Advances against cancer

A comprehensive overview of the disease in Spain

The term cancer covers hundreds of different pathologies. Almost 300,000 people are diagnosed each year in Spain, which has great personal, social and economic impact. Hand in hand with prevention, the latest advances in diagnosis and treatment are changing approaches to this health challenge.

- Approximately 40% of tumours could be prevented if risk factors were reduced.
- Screening programmes facilitate early diagnosis for some pathologies which are linked with better prognosis..
- Precision medicine for cancer, based on molecular diagnostics, among other techniques, enables more precise and effective treatment and improved outcomes.
- Tackling cancer requires a multi-disciplinary combination of therapies. In addition to surgery and chemotherapy:
  - Advances in radiation oncology offer treatments that are more effective, safer and more cost-effective.
  - Immunotherapy, despite not always being effective, has achieved significant increased survival for certain types of cancer..
  - Targeted therapies selectively attack the mechanisms that cause and maintain a tumour.
- European objectives promote changes towards a comprehensive treatment of cancer in Spain. Such as:
  - Concentrating patients in hospital units where there is a multi-disciplinary approach combining diagnosis, treatment and research.
  - Improving access to precision medicine, new drugs and clinical trials.
  - Improving the quality of life and prognosis of minors and young adults with cancer.
- In addition to further studying the genomics of cancerous cells, current research seeks to understand the relationship of the tumour with its immediate surroundings and the rest of the organism.

Production method

Reports C are brief documents on subjects chosen by the Bureau of the Congress of Deputies that contextualise and summarise the available scientific evidence on the analysed subject. They also inform about areas of agreement, disagreement, unknowns, and ongoing discussions. The reports are drafted based on an in-depth review of the literature, supplemented by interviews with experts on the subject.

To produce this report Oficina C referenced 198 documents and consulted 34 experts on the subject. The majority of these experts are science or healthcare professionals specialised in different disciplines: 19% also have training in social sciences or humanities; 85% work in Spanish institutions or centres, whereas 15 % have affiliations abroad.

Oficina C is responsible for the publication of this report.

Researchers, scientists and experts consulted* (in alphabetical order)

Abad, María[1]. Principal Investigator at the Vall d'Hebron Institute of Oncology (VHIO).

Arroyo, Rocío[1]. Coordinator of the working group: Advanced Diagnosis and Personalised Medicine at the Spanish Bioindustry Association (Asociación Española de Bioempresas - ASEBIO), CEO, Amadix.

Barbacid, Mariano[1]. AXA-CNIO Professor of Molecular Oncology. Group leader of Experimental Oncology, Spanish National Cancer Research Centre (Centro Nacional de Investigaciones Oncológicas - CNIO).

Barragán, María Begoña[1]. President of the Spanish Group of Patients with Cancer (Grupo Español de Pacientes con Cáncer - GEPAC).

Borras, Josep Maria[1]. Director of the Oncology Master Plan of the Catalan Regional Government and scientific coordinator of the Catalan Health Service Cancer Strategy.

Castell, Joan[1]. Former President of the Spanish Society of Nuclear Medicine and Molecular Imaging (Sociedad Española de Medicina Nuclear e Imagen Molecular - SEMNIM) Director of Nuclear Medicine at SIMM-Atrys, Barcelona.

Cañete, Adela1. Paediatric Oncology and Haematology Section, La Fe Hospital. Vice-president of the Spanish Society of Paediatric Haematology and Oncology (Sociedad Española de Hematología y Oncología Pediátricas - SEHOP). Scientific director of the Spanish Registry of Children with Tumours of the Spanish Society of Paediatric Haematology and Oncology (Registro Español de Tumores Infantiles - RETI-SEHOP).

Chiarle, Roberto. Professor and Principal Investigator at Boston Children's Hospital and Harvard Medical School. United States. Professor at the University of Torino. Italy

Conde, Antonio J[1]. Head of Radiotherapy Oncology Service, La Fe University and Polytechnic Hospital.

de Álava, Enrique1. Director of the Anatomical Pathology Unit, Virgen del Rocio University Hospital, Biomedicine Institute of Seville. Coordinator of the Precision Medicine Strategy for the Andalusian Government Department for Health and Consumption.

Díaz-Rubio, Eduardo1. Emeritus Professor of medical oncology, president of the Spanish Royal Academy of Medicine.

Fabregat, Isabel[1]. Principal Investigator, Bellvitge Biomedical Research Institute (Instituto de Investigación Biomédica - IDIBELL)

Felip, Enriqueta[1]. Head of section, Vall d'Hebron University Hospital. President of the Spanish Society of Medical Oncology (Sociedad Española de Oncología Médica - SEOM).

Fernández-Teijeiro, Ana[1]. President of the Spanish Society of Paediatric Haematology and Oncology

García-Foncillas, Jesús. Professor of Oncology, Director of the Oncology Department, Jiménez Díaz Foundation University Hospital, Autonomous University of Madrid.

Gros, Alena. Principal Investigator, Vall d'Hebron Institute of Oncology (VHIO)

Gómez Caamaño, Antonio[1]. Head of Radiation Oncology Service, Santiago de Compostela University Hospital. President of the Spanish Society of Radiation Oncology (Sociedad Española de Oncología Radioterápica - SEOR)

Massagué, Joan[1]. Director of Sloan Kettering Institute, Memorial Sloan Kettering Cancer Center. United States.

