*

A survey undertaken as part of the Joint Action on Rare Cancers (JARC) has shown that children and adolescents with cancer in Europe still experience issues of access to medicines that the scientific and patient community defines as essential⁷⁹⁸. Based on the survey results, urgent action is needed to address shortages, availability of safe age-appropriate oral formulations, and consistent supply on inexpensive pain management medicines. Financial accessibility of newer expensive medicines and the need to devise appropriate reimbursement strategies reflecting the specificities of the paediatric population are another emergent orientation.

ii. *Development of new therapies and access to clinical trials*

The paediatric cancer field is facing the challenges inherent in the rare disease area, making market-driven innovation limited relative to advancements in the more common cancers.

Market-driven innovation

From a regulatory perspective, the EU Orphan Medicines Regulation has been ineffective for paediatric cancer medicine development⁷⁹⁹. The Paediatric Regulation (EC) N° 1901/2006 has been a potentially more relevant instrument, but also faced challenges in addressing the needs of paediatric cancer patients⁸⁰⁰. Only 9 innovative, specific paediatric drugs have been approved so far in contrast to over 150 new medicines for adult cancers since 2007, suggesting that the regulatory environment is not adequately fostering investment in the development of specific paediatric drugs.

The obligation to undertake a paediatric investigation plan under the Paediatric Regulation is currently driven by the medicine's indication in adults, rather than by biological reasons, although there is large evidence that medicine targets in adult cancers can be relevant also in paediatric malignancies⁸⁰¹. The RACE for Children Act in the United States will require that new cancer medicines be studied in any paediatric cancer for which the molecular target of the medicine is substantially relevant⁸⁰². This is a development that can be of high relevance to boost therapeutic innovation in childhood cancers in the global regulatory environment.

⁷⁹⁶ Janssens G.O., Timmermann B., Laprie A. et al., Recommendations for the organisation of care in paediatric radiation oncology across Europe: a SIOPE–ESTRO–PROS–CCI–Europe collaborative project in the framework of the JARC. *Eur J Cancer* 2019; 114: pp. 4–54.

⁷⁹⁷ SIOPE Europe. European Standards of Care for Children with Cancer. 2009: <https://siope.eu/european-research-and-standards/standards-of-care-in-paediatric-oncology/> (Accessed March 2020).

⁷⁹⁸ Joint Action Against Rare Cancers (2019). Report summarising the result of the survey on accessibility of standard treatment and recommendations to Member States and Europe to overcome bottlenecks. (Deliverable 9.1.)

⁷⁹⁹ Vassal G., Kearns P., Blanc P. et al., Orphan Drug Regulation: A missed opportunity for children and adolescents with cancer. *Eur J Cancer* 2017; 84: pp. 149–158.

⁸⁰⁰ Vassal G., Schrappe M., Pritchard-Jones K. et al., The SIOPE strategic plan: A European cancer plan for children and adolescents. *J Cancer Policy* 2016; 8: pp. 17–32.

⁸⁰¹ SIOPE Europe, Unite2Cure, CRUK. Paediatric Cancer Medicines-Urgent need to speed up life-saving innovation Position statement. 2016: <https://siope.eu/news-and-resources/position-papers/> (Accessed March 2020).

⁸⁰² Bennet MF. 115th Congress (2017-2018): RACE for Children Act. 2017: <https://www.congress.gov/bill/115th-congress/senate-bill/456> (Accessed March 2020).

Another issue is that the development of several drugs has been stopped in adults for inefficacy, but they have not been considered for a development in the paediatric population even though there was scientific and medical reasoning. Repurposing of molecules originally meant for development in adults may provide opportunities for further studies and potential therapeutic benefit in paediatric cancers.

In particular, the ACCELERATE platform gathers all stakeholders, including academia, industry, parents, and regulators, to develop solutions for faster development of novel potentially life-saving medicines for children with cancer. Initiatives include running the Paediatric Strategy Forums jointly coordinated by ACCELERATE and the EMA, more recently also involving the US Food and Drug Administration (FDA), to share information and advance learning in a pre-competitive setting, and contrasting the "18-years dogma" for participation in clinical trials⁸⁰³. This work is closely aligned with ERN PaedCan.

Due to the above challenges in innovative medicine development for children in the pre-marketing authorisation phase, the paediatric cancer sector has so far been less active in the pricing debate. This topic is due to become more relevant with the advent of newly authorised immunotherapy medicines for children with cancer⁸⁰⁴.

Recommendation: Accelerating therapeutic innovation in paediatric cancers

Revisit the EU regulatory environment to address the unmet needs of children and adolescents with cancer and make medicine development for this group faster, more efficient, and in line with the rate of innovation observed in the adult cancer sector.

Academic research driven innovation

Paediatric cancers therapies can be defined as an area of relative market failure due to their rarity and limited number of new medicines developed commercially over the last decade. Most standard therapies in paediatric oncology have been established through European and international cross-border academic-driven clinical research, often supported by project-based EU funding programmes. The concept of national and international networks has been fundamental to make this progress possible and provided a basis for current best practices in paediatric haematology and oncology, **allowing substantial improvements in survival rates over the past 50 years (although persisting inequalities across Europe have been underlined and require urgent attention)**⁸⁰⁵.

Public funding is instrumental to further build on these important achievements of the European academic research by enabling the utilisation of innovative technologies and methods, further integration of care and research, and support to permanent and sustainable clinical trial platforms within international collaborations.

The EU is ideally placed to take the lead in redressing unequal allocation to paediatric cancer research funding documented globally⁸⁰⁶.

