Critical Appraisal: Cancer

Andalusian School of Public Health (Escuela Andaluza de Salud Pública, EASP)

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Mapping Chronic Non-Communicable Disease Research Activities and their Impact
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Abbreviations

CA	Critical Appraisal
COPD	Chronic Obstructive Pulmonary Disease
CRD	Chronic Respiratory Disease
CVD	Cardiovascular Disease
EASP	Escuela Andaluza de Salud Pública
IARC	International Agency for Research on Cancer
ECRM	European Cancer Research Managers Forum
EU	European Union
EUR	Europe
FDA	Food and Drug Administration
FP6	Framework Programme
FP7	Framework Programme
HTA	Health Technology Assessment
LSE	London School of Economics and Political Science
MD	Medical Device
MS	Member States
NCD	Non Communicable Disease
OECD	The Organization for Economic Co-operation and Development
ONCOL	Oncology
RFO	Research Funding Organization
US	United States
WHO	World Health Organization
WCRF	World Cancer Research Fund
WP5	Work Package

Executive Summary

Cancer is among the leading causes of morbidity and mortality in Europe, with an estimated 3.45 million new cancer cases (excluding non-melanoma skin cancer) and 1.75 million deaths from cancer in 2012. In the future, the burden of cancer will become higher. Today, Europe as a whole is working together in the area of cancer policy initiatives and research in order to understand the underlying causes of cancer, to ensure the improved management of this disease and to study its social impact.

Across Europe, the EU and its MS have mainly supported research on dissecting the causes and mechanism of cancer, translating this basic knowledge into clinical applications and supporting clinical research on new and improved interventions. Other issues related to cancer have been also covered, but have received a considerably lower attention (e.g. cancer control, prevention, patient care, etc.). Thus, room is left for cancer research aimed at improving existing treatments as well as studies of the organization of care, and methods to enhance quality of life and prevention.

The European pharmaceutical sector has five companies in among the world's top ten pharmaceutical firms. The research pipeline for the top 10 European pharmaceutical companies suggests that firms seem to specialize in certain NCD categories. For example, pipeline data shows that NOVO-NORDISK, preferring to focus on other areas, does not have any CANCER relevant molecules under development; other firms like NOVARTIS or ROCHE, however, are developing several.

Overall, the European pharmaceutical sector has increased its commitment to R&D over the past four years. GSK is the only top 10 company to record a shrinking commitment to research investment. Some companies, like AstraZeneca, have recorded a massive increase in R&D spending. But most companies have recorded progressive of steady increases. By contrast, US levels of investment in R&D have been more mixed.

Interviews with stakeholders revealed several major themes with regard to the future of research in the area of Cancer. In the main, researchers find funding very complex and limited. They hold that most funding focuses on basic research which although it has an impact in the academic research of Europe, it also limits the capacity to compete with US. Researchers are concerned about lack of funding for independent clinical studies and a lack of independent funding sources.

Cancer is the first leading cause of lost DALYs across Europe in terms of NCDs (17.68 %). Breaking down the category into its major diseases, Leukaemia is the largest cause of lost DALYs by comparison with Kidney. In the past few years, research investment in Cancer was well adjusted to reflect their relative burden.

In terms of the effectiveness of research investment, Cancer funding is among the top three with an average of 38% of paper published for Cancer are of European origin, behind RESPI(56%) and CARDI (42%). According to the results in Europe, Cancer is a big subject area, averaging 11.5 % of the papers in biomedicine overall. Cancer research represents just over one ninth of all European biomedical research output, but one eighth of world biomedical output.

Germany has the highest output in terms of Cancer papers, highlighting that genetics is the dominant research type, followed by chemotherapy, prognosis and surgery. On the other hand, Malta is publishing very little and Germany, Italy and UK are the ones most publishing in cancer research, being correlative within is level of GDP.

1 European Research Programs

Cancer is among the leading causes of morbidity and mortality in Europe, with an estimated 3.45 million new cancer cases (excluding non-melanoma skin cancer) and 1.75 million deaths from cancer in 2012 (Ferlay et al. 2013)[1]. In the future, the burden of cancer will become extremely higher. The European Commission became soon aware of the cancer problem and made a strong commitment to support cancer research at the UE-level through the different Framework Programmes. Today, Europe as a whole is working together in the area of cancer policy initiatives and research in order to understand the underlying causes of cancer, to ensure the improved management of this disease and to study its social impact.

Europe has a long tradition of funding cancer research at the national and at the European level. The ECRM surveys and our previous Impact Assessment Report have highlighted various differences in the funding scheme and funding priorities of the Member States (MS). Indeed, despite the majority of public funding in cancer research being concentrated in public funding organizations (41% public and 7% private-public sectors), each country has its own funding system. The priorities set for cancer research funding generally matches the ones set by the EU Frameworks Programmes. As regards the EU level, within the Sixth Framework Programme (FP6; 2002-2006), for example, cancer-related research was attributed a budget of approximately €450 million. Whereas in the previous 5th Framework Programme (1998–2002) cancer research focused mainly on molecular mechanisms underlying the disease, the 6th Framework Programme implemented a patient-oriented, ‘‘translational’’ research approach, aiming at bringing basic knowledge into medical practice more rapidly. This translational concept was also applied in the 7th EU Framework Programme (FP7; 2007-2013) (Jungbluth et al. 2007)[2]. The total EU funding for cancer research in the FP7 Cooperation Programme, taking into account all cancer-related projects, including not only the thematic "cancer" area but also other areas, i.e. diagnostics, nanotechnology, etc. is estimated to be over EUR 500 million.

1.1 Summary of RFO Research Projects

This section presents a selection of 139 cancer research projects (a purposive sample) at national levels (MS) and EU-level, with the aim to provide a general description of funded research programs/projects in cancer across the EU. For the EU-level, the selection was based on the first three calls for proposals launched in the FP6 (Thematic Priorities: Life sciences, genomics and biotechnology for health, as well as in the FP7 (under the thematic "cancer" area). For the MS-level, the main research funding organizations (RFOs) dedicated to cancer research were selected.

[1] Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, Forman D, Bray F. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013;49(6):1374-403.

[2] Jungbluth S, Kelm O, van de Loo JW, Manoussaki E, Vidal M, Hallen M, Trias OQ. Europe combating cancer: The European Union´s commitment to cancer research in the 6th Framework Programme. Mol Oconol 2007;1:14-8.

In brief, the methodology followed to select these funded research program/projects in cancer was based on three parameters:

i. A time limitation of 2006-13 in order to include projects under FP-6 and because there is a large number of projects funded for the study period. Considering as time period 2006-2013 limited the sample considerably;
ii. A selection of range of RFOs in cancer across the different European Countries and the most relevant projects funded by EU or at EU Level;

In order to provide a reliable picture of cancer research funded programs/projects in Europe, those being the major research programs/projects funded were selected. Therefore, about 80% of the selected programs/projects were those funded by the EU. For the remaining 20% of the selected programs/projects, the selection was based on the amount of funding dedicated by the countrie´s main RFOs.

The variables collected for each cancer research funded programs/projects were:

- Funder: main funding organisations of research projects on European and national level. Example: EC, DG Sanco, AECC (Asociación Española contra el cancer), etc…
- Recipient: the type(s) of institution receiving the funds, n=number of partners
- Level of Collaboration: whether the research institutions involved in the project are from one country, a number of European countries, or European and non-European countries.
- Partner countries: the countries involved in the project
- Project Title: the project's name
- Research Area: the type of research, ex: prevention, diagnostic, treatment, management, policy etc…
- Project timeline: the years during which the project is undertaken
- Summary description: overview of what the project is focusing on and its objectives
- Achieved/Anticipated Outcomes: the main results achieved or likely to be achieved, ex: development of a new treatment for prostate cancer, or change in policy, etc…
- Amount of funding: the amount of funding the project received (if available)

Once this data was collected, a mixed quantitative (deriving summary statistics) and qualitative analysis was performed.

The creation of a "Purposive Sample" of European funded projects/programs involves several limitations. Firstly, this purposive sample does not strictly retrieve all the projects funded across EU on cancer. Since this would have been unfeasible, a sampling of the main projects/programs was carried out. Secondly, it was sometimes not possible to distinguish between basic and applied research projects via the database queries. Moreover, often the basic research such as microbiology and fundamental chemistry is not specifically directed to a group of cancers or a specific cancer site, but is directed towards a wide range of cancer sites and applications for treatment, diagnosis or prevention of the disease. For this reason, it was decided to not separate research projects by cancer sites.

Thirdly, the website query has intrinsic limitations related to the public availability of information. Often, RFOs do not clearly state the levels of funding for individual projects/program or do not list

research projects/programs of earlier years (the most recently funded ones were more commonly listed). For all these reason, we selected at a first stage RFOs for which information was available. However, by doing this, lack of data for some variables was still a major issue. For instance, the classification of research projects/programs into areas of research was given for some projects only. When this information was not provided, the most suitable area or field of research was assigned. Otherwise, it was specified that the information (for this or other variables) is not available.

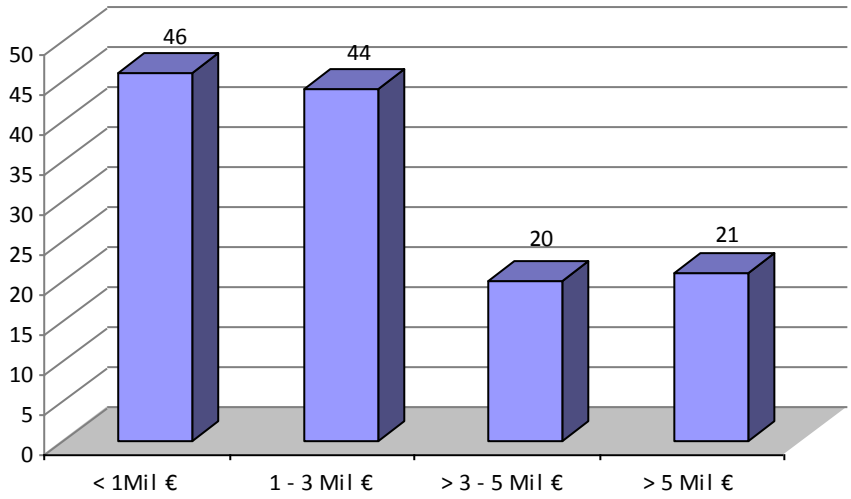
1.2 Major European Research Programs Receiving Funding

Under the FP6 (2002-2006), the EU devoted 480 million € of funding to 139 cancer research projects. A selection of 40 major funded research projects is shown in table 1. The FP7 (2007-2013) funded a similar number of projects for a total amount of over 500 million €. Further 40 research projects under this programme are shown in the same table.

Across the EU, the main research programs/projects of each MS are shown in table ii. About 2-3 research programs/projects are provided for each MS. A higher number of research programs/projects was collected for Spain and Portugal, because there are the countries for which WP5 (EASP) was responsible for the identification of RFOs and retrieval of funding activities.

Looking at the average life-time of the projects, the average life of grant is of 28 months with a minimum time of 12 months and a maximum of 60 months per project (mostly in the case of EU-funded research projects/programs). The total funding allocated to the selected research projects/programs is 278,947,893 € (2,582,850 per research project/program). The funding allocated for the majority of the selected projects (68%) was under 3 million €, whereas for a relatively smaller number of projects (16%) the funding allocated reached 5 million € (Figure i).

Figure i : Total funding allocated projects by Europe (2002-2013)



The most important area in which the RFOs were interested was in relation to the therapeutic and drug developments, specifically research areas of biology, scientific models and aetiology, whereas the health care research and economic health research are almost not existent. Indeed, a high number of projects (13% of the research projects with information available on research area) addresses genetic or cellular biology (research areas of biology), with the aim of finding the causes of chemical and biological mechanisms so as to develop new strategies in therapeutic and pharmaceutical care of cancer patients. Research into the molecular and cellular biology of cancer,

leading to major improvements in personalized cancer medicine, has also received a major attention in the past few years. For instance, EU-funded projects in this area were ANGIOTARGETING (Multidisciplinary research to explore and validate molecular targets for innovative treatments), and MOL CANCER MED (Developing molecular medicines for cancer), to name a few.

In addition, of the EU-funded projects, only six projects addressed the quality of life for cancer patients (are of Cancer control, Survivorship and outcomes research, such as the EUROCHIP project - European Cancer Health Indicator Project-III), and only a small percentage of the research projects/programs addressed the economic consequences of cancer. All EU funded projects/programs involved a consortium or multiple partners across Europe. Recipients of funding were universities, as well as the private sector and NGOs, with several partners from different countries collaborating (except one project of the private sector only, the "European Consortium for Anticancer Antibody Development"). These projects had particular relevance to the shaping of national and European policy on cancer given the larger level of funding investment involved, and the inclusion of research groups from several universities, research institutions and private companies and Charities.

MS, at national level, used to fund research projects/program of 1 to 2 years, and on an individual basis (most of the projects/programs funded were not multicenter or collaborative). Most of the RFOs (n=90%) tend to fund only 1 organization. Overall, the topics funded fall within similar research areas (therapeutic and drug development). Most of the recipients of funding were universities or research centers (around 90%), whereas the private sector and NGOs conducted research projects mainly in Northern European countries. Although private companies and charities were commonly participating as members of larger consortiums (led by universities or public research institutions), there are several research projects/programs (as stated, typically from Northern Europe) led by the private sector solely (e.g. CAMELIAT and ESCAPE, funded by the French RFOs).

In terms of the level of collaborations among RFOs of the MS, results highlighted the absence of trans-border collaboration. Indeed, all the projects were funded within the RFOs of the MS. In other words, at national level, none of the selected RFOs funded any multicentric international project. This observation may indicate a need for larger collaborations within the Ms in order to enhance the quality of research in cancer, but also to avoid duplicate efforts (funded projects by the EU and MS may have overlapping aims because similar research areas are funded).