Mayan, María D[1]. Group leader, A Coruña Biomedical Research Institute (Instituto de Investigación Biomédica de A Coruña - INIBIC) CHUAC- SERGAS.

Morales, Andrés[1]. Paediatric oncologist and Director of Healthcare, Paediatric Cancer Centre, Barcelona. Sant Joan De Deu Hospital.

Moreno, Gema[1]. Professor of the Biochemistry Department, Medical Faculty, Autonomous University of Madrid. Director of the Cancer Research Laboratory, MD Anderson Foundation.

Nadal, Ernest[1]. Head of section, Thoracic, Head and Neck Tumours, Duran I Reynals Hospital. Catalan Institute of Oncology.

Nieto, Patricia[1]. Research Project Manager, Scientific Foundation of the Spanish National Association Against Cancer (Asociación Española Contra el Cáncer - AECC)

Nik-Zainal, Serena. Professor of Genomic Medicine and Bioinformatics, Early Cancer Institute, University of Cambridge. Department of Medical Genetics, University of Cambridge. United Kingdom.

Paz-Ares, Luis[1]. Head of Medical Oncology Service, 12 de Octubre Hospital. President of the Spanish Association for Cancer Research (Asociación Española de Investigación sobre el Cáncer - ASEICA).

Peinado, Héctor[1]. Principal Investigator, Spanish National Cancer Research Centre (Centro Nacional de Investigaciones Oncológicas - CNIO).

Piris, Alejandro[1]. Scientific Research Manager, Vall d'Hebron Institute of Oncology (VHIO).

Puyol, Marta[1]. Scientific director, Scientific Foundation of the Spanish National Association Against Cancer (AECC)

Ramón y Cajal, Santiago[1]. Head of Anatomical Pathology Service, Vall d'Hebron University Hospital. Group leader, Translational Molecular Pathology Service, Vall d'Hebron Research Institute (Vall d'Hebron Instituto de Investigación - VHIR). President-elect of the Spanish Society of Anatomical Pathology.

Santamaría, David. Principal Investigator at the Cancer Research Centre (Centro de Investigación del Cáncer CIC-IBMCC).

Stevens, Lisa. Director, Division of the Programme of Action for Cancer Therapy, International Atomic Energy Agency (IAEA), Austria.

Tabernero, Josep[1]. Head of Medical Oncology, Vall d'Hebron University Hospital. Director, Vall d'Hebron Institute of Oncology (VHIO).

Vousden, Karen. Principal Investigator, Francis Crick Institute, former chief scientist at Cancer Research UK. United Kingdom.

Weiderpass, Elisabete[1]. Director of the International Agency for Research on Cancer (IARC), World Health Organisation (WHO) France.

** The experts have not declared any conflicts of interests.*
1 Specialists who also participated in the full or partial review of the report.

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Graphical abstract

Introduction

It is estimated that around 280,100 people will be diagnosed with cancer in Spain during 2022[1]. Taken as a group, this type of disease is the second cause of mortality among the general population, responsible for 112,741 deaths in 2020 and second only to cardiovascular diseases[1,2]. Forecasts indicate that if incidence trends for the main types of cancer continue, by 2070 the number of cases will have doubled compared to the figures for 2020[3].

Spanish society perceives cancer as the most serious disease, and it is the one that causes most fear, according to the latest survey on perceptions of cancer (the Oncobarometro)[4]. Calculations are that 1.5 million people suffer or have suffered cancer in Spain, with a consequent impact on physical and emotional health, in addition to the social and economic repercussions[5]. If calculations include direct costs (medical and pharmacological), indirect costs (loss of productivity due to premature death or sick leave), and the cost of informal care by family and friends, the total European Union investment in 2018 reached 199,000 million euros. During the same period, the cost for Spain alone is estimated to have been 12,164 million euros[6]. Direct costs were 5,245 million euros, an increase on the figures for 2015[7]. Another report measuring similar, broader, categories estimates the national cost at 19,300 million euros, of which 45% was met by families and patients[5].

According to the latest available data for Spain (2008-2013), mean 5-year survival is around 60%[8]. This is higher for women since, among other factors, some of the tumours with the highest incidence and worst prognosis, like lung cancer, are more frequent among men 8. Compared to the previous period, overall survival improved and, while extremely high for some cancers, such as thyroid or prostate, for others, like pancreatic, oesophageal, liver and lung, it remains low[8].

To tackle this challenge, The European Commission launched its Europe's Beating Cancer Plan[9], which runs until 2030 and has a budget of 4000 million euros. The Horizon Europe programme mission devoted to the disease will organise the corresponding research[10]. In Spain, the National Health System's Cancer Strategy, which began in 2006, was updated in 2021[2]. The same year saw the launch of the Strategic Project for Recovery and Economic Transformation (PERTE, in Spanish) focused on state-of-the-art health[11].

Prevention, a key tool

It is estimated that 44.4 % of tumours and the associated costs could be prevented by limiting risk factors[12]. Likewise, prevention programmes can reduce mortality by a third[13].