⁸⁰³ Vassal G., Rousseau R., Blanc P. et al., Creating a unique, multistakeholder Paediatric Oncology Platform to improve drug development for children and adolescents with cancer. *Eur J Cancer* 2015; 51(2): pp. 218–224.

⁸⁰⁴ Joint Action on Rare Cancers (2019). *Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers* (Ch. 8).

⁸⁰⁵ Joint Action on Rare Cancers (2019). *Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers* (Ch. 5).

⁸⁰⁶ Loucaides E.M., Fitchett E.J.A., Sullivan R., Atun R., Global public and philanthropic investment in childhood cancer research: systematic analysis of research funding, 2008–16. *The Lancet Oncology*. 2019. p. e672–84.

 Recommendation: Making the EU a global leader in paediatric cancer research

A clear and specific EU funding stream should be dedicated to paediatric cancer research and budget allocations earmarked across all relevant EU programmes in order to redress allocation of investment in the area of paediatric cancer.

Another critical aspect is ensuring access to innovative therapies delivered in early clinical trials, which can be lifesaving for children with relapsed or refractory non-curable malignancies. The ITCC network of excellence (Innovative Therapies for Children Cancer) is a hub of expertise on innovative therapies delivered in early clinical trial settings uniting academic centres running such trials across Europe. A number of ITCC centres are members of ERN PaedCan, thus maximising synergies between the two initiatives⁸⁰⁷.

d. Survivorship

With an 80% survival at five years, the number of childhood cancer survivors (currently estimated to be more than 300,000 in Europe) is likely to continue to increase. Improving the quality of life of these survivors is a major goal. Two-thirds of survivors have late-occurring side effects due to their treatments, which are severe in half of them, and have a strong impact on their daily lives. It is anticipated that in 2030 there will be around 750,000 paediatric cancer survivors in Europe⁸⁰⁸.

Long-term follow-up of childhood cancer survivors is key to address this issue, as health sequelae and long-term complications of treatment are of major concern in childhood cancers. In this regard, **JARC recommends the roll-out of a European Unique Patient Identifier, in order to ensure monitoring of long-term outcomes in childhood cancer survivors in a cross-border setting**⁸⁰⁹.

Long-term quality of care models for cancer survivors across the EU should also be fostered, through the development of high-quality guidelines⁸¹⁰ and by tapping the full potential of the cross-border nature of ERN PaedCan. Such models should allow for coordinated transition from paediatric to adult care settings, appropriate surveillance of late effects, and empowering childhood cancer survivors with information about future risks and available care settings and guidelines⁸¹¹.

Recommendation: Addressing the needs of childhood cancer survivors

The implementation of the Survivorship Passport model across Member States should be supported, alongside sustained development of long-term surveillance and research through EU programmes.

Healthcare structures should be modified to better satisfy the special care needs after childhood cancer treatment, including psychosocial aspects, to maximise quality of life.

Policies are needed to address societal equity needs that arise for childhood cancer survivors including education and career opportunities, income, starting a family, and access to financial services such as insurance.

⁸⁰⁷ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 5).

⁸⁰⁸ Vassal G., Schrappe M., Pritchard-Jones K. et al., The SIOPE strategic plan: A European cancer plan for children and adolescents. *J Cancer Policy* 2016; 8: pp. 17–32.

⁸⁰⁹ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 2).

⁸¹⁰ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 3).

⁸¹¹ Joint Action on Rare Cancers (2019). Rare Cancer Agenda 2030: Ten Recommendations from the EU Joint Action on Rare Cancers (Ch. 10).

4.2.4. The role of patient organisations in paediatric cancers

Patient engagement in paediatric cancers has specificities attributable to a particularly heterogeneous patient population with different needs, the central place of not only young patients but also their parents and caregivers, and the distinct needs of adolescents as well as adult survivors of childhood malignancies.

In addition and importantly, the paediatric cancer sector is characterised by a long-term organised cooperation between parent/patient/survivor representatives and professionals that pre-dates the formation of the ERNs. Indeed, a network of patient representatives and healthcare professionals working in paediatric haematology and oncology has been built over several decades in Europe.

Whereas core asks including meaningful participation and funding sustainability to play their essential role, specific priorities apply from the paediatric cancer patient perspective.

In the light of the potential burden on families with seriously ill children seeking cross-border health care, ERN PaedCan prioritises mechanisms to move information and knowledge rather than patients. Nevertheless, as cross-border travel might be required to receive highly specialised care and, for patients in treatment failure or relapse, to participate in early clinical trials, appropriate reimbursement of the interventions, travel and accommodation is needed for parents and their child. **Exchanges are needed to streamline the current rules for cross-border healthcare reimbursement and their implementation, to foster reimbursement predictability, avoid unnecessary burden on families at an already challenging time, and ensure access to potentially life-saving clinical trials.**

The right of the hospitalised child to "constant and continuous parental involvement" is defined in the European Standards of Care for Children with Cancer developed in the European Partnership Against Cancer Joint Action (EPAAC, EU Health Programme). A parent's presence during the child's treatment is essential.

Recommendation: Upholding the rights of children with cancer and their families

In the aim of upholding the rights of children with cancer and their families, awareness of the importance of parental involvement and financial security for families caring for children and adolescents with cancer should be fostered.