Table i: Cancer funded research programs/projects at the EU-level (FP6 and FP7)

Funder	Recipient Type	Level of Collaboration (National – European - Global)	Partner Countries	Project Title	Research Area (focus)	Project Timeline (years)	Summary Description (Project aim)	Achieved/ Anticipated Outcomes	Amount of Funding
European Commission- FP6 projects	University, NGO, Private, n= 19	GLOBAL	FR, GER, IT, NE, SWE,UK, DK, IL	Manipulating tumour suppression: a key to improve cancer treatment	Biology	2004-2009	To ease both diagnosis and prognostic classifi cation, as well as the efforts towards novel therapy regimens to treat patients suffering from breast cancer and neuroblastoma.	To provide a basis for the re-activation of tumour suppression and the design of novel therapeutic approaches to combat cancer. In particular, we are aiming at modulating p53 family activities to decrease resistance of tumour cells to anti-cancer treatments	€ 6,000,000
European Commission- FP6 projects	University, NGO, Private, n= 14	European	GER, NE, SWE, UK, DK, LU, NOR, CZ, FI	Multidisciplinary research to explore and validate molecular targets for innovative treatments	Biology	2004-2009	The identification and validation of new therapeutic targets directed towards tumour vascularmatrix interactions.	To the identification of a number of potential targets towards the tumour vasculature.	€ 6,000,000
European Commission- FP6 projects	University, NGO, Private, n= 8	GLOBAL	GER, NE, SW, DK, AT, IL	Modulation of the Recruitment of the Vessels and Immune Cells by Malignant Tumours: Targeting of Tumour Vessels and Triggering of Anti-Tumour Defence Mechanisms	Biology	2005-2008	To design and evaluate strategies of anti-tumour angiogenesis and anti-tumour immune therapies and their combination in murine models of some of the most prevalent forms of human solid	All expected findings with the angiogenesis inhibitors and immune stimulators will be important to improve understanding of the role of vessel formation and of anti-tumour immune responses for cancer.	€ 3,005,000

							tumours		
European Commission- FP6 projects	University, NGO, Private, n= 11	European	FR, GER, NE, SW DK, BEL	Identification of molecular pathways that regulate the organ-specific metastasis of breast cancer	Biology	2004-2007	- To identify genes that are specifically up- or down regulated in breast cancer metastases in specific organs. - To identify gene expression signatures in primary breast tumours that predict metastasis to specific organs or predict the prognosis of ductal carcinoma in situ (DCIS). - To determine whether genes already associated with breast cancer invasiveness and metastasis are expressed in metastases in all or only a subset of organs.	The gene expression signatures in primary tumours identified in this project that predict organ-specific metastasis and the prognosis of DCIS will have obvious potential for clinical application in diagnosis and prognostic assessment.	€ 3, 430, 273
European Commission- FP6 projects	University, NGO, Private, n= 8	European	GER, SW DK, AT, UK, EE, ES	Combating cancer through novel approaches to protein-protein interaction inhibitor libraries	Biology	2007-2010	To develop a series of innovative small ligand tools and libraries that allow new approaches to the inhibition of protein-protein interactions in cancer	Five different PPI-inhibitor library creation tools, based on five complementary approaches: • in silico; • genetic chemistry; • advanced natural product technologies; • retro-synthesis of natural scaff olds; • ADME improvement.	€ 3, 361, 300
European Commission- FP6	University, NGO,	GLOBAL	GER, ES, BEL, IL, HU	An Integrative Approach to Cellular Signalling and Control	Biology	2004-2007	To simulate a whole cell. Rather our	The generation of the guidelines described	€ 1,998,000

projects	Private, n= 9			Processes – Bringing Computational Biology to the Bench			project aims to bring computer models and simulations to the experimental community	above should make a fundamental contribution to the area of functional genomics, and provide ways for elucidating the mechanisms of action of pharmacological compounds.	
European Commission- FP6 projects	University, NGO, Private, n= 8	European	SWE, DK, FI, UK, NE	New molecular methods and image analysis tools for analysis of cancer biomarkers in situ	Biology	2006-2009	To develop new molecular methods and assays for the analysis of individual DNA and protein molecules in situ.	To provide new means to study biomarkers for oncogenesis, and to generate novel insights in cancer biology.	€ 2,978,810
European Commission- FP6 projects	University, NGO, Private, n= 12	European	IT, NE, ES, FR, UK, FI, GER	Epigenetic treatment of neoplastic disease	Biology	2005-2010	To validate and extend the concept of 'epigenetic therapy' of cancer.	In their entirety, the studies performed in AML, breast, skin and colon cancer preclinical models will provide a framework for a detailed molecular definition of 'epigenetic therapy', which will pave the way to more focused and appropriate protocols for future clinical trials.	€ 10,904,474
European Commission- FP6 projects	University, NGO, Private, n= 6	European	SW, UK, DK	Targeting Cancer Stem Cells for Therapy	Biology	2007-2010	To use functional analysis and gene profiling of purified human cancer stem cells and genetic modelling in the mouse to identify molecular targets that may be used to	To identify and validate target molecules with activity against cancer stem cells in AML, call and breast carcinoma.	€ 1,900,000

							selectively eradicate or inactivate the malignant stem cells that sustain tumours.		
European Commission- FP6 projects	University, NGO, Private, n= 11	European	IT, NE, AT, GER, ES, SW, UK, FR, HU	Identification of novel targets for cancer therapy	Biology	2004-2008	Use large-scale functional genomics, in particular genome wide loss of-function screens, to identify novel mechanisms, including novel oncogenes and tumour suppressor genes, involved in the development of human cancer;	To develop novel high-throughput technologies for the functional annotation of the human genome and will apply these technologies to develop novel therapies to treat human cancer.	€ 8,200,000
European Commission- FP6 projects	University, NGO, Private, n= 10	European	NE, UK, FR, GER, IT, DK	Selecting and validating drug targets from the Human kinome for high risk paediatric cancers	Biology	2006-2009	To systematically explore the human kinase family for targeted therapy development for children with cancer	To contribute to a better understanding of the unique pediatric tumor biology and to the development of new drugs.	€ 3,415,414
European Commission- FP6 projects	University, NGO, Private, n= 13	European	FR, SWE, AT, IT, SW, GER, BEL, FI	Genome-wide Discovery and Functional Analysis of Novel Genes in Lymphangio genesis	Biology	2004-2009	To discover novel genes important for lymphatic vascular versus blood vascular development and function, and to study the functional role and therapeutic potential of their gene products in lymphangio genesis using state-of-the-art technologies	Novel therapies for cancer, infl ammatory diseases, lymphedema and tissue ischemia.	€ 9,000,000
European Commission- FP6	University, NGO,	European	IT, FR, NE, IL, POL, UK, ES,	Molecular mechanisms involved in organ-specific metastatic growth	Biology	2004-2008	To discover new gene and protein	To identify novel molecular	€ 4,005,295

projects	Private, n= 11		BEL	processes in breast cancer			markers, which can be used for diagnosis as a signature of metastasis to specific organs, and also be targeted for therapy.	mechanisms that may be targeted for therapy of metastatic disease in breast cancer.	
European Commission- FP6 projects	University, NGO, Private, n= 10	European	GER, IT, FR, UK	Regulation of Mitosis by Phosphorylation – A Combined Functional Genomics, Proteomics and Chemical Biology Approach	Biology	2004-2009	-To identify all human protein complexes required for mitosis; - To analyse how these complexes are regulated through phosphorylation by mitotic kinases; - To evaluate the potential of mitotic kinases as diagnostic or prognostic markers in clinical oncology	To generate knowledge relevant for diagnostics and biomarker research as well as for target identifi ation for new antiproliferative pharmaceuticals	€ 8,578,177
European Commission- FP6 projects	University, NGO, Private, n= 13	European	UK, IT, FR, SW, GER, ES, DK, SWE	Developing molecular medicines for cancer in the post-genome era	Biology	2004-2009	To fully exploit the results of recent fundamental advances in understanding the role of telomerase and telomere maintenance mechanisms in human cancer development	The understanding and definition of biochemical response pathways underpinning the telomere checkpoint for somatic cell proliferation	€ 4,000,000
European Commission- FP6 projects	Private, n= 2	European	POL, TK	Advancing International Co-operation and Developing Infrastructure for Targeted Screening of Prostate Cancer in Men with Genetic Predisposition	Aetiology	2005-2007	To expand the IMPACT study collaboration into the Associate Candidate Countries through advertising the study both to the general population	To host an international conference to bring all collaborators together and meet and share knowledge. To identify and	€ 330,057

							and to researchers using media, establishing a website and holding an international conference.	recruit new centres in ACCs. To recruit ACC members onto the IMPACT study, and specialist and steering committees.	
European Commission- FP6 projects	University, NGO, Private, n= 19	GLOBAL	NE, AU, E S, SWE, UK, IT, FR, USA, GER, IL, LV, SL, POL	Genetic and environmental determinants of melanoma: translation into behavioural change	Aetiology	2006-2011	To understand the genetic causes of melanoma and how the identified susceptibility genes interact with the environment, predominantly with sun exposure.	To improve on the ranking of risk factors for melanoma and to understand the phenotypic markers of those susceptibility genes.	€ 10,452,723
European Commission- FP6 projects	University, NGO, Private, n= 26	European	GER, UK, SWE, FR, PT, DK, AT, BEL, IT, GR, FI, HU, SW	The role of chronic infections in the development of cancer	Aetiology	2006-2010	To investigate the role of six of these infectious agents – EBV, KSHV/HHV8, HPV, HTLV-I, HCV, and HP – in the pathogenesis of infection-associated cancer. In addition, the co-factor role of enterohepatic HP will also be investigated	To develop and validate animal models to study chronic inflammation and cancer progression, and new diagnostic procedures for the identification of infected individuals likely to develop infection-associated malignancies.	€12, 400,000
European Commission- FP6 projects	University, Private, n= 3	European	UK, DK, NE	Inherited risk of breast and prostate cancer	Aetiology	2005-2008	To determine the contribution of polymorphic variants in a large number of candidate genes to the risk of breast and prostate cancer, and to develop efficient statistical and computational methods for the	To confirm or exclude the association of multiple candidate cancer genes with breast and prostate cancer in the Icelandic and Dutch populations	€ 2,962,908

							analysis of genetic and association data		
European Commission- FP6 projects	University, NGO, Private, n= 25	European	NE, UK, DK, NOR, IT, GR, ES, FR, GER, SWE	European Prospective Investigation into Cancer, Chronic Diseases, Nutrition and Lifestyle	Prevention	2006-2010	To reinforce and expand the collaboration between 27 European institutions so as to ensure that there is a major European resource	New scientific knowledge will be gained on the roles that diet, obesity, physical activity, alcohol, tobacco and socioeconomic factors play in the risk of developing cancer, coronary heart disease and stroke in the ten European countries studied.	€ 999 ,745
European Commission- FP6 projects	University, NGO, Private, n= 11	European	NE, NOR, ES, FR, GER, IT, FI, DK, GR, POL	Key determinants of the future incidence of cancer across Europe: impact of prevention	Prevention	2005-2009	To underpin and promote implementation of European and national policies to prevent cancer by providing estimates of the potential impact that interventions directed at key determinants of the incidence of this disease may have on the future burden of cancer in the various parts of Europe up to 2040	To be that a perspective for cancer prevention is shown, which makes maximal use of existing knowledge in such a way that policy-makers are persuaded to invest more in effective long-term prevention efforts	€ 987,963
European Commission- FP6 projects	University, NGO, Private, n= 7	European	GER, ES, PT, SWE, NE	Mammography with molecular imaging	Prevention	2007-2011	Design and development of a dedicated low cost PET camera prototype for breast examination with an intrinsic resolution	To proposes a new PET device specifically designed for breast cancer diagnosis and evaluation of therapy response	€ 2 ,500, 000

							of less than 1 mm, high sensitivity, and tomographic 3D reconstruction.		
European Commission- FP6 projects	University, NGO, Private, n= 18	European	GER, UK, ES, IT, EE, SWE, IE	Novel Molecular Diagnostic Tools for the Prevention and Diagnosis of Pancreatic Cancer	Early Detection, Diagnosis and Prognosis	2006-2009	To integrated project joining leading groups in European pancreatic cancer research, SMEs and industry to develop novel molecular diagnostic approaches for the prevention, early diagnosis and risk stratification of pancreatic cancer.	These approaches will be developed based on large-scale transcriptome, genome and proteome analyses that have been performed by members of the consortium in recent years in two subsequent EU funded concerted actions	€ 8,500,000
European Commission- FP6 projects	University, NGO, Private, n= 8	European	NE, UK,FR, GER, SW	Prostate cancer molecular-oriented detection and treatment of minimal residual disease	Early Detection, Diagnosis and Prognosis	2006-2010	The progress made in the treatment of the primary tumour by surgery o radiotherapy, mortality in cancer patients is increasingly linked to metastatic disease.	To identify genes up- or down-regulated in minimal residual disease with a potential for use in diagnostics and therapeutic strategies	€ 4,034,200
European Commission- FP6 projects	University, NGO, Private, n= 12	European	FI, NE, SWE, UK, GER, FR	High Resolution X-Ray Imaging for Improved Detection and Diagnosis of Breast Cancer	Early Detection, Diagnosis and Prognosis	2007-2010	To solve the current dilemma in mammography by increasing the image quality in terms of contrast and spatial resolution while lowering the radiation dose.	An increase in breast cancer detection rate in screening of just 1% in Europe would mean that in the order of 500 otherwise undetected cases would be diagnosed annually, with a potential of 100-300 lives saved.	€ 3,635,200

European Commission- FP6 projects	University, NGO, Private, n= 16	European	FR,E S, NE, IT, UK SWE, BEL, GER	Molecular mechanisms underlying chemotherapy resistance, therapeutic escape, efficacy and toxicity	Treatment	2007-2012	To improve the outcome of cancer chemotherapy by developing novel tools to predict tumour response to treatment as well as individual toxicity to chemotherapy.	To lead to new tools for prediction of treatment outcome as well as toxicity of chemotherapy. To identify and prepare for pre-clinical development of potential novel modulators of drug resistance based on validated mechanisms and pathways.	€ 8,710,300
European Commission- FP6 projects	University, NGO, Private, n= 9	European	FR, UK, IT, NOR, GER, NE	Chimaeric T cells for the treatment of paediatric cancers	Treatment	2006-2010	To builds on the excellence of a network of EU-based partners with broad experience in the field of paediatric haematology and oncology, immunology and cell and gene therapies	To exploit the Immuno stimulatory properties of EBV-CTLs and retarget them to leukaemia/lymphoma cells, which themselves lack many of the costimulatory molecules needed to activate CTLs	€ 3,208,760
European Commission- FP6 projects	University, NGO, Private, n= 6	European	IT, UK, ES, FR	Designing Therapeutic Protein-Protein Inhibitors for Brain Cancer Treatments	Treatment	2007-2010	To provide more effective anti-tumour therapies by developing targeted small ligand libraries with appropriate physico-chemical properties for therapeutic effect targeted against Protein-Protein interactions implicated in various tumour types	The successful integration of the various aspects of this proposal will provide a robust knowledge-based strategy for exploiting Protein-Protein interactions as drug targets in the treatment of brain tumours	€ 3,640,293