Prevención para disminuir la incidencia

The European Code Against Cancer[14] identifies twelve ways of reducing risk. These include not smoking any type of tobacco, maintaining a healthy weight, being physically active, following a diet rich in fruit and vegetables, and limiting consumption of red meat, processed foods and refined sugars, avoiding alcohol, and avoiding overexposure to the sun. The code also recommends protecting ourselves from cancer-causing substances in the workplace and taking measures to reduce exposure to the gas radon, which is found at high levels inside buildings in several Spanish provinces[15,16]. Estimations attribute responsibility for 2-5 % of work-related cancers with the presence of cancer-causing substances in the workplace[17]. Among these substances are asbestos, forbidden in Spain since 2002[18], respirable crystalline silica, and hardwood dust[19].

Worldwide, the most prejudicial factor for both sexes is tobacco consumption, followed by alcohol and a high body mass index[12]. If exposure to risk factors were reduced, lung, oral cavity and oesophageal tumours would potentially be avoidable in 90% of cases, and in 75% of stomach cancer and melanoma, with figures between these for other types of tumour[23].

Hormone Replacement Therapy: treatment with drugs, mainly oestrogens, to relieve the symptoms of menopause.

In addition, among the protective factors the European Code Against Cancer highlights are breastfeeding, limiting the use of hormone replacement therapy, and vaccination against oncogenic viruses like the human papillomavirus (**Key point 1**) or hepatitis B[14,22].

Vaccines are currently in development against other oncogenic viruses, like Epstein-Barr[24,25], which figure in the aetiology of approximately 1.5% of cancer cases, as well as other diseases[26].

Key point 1. The vaccine that could eradicate cervix cancer.

In 2008, Harald zur Hausen was awarded the Nobel Prize in Physiology or Medicine for his discovery of the human papillomavirus. This sexually transmitted virus is the cause of almost all cases of cervical cancer and is related with others, like anal or head and neck cancer[20]. Since the introduction of this vaccine over a decade ago, both precancerous lesions and incidence have reduced, particularly among girls who were vaccinated at 12-13 years. In countries with vaccination, cervical tumours have disappeared in women born after 1995[21]. The vaccine will also be administered to boys aged 12 years in Spain from 2023.

Early detection among populations at risk

The likelihood of successful treatment for a tumour increases when early diagnosis exists[28,29], which highlights the importance of establishing detection and screening programmes for the populations at risk.

In Spain, the National Health System (NHS) has offered screening programmes for breast, and cervix cancer since 2006. Currently, eight of every ten women have had a mammogram or a cervical smear test within the recommended intervals[30].

Since 2014[2], the Spanish NHS has had a screening programme for colorectal cancer, which consists of detecting small amounts of blood in a stool sample. Patients who test positive undergo a colonoscopy to identify the origin of the bleeding and confirm or rule out pre-cancerous lesions or cancer. Despite the fact that this disease has a higher incidence in Spain than the European average[2], and that it is the second most lethal cancer[1], only two in every ten people between the ages of 50 and 70 have had a faecal occult blood test[30] and notable differences exist in these figures for each autonomous community[31].

Additionally, since 2014, the Spanish NHS has offered a genetic counselling service to assess the risk of hereditary tumours (5-10% of the total) for people with a family history[2].

According to the findings of the recent report of the consortium, Science Advice for Policy by European Academies (SAPEA), all of these screening programmes could be improved. The consortium's recommendations include starting mammograms at 45 years and using magnetic resonance imaging (MRI) for women with dense mammary tissue, for which mammograms are less sensitive[29]. To prevent cervical cancer, directly testing for the presence of the human papillomavirus is advisable, as the test is extremely sensitive and offers up to six years protection[29]. The frequency of colon cancer screening could be optimised depending on sex, age and the results of previous tests[29]. And, for early diagnosis of prostate cancer, it would be useful to introduce the PSA test, which detects levels of the protein prostate-specific antigen in blood, followed by other filters or tests to reduce overdiagnosis and overtreatment[29].

Additionally, the SAPEA report mentions two large-scale randomised clinical trials, one Dutch-Belgian and the other in the United States, which indicate that lung cancer screening with low-dose computerised tomography reduces mortality in this disease[29] (**Key point 2**).

Key point 2. Lung cancer screening.

The NEderlands Leuvens Screening ONderzoek (NELSON) trial, with sufficient statistical power in men 2, detected 60% of cancers at the early stage, compared to 13% in the control group, and observed a reduction of mortality for lung cancer of 24% in men and 59% in women, eight years after the start of the study[29,36]. Prevention guidelines in the United States recommend the introduction of annual screening for adults between the ages of 50 and 80 years who have a 20-pack year smoking history (which corresponds to having smoked one packet a day for 20 years, two packets a day for ten years, or the equivalent). The trial included smokers and ex-smokers who had stopped smoking at least 15 years previously[37]. These trials propose using low dose **computerised tomography (LDCT)**, which irradiates less than traditional CT[29]. No tobacco census exists for Spain, and it is difficult to identify the target population for this type of screening[2]. There is also the belief that there may be false positives or a complicated follow-up for suspicious lung nodules. While the SAPEA report recommends introducing screening[29], other health technology assessment agencies disagree and believe that the supporting evidence is insufficient[2,38]. Lung cancer is currently the third most frequent, and is notably the most lethal, in terms of survival[2]. The European Commission's proposal for a Council Recommendation already advises this type of screening[32], which the United Kingdom has just approved[39]. Experts consulted for this report recommend initiating a pilot programme in Spain, like those of other European countries[29].

Computerised tomography (CT): technique employing a beam of X-rays that spins around the patient to obtain sections that are subsequently processed by computer to obtain a 3D image.