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ANNEX 1: EPIDEMIOLOGY OF MOST COMMON CANCERS IN 2018 IN THE EU

Table 6: Incidence and mortality of the 15 most common cancers in 2018 in the EU

Organ site/Cancertype	INCIDENCE Estimated new cases in 2018 in the EU27	MORTALITY Estimated deaths in 2018 in the EU27
Breast	349,481	86,906
Colorectum	330,553	152,276
Prostate	319,441	68,397
Lung	312,281	258,452
Bladder	152,232	46,822
Skin melanoma	102,653	17,225
Pancreas	88,631	85,330
Kidney	85,531	34,600
Non-Hodgkin lymphoma	81,452	33,908
Stomach	73,841	54,007
Corpus uteri	68,243	16,366
Leukaemia	63,589	42,549
Liver	57,956	52,650
Thyroid	53,497	4,500
Brain, central nervous system	43,183	33,906
All cancers	2,835,930	1,246,462

Source: IARC Global Cancer Observatory <https://gco.iarc.fr/> (accessed June 2020).

ANNEX 2: SHARE OF PREVENTABLE CANCERS AMONG MOST COMMON CANCER TYPES IN EUROPE



Source: Adapted from Cancer Prevention Europe's website <https://cancerpreventionEurope.iarc.fr/preventable-cancers/> (accessed March 2020).

Note: NHL: Non-Hodgkin's Lymphoma.

Data on estimated incidence in 2012 retrieved from International Agency for Research on Cancer's Global Cancer Observatory: <https://gco.iarc.fr>.

Data on risk factor attributable fraction retrieved from Brown KF, Runggay H, Dunlop C, et al. The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. *Br J Cancer*. 2018 Apr; 118(8): pp. 1130-1141.

ANNEX 3: THE EUROPEAN CODE AGAINST CANCER (4TH EDITION)

European Code Against Cancer

12 WAYS TO REDUCE YOUR CANCER RISK

You are here: Home Print the Code

1. Do not smoke. Do not use any form of tobacco.
2. Make your home smoke free. Support smoke-free policies in your workplace.
3. Take action to be a healthy body weight.
4. Be physically active in everyday life. Limit the time you spend sitting.
5. Have a healthy diet:

 - Eat plenty of whole grains, pulses, vegetables and fruits.
 - Limit high-calorie foods (foods high in sugar or fat) and avoid sugary drinks.
 - Avoid processed meat; limit red meat and foods high in salt.
6. If you drink alcohol of any type, limit your intake. Not drinking alcohol is better for cancer prevention.
7. Avoid too much sun, especially for children. Use sun protection. Do not use sunbeds.
8. In the workplace, protect yourself against cancer-causing substances by following health and safety instructions.
9. Find out if you are exposed to radiation from naturally high radon levels in your home. Take action to reduce high radon levels.
10. For women:

 - Breastfeeding reduces the mother's cancer risk. If you can, breastfeed your baby.
 - Hormone replacement therapy (HRT) increases the risk of certain cancers. Limit use of HRT.
11. Ensure your children take part in vaccination programmes for:

 - Hepatitis B (for newborns)
 - Human papillomavirus (HPV) (for girls).
12. Take part in organised cancer screening programmes for:

 - Bowel cancer (men and women)
 - Breast cancer (women)
 - Cervical cancer (women).

The European Code Against Cancer focuses on actions that individual citizens can take to help prevent cancer. Successful cancer prevention requires these individual actions to be supported by governmental policies and actions.

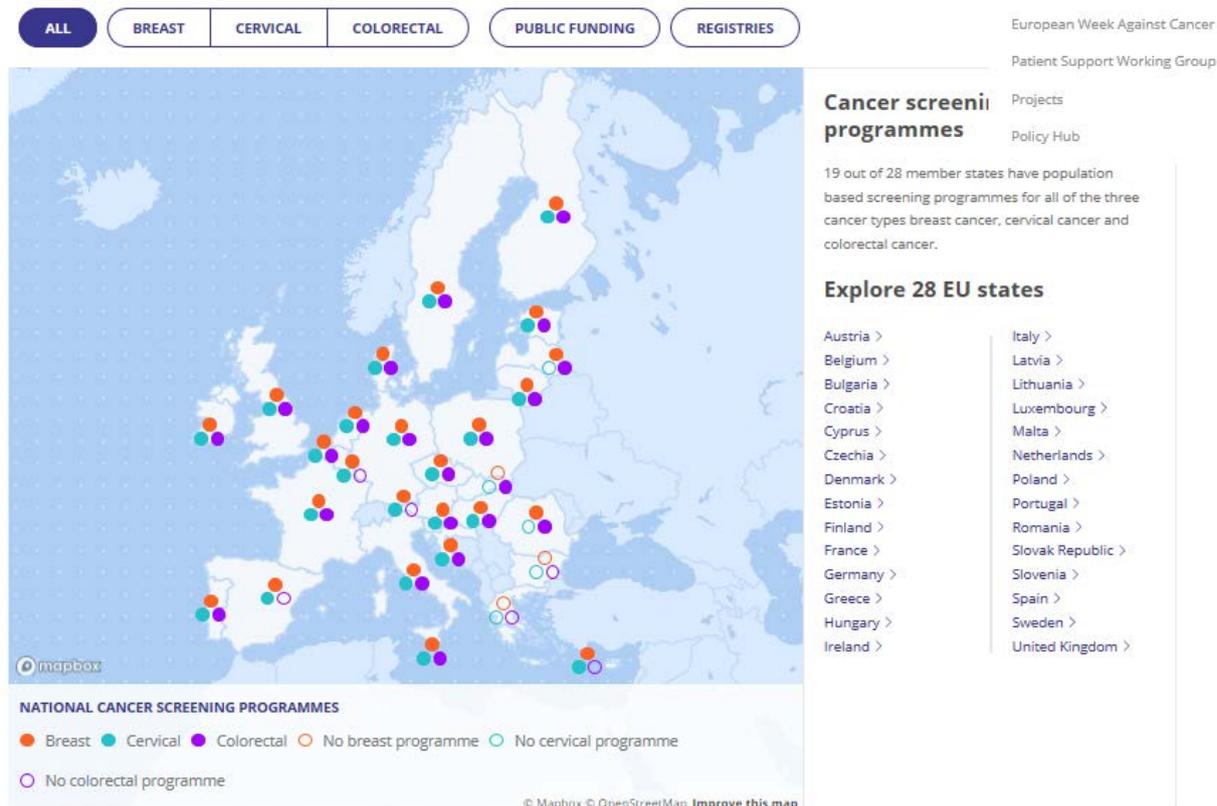
These recommendations are the result of a project coordinated by the International Agency for Research on Cancer and co-financed by the