European Commission- FP6 projects	University, NGO, Private, n= 7	European	UK, IT, SW, GER, CY	Immunophoto dynamic therapy of cancer: concepts and applications	Treatment	2006-2009	The synthesis and conjugation of novel infrared hotosensitisers to the most promising antibodies against vascular tumour antigens obtained by human antibody technology, the immuno histochemical characterisation, the biodistribution and imaging targeting in vivo.	Immuno-PDT procedures promise to be invaluable for the selective ablation of inoperable superficial neoplastic lesions, such as certain head&neck, gastrointestinal, urogenital and gynecological tumours	€ 3,000,000
European Commission- FP6 projects	University, NGO, Private, n= 6	European	IE, ES, NE	Therapeutic molecules for treatment of solid tumours by modulating death receptor-mediated apoptosis	Treatment	2006-2009	To develop novel molecules that target critical apoptotic signalling pathways important in the formation of various solid tumours	The anticipated deliverables include the development of novel diagnosis technologies and novel therapeutics for intervention in cancer progression through activation of apoptosis as well as technologies to advance a more rational approach to the design of 'tailor-made' therapeutic drugs	€ 2,069,000
European Commission- FP6 projects	University, NGO, Private, n= 6	European	NOR, SWE, IT, NE, UK	Development of optimised recombinant idiotypic vaccines for subset-specific immunotherapy of B cell lymphomas	Treatment	2007-201O	The development and production of optimised recombinant idiotypic vaccines for the treatment of subgroups of lym phoproliferative disorders expressing molecularly	Establishment of a large database including sequences of idiotypic VH and VL genes expressed by a variety of lympho-proliferative disorders, including low grade B-NHL, autoimmunity-	€ 2,050,000

							correlated idiotypes	associated lympho-proliferations, and chronic lymphocytic leukemia.	
European Commission- FP6 projects	University, NGO, Private, n= 8	GLOBAL	FI, HU, IL, IT, ES	Grid-aided computer system for rapid anti-cancer drug design	Treatment	2007-2010	To develop and refine methods for the enrichment of molecular libraries to facilitate discovery of potential anti-cancer agents	Novelties and added values of the project: • virtual focused libraries of anti-cancer agents; • potential anti-cancer agents; • HTS technology; • data for model building purposes; • models able to predict anti-cancer properties; • CancerGrid System	€ 2,804,075
European Commission- FP6 projects	University, NGO, Private, n= 10	European	UK, IT, SW, GER, AT, NOR	The European Palliative Care Research Collaborative: improved treatment of pain, depression and fatigue through translation research	Cancer control, Survivorship and outcomes research	2006-2009	To develop novel genetic methods for prediction of opioid responses and individual variation of fatigue (cachexia), and methods for assessment and classification of pain, fatigue (cachexia), and depression	- Identification of profiles of genetic markers that best predict pain treatment responses, with specific emphasis on opioids. - Increased understanding of the molecular basis for cachexia and identifi cation of genetic factors that may predict patients at particular risk.	€ 2,799,910
European Commission- FP6 projects	University, NGO, Private, n= 10	European	IT, BEL, POL, HU, GR, GER	Development of new therapeutic substances and strategies for treatment of pain in patients with advanced stages of cancer	Cancer control, Survivorship and outcomes research	2006-2009	Chemistry, in vitro biopharmacology and in vivo pharmacology that will be accomplished by multidisciplinary	Reduce side effects generated by traditional opioids in central nervous system, including tolerance, dependence, constipation,	€ 2,182,325

							teams integrated in the project.	euphoria, etc	
European Commission- FP6 projects	University, NGO, Private, n= 5	European	NE, GER,HU	High-throughput Tools for Biomedical Screens in Zebrafi sh	Scientifi c Model Systems	2007-2010	To develop a case study for an anti-tumor drug screening system, based on the implantation of fl uorescently labeled tumor cells into zebrafi sh embryos	The development of a zebrafish embryo screening system as an innovative genomics tool.	€ 1,739,000
European Commission- FP6 projects	University, NGO, Private, n= 11	GLOBAL	AT, GER, IL, UK, ES, HU	Identification, development and validation of novel therapeutics targeting programmed cell death in tumours	Biology	2006-2010	At restoring these failsafe programmes, in particular apoptosis, in established solid tumours have emerged as an important approach to cancer therapy.	- An understanding of the pathways that signal apoptosis in solid tumours; - Their validation as viable targets for tumour suppression or regression in animal models in vivo.	€ 3,531,507
European Commission- FP6 projects	University, NGO, Private, n= 21	European	GER, FR, SW, UK, NE, ES, BEL, IT	Cancer immunology and immunotherapy	Treatment	2002-2016	Integrated Project is to develop a therapeutic cancer vaccine with defined tumour antigens that would provide a clinical benefit in at least 40% of patients	Vaccines with a greater immunogenicity, such as those we plan to investigate, will also have a greater clinical efficacy	€12,185 ,102
European Commission- FP7 projects	University, NGO, Private, n= 9	European	UK, IT,FR	Oral Off-patent Oncology Drugs for Kids	Treatment	2008-2011	The goal of the O3K consortium is to develop oral liquid formulations of cyclophosphamide and temozolomide, important chemotherapeutics which have been identifi ed in the list of paediatric needs	To provide access to curative drugs for all children with cancer, improving compliance, ensuring safety for both patient and environment, and allowing the development of essential ambulatory	€ 5,958,419

							by EMEA.	treatments.	
European Commission- FP7 projects	University, NGO, Private, n= 9	European	IT, SW, GER, UK, BEL, NE	Antibody Derivatives as Molecular Agents for Neoplastic Targeting	Treatment	2008-2011	To generate anticancer agents of superior quality that rely on the antibody-based delivery of cytotoxics, radionuclides or immunostimulatory cytokines to either vascular tumour antigens or to tumour cell membranes.	Therapy studies in tumour-bearing mice, featuring the use of antibody derivatives in combination with other anti-cancer drugs (cytotoxic, biological, vascular disrupting agents.	€ 3,000,000
European Commission- FP7 projects	University, NGO, Private,, n= 8	European	UK, FR, IT, GR, HU, GER, BEL	Monoclonal Antibody-targeted Carbon Nanotubes against Cancer	*NA	2008-2011	To enhance the therapeutic potency of the antibody and establish a new paradigm for oncology therapeutics	*NA	€ 2,967,008
European Commission- FP7 projects	University, NGO, Private, n= 7	European	HU, GER, IE	Automatic Cancer Screening based on Real-time PCR	*NA	2008-2011	To develop a novel rapid real-time PCR/probe technology in a microarray biochip format, with the corresponding automated instrumentation for use as a rapid point-of-care diagnostic device	*NA	€ 2,999,669
European Commission- FP7 projects	University, NGO, Private, n=6	European	ES, BEL, NE, IT, GER,	The Use of Methylated DNA Immunoprecipitation MeDIP in Cancer for better Clinical Management	*NA	2008-2011	To use a novel technique based on chromatin Immuno precipitation, the Methylated DNA Immunoprecipitation	*NA	€ 2,999,994

							(MeDIP) technique, which will readily produce an epigenomic profile to personalise cancer treatment and facilitate tumour diagnosis, prognosis and monitoring		
European Commission- FP7 projects	University, NGO, Private, n= 8	European	UK, GER, AT, HU	Developmental Molecular Pathways in Drosophila as a Model for Human Cancer	Treatment	2008-2011	To identify novel targets and drug-like molecules for therapeutic application	To establish high-throughput cell-based assays for regulators of the major developmental oncogenic signalling pathways	€ 2,995,295
European Commission- FP7 projects	University , NGO, Private n=12	GLOBAL	UK, ES, PT, MJ, CB, BR, AG, UR	Genetic study of Common Hereditary Bowel Cancers in Hispania and the Americas	*NA	2009-2013	To detect SNPs with eff ects in both Latin America and Europe, but also SNPs with eff ects specifi c to Latin Americans. To develop a polymorphism panel for predicting the risk of CRC in the general population, so that those at increased risk can be off ered eff ective measures to prevent cancer	To be a focus for education about CRC, especially in Latin America, and will also provide training for young researchers there	€ 2,974,288
European Commission- FP7 projects	University, NGO, Private, n=16	European	SWE, UK, AU, GER, ES, FI, NE, DK, BEL, FR	Collaborative Oncological Gene-environment Study	*NA	2009-2013	To identify individuals with an increased risk of breast, ovary or prostate cancer.	To the development of new tests for risk prediction of breast, ovarian and prostate cancer	€ 11,715,501
European Commission- FP7	University, NGO, Private, n= 8	European	GR, SW, FR, ES, GER, LU	Novel MS-based Strategies to Discover and Evaluate Cancer Biomarkers in Urine: Application	*NA	2008-2012	To implement a strategy for protein biomarker discovery	To establish a whole experimental pipeline, from the	€ 2,907,412

projects				to Diagnosis of Bladder Cancer			and validation relying on state-of-the-art mass spectrometry instrumentation for the quantitative analysis of proteins	search for new bladder cancer biomarker candidates to their thorough evaluation and validation in a clinical environment.	
European Commission- FP7 projects	Private, n= 4	European	AT, GER	Diseminate Research funded by EC improving Treatment options for children suffering from cancer	*NA	2008-2010	To raise the interest in, and understanding of, health research. The approach is based on carefully selected projects in paediatric oncology and a mountaineering event that will highlight the good physical condition of former patients	To show a link between EC-funded research and the health of young people who have recovered from cancer	€ 618,000
European Commission- FP7 projects	University, Private N= 10	European	UK, GER, IT, ES, FR	European Paediatric Oncology off-patent medicines Consortium	*NA	2009-2013	Provide data that will guide the optimal use of doxorubicin in the clinic, particularly in patients of under three years.	*NA	€ 1,997,862
European Commission- FP7 projects	Private n= 9	European	SWE, IT, GER, SW, BEL, FR	European Consortium for Anticancer Antibody Development	Treatment	2008-2012	To the discovery and evaluation of new antibodies for therapy in human cancers	The development and evaluation of antibodies against new target structures on tumour cells, and blood vessels supplying tumours, responsible for tumour angiogenesis, progression and metastasis	€ 5,989,862

European Commission- FP7 projects	University, NGO, Private n= 15	European	NE, RO, EE, AT, BEL, DK, FI, IS, IT, SWE, IE, ES	Europe against Cancer: Optimisation of the Use of Registries for Scientific Excellence in research	Cancer control, Survivorship and outcomes research	2009-2012	To optimise the use of cancer registration data for the amelioration of cancer control and the strengthening of population-based cancer research in Europe	*NA	€ 1,999,408
European Commission- FP7 projects	University, NGO, Private n= 12	European	SWE, GER, IE, FI, NE	Ultra-high Resolution and ultra-sensitive Fluorescence Methods for objective sub-cellular Diagnosis of early Disease and Disease Progression in Breast and Prostate Cancer	*NA	2008-2012	To develop and validate a quantitative, minimally invasive diagnostic tool for early and conclusive detection, diagnosis and monitoring of disease and disease progression in breast and prostate cancer	To improved, early and reliable diagnosis of breast and prostate cancer will be possible from amounts of sample material small enough to permit a minimally invasive procedure such as Fine-Needle Aspiration (FNA)	€ 4,197,774
European Commission- FP7 projects	University, NGO, Private, n= 11	European	SW, GER, DK, ES, GR, UK, FI, IT	Genomic Instability in Cancer and Precancer	*NA	2008-2011	To Study the role of DNA replication stress and short telomeres in driving genomic instability, particularly in human precancerous lesions	*NA	€ 2,994,979
European Commission- FP7 projects	University, NGO, Private n= 11	European	AT, IT, GER, FR, UK	Genomic Instability and genomic Alterations in pre-cancerous Lesions and/or Cancer	*NA	2008-2011	To identify markers for novel therapeutic and/or preventative strategies, as well as facilitate tumour diagnosis, prognosis and monitoring	*NA	€ 2,995,569
European Commission- FP7 projects	University, NGO, Private, n= 21	European	GR, AT, IL, IT, CZ, FR, UK, GER, HR	Understanding Inflammation-associated Tumorigenesis for the rational Design of novel anti-cancer therapeutic Strategies	*NA	2009-2013	To identify molecular and cellular targets for cancer therapy through the	Investigae the nature of the progression from normal to inflamed and	€ 11,999,889

							development and systematic study of state-of-the-art preclinical models of infl ammation-driven cancer	cancerous tissue. Another component of the programme will use cutting edge technology to considerer how changes in our genes coding can relate to how patients progress with cancer disease and how they will respond to therapy	
European Commission- FP7 projects	University, NGO, Private, N=11	European	FR, DK, IE, GER	Development of 6-mercaptopurine and methotrexate oral liquid Formulations for the Maintenance Treatment of Acute Lymphoblastic Leukæmia in Children	*NA	2008-2011	O4CP will undertake the non-clinical and clinical development of methotrexate and 6-mercaptopurine oral liquid formulations adapted for maintenance treatment of paediatric acute lymphoblastic leukaemia, with the crucial objective of making these adapted formulation available by 2011 at the latest	*NA	€ 3,316,415
European Commission- FP7 projects	University, NGO, Private, n= 8	GLOBAL	UK, USA, FI, DK, SK, POL	Identification and Validation of new Breast Cancer Biomarkers based on Integrated Metabolomics	*NA	2008-2011	To test the hypothesis, that alterations in the level of metabolites can be used for a molecular classification of breast cancer as well as for the Identification of new prognostic and	To go beyond the metabolite level, and identify and validate selected protein and mRNA biomarkers relevant to metabolic alterations	€ 2,873,205

							predictive biomarkers.		
European Commission- FP7 projects	University, NGO, Private, n=9	European	IT, FI, ES, SWE, FR, NE	Understanding and fighting Metastasis via Dissection of the Core Invasive Machinery	*NA	2008-2011	To study to understand the dissemination and outgrowth of metastasis through systematic analysis of the Core Invasive Machinery contained within integrin-mediated ECM attachment structure: this includes a large and discretely localised intracellular signalling network which drives migration and invasion	*NA	€ 2,999,609
European Commission- FP7 projects	University, NGO, Private, N=21	European	NOR, NE, UK, DK, IT, SWE, ES, GER, SK, LT	Metastatic tumours facilitated by hypoxic Tumour Micro-Environments	*NA	2009-2014	To clarify the roles and functions of the hypoxic tumour micro-environment in relation to the survival of solid tumours that are likely to metastasise	To identify and develop advanced imaging techniques and biomarkers and identify micro-metastases in the bone marrow of patients, in order to assist in the selection of appropriate stratifi cation of the actual primary tumours' and metastases' micro-environmental conditions.	€ 11,998,300
European Commission- FP7 projects	University, NGO, Private, n= 21	European	BEL, NOR, NE, UK, DK, IT, ES, GER, LT, LT	Understanding and Fighting Metastasis by Modulating the Tumour Microenvironment through Interference with the Protease Network	*NA	2008-2012	To identify molecular pathways involved in the regulation of metastatic dissemination	*NA	€ 2,999,689

							to lung, liver, lymph node and bone		
European Commission- FP7 projects	University, NGO, Private, N=5	European	NE, FR, GER, SW,	Characterisation and quantitative Modelling of DNA mismatch Repair and its Role in the Maintenance of genomic Stability and Cancer Avoidance	*NA	2008-2012	To adopt and exploit a systems biology approach, combining European expertise in DNA mismatch repair with sophisticated multidisciplinary technology and expertise in quantitative modelling, in order to describe this DNA repair process at diff erent levels of complexity	*NA	€ 3,000,000
European Commission- FP7 projects	University, NGO, Private n=5	European	IT, SL, UK, NE, GER	Targeted Nanosystems for Improving Photodynamic Therapy and Diagnosis of Cancer	*NA	2008-2011	The development of one or more nanosystems loaded with Foscan® and conjugated to cancer-cell-specifi c ligands to improve the effi cacy and selectivity of photodynamic therapy (PDT) and optimise a fluorescencebased tumour imaging approach	*NA	€ 2,453,118
European Commission- FP7 projects	University, NGO, Private n=6	European	BEL,ES, IL, DK, FR, GER	MicroRNAs and Cancer: From Bench to Bedside	*NA	2008-20163	To identify and expose novel miRs and components of their biogenesis machinery, and investigate links	*NA	€ 2,992,227

							between these molecules and human cancers		
European Commission- FP7 projects	University, NGO, Private n= 9	GLOBAL	UK, GER, NE, IT, SWE, SL, SW, AG, NL	A European Collaboration to optimise Research for the Care of Cancer Patients in the last Days of Life	Cancer control, Survivorship and outcomes research	2008-2011	To explore, share and collate existing knowledge and practice relating to each of the key themes identified within the work programme. To reach consensus based on current practice and available research evidence on the optimum care to be delivered in the last days of life and on the gaps in the knowledge base	*NA	€ 2,224,007
European Commission- FP7 projects	University, NGO, Private n= 5	GLOBAL	UK, DK, FR, GER, PT	Discovery of novel Cancer Serum Biomarkers based on aberrant Post-Translational Modifications of O-glycoproteins (O-PTM-Biomarkers) and their application to early detection of cancer	*NA	2008-2011	- To use a novel glycopeptide microarray technology to identify, evaluate and validate an O-PTM auto-antibody signature as an early diagnostic biomarker, focusing on breast, ovarian, pancreatic and lung cancers. - To develop and validate novel ELISA-type assays for cancer-specific glycoforms of the MUC1 and MUC16 glycoproteins.	*NA	€ 2,848,153