The recent European Commission proposal for a Council Recommendation advises increasing screening to prostate, lung and gastric cancer[32]. For gastric cancer, the recommendation is aimed at regions with a high incidence and mortality for stomach cancer. Screening consists of detecting the bacteria Helicobacter pylori, and controlling pre-cancerous lesions. Chronic infection from this pathogen, considered a group[1] carcinogen, causes ulcers and in some cases cancer, but is possible to eliminate with antibiotic treatment[33]. Spain has a mid to low incidence of gastric cancer compared to other European countries[34], although some inland areas have higher rates[35].

Likewise, the development of new screening and early diagnosis procedures and technologies is a priority of the EU Cancer Mission[10]. New methods exist that attempt to simultaneously identify different types of tumours. To do so, they examine markers in blood or other fluids where DNA, proteins or cancer-causing cells circulate[40-43]. Although promising, the sensitivity of such technologies needs to improve tenfold to be able to detect initial-stage tumours[29].

Towards precision diagnosis

Cancer can be detected with methods to explore organs or their activity (imaging methods), with more precise characterisation after the analysis of tumour cells. The following are some of the most important diagnostic methods used in oncology.

Imaging

Positron emission tomography (PET): a medical imaging technique that provides information about the metabolic activity of tissues. Most PET scans use an injection of the radioisotope fluorine-18. In recent years, research has facilitated the development of new specific radiopharmaceuticals to follow-up particular tumours

Computerised tomography (CT) or MRI offer information about the anatomy of lesions. The difference is that MRI produces more detailed images and does not irradiate, unlike CT, which uses X-rays[44,45]. **Positron emission tomography (PET)** is another tool that provides metabolic information about cellular activity[46]. Tumour cells consume great amounts of glucose, and the technique uses this fact to highlight lesions in contrast to healthy tissue[46]. PET scans are high resolution and allow differentiation between lesions smaller than 1 cm, which enables detection of tumours or dissemination at early stages[47]. This technique is usually used in conjunction with CT to combine anatomic and metabolic information.

In Spain, the Plan for Investment in Healthcare High-Tech (known as INVEAT) promoted by the Ministry of Health through the Plan for Recovery, Transformation and Resilience (PERTE) aims to renew the equipment used in diagnostic test systems for imaging, which at present are mostly obsolete and have lost resolution[48,49].

Towards precision anatomic pathology

Anatomic pathology services study and diagnose based on biopsies and cytology. A two-coloured tissue staining is a basic technique in the microscopy diagnosis of tumours[50,51]. It is a cheap (10 cents of a euro) and informative method when an experienced pathologist interprets the results. It provides information about whether the tissue is a tumour, if it is malignant, the tumour type and whether it has spread to other parts of the body[52].

Digitising anatomic pathology samples using a scanner helps reduce diagnosis time, exchange information, images and opinions, view results, promote cooperation and reduce differences of opinion [53]. Along with genomic information and imaging, digitisation of samples will form the basis for future applications of artificial intelligence in diagnosis supervised by clinicians[54-58].

Therapeutic target: the molecular target that a drug or therapeutic strategy acts on. For instance, a drug may inhibit a protein with cancer-causing mutations.

Immunohistochemistry: a laboratory method that uses antibodies to specifically detect certain elements in a sample.

DNA sequencing: a laboratory method to determine the order of components (nucleotides) in DNA, in a more efficient and cost-effective way than traditional sequencing. In diagnostics, it allows determination of cellular DNA

On the other hand, to specify the type of cancer and identify **therapeutic targets**, complementary techniques such as **immunohistochemistry** and **DNA sequencing** may be used. Sequencing is interpreted by personnel who are experts in pathology, genetics or molecular biology. It represents a key tool in precision medicine against cancer and seeks to identify molecular alterations for the selection of more precise, effective treatments, with better outcomes and fewer side effects. An extensive molecular study enables determination of the optimum treatment for each patient, which is essential in some types of cancer[59-62] (see "Targeted therapies" and "Access to innovation" sections).

Another recently used technique is liquid biopsy for the non-invasive analysis of molecular alterations in fluids like blood[63]. This procedure is employed in addition to a traditional tumour biopsy, and when little material can be extracted from the tumour.It is particularly useful to track response to treatment, understand how the disease becomes resistant to therapy, and detect residual disease or relapse[64,65].

Treatments

Patients usually undergo a combination of therapies. As a first step, if the tumour is operable, there is an operation to remove it. Of additional treatments, some of the most successful and frequently used are chemotherapy and radiotherapy[66], whose cytotoxic capacities eliminate tumour cells. The problem with chemotherapy is that, despite its efficacy, it has little specificity[67] and causes major side effects (fatigue, nausea, vomiting, temporary hair loss, anaemia, infections, fertility problems, etc.)[68]. Likewise, conventional radiotherapy damages neighbouring tissue and could increase the risk of developing new tumours in the irradiated area[68].

The following sections describe current advances in radiotherapy and the newest treatments, such as immunotherapy and targeted therapies.