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Source: Adapted from the European Code Against Cancer's website: <https://cancer-code-europe.iarc.fr/index.php/en/> (accessed June 2020).

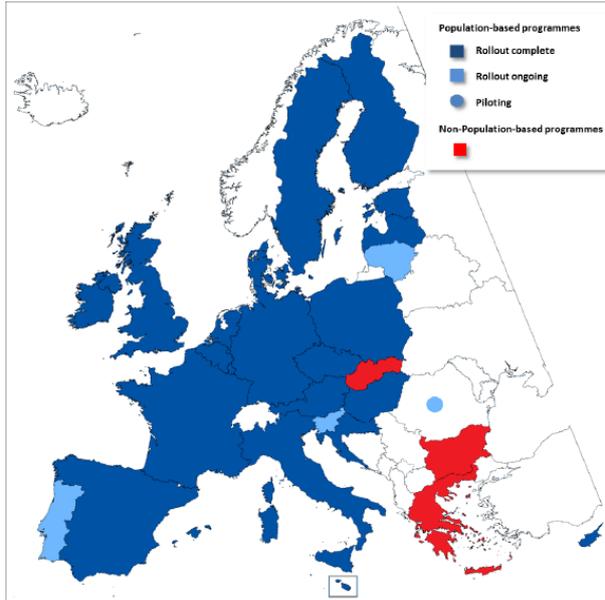
ANNEX 4: IMPLEMENTATION OF RECOMMENDED SCREENING PROGRAMMES (1/2)



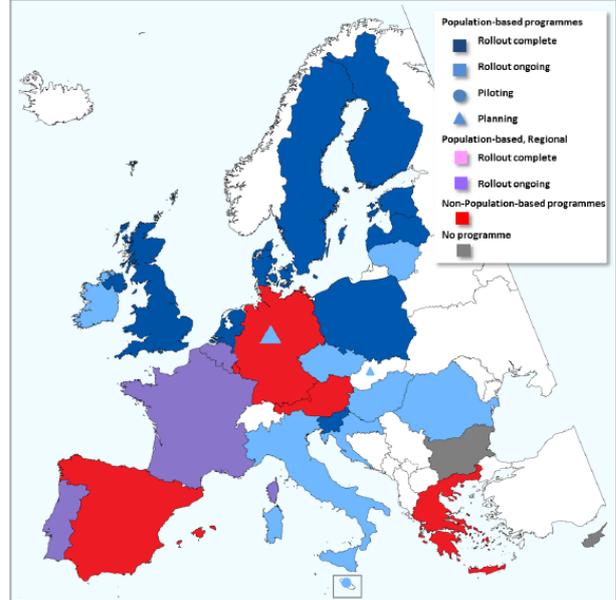
Source: European Cancer Leagues' interactive map of national efforts regarding implementation of cancer screening programmes, within the frame of policies addressing European Code Against Cancer's recommendations to reduce cancer risk; extracted from: <https://www.europeancancerleagues.org/cancer-prevention-ecac-map/#12> (accessed March 2020).

ANNEX 5: IMPLEMENTATION OF RECOMMENDED SCREENING PROGRAMMES (2/2)

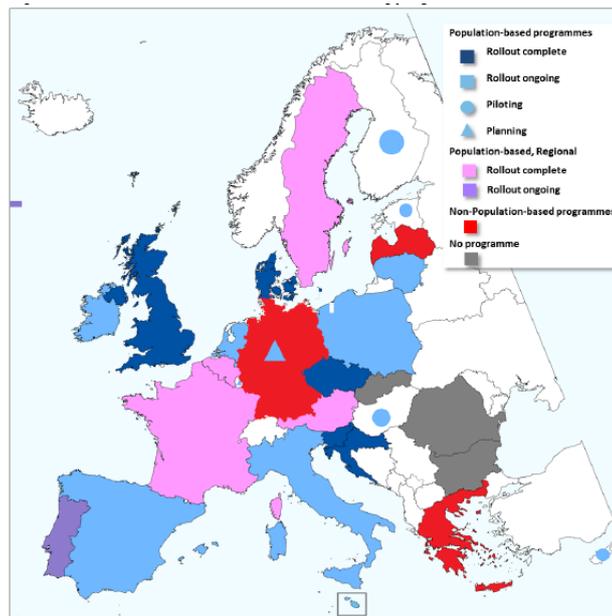
Breast cancer screening



Cervical cancer screening



Colorectal cancer screening



Source: Cancer screening in the European Union: Report on the implementation of the Council recommendation on cancer screening (2nd edition). International Agency for Research on Cancer; 2017. Available at: https://ec.europa.eu/health/sites/health/files/major_chronic_diseases/docs/2017_cancerscreening_2ndreportimplementation_en.pdf

ANNEX 6: ORGANISATION OF RECOMMENDED CANCER SCREENING PROGRAMMES

Table 7: Adoption of recommended target populations and screening intervals within recommended cancer screening programmes across EU Member States and the UK in 2017

	Breast cancer screening		Cervical cancer screening		Colorectal cancer screening	
	Target population (women 50-69)	Screening interval (2 or 3 years)	Target population (women 30-59 ⁸¹²)	Screening interval (3-5 years)	Target population (men & women 50-4)	Screening interval (2 years) ⁸¹³
Wider population/ Shorter interval	9	0	20	2	2	2
Exact population/ Interval	15	25	1	20	7	20
Narrower population/ Longer interval	1	0	1	0	14	0

Source: Cancer screening in the European Union: Report on the implementation of the Council recommendation on cancer screening (2nd edition). International Agency for Research on Cancer; 2017.