European Commission- FP7 projects	University, NGO, Private, n= 11	GLOBAL	UK, ES, PT, GER, NOR, NE, IT, BEL, AF	Reflecting the Positive diveRsities of European prIorities for research and Measurement in end of life cAre	*NA	2008-2011	To inform best practice and harmonise research in end-of-life care for cancer patients across Europe.	*NA	€ 1,650,898
European Commission- FP7 projects	University, NGO, Private, n= 8	European	FI, SWE, UK, NE, DK,	Prostate Cancer: Profiling and Evaluation of ncRNA	*NA	2008-2012	- To early identification of cases requiring aggressive curative Treatment. - The development of efficient therapies for hormone-refractory prostate cancer.	*NA	€ 2,986,216
European Commission- FP7 projects	University, NGO, Private, n= 7	European	UK, IT, GER	HGF/SF and MET in Metastasis	*NA	2008-2011	- Understand how the conditions of low oxygen tension (hypoxia) typical of growing tumours can cause activation of HGF/SF and MET and hence metastasis. -Understand how HGF/SF and MET cooperate with another signalling system. Namely the chemokines and their receptors, in promoting metastasis.	*NA	€ 2,927,011
European Commission- FP7 projects	University, NGO, Private, n= 6	European	GER, UK, IT	Multimodal Skin Inspection with hybrid acoustic and optical Spectroscopic Imaging	*NA	2008-2012	The development of a non-invasive multimodal hybrid imaging system with the capability to perform non-invasive high-resolution	The project will provide a novel unique tool for early diagnosis and treatment control of skin cancer and skin disease and thus significantly	€ 4,097,585

							three-dimensional clinical	contribute to the improvement of the European health care system.	
European Commission- FP7 projects	University, NGO, Private n= 10	European	FR, SW, GER, SWE, SL, FR, BEL	Targeting Alpha-particle emitting Radionuclides to Combat Cancer	*NA	2008-2011	To improving drug delivery to cancer cells by developing targeted radiotherapy with alpha-emitting radionuclides	The joint research will permit us to select alpha-radionuclide candidates for future preclinical and clinical developments and define the most promising setting for targeted alpha-radionuclide therapy in terms of vector properties and modes of administration.	€ 3,000,000
European Commission- FP7 projects	University, NGO, Private, n= 7	European	UK, GER, SWE, ES, FR, SW	Identification and Characterisation of novel Human Telomere-related Biomarkers that aid cancer management by improving patient diagnosis, treatment selection, response monitoring and drug development	*NA	2008-2011	- To look at proteins that make up the telomere structure using modern genomics and proteomics techniques to identify those that have diagnostic value	*NA	€ 2,848,490
European Commission- FP7 projects	University, NGO, Private, n= 15	European	GER, SW, NE, UK, IT, DK, BEL, FR	An integrated Concept of Tumour Metastasis: Implications for Therapy	*NA	2008-2012	- To understand how cancer stem cells behave in and contribute to metastasis, and how networks and pathways that are known to regulate metastasis affect their properties. - To determine how	*NA	€ 2,999,185

							a permissive microenvironment for metastasis formation is established in given organs		
European Commission- FP7 projects	University, NGO, Private, n= 7	European	DK, NE, ES, SWE	Prediction of Bladder Cancer Disease Course using Risk Scores that combine molecular and clinical Risk Factors	*NA	2008-2013	To combine the best markers of bladder cancer outcome in a prospective multi-centre validation study as genetic predictors. - To establishing mathematical predictive algorithms or nomograms that can help guide the clinical selection of therapeutic regimens and follow-up plans.	*NA	€ 2,995,347
European Commission- FP7 projects	University, NGO, Private n= 6	European	NE	Developing high-throughput Bioassays for Human Cancers in Zebrafish	*NA	2008-2011	To develop high throughput bioassays for target discovery and rapid drug screenings applicable in preclinical validation pipelines	*NA	€ 2,991,793
European Commission- FP7 projects	University, NGO, Private, n= 15	GLOBAL	AT, AU, CA, FR, GER, GR, IND, IL, IT, JP, COR, NZ, TW, NE, ES	Risk of brain cancer from exposure to radiofrequency fields in childhood and adolescence	*NA	2009-2014	To assess the potential carcinogenic effects of childhood and adolescent exposure to RF and ELF from mobile telephones on the central nervous system.	*NA	€ 3,499,748

European Commission- FP7 projects	University, NGO, Private, n= 24	European	IT, LV, LT, BG,RO, EE, CZ, FI, BEL, POL, NE, LU, PT, ES, SI,SK, IL, MT, DK, HR, AT, FR, UK, GR, HU	European Cancer Health Indicator Project-III	Cancer control, Survivorship and outcomes research	2008-2011	- To avoid avoidable deaths: an EU-solidarity based intervention on cervical screening in five Eastern European Member States (MS) - To improve the health information system: an EU-solidarity based promotion of cancer registration - To improve the health information system: promotion of the ECHI cancer indicator collection - To extend the health information system to emerging health needs: list of cancer rehabilitation indicators - To guarantee cancer care for all: a discussion on cancer cost/outcome ratio.	*NA	603,000 €

European Commission- FP7 projects	University, NGO, Private, n= 5	European	UK, NE, RO	Genetic Prostate Cancer Variants as Biomarkers of Disease Progression	*NA	2008-2013	The identification and functional analysis of prostate cancer biomarkers that predict disease progression and outcome	1) A collection of samples and clinical information from over 8,000 prostate cancer cases.2) A new prognostic test that predicts clinical outcomes for localized prostate cancer 3) Documentation of the association of genetic risk variants to clinical parameters and outcomes. 4) Increased understanding of carcinogenesis of the prostate.	€ 2,709,577
European Commission through DG SANCO	University, NGO, Private, n= more 15	European	IT	Surveillance of Rare Cancers in Europe	Cancer control, Survivorship and outcomes research	2007-2010	-To provide an operational definition of “rare cancers”, and a list of cancers that meet this definition -To estimate the burden of rare cancers in Europe -To improve the quality of data on rare cancers - To develop strategies and mechanisms for the diffusion of information among all the key players involved in Europe-wide surveillance on and treatment of rare cancers	*NA	*NA

*NA: Not Avalilable

Table ii: Cancer funded research programs/projects at the MS-level (for the main RFOs)

Funder	Recipient Type	Level of Collaboration (National – European - Global)	Partner Countries	Project Title	Research Area (focus)	Project Timeline (years)	Summary Description (Project aim)	Achieved/ Anticipated Outcomes	Amount of Funding
Scientific Foundation of the Spanish Association against Cancer (AECC)	Private n= 1	National	ES	Hereditary cancer: towards an accurate estimate of risk	*NA	2010-2015	(i) the incorporation of methodologies Next generation algorithms diagnostics; (ii) evaluation of new markers to identify and modify risk screening strategies; (iii) identification of new genes responsible for breast cancer and familial colon from different approaches genomics and integrative biology and (iv) increase adherence to screening measures reducing the emotional impact.	*NA	€235,000
Scientific Foundation of the Spanish Association against Cancer (AECC)	Private, n=1	National	ES	Hematological malignancies: therapy supported the diagnosis molecular	*NA	2010-2015	To take information about the molecular mechanisms pathogenesis of hematological malignancies, including common	*NA	€235,000

							mechanisms and specific events of each tumor type.		
Scientific Foundation of the Spanish Association against Cancer (AECC)	Private, n= 1	National	ES	Molecular mechanisms involved in the genesis of glioma and study of tumor stem cells. Identification of new therapeutic targets and markers for patient stratification and drug response	*NA	2010-2015	To study the mechanisms molecular involved in the development of glioma and will study the biology of tumor stem cells.	To improve the design of clinical trials currently providing markers up to The harmaco dynamic study of inhibitors and turn markers to stratify patients who enter a particular study	€235,000
Scientific Foundation of the Spanish Association against Cancer (AECC)	University, Private, n= 11	National	ES	Pharmacogenetics in pediatric tumors	*NA	2010-2015	The pursuit pharmacogenetic markers that are associated toxicity and / or response to treatment in patients children's cancer.	*NA	€150,000
Scientific Foundation of the Spanish Association against Cancer (AECC)	Private, n= 9	National	ES	Targets metastasis of pediatric osteosarcoma: validation functional, clinical and therapeutic impact in a multicenter approach and multidisciplinary	*NA	2010-2015	Identify and Characterize new targets of metastatic osteosarcoma Pediatric.	*NA	€150,000
Scientific Foundation of the Spanish Association against Cancer (AECC)	University, Private n= 5	National	ES	Molecular alterations associated with tumor progression in endometrial cancer	*NA	2011-2016	To find related molecular alterations development, progression and spread of the disease, as well as resistance to chemotherapy and radiation therapy, the purpose of such molecules they could pose a new set of markers	*NA	€1,200,000

							diagnostic, evolution and prognosis		
Scientific Foundation of the Spanish Association against Cancer (AECC)	Private n= 3	National	ES	Genomic analysis of intrahepatic cholangio carcinoma	*NA	2011-2016	To establish a molecular classification of cholangio carcinomas intrahepatic	*NA	€1,200,000
Scientific Foundation of the Spanish Association against Cancer (AECC)	Private, n=3	National	ES	Role of epigenetic mechanisms in tumor development Malignant peripheral nerve	*NA	2011-2014	To characterize these epigenetic mechanisms in the development of these tumors in human samples.	*NA	€150,000
Scientific Foundation of the Spanish Association against Cancer (AECC)	Private, n= 2	National	ES	New strategies to treat breast cancer positive for Her-2.	Treatment	2012-2017	To provide more effective and safer therapies for treating some cancers of the breast,	*NA	€1,200,000
Scientific Foundation of the Spanish Association against Cancer (AECC)	Private, n= 2	National	ES	Analysis of resistance markers in multiple myeloma and development	Treatment and cancer control	2012-2017	Achieve increased survival of the resistant patients and eventually cure a significant fraction of patients	*NA	€1,200,000
Scientific Foundation of the Spanish Association against Cancer (AECC)	Private, n=1	National	ES	Molecular mechanisms involved in the origin of children leukemias	Aetiology	2012-2017	Study of leukemia in infants under one year	*NA	€1,200,000
Scientific Foundation of the Spanish Association against Cancer (AECC)	Private, n= 1	National	ES	Disposal of cancer stem cells for children in neuroblastomas	*NA	2012-2017	Optimize treatments for neuroblastoma tumors type and improve the prognosis of patients	*NA	€150,000

Ministry of Economy and Competitiveness. Spain	Public n= 1	National	ES	Ultrasonic technology development of performance for the isolation of circulating tumor cells in peripheral blood	*NA	2011-2013	*NA	*NA	€242,000
Ministry of Economy and Competitiveness. Spain	Public n= 1	National	ES	Interference interaction between tumor cell and its microenvironment: a new therapeutic approach in the treatment of lymphoma follicular	*NA	2011-2013	*NA	*NA	€266,200
Ministry of Economy and Competitiveness. Spain	Private n= 1	National	ES	Functional analysis program general adult stem cells in intestinal epithelium and its role in metastasis and relapses in *NA colorectal cancer	*NA	2011-2013	*NA	*NA	€943,800
Ministry of Economy and Competitiveness. Spain	Public n= 1	National	ES	Structural biology of macromolecular machines involved in chromosome dynamics	*NA	2011-2013	*NA	*NA	€992,200
Ministry of Economy and Competitiveness. Spain	Public n= 1	National	ES	Signaling inhibition K-RAS oncogene IN Cancer	*NA	2011-2013	*NA	*NA	€1,427,800
Ministry of Economy and Competitiveness. Spain	Public n= 1	National	ES	Cell death in progression and treatment of melanoma	*NA	2011-2013	*NA	*NA	€677,600
Ministry of Economy and Competitiveness. Spain	Public n= 1	National	ES	Exocrine pancreas cancer: role of components and ductal acinar and development of animal models	*NA	2007	*NA	*NA	€ 847,000
Ministry of Economy and Competitiveness. Spain	Public n= 1	National	ES	Integration of signals from p38 mapk: physiological functions in vivo regulatory mechanisms tumor	*NA	2007	*NA	*NA	€625,710
Ministry of Economy and Competitiveness. Spain	Public n= 1	National	ES	Genotyping mass for the characterization genetics of patients with sporadic melanoma skin spanish population. Study of the response in vivo skin from uv radiation.	*NA	2007	*NA	*NA	€147,015

Ministry of Economy and Competitiveness. Spain	Public n= 1	National	ES	Aurora kinases and cancer: new models inducible and regulatory mechanisms animals	*NA	2007	*NA	*NA	€ 193,600
Ministry of Economy and Competitiveness. Spain	Private n= 1	National	ES	Reconnect human cancer gene networks	*NA	2010-2012	*NA	*NA	€ 387,200
Ministry of Economy and Competitiveness. Spain	Private n= 1	National	ES	Mechanisms investigation common cancer and aging	*NA	2010-2012	*NA	*NA	€169,400
Ministry of Economy and Competitiveness. Spain	Private n= 1	National	ES	Approach based networks to biology and breast cancer colorectal	*NA	2010-2012	*NA	*NA	€ 260,150
Ministry of Economy and Competitiveness. Spain	Private n= 1	National	ES	Mechanisms of er-positive breast cancer metastasis	*NA	2010-2012	*NA	*NA	€ 205,700
Ministry of Economy and Competitiveness. Spain	Public n= 1	National	ES	Structural determination of the architecture of cad, an anti-tumoral target that controls the biosynthesis of pyrimidines	*NA	2010-2012	*NA	*NA	€ 145,200
Ministry of Economy and Competitiveness. Spain	Public n= 1	National	ES	Decoding the uri role in the development of hepatocellular carcinoma (hcc)	*NA	2010-2012	*NA	*NA	€ 108,900
Ministry of Economy and Competitiveness. Spain	Public n= 1	National	ES	New genetic models for the study of mouse angiogenesis and lymphangiogenesis in tumors and development	*NA	2010-2012	*NA	*NA	€121,000
Ministry of Economy and Competitiveness. Spain	Public n= 1	National	ES	Implications type of mutation germinal in the forecast and treatment of patients with breast cancer carriers hereditary mutations in the gene brca1	*NA	2010-2012	*NA	*NA	€96,800
Ministry of Education and Science, and Foundation for	University, Private, n= 3	National	PT	Protein kinase wnk2 role as gene suppressor gliomas evil	Biology	2008	*NA	*NA	€ 109,062

Science and Technology Portugal									
Ministry of Education and Science, and Foundation for Science and Technology. Portugal	Private, n= 3	National	PT	Transcriptional mechanisms and post of transcriptional lrp1b inactivation in tumors non-medullary thyroid sporadic and family	Biology	2008	*NA	*NA	€ 129,072
Ministry of Education and Science, and Foundation for Science and Technology. Portugal	University, Private, n= 2	National	PT	Influence of thymic stromal cells chemokines and signs on the development of leukemia acute lymphocyte t	Biology	2008	*NA	*NA	€172,900
Ministry of Education and Science, and Foundation for Science and Technology. Portugal	Private, n= 2	National	PT	Research effect of anti-angiogenic dll4fc therapy with the tumor metastases training	Treatment	2010	*NA	*NA	€179,505
Ministry of Education and Science, and Foundation for Science and Technology. Portugal	Private, n= 3	National	PT	Dissecting the changes impact gain-of-function gene in leukemia t il7r	Biology	2010	*NA	*NA	€165,000
Fondation ARC pour la recherche sur le cancer. France	Private, n= 1	National	France	Melanoma: predict response to chemotherapy with certain immune parameters	Treatment	2011	*NA	*NA	€ 300,000
Enfants et Santé. France	Private, n= 1	National	France	Project CAMELIAT - Characterization acute leukemias mégacarioblastique - improving knowledge and treatment.	Treatment	2013	*NA	*NA	€100,000