Radiotherapy

Used to treat cancer since 1903[69], over 40% of patients with neoplasia receive radiotherapy at some point during their treatment[70-72]. It may be prescribed as a cure to eliminate the tumour or palliatively, to alleviate symptoms derived from tumour growth at advanced stages of the disease[73]. In recent years, advances in the technique have aimed to improve the specificity and efficacy of treatment and reduce toxicity. On the one hand, planning has been optimised. This uses CT imaging, acquired with the patient in the same position they will adopt for the treatment itself. The images are used to define tumour location and volume, its relation to neighbouring organs and any movement due to breathing or the internal displacement of organs. On the other, technological progress in dosimetry provides a more precise dose, which increases treatment efficacy and safety[73]. One type of treatment is proton beam therapy, which uses protons rather than photons as its source of radiation (**Key Point 3**).

Clinical trial: experimental assessment of a drug or medical procedure that aims to determine whether the treatment being tested is safe and more effective than the available treatments. After animal testing to ensure the drug is safe, the medication is tested on healthy humans (phase I) to ensure its safety. Phase II consists of tests on patients to verify efficacy. Phase III is similar to the previous one but includes a larger group of patients. Phase IV provides further information about how the pharmaceutical works in a much larger population

Key point 3. Proton beam therapy.

Protons allow concentration of radiation on the tumour and conserve the surrounding tissues better, which reduces the risk of sequelae, of causing other tumours[70] and of serious side effects[75]. **Clinical trials** are under way to obtain scientific evidence that proton beam therapy is more effective than conventional radiation in different tumours among adults[76, 77]. However, since there is evidence that it is safer, there is broad consensus indicating its use in paediatric cancers, particularly those that affect the central nervous system, and in adults for tumours close to the base of the cranium or of the spinal cord[73]. Moreover, as it is less aggressive, it is possible to irradiate more times if the tumour reproduces[78]. This technique not only requires an investment in equipment, but also the construction of specific facilities[76]. In addition to the two accelerators that already exist in private hospitals in the Community of Madrid[80], the Amancio Ortega Foundation has donated 10 proton beam therapy particle accelerators to the NHS[79]. There is also another proton beam therapy project under way in Cantabria[81].

But radiation can also be used internally, as occurs in brachytherapy, in which sources of radiation are placed in the tumour or tissue where the tumour was found. This is an extremely specific technique because radiation rapidly declines with distance, thus preserving neighbouring organs[74]. It also shortens treatment duration. Unlike other forms of radiotherapy, this technique is usually surgical and may require anaesthesia[74]. At present, Spanish technical equipment resources are updated by means of the INVEAT plan and private sector donations. Even so, regular planned renovation of obsolete radiotherapy equipment is advisable for several reasons. First, despite being a cost-effective therapy, acquiring new equipment requires a substantial initial investment. Moreover, its installation and staff training may involve closure of the service for several months and the transfer of patients to other treatment units[73]. Another factor to consider is that in order to increase treatment adherence, specialists suggest that there should be a reduction in the distances patients have to travel to receive conventional radiotherapy treatment[73].

Immunotherapy

The immune system eliminates foreign elements including pathogens and cancer-causing cells from the organism[82-83]. To form a tumour, mutated cells have to evade the body's immune system defences. The approach of immunotherapy consists of strengthening different components of the immune system so that they recuperate their ability to recognise and effectively attack cancer[84].

Today, immunotherapy has revolutionised oncology with treatments that significantly prolong patient survival for certain types of cancer for which, until recently, no effective alternative existed[83]. Nevertheless, a high percentage of people do not respond to the therapy or only do so temporarily, currently making it difficult to predict which patients this therapy will be effective for[85]. Although it is less toxic than other conventional therapies, immunotherapy may generate autoimmune reactions of varying severity 86,87. **Key point 4** describes the main immunotherapy treatments.

Targeted therapies

Some changes in the sequence of specific genes (genetic mutations or rearrangements) cause cells to become cancerous. Targeted therapies take advantage of the differences between healthy cells and tumour cells to selectively act on the diseased ones. Thus, this therapy reduces the toxicity of treatment and tackles cancer more effectively61. These therapies require an exhaustive knowledge of the tumour's molecular biology before they can be applied, along with a precise diagnosis that identifies the dominant mutations[106,107] (see "Towards precision anatomical pathology" and "Access to innovation" sections).

Today, the increased efficacy and safety of targeted treatment compared to conventional therapies, and greater knowledge of the molecular basis of cancer have been key for the inclusion of these therapies in clinical practice[106]. However, this therapy is not always effective and may only work temporarily. In time, resistance appears, which requires other approaches or its use in combination with other treatments[107,108]. A precision attack on the tumour may be performed using antibodies or with selective drugs[109].

Antibodies recognise tumour cells and induce their death[108,110]. Although certain antibodies have little anti-tumour effect on their own, their specificity is used to aim other drugs at the tumour[108]. They may be combined with chemotherapy medication, with specific inhibitors of cancer-causing cells or with radiopharmaceuticals (**Key point 5**), all of which have the capacity to eliminate cells. Anti-tumour antibodies are prescribed above all in cases of

lymphoma, breast cancer or colorectal cancer[110].

Secondly, targeted drugs are principally inhibitors of the gene mutations that initiate and maintain tumour progression. Dozens of molecules have been approved in the last 20 years, including some notably successful cases, even for proteins that it was not thought possible to inhibit[106,111]. Nevertheless, many genes that frequently appear with mutations are not yet susceptible to effective therapeutic intervention. Promising therapies based on new mechanisms are currently at the pre-clinical phase of development[112].