Note: Displayed numbers correspond to the number of EU Member States and the UK reporting the respective situation regarding the respecting cancer screening program.

⁸¹² No target age band is defined for cervical cancer screening by 2003 Council recommendations or subsequent European guidelines; however, this age group (women aged 30 to 59) is common to all population-based cervical cancer screening programmes implemented in EU Member States in 2017, except current pilot programme in Malta.

⁸¹³ Screening interval recommended for programmes using gFOBt (Guaiaac Fecal Occult Blood Test) or FIT (Fecal Immunochemical Test) as screening tests; therefore excluding Poland where only colonoscopy is offered.

ANNEX 7: PERFORMANCE OF RECOMMENDED CANCER SCREENING PROGRAMMES ACROSS THE EU (1/2)

Table 8: Screening coverage and participation rates for recommended cancer screening programmes across EU Member States and the UK in 2013

	Breast cancer screening ⁸¹⁴			Cervical cancer screening ⁸¹⁵			Colorectal cancer screening		
	E.C.R.	I.C.R.	P.R.	E.C.R.	I.C.R.	P.R.	E.C.R.	I.C.R.	P.R.
Austria	36.9%	INDI	INDI	NPBSP	NPBSP	NPBSP	ND	ND	ND
Belgium ^{816,817}	33.0%	99.7%	31.5%	3.9%	33.8%	11.6%	22.7%	81.4%	27.9%
Bulgaria	NPBSP	NPBSP	NPBSP	NSP	NSP	NSP	NSP	NSP	NSP
Croatia	45.1%	104.8%	43.1%	10.8%	105.1%	10.3%	15.3%	100.5%	15.3%
Cyprus ⁸¹⁸	16.5%	39.6%	37.7%	NSP	NSP	NSP	ND	ND	ND
Czech Republic	59.1%	INDI	INDI	ND	ND	ND	24.8%	NPBSP	NPBSP
Denmark	72.0%	82.3%	83.5%	45.4%	67.1%	67.7%	ND	ND	ND
Estonia	45.9%	69.2%	66.3%	44.4%	77.1%	57.5%	P	P	P
Finland ⁸¹⁹	76.1%	91.6%	83.0%	64.4%	97.9%	65.8%	6.9%	10.5%	66.6%
France ⁸²⁰	52.3%	102.7%	51.0%	12.2%	56.0%	21.9%	26.5%	99.1%	24.4%
Germany	52.7%	90.8%	56.3%	P	P	P	P	P	P
Greece	NPBSP	NPBSP	NPBSP	NPBSP	NPBSP	NPBSP	NPBSP	NPBSP	NPBSP
Hungary ⁸²¹	38.4%	78.5%	59.0%	4.6%	15.2%	30.1%	0.5%	1.5%	36.7%
Ireland ⁸²²	76.2%	110.5%	68.7%	ND	ND	ND	4.4%	10.9%	43.1%
Italy ⁸²³	39.1%	70.6%	55.4%	27.2%	65.1%	41.8%	23.8%	52.4%	45.7%
Latvia	33.6%	98.4%	53.8%	34.0%	92.7%	36.7%	11.1%	NPBSP	NPBSP
Lithuania	44.9%	INDI	INDI	36.4%	75.5%	48.2%	53.1%	AINSI	AINSI
Luxemburg	60.4%	107.5%	56.6%	NPBSP	NPBSP	NPBSP	P	P	P
Malta ⁸²⁴	36.4%	78.8%	58.1%	ND	ND	ND	10.2%	28.5%	35.7%
Netherlands ⁸²⁵	77.5%	96.7%	80.1%	63.8%	96.7%	66.0%	15.0%	20.2%	74.0%
Poland ⁸²⁶	44.0%	101.8%	63.1%	17.8%	97.7%	18.2%	2.1%	12.5%	16.7%
Portugal ^{827,828}	33.8%	55.4%	60.0%	11.7%	18.6%	NC	1.0%	1.6%	62.8%
Romania ⁸²⁹	0.2%	0.2%	82.0%	9.2%	65.0%	14.2%	NSP	NSP	NSP
Slovakia	NPBSP	NPBSP	NPBSP	P	P	P	NSP	NSP	NSP

⁸¹⁴ Breast cancer screening in Estonia, Hungary and Ireland: rolling out only in 50-64 target age band.

⁸¹⁵ Cervical cancer screening in Croatia, Poland, Portugal and Romania: data reported without age distribution, therefore not on 30-59 age band but on entire used target age bands (i.e. 25-59 for Poland and 25-64 for Croatia, Portugal and Romania).

⁸¹⁶ Cervical cancer screening in Belgium: rolling out only in the Flanders region.

⁸¹⁷ Colorectal cancer screening in Belgium: rolling out only on 56-74 age band in the Flemish region.