Enfants et Santé. France	Private, n= 1	National	France	Euro Ewing 2012	*NA	2013	*NA	*NA	€125,000
Erasme fund for medical research.Belgium	Private, n=1	National	Belgium	The cellular radiosensitivity, imaging of intracellular trafficking and the individual risk of radiation-induced pathologies.	Treatment	2011-2013	To study the mechanisms of radiosensitivity in the thyroid seeking potential links to radio-induced cancers. The second objective is to study the cellular radiosensitivity to improve labeling techniques for imaging cellular traffic.	*NA	€130,000
Fonds National de la Recherche Luxembourg	Private n= 1	National	Luxembourg	Identifying Tumor Escape Mechanisms after Anti-Angiogenic Treatment in Malignant Gliomas-ESCAPE	Treatment	2011-2013	To understand the molecular and metabolic mechanims that enable glioma cells to adapt to hypoxia and identify the key factors involved in the tumor specific metabolic switch allowing survival under stressful microenvironmental conditions.	*NA	€ 800,000
Dutch Cancer Society	Private, n= 1	National	The Netherlands	Designing and testing new intervention therapies for lung cancer and mesotheliomas	Treatment	2008	To develop better treatments for lung cancer and pleural cancer.	*NA	*NA
Dutch Cancer Society	Private, n= 1	National	The Netherlands	The biology of ageing in relation to acute myeloid leukaemia (AML) in older patients	Biology	2009	To gain more insight into the relationship between aging and cancer. In the first place, we want to create a list of genes,	*NA	*NA

							in addition to p16, which play a specific role in the development of AML in elderly patients		
The Federal Ministry of Education and Research, Germany	University, n= 1	National	Germany	Immunotherapy in mature peripheral T-cell lymphomas: The role of allogeneic stem cell transplantation and antibody therapy (an age-and risk-adapted approach)	*NA	2007-2014	*NA	*NA	€ 1,983,513
German Research Foundation	Private, n= 1	National	Germany	Epigenetic regulation of normal hematopoiesis and its dysregulation in myeloid neoplasia	*NA	2010	*NA	*NA	*NA
FWF Austrian Science Fund	Private, n= 1	National	Austria	Tailoring the therapy to the cancer	*NA	2007	*NA	*NA	*NA
FWF Austrian Science Fund	Private, n= 1	National	Austria	Ovarian Cancer: New Tumour Suppressor Gene Identified	*NA	2012	*NA	*NA	*NA
Swiss National Science Foundation	University, NGO, Private, n= 1	National	Switzerland	The educational situation in childhood cancer survivors in Switzerland	*NA	2002-2016	*NA	*NA	€ 57,391.87
Swiss National Science Foundation	University, NGO, Private, n= 1	National	Switzerland	Systems biology approach to molecularly characterize the lung cancer microenvironment	Biology	2012-2015	To gain novel knowledge on stromal cells that determine the growth supporting micro-environment of lung cancer	To identify critical target structures on lung cancer stromal cells and that this knowledge will foster the development of novel diagnostic and therapeutic avenues.	€ 95,653.12
Swiss National Science Foundation	Private, n= 1	National	Switzerland	The biology of cancer-initiating cells	Biology	2012-2015	*NA	*NA	€ 95,653.12
Italian Association for Cancer Research (AIRC)	University, Private, n= 1	National	Italy	Harnessing tumour cell/microenvironment cross talk to treat mature b-cell tumours	*NA	2010-2015	*NA	*NA	€ 2,011,957

Italian Association for Cancer Research (AIRC)	Unviersity, Private, n= 1	National	Italy	Targeting resistances to molecular therapies in metastatic colorectal carcinomas	*NA	2010-2015	*NA	*NA	€ 3,026, 666
Hungarian Scientific Research Fund.	Private, n= 1	National	Hungary	Effect of bacterial and chemoattractant therapy in metastasis regression	*NA	2010-2013	*NA	*NA	€ 9,983,000
Hungarian Scientific Research Fund.	Private, n= 1	National	Hungary	Tumor induced lymphangiogenesis in human non-small cell lung cancer: pathology and therapeutic implications	*NA	2007-2010	*NA	*NA	€ 9,000,000
Breakthroug Breast Caner	NGO, n= 1	National	UK	Understanding how to stop breast cancers becoming resistant to drugs	*NA	2013	To prevent cells from producing oestrogen or responding to it. But breast cancer tumours do not always respond to these drugs, or they can become resistant to them.	*NA	*NA
Breakthroug Breast Caner	NGO, n=1	National	UK	Investigating new ways to kill drug-resistant breast cancer cells	*NA	2013	*NA	*NA	*NA
Children with Cancer UK	NGO, n=1	National	UK	A novel combination therapy to treat metastatic Ewing sarcoma	*NA	2013	Assessment of physical function in survivors of childhood bone and soft tissue tumours	*NA	€ 340,000
Children with Cancer UK	NGO, n=1	National	UK	Assessment of physical function in survivors of childhood bone and soft tissue tumours	*NA	2013	*NA	*NA	€ 66,482
Children with Cancer UK	NGO, n=1	National	UK	**A new treatment approach in acute myeloid leukaemia**	*NA	2013	To detect bowel cancer as early as possible, so patients can be treated and	*NA	€60,589

							remain healthe		
Irish Cancer Society	NGO, n=1	National	Ireland	The inverse resistance relationship between planitum and taxane chemotherapy in ovarian cancer	*NA	2010-2013	*NA	*NA	€ 197,173
Irish Cancer Society	NGO, n=1	National	Ireland	Serological dection and biological validation of antibody based biomarkers specific to colorectal cancer	*NA	2010-2013	*NA	*NA	€ 219,985
Irish Cancer Society	NGO, n=1	National	Ireland	Integrating biomarkers for the stratification of patients into insignification prostate cancer	*NA	2011-2014	*NA	*NA	€ 750,000
Norwegian Cancer Society	University, n=1	National	Norway	Molecular Epidemiology of breast cancer risk and progression	*NA	2009	*NA	*NA	€ 150,000

*NA: Not Avalilable

1.3 Discussion and Conclusion

Under the FP6 and FP7, the EU aimed to develop improved patient-oriented strategies for combating cancer - ranging from prevention to more effective and earlier diagnosis, but focusing mainly on improving treatment (therapeutic and drug developments). In order to achieve these aims, the EU has supported research on dissecting the causes and mechanism of cancer, translating this basic knowledge into clinical applications and supporting clinical research on new and improved interventions. Other issues related to cancer have been also covered, but have received a considerably lower attention (e.g. ageing and cancer, childhood cancers, regional differences, psychosocial aspects, palliative care and guidance to support groups). Thus, room is left for cancer research aimed at improving existing treatments as well as studies of the organization of care, methods to enhance quality of life and prevention.

In the FP6 (2002-2006) the 'Combating Cancer' initiative within the 'Life Sciences, Genomics and Biotechnology for Health' thematic priority resulted in approximately 480 million € allocated to 108 translational cancer research projects all over Europe. As has been already envisaged, these projects have resulted in advances in our understanding of cancer, and has also served to improve and develop anti-cancer therapies.

The Seventh Framework Programme (FP7; 2007-2013), provided extensive financial support for different areas of collaborative cancer research, ranging from basic to pre-clinical, clinical and translational research. The focus was on disease aetiology, new medicines and therapies; identifying and validating drug targets and biological markers that aid in the prevention, early diagnosis and treatment; and assessing the effectiveness of preventive prognostic, diagnostic and therapeutic interventions. Over 100 projects were funded for over 500 million €e under the thematic "cancer" area. The EU funded cancer research in the FP7 Cooperation Programme, taking into account all cancer-related projects, included not only the thematic "cancer" area but also other areas, i.e. diagnostics, nanotechnology, etc. At national level, most funding is provided through governmental and charitable organizations and the health-care/university systems. Although some similarities with the EU funded projects/programs were noted (research areas prioritized), there were few multicenter and collaborative research projects funded. A shift from regional or national efforts to continent-wide collaborations, including collaborative research with the private sector, would be desirable, as well as to pursue the component of translational research in cancer.

Cancer is a complex disease caused by interactions of multiple factors such as genetic predisposition, environmental and lifestyle influences, infectious agents and ageing. The past Framework Programmes have witnessed an important progress in understanding the molecular mechanisms of cancer in the transformation of a normal cell into a cancer cell. Yet, intensive collaboration among scientific, medical and pharmaceutical communities is indispensable. Therefore, collaborative research on cancer is also considered to be a priority in the EU framework programmes. For instance, within the FP7, specific research programs allocated funds for this purpose (also including clinical trials), such as the Innovative Medicines Initiative (IMI). At national level, few RFOs consider the private sector as a recipient of funding. It is needed to pursue the component of translational research in cancer at this level.

Duplication of cancer research efforts between and even within Member States (MS) is very likely. As such, since research priorities defined by the EU (topics or thematic calls) were also adopted by the MS, several RFOs of MS may have fund (partially) projects funded by the EU. Therefore, an alignment of research efforts between the MS would be desirable. Efforts have been already made for a better coordinated research program within Europe. For instance, since 2011, ECCO is leading the European Partnership for Action Against Cancer’s (EPAAC) work package on research coordination, the objective of which is to devise methodologies to coordinate cancer research from all funding sources in Europe.

2 Private Sector Investment in Cancer

Investments in NCD research funding originate from a variety of sources: national governments, regional organizations, charities, non-governmental organizations and supranational organizations. While policy-makers regard the management of NCDs as an increasingly important issue and are engaged in sponsoring research and facilitating cooperation between these organizations for the purpose of developing useful collaborations; less is known about the industry response to NCDs in terms of research and development. In this section of the CA, we consider the background and specifics of private sector investment in NCD research, and in particular, Cancer.

2.0.1. Background: Private Sector Investment in Research and Development

Across the various sectors of industry, the world's top companies are increasing their commitment to research and development (R&D). After the 2009 financial crisis, the world's top 2500 companies, which account for 90% of the world's industrial investment in research and development, enjoyed a brief rebound in sales for the years 2010-11. Although growth stalled in 2012-13, companies continued to invest in R&D, which, overall, increased 4.9% in 2013 (Hernandez et al 2014, 6)[3]. Currently, the top 100 world companies are responsible for 53.1% of the total investment in R&D, which includes 31 companies based in the EU, 39 in the US and 17 in Japan. These companies are also responsible for about one third of all patents filed for approval in the US and EU, with the Electronic and Electrical Equipment sector (Samsung and IBM) being the most active (Hernandez et al 2014,12) [3]

The Pharmaceuticals & Biotechnology sector is one of the largest investors in R&D, claiming about a 18.0% share of total R&D investment for 2014 (Hernandez et al 2014, 47)[3]. However, the sector has a much less significant share of patents to R&D investment ratios. For example, the Electronic and Electrical Equipment sector, which enjoys the highest ratio, is about ten times larger than the ratio for Pharma & Biotech. Today, the production of safe and effective compounds requires substantial investment and cooperation between diverse companies across the sector, particularly bio-tech companies (Hernandez et al 2014, 39-40) [3]. Indeed, biotech companies are outstripping traditional pharmaceutical companies in terms of investment in R&D, which has increased 20.4%, against pharmaceutical, which has itself decreased investment by 0.2% (Hernandez et al 2014, 47) [3].

Although the Pharmaceutical and Biotechnology sector is among the largest in terms of global R&D investment; analysts have become concerned about the nature and quality of those investments. Decreased patent ratios, stalling investment in general R&D and the increasing role of biotech companies in discovering new molecules and bringing them to market are symptomatic of wider systemic shifts across the industry. The sector, they argue, is in the grip of major changes, which are weighing heavily on the capacity of industry to undertake investment in R&D and respond to the growing challenge of NCDs. These shifts are tectonic and include: changed paradigms for scientific research, new measures of productivity and a declining tolerance for risk (Cockburn, 2006[4]; Pammolli et al., 2011[5]).

[3] Héctor Hernández, Alexander Tübke, Fernando Hervás, Antonio Vezzani, Mafini Dosso, Sara Amoroso, Nicola Grassano (2014) EU R&D SCOREBOARD: The 2014 EU Industrial R&D Investment Scoreboard. Brussels: Eupopean Comission. Available online at: http://iri.jrc.ec.europa.eu/scoreboard14.html

[4] David MCockburn. How to make clinical decisions from statistics. Clin Exp Optom. 2006 May;89(3):176-83.

[5] Pammolli, Fabio,Laura Magazzini, Massimo Riccaboni (2011) "The productivity crisis in pharmaceutical R&D", Nature Reviews 10: 428-438

Today, new drug discovery is a high-risk and time-consuming process. Only 1 out of every 5000-10,000 compounds screened becomes an approved drug. And it takes an average of 10 to 15 years at an average cost of more than US$1 billion to develop a successful medicine (Merck 2015)[6]. Significant can losses occur where outputs are dependent on research interaction at the interface of various disciplines, and where there is no guarantee that new compounds will advance to clinical trials. Increased possibility of R&D failure is one of the main factors in the raised estimates of the costs per new molecular entity (NME), on the basis which analysts now question whether industry is in the grip of an R&D productivity crisis (Cockburn, 2006; Pammolli et al., 2011) [4, 5].
In past, analysts lauded the contribution of industry to the advancement of science and medical technologies. Today, however, where they measure productivity in terms of the ratio of the "output" of a process to some measure of "inputs", like rising R&D expenditures and falling or static counts of new drug approvals; they have identified a sharp decline in research productivity over the past decade (Cockburn 2007, 1)[7]. As such, old confidences in the industry and its product development pathway are fading. In 2004, the FDA expressed "growing concern that many of the new basic science discoveries made in recent years may not quickly yield more effective, more affordable, and safe medical products for patients," citing falling numbers of applications for approval of new drugs, and placing the blame squarely on an "increasingly challenging, inefficient, and costly" product development path (cited in Cockburn 2007, 3)[7]. In the 21st century, industry analysts are concerned that the decreasing levels of productivity confronts policy makers with tough questions. Where tax-payers continue to provide significant amounts financial support to industry led R&D, analysts are now asking whether these "poor outcomes justify continued public investment at its current scale?" (Cockburn 2007, 2-3) [7]

2.0.2. Mapping the Private Sector Research Pipeline

In this context, mapping private sector investment in NCD research funding becomes quite important. However, such a mapping exercise also involves unique challenges. For example, the details and strategic focus of public and third sector NCD research funding programmes are readily accessible and, in many cases, a matter of public record. By contrast, the activities of the private sector are not. Governed by the profit motive, the specifics of private sector investment in NCD research are more usually confidential. So, what is the commitment of European pharmaceutical companies to R&D investment in Cancer. How can we map the ways (types of technologies) in which industry has responded to the challenge of Cancer? And how can we assess, or make sense, of this response.

In order to map the industry response (activity, investment and initiatives) to Cancer in terms of research investment, we describe the research pipeline for major European pharmaceutical companies in terms of Molecules in Phase I, Phase II, Phase III, Submission and Approval. Data was collected from the four most recent annual reports available at the companies' global websites (2014-2011). Where data was not available for 2014, the range 2013-2010 was applied. Information was readily available on the web. Results are expressed in terms of phases of development for individual molecules, which are set out in the tables below. The tables also include the total amount of R&D expenses for the available period and the percentage of sales or revenues allocated to R&D.