Key point 4. Main immunotherapy treatments

Immune checkpoint inhibitors (ICI)

To avoid attacking healthy tissue, the immune system has developed mechanisms that distinguish healthy from cancerous cells and pathogenic microorganisms[88]. Before attacking, T cells check the nature of the suspicious cell, analysing the proteins on its surface. Malign cells use this checkpoint mechanism to make themselves invisible to the body's defences and produce proteins that slow down immune response[89]. This is where ICIs come into play; these antibodies function as a barrier, blocking the interaction of T cells with the inhibitor proteins produced by the cancerous cell. This allows the T cells to activate and eliminate tumour cells. The first drug of this type was approved in 2011, and currently the European Medicines Agency has approved several others[90,91]. They have been used to combat many types of cancer including early and advanced-stage solid tumours. One of these drugs has given 30% of patients with advanced melanoma a survival of over 5-years[89,92].

Cell therapy

Whereas ICI do not require personalisation, cell therapy uses the cells of each patient and requires more costly facilities to process them. In chimeric antigen receptor cell therapy (CAR-T), T cells extracted from the patient are genetically modified to express a protein (receptor) that will specifically recognise the tumour and enable its destruction[93]. This therapy has achieved 10-year complete remission among patients with blood cancers and cured certain cases of leukaemia[94]. Since 2017, five CAR-T medications have been approved to treat leukaemia, lymphoma and myeloma although, due to its difficulties, this method is still only a last resort[95]. In Spain it is funded by the NHS[96], does not require multiple applications, and has a good, though variable, response percentages[97]. Another type of cell therapy, tumour infiltrating lymphocytes (TIL), targets solid tumours. The immune system's lymphocytes that are found in the tumour can recognise the disease, but their capacity to eliminate it is inhibited by the tumour itself. TIL therapy consists of isolating them from the biopsy, selecting the lymphocytes that recognise the specific mutations of the tumour and expanding these populations before returning them to the patient[99,100]. Although still at an experimental stage, this treatment shows promising results[101,102].

Vaccines

In oncological treatment, the objective of vaccines is to awaken the immune response to cancer. Although this idea has been worked on for many years, its clinical efficacy is considerably lower than other immunotherapies[103,104]. The latest generation of vaccines is based on the injection of genetic material (mRNA) which is translated into tumour proteins once injected into the patient[105]. Several pharmaceutical companies are testing various products at phases I-III.

The preventive use of vaccines is also under investigation. They are being tested in healthy subjects who have hereditary mutations that increase their risk of developing the disease[103].

Key points 5. Radioligands

Tumour cells have some surface molecules that the other cells of the body do not. Radioligands use this property to supply radiation specifically to the cancer-causing cells. On the one hand, the ligand (for instance, an antibody) locates the tumour, recognising specific molecules. On the other, the radioisotope joined to the ligand can supply the radiation that will cause the death of tumour cells[113]. This targeted therapy treatment is potentially useful at late stages as it can treat multiple tumour locations simultaneously. It is currently indicated for inoperable gastroenteropancreatic neuroendocrine tumours[49,114]. This therapy has also been tested in cases of castration-resistant prostate cancer with bone metastasis, with an observed increase in patient survival and quality of life[115].

Radioligands can also serve for diagnosis and treatment (theragnostic use). The ligand can be combined with radiopharmaceuticals for PET-CT diagnosis (see "Imaging" section) or with tumoricidal radiation-emitting radioisotopes. This technology enables characterisation of the disease and assessment of the response to treatment in a precise, personalised way[116,117].

Planning is essential to cover the potential increase in demand when radioligand treatment becomes indicated in the highest-incidence tumours (prostate, breast, lung). Experts have reached a consensus on a series of recommendations for increasing infrastructure and training the professionals necessary to guarantee this service[49].

European objectives

Europe's Beating Cancer Plan 9 details several objectives for member states, among which are:

Comprehensive Cancer Centres

To ensure patients have access to quality-assured diagnosis and treatment, and to reduce inequalities of access between member states, the European Commission plans to establish networks of Comprehensive Cancer Centres (CCC) by 2025[9,118]. The objective is that 90% of patients have access to CCC by 2030[9].

These CCC are autonomously governed organisations that, on one site, provide cancer patient care (diagnosis, treatment and follow-up), research (clinical, translational and basic) and training for clinicians, researchers and patients[119]. They may be centres that focus on a single type of cancer or autonomously governed organisations within general hospitals.

Their chief characteristic is that they treat a large number of diverse cancers, adopt new therapies at early stages, standardise treatments and patient circuits, have greater access to multi-disciplinary consultation and can easily access clinical trials within the centre. All of these characteristics correlate with a more favourable patient outcome[120].

The requirements that CCC must fulfil have been defined by the accreditation programmes of the Organisation of European Cancer Institutes (OECI), the National Cancer Institute (NCI) in the USA and the Deutsche Krebshilfe in Germany[120]. Although the European Commission recognises OECI accreditations, there is no official EU accreditation. Other oncological societies offer certifications with different meanings and differing requirements[121,122].

Ten European Union member states, including Spain, have no centres recognised as CCC by the aforementioned organisations[119,123], although the Vall d'Hebron University Hospital is currently undergoing the OECI accreditation process. Our country already has one centre recognised as a Cancer Centre (CC), the Valencia Institute of Oncology (Instituto Valenciano de Oncología). This certification requires a lower degree of research than that of a CCC[124].