⁸¹⁸ Breast cancer screening in Cyprus: data on invitations only provided for the Nicosia region.

⁸¹⁹ Colorectal cancer screening in Finland: rolling out only on 60-69 age band.

⁸²⁰ Cervical cancer screening in France: data only provided for 13 districts, representing altogether 13% of the national target population.

⁸²¹ Colorectal cancer screening in Hungary: rolling out only in 50-70 age band.

⁸²² Colorectal cancer screening in Ireland: rolling out only in 60-69 age band.

⁸²³ Colorectal cancer screening in Italy: rolling out only in 50-69 age band.

⁸²⁴ Colorectal cancer screening in Malta: rolling out only in 60-64 age band.

⁸²⁵ Colorectal cancer screening in Netherlands: rolling out only in 55-75 age band.

⁸²⁶ Colorectal cancer screening in Poland: rolling out only in 55-64 age band.

⁸²⁷ Cervical cancer screening in Portugal: no data reported for the Azores region.

⁸²⁸ Colorectal cancer screening in Portugal: rolling out only in 50-70 age band.

⁸²⁹ Breast cancer screening in Romania: pilot running only in the Cluj region.

	Breast cancer screening			Cervical cancer screening			Colorectal cancer screening		
	E.C.R.	I.C.R.	P.R.	E.C.R.	I.C.R.	P.R.	E.C.R.	I.C.R.	P.R.
Slovenia ⁸³⁰	19.1%	20.9%	82.5%	ND	ND	ND	40.3%	80.0%	50.5%
Spain ⁸³¹	59.7%	84.7%	70.4%	NPBSP	NPBSP	NPBSP	7.2%	14.2%	52.2%
Sweden ^{832, 833}	76.5%	93.3%	73.2%	70.6%	79.9%	53.7%	5.1%	8.5%	60.2%
United Kingdom ^{834, 835, 836}	83.6%	111.0%	71.7%	62.1%	102.1%	59.4%	32.8%	58.7%	55.4%

Source: Cancer screening in the European Union: Report on the implementation of the Council recommendation on cancer screening (2nd edition). International Agency for Research on Cancer; 2017.

Note: E.C.R.: Examination Coverage Rate; I.C.R.: Invitation Coverage Rate; P.R.: Participation rate.

AISNI: Active Invitation System (call-recall) Not Implemented; INDI: Invitations Not Documented or Issued at the time of the index year; NC: Not Computed; ND: No Data provided; NPBSP: Non Population-Based Screening Program; NSP: No Screening Program; P: Planning phase of the screening program, no data provided.

Invitation Coverage Rates beyond 100% reflect variability between years within a screening interval. If the latter is 3 years, it can indeed be that, on the index year, more than one third of the target population gets invited to screening, resulting in Invitations Coverage Rates exceeding 100% when using the "annual target population" as a reference (i.e. the target population dividing by the screening interval).

⁸³⁰ Colorectal cancer screening in Slovenia: rolling out only in 50-69 age band.

⁸³¹ Colorectal cancer screening in Spain: rolling out only in 50-69 age band.

⁸³² Breast cancer screening in Sweden: participation rate computed using only data from the Stockholm Gotland region.

⁸³³ Colorectal cancer screening in Sweden: rolling out only in 60-69 age band, only in the Stockholm Gotland region.

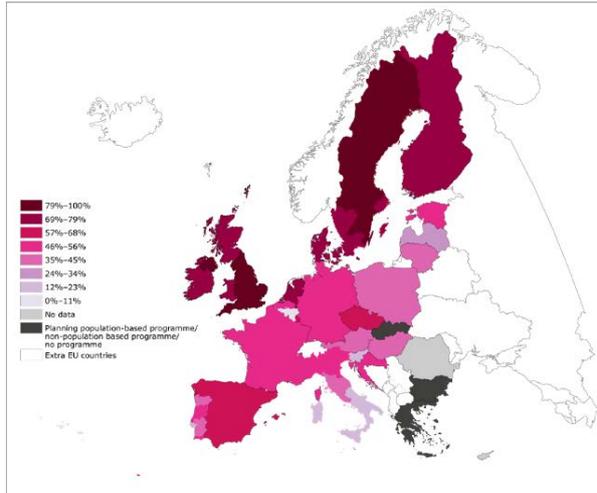
⁸³⁴ Breast cancer screening in the United Kingdom: data provided for target age 50-70; participation rate computed excluding Scotland.

⁸³⁵ Cervical cancer screening in the United Kingdom: no data provided on examinations for Scotland; participation rate computed considering only England and Northern Ireland.

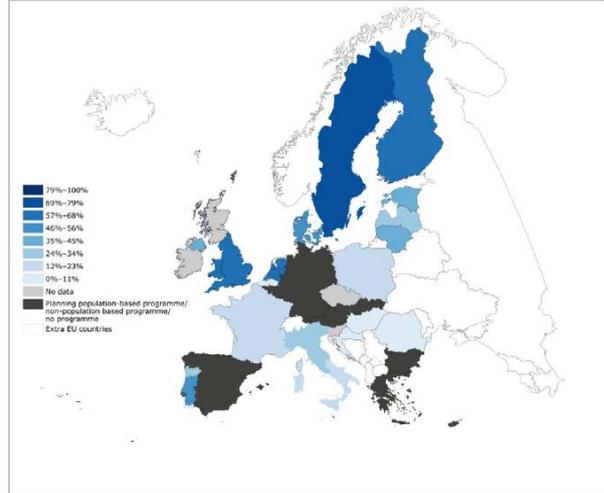
⁸³⁶ Colorectal cancer screening in the United Kingdom: rolling out only in 60-74 age band, except in Scotland (50-74).