In order to assess the industry response, we compare the top 10 European headquartered companies in terms of annual R&D investment against unmet European need for Cancer, and also against the response of the top 10 US headquartered companies to unmet US need for Cancer. Table iii details the top ten pharmaceutical companies based in the US and Europe by investment in R&D. In the sections that follow, we discuss unmet need for NCDs in both Europe and the US,

[6] MERK (2015) available on line at http://www.merck.com/index.html
[7] Cockburn, Iain M. (2007) "Is the Pharmaceutical Industry in a Productivity Crisis?" in Josh Lerner and Scott Stern (eds.) Innovation Policy and the Economy, Volume 7, Massachusetts: MIT Press. pp. 1 - 32

mapping and analyzing the commitment of each company to Cancer in terms of their individual research pipelines.

Table iii: Top 20 European and US Pharmaceutical Companies by R&D investment (2013)*

Pharma Co. Rank	**World Co. Rank**	**Company**	**Country**	**Total R&D Investment (Mil EURO)**	Pipeline Data Available
1	5	NOVARTIS	Switzerland	7173.5	Yes
2	6	ROCHE	Switzerland	7076.2	Yes
3	8	JOHNSON & JOHNSON	US	5933.6	Yes
4	12	MERCK US	US	5165.0	Yes
5	14	SANOFI-AVENTIS	France	4757.0	Yes
6	15	PFIZER	US	4750.2	Yes
7	21	GLAXOSMITHKLINE	UK	4154.3	Yes
8	23	ELI LILLY	US	4010.8	Yes
9	34	BAYER	Germany	3259.0	Yes
10	37	ASTRAZENECA	UK	3202.8	Yes
11	38	AMGEN	US	2960.6	Yes
12	39	BOEHRINGER INGELHEIM	Germany	2743.0	Yes
13	40	BRISTOL-MYERS SQUIBB	US	2705.4	Yes
14	52	ABBVIE	US	2059.3	Yes
15	65	CELGENE	US	1603.4	Yes
16	66	NOVO NORDISK	Denmark	1567.4	Yes
17	68	GILEAD SCIENCES	US	1537.1	Yes
18	70	MERCK & CO	Germany	1504.3	No
19	95	ABBOTT LABORATORIES	US	1052.9	Yes
20	96	BIOGEN IDEC	US	1047.1	Yes

*'The 2014 EU Industrial R&D Investment Scoreboard' available at: http://iri.jrc.ec.europa.eu/scoreboard.html

2.1 Unmet Need for Cancer and the Pharmaceutical Sector (EUR)

As it was explained in the previous Impact Assessment Report, although Europe comprises only one eighth of the world's population, it suffers a quarter of the global burden of cancer, in terms of incidence. In 2012, there were an estimated 3.45 million new cases of cancer (excluding non-melanoma skin cancer) and 1.75 million deaths from cancer (Ferlay et al. 2013)[1].

Cost of cancer treatments and research & development on this disease have become a dominant factor in policy making decisions. There is concern about the high cost of new treatments for cancer, probably because most of them are developed by profit institutions.

The current trends of cancer research tend to development of new drugs and therapies, there remains tremendous scope and mileage in cancer research aimed at improving existing treatments as well as studies of the organization of care, methods to enhance quality of life and prevention. Organizational strategies should cover the broad spectrum that makes up cancer research and should fit the objectives of individual Member States as well as the broader European vision for cancer control (Coleman et al. 2008)[8].

The final aim of any cancer research is to improve cancer control for each patient and in society as a whole. In order to translate research findings into strategies that will ultimately improve the prevention, diagnosis, treatment and rehabilitation of cancer, it is not only scientists, but also the lay public and patients' organizations, who must be widely informed about the conduct and the results of research (EPAAC, 2014)[9].

There is a consensus that prevention activities are cost - effectiveness actions for the health care systems. To set cancer prevention priorities in cancer research policies, some actions could be (Vineis and Wild, 2014)[10]:

- To develop and test effective preventive strategies based on structural interventions (including bans, taxation, and urban planning) that integrate with individual health promotion
- To study and test the best organizational ways to integrate primary prevention into health services
- To identify the unknown causes of cancer (including frequent cancers such as colon and breast cancer) with novel methods; in particular, the so-called omics technologies used to probe the genome, epigenome, transcriptome, proteome, and metabolome
- To assess the extent of preventable cancers in all countries, taking into account their specific and changing exposure profiles (e.g., infectious agents)

Burden of disease analysis is a technique used to assess and compare the fatal and non-fatal effects of different diseases (such as prostate cancer) among population groups and over time. It combines data around premature death, measured by the years of life lost (YLL) and non-fatal health outcomes, measured by years lost due to disability (YLD) into a summary measure called the DALY (disability-adjusted life years). This allows the effects of different diseases (such as cancer) and injures to be compared on an equal basis.

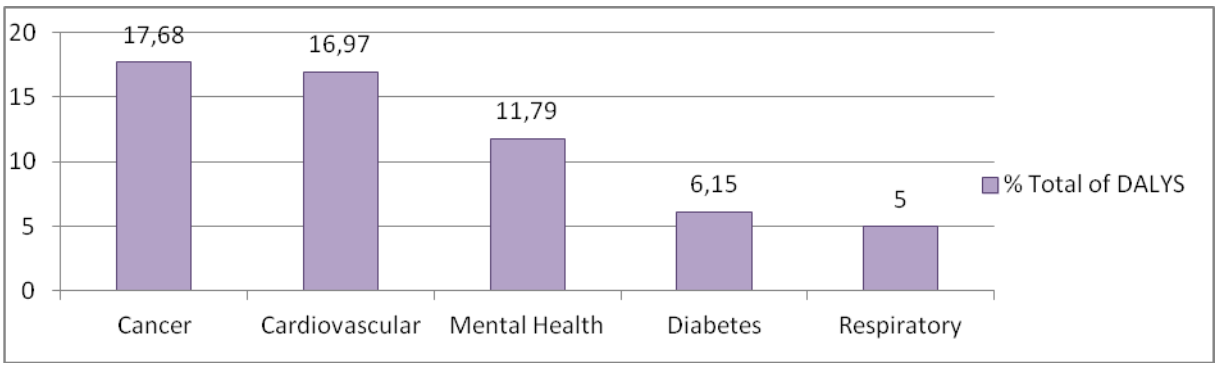
[8] Coleman MP, Alexe DM, Albreht T, McKeee M. Responding to the challenge of cancer in Europe. Ljubljana: Institute of Public Health of the Republic of Slovenia, 2008

[9] EPAAC 2014. Implementation of the Communication from the Commission, from 24 June 2009, on Action Against Cancer: European Partnership [COM (2009) 291 final] and Second Implementation Report on the Council Recommendation of 2 December 2003 on cancer screening (2003/878/EC) http://ec.europa.eu/health/major_chronic_diseases/docs/2nd_implreport_cancerscreening_co_eppac_en.pdf [Accessed March, 30 2015]

[10] Vineis P1, Wild CP2. Global cancer patterns: causes and prevention. Lancet. 2014;383(9916):549-57.

As you can see in the figure ii, Cancer is estimated to be the first cause of the burden of disease in NCDs in Europe by percentage of lost of DALYs (17,68% of the total DALYs), followed by cardiovascular disease (16,97%), mental health (11,79%), diabetes (6,15%) and respiratory (5%).

Figure ii: NCDs in Europe 2010: Percentage of Lost DALYs by Disease Category*



*Sourced at: http://vizhub.healthdata.org/gbd-compare/

In 2013 there were 14.9 million incident cancer cases, 8.2 million deaths, and 196.3 million DALYs. Prostate cancer was the leading cause for cancer incidence (1.4 million) for men and breast cancer for women (1.8 million). Tracheal, bronchus, and lung (TBL) cancer was the leading cause for cancer death in men and women, with 1.6 million deaths. For men, TBL cancer was the leading cause of DALYs (24.9 million). For women, breast cancer was the leading cause of DALYs (13.1 million).

2.2 European Pharmaceutical Sector: Research Pipeline for Cancer

The European pharmaceutical sector has five companies among the world's top ten pharmaceutical firms. And indeed, across Europe, the sector is major investor in R&D. According to the European Federation of Pharmaceutical Industries, the European pharmaceutical sector invested an estimated €30,630 million in R&D across Europe for the year 2013 (EFPI 2014)[11]. The industry also employs about 690,000 people and supports between three and four times than number of jobs across the EU area. The EFPI also asserts that the sector has suffered from the impact of European austerity measures introduced in response to the financial and debt crisis of 2008-9 (EFPI 2014)[11].

2.2.1. NOVARTIS (EUR)

Novartis is a Swiss based company headquartered in Basel. It was formed in 1996 through the merger of Sandoz and Ciba-Geigy. In 2003, Novartis reintroduced the Sandoz brand as a single subsidiary in which it consolidated its generic drugs businesses. Novartis divested its agrochemical and genetically modified crops business in 2000 with the spinout of Syngenta in partnership with AstraZeneca, which also divested its agrochemical business. Today, Novartis focuses its business on three leading divisions: pharmaceuticals (Novartis), eye care (Alcon) and generics (Sandoz). Novartis is currently expanding its presence in the emerging markets of Asia, Africa and Latin America, where there is fast-growing demand for access to high-quality medicines and healthcare. The company has more than 119.000 employees in over 150 countries.

Table iv: NOVARTIS (EUR) Total Research and Development Investment

[11] [EFPI] The European Federation of Pharmaceutical Industries (2014) "The Pharmaceutical Industry in Figures-Key Data 2014. Brussells: EFPI available online at http://www.efpia.eu/uploads/Figures_2014_Final.pdf

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	9900	17.1	9640	16.6	9120	16.1	9240	15.8
% Change	+2.7		+5.7		-1.3			

Since 2012, Novartis has marginally increased its commitment to R&D activities, and has a important number of molecules in cancer in different stages of development. Novartis has a important pipeline of medicines in cancer in phase I and phase II that probably will be in the market around 2020 or later.

Table v: NOVARTIS (EUR) Research Pipeline: Oncology

Year	Product Name	Indication	Phase
2014	Jakavi (ruxolitinib)	Myelofirosis, policytemia vera	Submission
2014	Panobinostat	Multiple Myeloma, hematological cancer	Submission
2014	Alpelisib	Solid tumors	I
2014	Zykadia (ceritinib)	Non-small cell lung cancer	Submission
2014	Encorafenib	Melanoma	II
2014	Ribociclib	Breast cancer, solid tumors	III
2014	EGF816	Solid tumors	II
2014	Capamatinib	Solid tumors	II
2013	Luminespib	Solid tumors	II
2013	Sonidegib	Basal cell carcinoma	II
2013	Binimetinib	Solid tumors	III
2013	Tasigna (nilotinib)	Metastatic melanoma c-KIT +	II
2013	Dovitinib lactate	Renal cell cancer	II
2013	BGJ398	Solid tumors	II
2013	LJM716	Solid tumors	I
2012	Buparlisib	Breast cancer, solid tumors	III
2012	Exjade (deferasirox)	Thalassemia	Approved
2012	Midostaurin	Mastocytosis, acute myeloid leukemia	III
2012	Signifor LAR (pasireotide)	Carcinoid syndrome	III
2012	BEZ235	Solid tumors	II
2012	CTL019	Leukemia	II
2011	HCD122	Hematological tumors	I
2011	LCI699	Solid tumors	II
2011	Everolimus	Breast cancer, hepatocelular carcinoma, lymphoma	Submission
2011	Dovitinib lactate	Renal cell cancer, solid tumors	III

2.2.2. ROCHE (EUR)

ROCHE is Swiss pharmaceutical company headquartered in Basel, Switzerland. Founded in 1896 by Fritz Hoffmann-La Roche, it is the largest European pharmaceutical company in terms of investment

in R&D. Today, Hoffman's descendants own close to half the company's bearer shares with voting rights (45%). ROCHE owns several important biotechnology companies, like Genentech and Ventana in the US, and Chugai Pharmaceuticals in Japan. In its early years, ROCHE gained a reputation for being the first company to mass-produce synthetic vitamin C in 1934. Today, it is a market leader in cancer research and in-vitro diagnostics. They have over 88.000 employees across more than 150 countries. Since 2012, ROCHE's total investment in R&D had been increasing at an average of 3.36%. ROCHE is focused on disease areas such as oncology, neuroscience and infectious diseases, immunology and cardiovascular diseases.

Table vi: ROCHE (EUR) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	8900	18.6	8700	18.6	8500	18.6	8100	19.0
% Change	+2.30		+2.35		+4.94			

ROCHE has increase the R&D expenditure around 3% as average during the last three years. As on of the largest pharmaceutical company in Europe, ROCHE has an important number of cancer medicines in its pipeline, that is probably one of its main area of research. Some of them has been approved recently, but other are in early stages (phase I and II).

Table vii: ROCHE (EUR) Research Pipeline: Oncology

Year	Product Name	Indication	Phase
2014	Venetoclax	Blood cancer and solid tumors	III
	Polatuzumab vedotin	Non-Hodgkin's Lymphoma	II
	RG7155	Breast and ovarian cancer	Ib
	RG7813	Anti IL-2 Cancer	I
	RG7446	Methastatic urothelial bladder cancer	I
	RG6046	Breast cancer	I
	Cobimetinib (+ Zelboraf)	Melanoma	III
2013	Gazyva (Obinutuzumab)	Chronic Lymphocytic Leukemia	Approved US
	Obinutuzumab		III
	Kadcyla (trastuzumab emtansine)	HER-2+ metastatic breast cancer	Approved US - EU
2012	Trastuzumab		III
2011	Pertuzumab		III
2012	Perjeta (pertuzumab)	HER-2+ breast cancer HER-2+ breast cancer	Approved US – EU
2013	Herceptin subcutaneous		Approved EU
2013	Tarceva (erlotinib)	Non-small cell lung cancer	III
	Alectinib		I/II
	Avastin (bevacizumab)	Advanced cervical cancer + other	III
2011	Erivedge (vismodegib)	Advanced basal cell carcinoma	II, approved in US 2012 Regulatory filing Switzerland
2012	Zelboraf (vemurafenib)	Metastatic melanoma	Approved EU
	Rituxan (rituximab)	Non Hodgkin's Lymphoma	Regulatory Approval US
2011	Xeloda (capecitabine)	Advanced-recurrent stomach cancer	Regulatory Approval in Japan

2.2.3. SANOFI-AVENTIS (EUR)

Sanofi-Aventis is a French pharmaceutical company currently headquartered in Paris. It was formed in 2004 when Sanofi-Synthélabo acquired Aventis via a hostile takeover bid in which the French government played a major role in resolving. Today, the company is focused on the seven strategic growth platforms: diabetes, vaccines, consumer healthcare, rare diseases & multiple sclerosis. They have 45000 employees across 40 countries.

Table viii: SANOFI-AVENTIS (EUR) Total Research and Development Investment

Mil Euro	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	4824	14.3	4770	14.5	4922	14.1	4811	14.4

% Change	+1.13	-3.09	+2.31	

R&D in Sanofi-Aventis has been irregular during the last years, where in some it has been some increase with respect to the previous year, but in some other it has been decrease (on the other hand, % of sales has been constant). Cancer medicines is one of the main areas of interest for Sanofi-Aventis, having as a consequence an important pipeline. During the last year, a number of products has stopped on the research.