However, even without the certifications mentioned above, there are many oncology services in Spain that offer single-site diagnosis, treatment and research. This allows treatment of large numbers of patients in a multi-disciplinary, comprehensive way, which improves survival[125-133].

For more complex, rarer cases, the Ministry of Health has designated Reference Centres, Services and Units (CSUR, in Spanish) with the aim of concentrating patients around multi-disciplinary specialist teams working in a network[2].

On the other hand, since cancer is increasingly a chronic disease, with patients under continuous or intermittent treatment, there is also an increase in the symptoms and sequelae derived from the therapies themselves[123]. For instance, pain is prevalent among 60-70 % of advanced cancer cases and stands at 46-65 % throughout the course of the disease[134]. To improve people's quality of life, some evidence suggests the positive effects of integrating palliative care from early stages of the disease rather than just in its final stages[123, 135,136].

Access to innovation

Biomarker: a biological characteristic of the body that can be measured and objectively quantified.

Characterising a tumour at molecular level enables precise diagnosis and, therefore, the definition of therapeutic targets, prescription of more effective treatments with lower toxicity, avoidance of ineffective therapies, and a survival prognosis[137]. To achieve characterisation, the status of specific genes and proteins in the tumour (**biomarkers**) is analysed to discover its mutations and characteristics, and design the most suitable therapy (see "Towards precision anatomical pathology" and "Targeted therapies" sections). Molecular diagnostics therefore represents the key to accessing specific treatments and improving survival[62,138,139].

At present, the catalogue of biomarkers that received Spanish NHS funding approval in 2014 focuses on genetic diseases, and the different types of cancer are under-represented[140]. There are also notable differences between the different autonomous communities, and even between hospitals, with pharmaceutical companies playing a decisive role in funding[141]. Specialists call for an extensive, single, national portfolio that is kept up to date[141].

Another tool to analyse genetic anomalies is cancer genome sequencing. This enables the simultaneous analysis of the status of many genes. In services that have a large enough concentration of patients, this technique also saves time, costs, and tissue compared to the analysis of individual genes[142]. Although there is recognition of the need to introduce precision medicine in Spain, how this should be done within the health system has not been defined[2]. Access is not the same in each region: in 2019 the autonomous communities of Andalusia, Castile and Leon, Catalonia, Galicia and the Basque Country had advanced most in the introduction of precision medicine in healthcare, including the field of oncology 143-143. Gene sequencing panels are currently only included in the portfolios of the Cantabrian and Catalan Health Services. These autonomous communities have designated reference centres to centralise testing and guarantee quality[145,147].

At a national level, according to a European Federation of Pharmaceutical Industries and Associations (EFPIA) report, access to biomarker analysis in Spain is at an intermediate level compared to other European countries[148].

In order to promote new techniques, it is vital to count on expert personnel in the fields of molecular biology and bioinformatics within the hospital system, and to train medical students in molecular biology and research. There is also a need to generate infrastructure to store genomic data, extract information efficiently and share it between parties in a secure way 9. Data science is one of the central points of the Infrastructure of Precision Medicine

Associated with Science and Technology programme (known as IMPaCT in Spanish)[149].

Another challenge is the time that passes between the approval of cancer medication by the European Medicines Agency and the date when it becomes available for patients. According to the EFPIA's Waiting to Access Innovative Therapies report, based on 2017-2020 data, Spanish patients wait an average 469 days before an oncological medication becomes available on the NHS[150], 56 days more than in 2016-2019. According to the Ministry of Health, which divides the process into phases with data from the last five years, the mean time is estimated at 415.98 days[151]. This is a complex process, and one which is not the same in all European countries. The fastest country, Germany, takes a mean 100 days, whereas in Romania, the slowest, it can be 964 days. Spain occupies the 16th position of the 35 countries analysed[150]. Other countries such as France have mechanisms to accelerate the availability of key medication. In the United Kingdom there is a fund to finance promising medicines while scientific evidence is compiled[152].

Another factor to consider is the cost of oncological medication, which has increased considerably. In addition, the approval of international agencies does not always follow the criterion of high clinical benefit, which means that a treatment substantially improves patient survival or quality of life[153,154]. To achieve a sustainable system, recommendations are to finance cost-effective therapies that enable the patient to live longer, better or both[155].

Spain occupies one of the top positions in attracting clinical trials[156,157]. These are mostly sponsored by pharmaceutical companies [156], although there are also trials developed by researchers or cooperative groups. Trials are an opportunity to access innovative treatments before they receive approval.

Paediatric cancer

One of the Europe's Beating Cancer Plan objectives is to better protect children and young people from cancer[9]. In the European Union, 15,500 children and adolescents are diagnosed with some type of malignant tumour each year. In Spain, 1,100 minors under the age of 14 are diagnosed with cancer annually[158]. Despite the fact that these are infrequent diseases, they are the highest cause of death among children under the age of one, and the first cause of non-traumatic death in infancy 9,159.

The causes of infant cancer are not clear, except for the 5-10 % of cases with a genetic origin or those caused by ionising radiation[159,160]. Most cases are considered sporadic, random events that are not currently preventable[161]. So early detection of the first signs and symptoms by primary care paediatricians plays an essential role[162].

Paediatric tumours are different to those of adults. They usually have their origin in a different type of cell[163,164], are more sensitive to chemotherapy and radiotherapy, have a mutation rate 14 times lower, and only 45% of DNA alterations coincide with those of adult tumours. The other 55% are specific to paediatric tumours[165-167]. These differences highlight the need to consider paediatric cancers as a separate entity[9] and develop concrete treatments based on the specific molecular alteration and not on patient age[168].