ANNEX 8: PERFORMANCE OF RECOMMENDED CANCER SCREENING PROGRAMMES ACROSS THE EU (2/2)

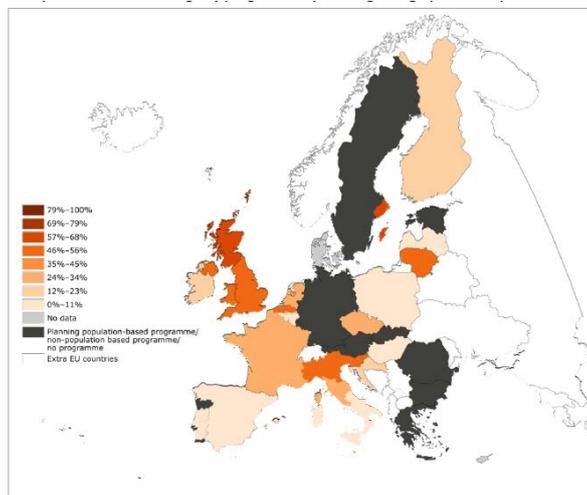
Breast cancer screening



Cervical cancer screening



Colorectal cancer screening



Source: Cancer screening in the European Union: Report on the implementation of the Council recommendation on cancer screening (2nd edition). International Agency for Research on Cancer; 2017.

Note: Examination coverage rates for recommended cancer screening programmes within the target populations (except for cervical cancer screening; examination coverage rate within all women) is depicted for each EU Member State.

ANNEX 9: EPIDEMIOLOGY OF CANCER ACROSS EU MEMBER STATES

Table 9: Cancer incidence, mortality and survival estimates across EU Member States

	SURVIVAL Age-standardised 5-year relative survival rate in 2000-2007 (%)	INCIDENCE Relative change of age- standardised incidence rate in 2018, as compared to EU28 average (%)	MORTALITY Relative change of age- standardised mortality rate in 2018, as compared to EU28 average (%)
Austria	60.10	-17.47	-8.74
Belgium	60.44	12.13	-3.10
Bulgaria	38.72	-21.34	-3.63
Croatia	46.23	-2.36	24.77
Cyprus	ND	-12.97	4.99
Czech Republic	50.66	2.37	-0.98
Denmark	50.92	16.26	14.67
Estonia	45.99	-0.53	9.49
Finland	61.36	-6.17	-18.84
France	58.62	10.79	0.42
Germany	59.09	1.28	-1.74
Greece	ND	-3.94	2.27
Hungary	ND	20.32	30.14
Ireland	53.95	19.03	2.91
Italy	56.77	-2.97	-9.23
Latvia	41.69	3.87	12.90
Lithuania	46.06	-5.54	9.34
Luxemburg	ND	4.45	-10.29
Malta	52.93	-9.63	-14.64
Netherlands	54.57	8.10	6.92
Poland	40.59	-11.93	18.08
Portugal	56.39	-13.60	-6.73
Romania	ND	-24.76	1.13
Slovakia	44.75	3.41	30.30
Slovenia	47.79	5.24	11.88
Spain	52.82	-9.44	-14.26
Sweden	64.75	-0.93	-11.08
European average	53.23	0.00	0.00

Source: The European Cancer Information System (ECIS): <https://ecis.jrc.ec.europa.eu/index.php> (accessed June 2020).

Note: ND: No Data.

ANNEX 10: EPIDEMIOLOGY OF RARE CANCER FAMILIES

Table 10: Incidence, prevalence and survival estimates across individual rare cancer families in the EU

	INCIDENCE		PREVALENCE	SURVIVAL
	Crude incidence rate per 100,000 people in 2000-2007	Estimated new cases in 2013 in the EU	Estimated prevalent cases in 2008 in the EU	Estimated 5 year relative survival in 2000-2007
All rare tumours	114.99	636,753	5,085,137	48.5%
Head and neck cancers	18.82	84,989	598,903	52.1%
Digestive cancers	21.94	112,351	226,227	15.3%
Thoracic cancers	6.80	37,277	80,002	13.4%
Female genital cancers	22.73	113,796	1,263,296	57.7%
Male genital and urogenital cancers	7.09	38,138	611,401	73.6%
Neuroendocrine tumours	3.51	19,587	159,889	53.5%
Cancers of the endocrine organs	5.35	28,322	371,695	88.1%
Sarcomas	5.86	31,916	340,916	59.5%
Cancers of the CNS ⁸³⁷	7.56	36,343	216,580	21.3%
Skin cancers and non-cutaneous melanoma	1.22	7,086	78,812	70.2%
Paediatric cancers ⁸³⁸	0.34	1,822	36,987	78.6%
Haematological malignancies	27.73	156,099	1,205,475	50.5%

Source: Gatta G, Capocaccia R, Botta L, et al. Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet-a population-based study. *Lancet Oncol* 2017 Aug; 18(8): pp. 1022-1039. RARECAREnet website's online analysis tool. <http://www.rarecarenet.eu/analysis.php> (accessed February 2020).

⁸³⁷ Central Nervous System.

⁸³⁸ This family does not encompass the entire burden of paediatric cancers; it indeed comprises a number of blastomas known to occur in the paediatric population, however the latter are also affected by rare tumour entities included under other labels (see Annex 2³¹), or even by tumour entities classified as common within the total population, but affecting children with a rare incidence. The International Childhood Cancer Classification (ICCC3) is most often referred to in the paediatric cancer sector (see Section 4.2).