Table ix: SANOFI-AVENTIS (EUR) Research Pipeline: Oncology

Year	Product Name	Indication	Phase
2014	SAR260301	Solid tumors	Stopped
2014	SAR256212 (MM-121)	Breast, lung and ovary cancer	Stopped
2014	SAR245408 (XL147)	Solid tumors	II
	SAR650984	Multiple myeloma	II
	SAR124844	Solid tumors MET+	I
2014	SAR408701	Adenocarcinoma	I
	SAR566658	Solid tumors	I
	SAR153192	Solid tumors	Stopped
2013	Fedratinib	Solid tumors	Stopped
2013	Iniparib	Non-small-cell lung cancer	Stopped
2013	SAR245409	Lymphoma and leukemia	II
	Coltuximab ravtansine	Malignant b-cell tumors	II
2012	SAR405838	Solid tumors	I
2012	GC 1008	Solid tumors	Stopped
2011	Colar/Evoltra	Acute myeloid leukemia	III
2011	Clofarabine	Pediatric Acute lymphoblastic leukemia	I
	GENZ-644282	Solid tumors	I
	GC1008	Solid tumors	I
	SAR307746 (REGN910)	AML	Stopped
	Zaltrap (afilbercept)	Colorectal cancer	III
	Ombrabulin	Sarcoma	III

2.2.4. **GLAXO** SMITH KLINE **(EUR)**

GSK is a British multinational pharmaceutical company currently headquartered in Brentford. It was established in 2000 by a merger of Glaxo Wellcome and SmithKline Beecham. GSK has a portfolio of products for major disease areas such as asthma, cancer, infections, mental health, diabetes and digestive conditions. In March 2015, they acquired Novartis's vaccines business (excluding influenza vaccines). Today, GSK has more than 100000 employees across 110 countries.

Table x: GLAXO SMITH KLINE (EUR) Total Research and Development Investment

Mil GBP	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	3100	13.5	3400	12.8	3500	13.2	4000	14.6
% Change	-8.82		-2.86		-12.5			

As its statement of focus suggests, GSK has a number of molecules in development that are relevant to cancer. There are a few products that have been approved recently in US and Europe, and some medicines now in phase III. However, GSK seems to have progressively decreased its commitment to R&D activities over the period (2011-4), and this can be the reason because there is just only one product in early stages of research.

Table xi: GLAXO SMITH KLINE (EUR) Research Pipeline: Oncology

Year	Product Name	Indication	Phase
2014	Afuresertib	Multiple Myeloma	I
2014	Arzerra (ofatumumab)	Blood cancer	III
2014	Revolade/Promacta (eltrombopag)	Myelodysplastic syndrome	III
		Severe aplastic anaemia	Approved
2013	Tafinlar (dabrafenib)	BRAF + Metastatic melanoma	Approved US - EU
	Mekinist (trametenib)		Approved US
2013	Tyverb/Tykerb (lapatinib)	Breast cancer	III
2013	Votrient (pazopanib)	Ovarian cancer	Field
		Renal cell cancer	III
2011	Xgeva (denosumab)	Bone metastatic disease	Approved
2010	Prolia (denosumab)	Bone loss in prostate cancer patients	Approved

2.2.5. BAYER (EUR)

Founded in 1863, Bayer is a German chemical and pharmaceutical company headquarter in Leverkusen, Germany. In the Aftermath of World War One, Bayer became part of IG Farben, which in the aftermath of World War Two, was broken up following its participation in Nazi war crimes. In 1978, the company retook the name 'Bayer'. Today, Bayer is active in healthcare, but also has major divisions in material and crop science. The company is mainly focused on familiar over-the-counter consumer health care products and prescription medicines. The company has about 118900 employees across 75 countries.

Table xii: BAYER (EUR) Total Research and Development Investment

Mil EURO	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	3574	8.5	3406	8.5	3013	7.6	2932	8.0

% Change	+4.9	+13.0	+2.8	

Bayer is progressively increasing its commitment to R&D investment. We can see an important increase (+13 %) in R&D between 2012 and 2013. It is also important the Bayer's pipeline in oncology treatments, where it can be observed that some product has been submitted during the last years for marketing authorization and some other are in previous phase (II and III).

Table xiii: BAYER (EUR) Research Pipeline: Oncology

Year	Product Name	Indication	Phase
2014	Copanlisib	Non-Hodgkin's lymphoma	II
2014	ODM-201	Prostate cancer	III
2014	Roniciclib	Small-cell-lung cancer	II
2013	Nexavar (sorafenib)	Breast, non-small-cell lung, kidney and thyroid cancer	Submited for approval
2013	Stivarga (regorafenib)	Colorectal and inoperable gastrointestinal stromal tumors	Submitted for approval
2013	Refametinib	Cancer	II
2012	Xofigo (Radium-223 dichloride)	Bone metastases	Sumitted for approval
2011	Alpharadin	Bone metastases in prostate cancer	III
2011	Regorafenib	Cancer	II

2.2.6. ASTRAZENECA PLC (EUR)

AstraZeneca PLC is a British-Swedish company with its headquarters in London. Founded in 1999 by the merger of Astra AB (Swedish) and the Zeneca Group (British), AstraZeneca focusses on three areas of healthcare: CVDs, Oncology, CRDs, Inflammation and Autoimmunity. The company is also active in the Infection, Neuroscience and Gastrointestinal disease areas. AstraZeneca also collaborates and cooperates with other leading companies in the sector. In 2012, it announced a collaboration with the American company Amgen on inflammatory disease treatments. The same year, it announced a joint acquisition of the biotechnology company Amylin Pharmaceuticals with American company Bristol Myers Squibb. Today, the company has about 57500 employees across 100 countries.

Table xiv: ASTRAZENECA (EUR) Total Research and Development Investment

Mil USD	**2014**		**2013**		**2012**		**2011**	
Total R & D Expense	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**
	5579	21.4	4821	18.8	5243	18.7	5523	16.4
% Change	+15.7		-8.0		-5.1			

Of the top 10 European pharmaceutical companies, AstraZeneca PLC has a large commitment to oncology by products in development. It demonstrates a greater commitment to oncology, where there are around 25 oncology products in pipeline in different phases. In 2014, the company

massively increased its commitment to R&D, almost tripling its aggregate investment of 2012, making it the third-largest European investor in R&D for 2014. The increase may be related to its joint acquisition of Amylin Pharmaceuticals.

Table xv: ASTRAZENECA PLC (EUR) Research Pipeline: Oncology

Year	Product Name	Indication	Phase
2014	AZD9496	Breast cancer	I
2012	MEDI0639, 6469	Solid tumors	I
2014	Volitinib		II
2011	AZD5363, 8330	Solid tumors	I
2011	MEDI-565		I
2014	MEDI-573, AZD4547		II
2011	MEDI3617, 0680, 4736		I
2014	Lynpraza (Olaparib)	Solid tumors	III
2014	AZD3750	Non-small-cell lung cancer	I
2013	Selumetinib	Solid tumors	III
2011	Tremelimumab		II
2011	AZD1480		I
2013	AZD2014		II
2012	AZ1208	Haematological malignancies	I
2012	AZD150, 9150		I
2013	MEDI-551		II
2013	AZD1775	Ovarian cancer	II
2013	AZD8186, 9291, 5312, 6738, 8835	Solid tumors	I
2012	MEDI-575	Glioblastoma, Non-small-cell lung cancer	II
2011	Faslodex (fulvestrant)	Breast cancer	III
2011	Iressa (gefitinib)	Tumor progression	III
2011	Caprelsa (vandetanib)	Tyroid cancer	III
2011	Ranmark (denosumab)	Bone metastasis	III
2011	AZD8931	Breast cancer	II
2011	Fostamatinib	Haematological malignancies	II
2011	AZD3514	Prostate cancer	I
2011	Moxeturnomab pasuadotox	Haematological malignancies	I

2.2.7. BOEHRINGER-INGELHEIM (EUR)

Originally founded in 1885 by Albert Boehringer, Boehringer Ingelheim is a German pharmaceutical company headquartered in Ingelheim, Germany. Today, Boehringer Ingelheim remains a family owned company. Its focus is on CRDs, metabolism, immunology, oncology and central nervous system diseases. The company claims a reputation for providing effective products for the treatment of COPD. It has about 47700 employees across 146 affiliates.

Table xvi: BOEHRINGER-INGELHEIM (EUR) Total Research and Development Investment

Mil EURO	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	2654	19.9	2743	19.5	2795	19.0	2516	19.1

% Change	-3.24	-1.9	+11.0	

Boehringer Ingelheim is a pharmaceutical company where the commitment to R&D investment has been reduced in the 2013 compare to the previous year. The company has just a few products in the cancer pipeline, one of them submitted and the others in latter stages in the research pipeline.

Table xvii: BOEHRINGER-INGELHEIM (EUR) Research Pipeline: Oncology

First launch	Product Name	Indication	Phase
2015	Vargatef (nintedanib)	Non-small-cell lung cancer	Submited in EU
	Nintedanib	Ovarian cancer	III
2013	Giotrif/Gilotrif (afatinib)	Head and neck cancer	III
	Volasertib	Acute Myeloid Leukemia	III

2.2.8. NOVO-NORDISK (EUR)

Founded in 1989 through the merger of the smaller Danish companies Nordisk Insulinlaboratorium and Novo Terapeutisk Laboratorium, Novo Nordisk is a Danish pharmaceutical company currently headquartered in Bagsvaerd, Denmark. The company's major product lines address the disease areas of diabetes, hemostasis and also growth hormone therapy and hormone replacement therapy. The company manufactures pharmaceutical under various brand names, which include Levemir, NovoLog, Novolin R, NovoSeven, NovoEight and Victoza. Today, the company has about 39000 employees across 75 countries. Importantly, the company records its results in Danish currency.

Table xviii: NOVO-NORDISK (EUR) Total Research and Development Investment

Mil DKK	2014		2013		2012		2011	
Total R & D Expense	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**
	13800	15.5	11700	14.0	10900	14.0	9300	14.5
% Change	+17.94		+7.33		+17.2			

With its focus on other disease areas, Novo Nordisk does not have any Cancer relevant molecules in development. But, since 2011, the company has progressive increased its commitment to R&D.

2.2.9. Merck KGaA (EUR)

Founded in 1668 in Darmstadt, Merck is the world's oldest pharmaceutical and chemical company. The 1887 establishment of an office in New York gave rise to the subsidiary Merck & Co. four years later. Since the end of World War I in 1917, the two companies have been separate. The original company, Merck of Darmstadt, Germany, holds the global rights to the name and the trademark MERCK, except in North America, where the company's brand is EMD ("Emanuel Merck Darmstadt"). The Merck family still controls a majority 70.3% of the company's shares. In 2006, Merck KGaA acquired Serono, which since January 2007 has operated as Merck Serono International SA, with headquarters in Darmstadt. Merck Serono's therapeutic focus is on oncology, immune-oncology, immunology, multiple sclerosis, fertility, endocrinology, biosimilars and neglected diseases.

Table xix: Merck KGaA (EUR) Total Research and Development Investment

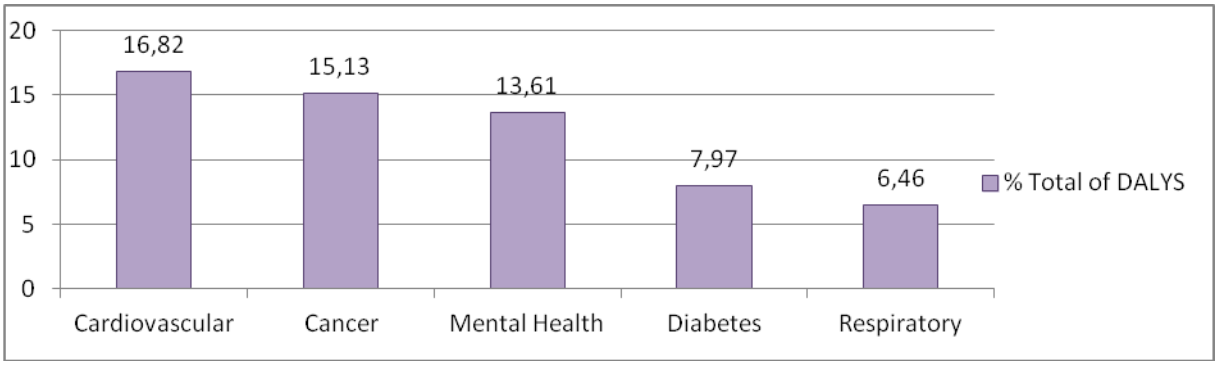
Mil DKK	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	1704	15.0	1504	14.0	1511	14.0	1517	15.3
% Change	+13.30		-0.50		-0.40			

In May 2013, Quintiles, the largest contract research organization (CRO), signed a five-year deal as Merck Serono's sole clinical development provider, and the significant increase in R&D expenditure in 2014 may be attributable to this partnership. Merck KGaA/Merck Serono are not active in MHDs.

2.3 Unmet Need for Cancer and the Pharmaceutical Sector (US)

In the United States, the burden of disease associated with cancer is lower than that of Europe. According to the GBD, the US seems to have larger problems with categories like diabetes and mental health than Europe; and the situation for CVDs and Cancer is somewhat reversed. In the US, CVDs are the largest disease category in terms of lost DALYs, but the levels of lost DALYs in Europe and the US are about the same.

Figure iii: NCDs in United States 2010: Percentage of Lost DALYs by Disease Category*



**Sourced at: http://vizhub.healthdata.org/gbd-compare/*

Breaking into disease areas, cancer remains the second largest contributor to lost DALYs in the US, with 15,13% of the total DALYs (In Europe was the first cause). The first cause is cardiovascular (16,92%). Mental health (13,61%), diabetes (7,97%) and respiratory (6,46%) are the third, fourth and fifth cause, respectively.

2.4 US Pharmaceutical Sector: Research Pipeline for Cancer

Five of the world's top ten pharmaceutical companies have their headquarters in the US, which is also the world's largest market for pharmaceuticals, and a world leader for investment in R&D. U.S. firms carryout the majority of global R&D and hold the intellectual property rights on most new medicines. Considered as an aggregate, the US research pipeline has approximately 3,400 compounds currently under development in the United States, which is significantly more than any

other region (PHRMA 2015)[12]. According to Pharmaceutical Research and Manufacturers of America, the US biopharmaceutical industry employs more than 810,000 people, supporting another approximately 3.4 million jobs nationally. In addition, the US biopharmaceutical sector is one of the most R&D-intensive sectors in the United States and around the world. In the US, the industry invests more than 10 times the amount of R&D per employee than all manufacturing industries overall (PHRMA 2015)[12].

2.4.1. JOHNSON AND JOHNSON

Founded in 1886, Johnson & Johnson is a U.S. medical devices, pharmaceutical and consumer healthcare products company currently headquartered in New Brunswick, New Jersey. Its consumer division provides well known over the counter medicines and a range of baby care and skin care products. Its medical devices division, which we consider in the next section, specialises in orthopedics, neurological disease, diabetes care, infection prevention, and cardiovascular disease. And its pharmaceutical division focusses on oncology, immunology, neuroscience, diabetes and cardiovascular diseases.

Table xx: Johnson & Johnson (US) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	8494	11.4	8183	11.5	7665	11.4	7548	11.6
% Change	+3.8		+6.8		+1.6			

Johnson & Johnson does have several molecules in development for cancer. Some of them have been approved during the last years, but other are in the last stage of development (phase III). As a side note, however, in December 2012, the company received approval for tuberculosis drug, Sirturo (bedaquiline), which is the first new medicine to combat the infection in over forty years. The company has been progressively increasing its commitment to R&D investment since 2011.