Although there is no single registry of tumours in adults, the Spanish Registry of Childhood Tumours, RETI-SEHOP[158], which compiles data from all paediatric oncology and haematology units, currently has close to 100% coverage[158]. Overall, 5-year survival of affected children increased 23 points in Spain between 1980 and 2004, reaching 77%[158,161], almost as much as the European average, but lower than the figures for Central Europe[169]. In recent years, this increase has slowed down, reaching 82% in 2022, in line with other developed countries[158]. Meanwhile, several types of cancer, above all those affecting the central nervous system, have modest survival rates throughout Europe[169].

Approximately 60% of survivors will have at least one long-term sequela derived from the cancer or its treatment, which may affect their growth, development and maturation[170,171]. In addition, thirty years after diagnosis, four out of ten survivors suffer severe, incapacitating or fatal sequelae[9,171,172]. The follow-up model for long-term survivors of childhood cancers is not yet defined, although there have been initiatives to compile clinical data whilst conserving privacy[9,171].

In this context, the objective of paediatric oncology units is not only to cure but also to cure better, to increase survival and minimise sequelae. Many studies indicate that children and young people treated in hospitals with a large volume of patients, more resources and higher specialisation have longer survival and fewer later complications[173-176]. On the other hand, to gain sufficient clinical experience, a paediatric healthcare unit should receive a minimum of thirty new patients a year[162], a condition met by 12 of the 43 existing units of this kind in Spain[161]. The creation of specific units for adolescents and young adults, separate from paediatric ones, would be advantageous in environmental, psychological and social terms. The low number of cases makes this measure difficult to introduce[161].

Towards the future: state-of-the-art research

Genomics has heralded the multiplication of targeted therapies[106,111,177,178], but there is still a long road ahead before cancer is understood at molecular level. In many cases, science does not know the genes that start the tumour or how the mutation's relevance changes in different organs. There are also some low frequency mutations that have not been studied in depth[107]. To date, characterisation of cancer has analysed whether the dominant mutations are present or absent. However, it may be necessary to consider a wider set of mutations in order to better predict the behaviour of a given tumour [179,180].

Another obstacle for researchers is the heterogeneity of tumours. The cells that constitute them are not identical in genetic or molecular terms and present a different response to treatment[181]. Current attempts to understand this variability seek to overcome the resistance to treatment that enables the cancer to reproduce.

As advances have given a better understanding of cancer cell genetics, there has been a change in paradigm which has presented many therapeutic opportunities; researchers are broadening their focus and seek to understand cancer in its context. This implies knowledge of how a tumour relates with its surroundings, both the cells that surround and

support it, and the rest of the body as a whole[182–185].

On the one hand, tumour cells are very plastic and have a great capacity to change their properties, adapt to the cellular atmosphere and avoid treatments[65], but the mechanisms that confer this plasticity are not yet known in depth[186]. It is also the case that some neighbouring cells may favour the progression of cancer[187]. Modulating the immediate environment of cancer-causing cells may increase the efficacy of treatments like immunotherapy. In this field, the factors that favour the effectiveness of treatment need to be discovered[188]. Work is also being done to broaden the therapeutic arsenal and components of the immune system beyond T cells, and in using cells of compatible donors[83,97].

The human microbiome: bacteria, virus, fungus and other forms of life that interact with the organs of the body they inhabit. Among other areas, there are studies into the influence of the microbiome in treatment response or as a tool for the early detection of cancer.

As well as systemic immunity, research is also investigating how the metabolism[182–192], stress[193] or the **microbiome**[194,195] impact on the development of the disease and response to therapy. In the case of the metabolism, one of the strategies is precision nutrition, which has been tested in mice. This consists of first analysing the genetic details of the tumour and then determining the nutrients that should be temporarily eliminated so as to optimise the prescribed treatment[189,190].

Regarding treatment, the professionals consulted indicate a need to progress in basic and clinical research in radiotherapy, and research more minority tumours such as childhood cancers.

Metastasis is another key area of research: although it is responsible for 90% of cases where death is due to cancer, the biological processes are not known in detail[196]. The cells that form metastases are capable of surviving the journey to other organs, remaining dormant for long periods of time whilst avoiding detection by the immune system, coercing neighbouring cells and, finally, reproducing the tumour with tissue regeneration mechanisms[197]. Discovering their properties and vulnerabilities is essential to develop new prevention strategies and treatment[197], some of which are already being tested[198].

The basic research undertaken in Spain is outstanding. Even so, in order to maximise results, experts recommend increasing resources, establishing research priorities, and reinforcing the transfer of innovation to the patient[156].

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Oficina C Team (in alphabetical order)

Ana Elorza*. Oficina C Coordinator at the Fundación Española para la Ciencia y la Tecnología.
Izaskun Lacunza. Oficina C Coordinator at the Fundación Española para la Ciencia y la Tecnología.
Maite Iriondo de Hond. Scientific and Technological Evidence Officer
Rüdiger Ortiz-Álvarez. Scientific and Technological Evidence Officer
Sofía Otero. Scientific and Technological Evidence Officer
Jose L. Roscales*. Scientific and Technological Evidence Officer
Cristina Fernández-García. Scientific Community and Society Connections Office

*contacts for this report

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