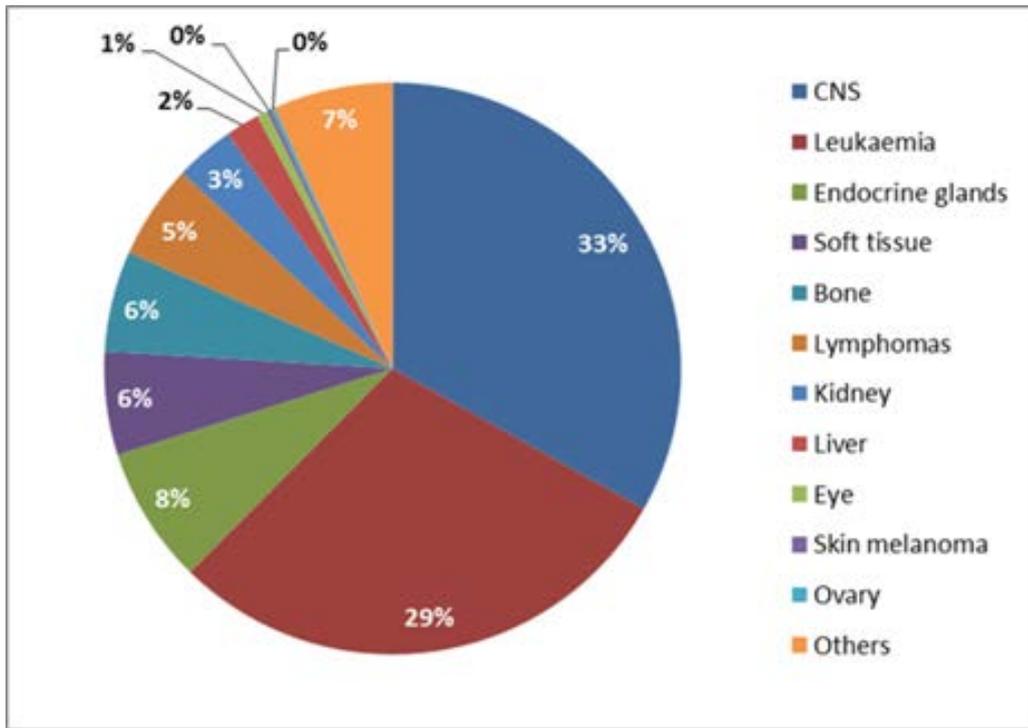
ANNEX 11: EPIDEMIOLOGY OF CHILDHOOD CANCERS

Table 11: Incidence and mortality estimates for childhood cancers in Europe in 2018

		WHO Europe region	EU27	WHO Europe region	EU27
All types of cancer	0 – 24	38,370	24,075	6,337	3,367
	0 – 19	25,094	15,350	4,482	2,325
	0 - 14	17,455	10,256	3,256	1,606
By type of cancer	0 – 24				
Leukaemia	0 – 24	7,242	4,175	1,653	843
Brain, nervous system	0 – 24	4,252	2,561	1,598	909
Hodgkin lymphoma	0 – 24	3,719	2,369	406	235
Testis	0 – 24	3,505	2,637	148	65
Thyroid	0 – 24	3,135	2,113	135	62
Melanoma of skin	0 – 24	2,422	1,899	117	54
Non-Hodgkin lymphoma	0 – 24	2,415	1,504	108	69
Other cancers	0 - 24	11,680	6,817	2,172	1,130
By type of cancer	0 - 19				
Leukaemia	0 - 19	6,509	3,713	1,318	645
Brain, nervous system	0 - 19	3,411	2,029	1,284	727
Hodgkin lymphoma	0 - 19	2,193	1,404	242	135
Non-Hodgkin lymphoma	0 - 19	1,679	1,026	92	36
Thyroid	0 - 19	1,276	848	92	43
Testis	0 - 19	1,276	947	53	20
Kidney	0 - 19	1,117	619	23	12
Other cancers	0 - 19	7,633	4,764	1,378	707
By type of cancer	0 - 14				
Leukaemia	0 - 14	5,670	3,183	1,038	578
Brain, nervous system	0 - 14	2,720	1,591	1,010	459
Non-Hodgkin lymphoma	0 - 14	1,196	716	138	68
Kidney	0 - 14	1,060	589	85	38
Hodgkin lymphoma	0 - 14	1,004	634	69	24
Thyroid	0 - 14	341	213	13	2
Liver	0 - 14	293	152	8	1
Other cancers	0 - 14	5,171	3,178	895	436

Source: International Agency for Research on Cancer. (2018). Cancer Today. Retrieved from Cancer Today website: <https://qco.iarc.fr/today/home>.

ANNEX 12: CAUSE OF DEATH IN THE PAEDIATRIC POPULATION BY TYPE OF CANCER



Source: Courtesy of Eva Steliarova-Foucher IN Vassal G, Schrappe M, Pritchard-Jones K et al. The SIOPE strategic plan: A European cancer plan for children and adolescents. *J Cancer Policy* 2016;8: pp. 17–32.

Note: Percentage of all cancer deaths in children (age 0-14) in all 50 areas covered by population-based cancer registries contributing data for years 2000-2007 to the European Cancer Observatory (N=6256). Causes of deaths are classified according to the tenth edition of the International Classification of Diseases (ICD-10; WHO, 1992).

This study provides an overview of the current state-of-play in Europe in respect to cancer. It focuses in particular on four main areas: causation of cancer; cancer screening and early diagnosis; access to cancer treatment, care and research; and rare and childhood cancers. It provides key findings and recommendations in each of these areas.

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