Table xxi: Johnson & Johnson (US) Research Pipeline: Oncology

Year	Product Name	Indication	Phase	Comments
NA*	ZYTIGA® (abiraterone acetate)	Metastatic advanced prostate cancer and metastatic castration-resistant prostate cancer	Approved	First approved in 2010. In 2012 extended indication's approval
	IMBRUVICA™ (ibrutinib)	Previously treated Mantle Cell and Lymphoma and CLL	Approved	In Phase III for several other indications
	SYLVANT® (siltuximab)	Multicentric Castleman's disease	Approved	Approved in 2014
	HuMax-CD38® (US)	Refractory multiple myeloma	Phase III	Plans for filling

[12] [PHRMA] Pharmaceutical Research and Manufacturers of America (2015) "The Biopharmaceutical Industry: Creating Research, Progress and Hope", online at: http://www.phrma.org/about/biopharmaceutical_sector (accessed 29.05.2015)

	(daratumumab)		concluded	for approval from 2014 to 2017. ARN-509 is also in Phase I for the treatment of castration-resistant prostate cancer.
	YONDELIS® (US) (trabectedin)	2nd line for soft tissue sarcoma		
	ARN-509 (androgen receptor antagonist)	Pre-metastaic prostate cancer		

*NA: Not Avalilable

2.4.2. MERCK & CO (US)

Merck US is headquartered in Kenilworth, New Jersey. The company was established in 1891 as a US subsidiary of the German company Merck, which was originally founded in 1668. During the First World War, the US government confiscated Merck and reestablished it as an independent American company. In 2013, Merck invested $7,500 million in R&D, which represents the largest amount in the sector both globally and the US. However, Merck's overall investment level in R&D has been progressively falling over the period (2010-2014), with a major fall of 22.7% in 2011.

Table xxii: MERCK & CO (US) Total Research and Development Investment

(Mil USD)	2014		2013		2012		2011	
Total R & D Expense	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**
	7180	16.9	7500	17.0	8200	17.4	8500	17.7
% Change	-4.30		-8.54		-3.53			

Merck **& Co** is the largest US pharmaceutical company by R&D investment, but has only two products in the pipeline. One of them (Pembrolizumab) was approved in 2014 and the other (Vintafolide) is in phase III in the US. During the last years, Merck commitment on R&D has been reduced significantly.

Table xxiii: MERK (US) & CO Research Pipeline: Oncology

Year	Product	Indication	Phase	Comments
NA*	Vynfinit® (vintafolide)	Ovarian cancer and non small cell lung cancer	Filled-EU Phase III - US	The EU has granted Vintafolide with Orphan Drug status.
	Keytruda® (pembrolizumab)	Advanced melanoma and other tumor types	Approved in 2014	Other types: bladder, non-small cell lung cancer and head and neck cancer.

*NA: Not Avalilable

2.4.3. PFIZER (US)

Founded in New York in 1849 by Charles Pfizer and Charles F. Erhart, Pfizer is American pharmaceuticals company currently headquartered in New York. Since 2004, the company's shares have been listed a component of the Dow Jones Industrial Average. Recently, Pfizer has also been the subject prosecutions for illegal and off-label marketing in relation to the arthritis drug Bextra, paying the US government multi-billion dollar settlements. Pfizer produces medicines for a wide 0range of disease areas, including: oncology, diabetes, cardiovascular disease and neurology

Table xxiv: PFIZER (US) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	8393	16.9	6678	12.9	7870	13.7	8681	14.2
% Change	+25.7		-15.1		-9.34			

Pfizer has several oncology relevant molecules in development, as cancer is one of the major disease areas of research in Pfizer. In the pipeline there are different products in the diverse phases. It is really interesting that Pzifer, as innovative company, is working in preparing a trastuzumab biosimlar probably because biosimilar market is a potential sector where is needed more investment. The company's commitment to R & D has been decreasing progressively since 2011 to 2013. Beginning in 2014, there is a significant increase of 25%.

Table xxv: PFIZER (US) Research Pipeline: Oncology

Year	Product Name	Indication	Phase	Comments
NA*	Tanezumab	Cancer pain	Phase II	Biologic
	Dacomitinib (PF-00299804)	Previously treated and 1st line advanced non-small lung cancer	Phase III	
	Palbociclib (PD-0332991)	1st line advanced breast cancer and recurrent advanced breast cancer	Phase III	
	PF-05280014	Metastatic Breast Cancer	Phase I	A trastuzumab biosimilar
	Sutent	Renal Cell Carcinoma Adjuvant	Phase III	
	Xalkori (crizotinib)	ALK positive 1st and 2nd line and Non-small cell lung cancer	Phase III	Supports potential full approval in the U.S.
	Inlyta (axitinib)	Liver cancer	Phase II	
	PF-03446962	2nd line hepatocellular Carcinoma	Phase II	Biologic

*NA: Not Avalilable

2.4.4. ELI LILLY (US)

Eli Lilly was founded in 1877 by Eli Lilly, a pharmaceutical chemist and veteran of the American Civil War, who was company president until his death in 1898. Eli Lilly was the first pharmaceutical company to mass produce break-through drugs like insulin, polio vaccine and penicillin. Today, the company remains the largest manufacturer and distributor in the world of psychiatric medications. In 2009, Eli Lilly paid a $515 million fine in relation to the off-label marketing of the dementia drug, Zyprexa. Today, the company's focus is on the disease areas of autoimmunity, cardiovascular disease, musculoskeletal disorders, neuroscience, oncology and diabetes.

Table xxvi: ELI LILLY (US) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	4734	24.1	5531	23.9	5278	23.4	5021	20.7
% Change	-14.4		+5.0		+5.0			

Eli Lilly does have several molecules in development for cancer, most of them in phase III that probably will be in the market in the next years. The company's levels on investment in R&D have steadily decreased since 2011, but dropped substantially (around 14%) in 2014.

Table xxvii: ELI LILLY (US) Research Pipeline: Oncology

Year	Product Name	Indication	Phase	Comments
NA*	Tanezumab	Cancer related bone pain	Phase III	Co- developed with Pfizer. Also in Phase III for moderate-to-sever chronic osteoarthritis pain.
	CDK 4\6 inhibitor	Cancer	Phase III	
	Enzastaurin	Diffuse large B-cell lymphoma	Phase III	
	Ramucirumab	Advanced Gastric Cancer	Registration	Submission for approval in 2013
		Solid Tumors	Phase III	
	Necitumumab	Metastatic squamous non-small cell lung cancer (NSCLC)	Phase III	Sublimited In 2014 for approval as a 1st line treatment for squamous NSCLC.

*NA: Not Avalilable

2.4.5. AMGEN (US)

Amgen is one of the world's leading independent biotechnology companies and it is committed to unlocking the potential of biology for patients suffering from serious illnesses by discovering, developing, manufacturing and delivering innovative human therapeutics. Amgen uses tools like advanced human genetics to unravel the complexities of disease and understand the fundamentals of human biology. According to its website, Amgen focuses on areas of unmet medical need. Amgen works to fight against cancer, kidney disease, rheumatoid arthritis, bone disease and other serious illnesses (Amgen website).

Table xxviii: AMGEN (US) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	4297	21.4	4100	22.5	3400	20.4	3200	20.9
% Change	+4.8		+20.6		+6.25			

Amgen has increased its investment in R&D during the last years, with important years as 2013 (+20.6%). In the pipeline there is a few products for cancer in phase III, but probably, taking into account the amount of investment during the last years, Amgen will have more products in the pipeline in early stages soon.

Table xxix: AMGEN (US) Research Pipeline: Oncology

Year	Product Name	Indication	Phase
2013	Talimogene laherparepvec	metastatic melanoma	Phase III
2013	Trebananib	Ovarian Cancer	Phase III
2014	Bilinatumomab	ALL (acute lymphoblastic leukemia)	Approved
2013	Rilotumumab	gastric cancer	Phase III
2011	Ganitumab	Pancreatic cancer	Phase III
2010	XGEVA™	Bone metastases from solid tumors	Approved

2.4.6. BRISTOL MYERS SQUIBB (US)

Founded in New York in 1858 by Edward R. Squibb, Bristol-Myers Squibb is a US based pharmaceutical company currently headquartered in New York City. During the American Civil War, the company was an important source of medicines for the Union Army, manufacturing the famous Squibb pannier, a compact wooden medicine chest for use by US army surgeons on the battlefield which filled with about 50 medicines, including chloroform for use in amputations. Today, Bristol-Myers Squibb manufactures pharmaceutical products in a number of disease areas including: cancer, HIV/AIDS, cardiovascular disease, diabetes, hepatitis, rheumatoid arthritis, fibrotic diseases and psychiatric disorders.

Table xxx: BRISTOL MYERS SQUIBB (US) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	4534	28.5	3731	30.3	3904	28.6	3839	21.8
% Change	+21.5		-4.4		+1.7			

Except in 2013 (-4.4%), the investment in R&D has increase during last years by Bristol Myers Squibb. In cancer there are several products in the pipeline, some of them just approved or under the registration process, but other in the different stages of the research (phase I, II and III).

Table xxxi: BRISTOL MYERS SQUIBB (US) Research Pipeline: Oncology

Year	Product Name	Indication	Phase	Comments
NA*	Yervoy® (ipilimumab)	Advanced Melanoma	Approved	Studies for Lung cancer.
	Opdivo® (nivolumab)	Non-small cell lung cancer, advanced melanoma and renal cell carcinoma	Registration Trials	Advanced immuno-oncology agent with a development program that compromises more

				than 30 studies.
	Urelumab & Lirilumab	Cancer	Phase I/II	Anti-CD137 and anti-KIR monoclonal antibody.
	HuLuc63 (elotuzumab)	Multiple myeloma	Phase III	Monoclonal antibody.
	Sprycel® (dasatinib)	Lung Cancer	Phase II	Approved in the U.S. for CML.
	Brivanib	Hepatocellular carcinoma.	Phase III	BMS-582664 is the trade name.

*NA: Not Avalilable

2.4.7. ABBVIE (US)

Formed in 2011, Abbvie is a US biopharmaceuticals company headquartered in Chicago, Illinois. Abbvie was formed via a divestment from Abbot Laboratories. Whereas Abbott Laboratories focuses on diagnostic equipment, medical devices and consumer health care products; AbbVie operates as a research-based biopharmaceutical company. The company claims the development of two important breakthrough medications for the treatment of HIV. Today the company's research focus is on areas such as: immunology, oncology, neuroscience, kidney and disease, and women's health

Table xxxii: ABBVIE (US) Total Research and Development Investment

Mil USD	**2014**		**2013**		**2012**		**2011**	
Total R & D Expense	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**
	3297	16.5	2855	15.19	2778	15.11	2618	15.0
% Change	+15.48		+2.77		+6.11			

Abbvie's commitment to R&D investment has been gradually increasing since 2011, highlighting the year 2014 where the increase was more than 15%. There is just 4 product in Abbvie's pipeline, all of them in phase III, so the products can be in the market in the next few years.

Table xxxiii: ABBVIE (US) Research Pipeline: Oncology

Year	Product Name	Indication	Phase	Comments
NA*	ABT-199	Chronic lymphocytic lymphoma	Phase III	
	Veliparib	Triple-negative breast cancer	Phase III	In 2012 it was in Phase II for the treatment of other solid tumors, like: brain metastases from non-small-cell lung cancer being treated with

				radiation therapy and non-small-cell lung cancer in combination with chemotherapy
	Elotuzumab	Multiple myeloma	Phase III	Collaboration with BMS
	ABT-199	Chronic lymphocytic leukemia	Phase III	Collaboration with Roche Holding AG

*NA: Not Avalilable

2.4.8. CELGENE´S (US)

Founded in 1986, Celgene is a US based biopharmaceutical company currently headquartered in Summit, New Jersey. Celgene's research focus is on the areas of cancer, immune and inflammatory disorders. Major compounds in development concern the treatment of hematological and solid tumor cancers, together with chronic lymphocytic leukemia, non-Hodgkin's lymphoma, small cell lung cancer and prostate cancer.

Table xxxiv: CELGENE (US) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	2431	32.13	2226	34.99	1724	32.0	1600	34.04
% Change	+9.2		+29.12		+7.75			

Cancer is one of the area where Celgene is focus its research. The company has an important pipeline in the different phases of research. In some of the products the company is looking for a different indication. Celgene has recorded the second largest percentage increase in terms of investment in R&D of the top 10 US pharmaceutical companies. Since 2011, its level of investment has increased around of 50 %

Table xxxv: CELGENE (US) Research Pipeline: Oncology

Year	Product Name	Indication	Phase	Comments
NA*	ABRAXANE ® (paclitaxel)/gemcitabine	Pancreatic cancer for patients who have successfully undergone surgery	Phase III	In 2012 it was in Phase III for metastatic pancreatic cancer
	ABRAXANE ® (paclitaxel)	Triple-negative metastatic breast cancer and lung, ovarian and colorectal cancer	Different Phases	
		Advanced non-small cell lung	Approved	Approval in 2012

		cancer		
		Metastatic Melaoma	Phase III	It has shown a clinically superior result compared to a standard of care
	REVLIMID ® (lenalidomide)	Newly diagnosed myeloma patients not eligible for transplant	Sublimited (2013)	Commitment in fighting Myeloma
		Non-delecton 5q myelodysplastic syndromes (MDS)	Phase III	Studies as maintenance therapy in diffuse large B-cell lymphoma
	RELEVANCE ® (lenalidomide+rituximab)	Follicular Lymphoma	Phase III	
	MOR 202 (monoclonal a.b)	Multiple myeloma and certain leukemias	Phase I/IIa	Collaboration with Morphosys
	ACY-1215 (HDAC 6 inhibitor)	Heavily treated myeloma patients	Phase II	It has shown activity in combination with REVLIMID ® . Collaboration with Acetylon
	CC-486 (oral epigenetic therapy)	MDS and acute myeloid leukemia	Phase III	In Phase II to evaluate different priming strategies in solid tumors.

*NA: Not Avalilable

2.4.9. GILEAD (US)

Founded in June 1987 by the then 29 year old Michael Riordan, Gilead Sciences is US based biotechnology currently headquartered in Foster City, California. Gilead's research focus in on HIV/AIDS, liver diseases, cancer, CRDs and CVDs. The company also boasts the first complete treatment regimen for HIV infection via a single pill taken once-daily, together with the first oral antiretroviral pill for reducing the risk of HIV acquisition.

Table xxxvi: GILEAD (US) Total Research and Development Investment

Mil USD	**2014**		**2013**		**2012**		**2011**	
Total R & D Expense	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**
	2854	11.4	2120	19.6	1760	18.72	1230	15.19
% Change	+34.62		+20.45		+43.08			

Gilead has just a few products in the pipeline for oncology treatments. One of them was approved in 2014, and the others are in phase II and III. Gilead has narrowly recorded the largest percentage increase of US pharmaceutical companies in terms of investment in R&D. Since 2011, its level of investment has doubled. Taking into account the important investment of Gilead in R&D, it is looked like that oncology is not one of the main area of disease for this company.

Table xxxvii: GILEAD (US) Research Pipeline: Oncology

Year	Product Name	Indication	Phase	Comments
NA*	Idelalisib	Indolent non-Hodgkin`s lymphoma (iNHL) and chronic lymphocytic leukemia (CLL)	Approved (2014)	Monoclonal antibody, it is also being studied in various Phase II studies for liver fibrosis and solid tumors.
	Simtuzumab	Pancreatic cance and colorectal cance	Phase II	PI3K delta inhibitor. It received "breakthrough designation" by the FDA for relapsed CLL
	GS-9973	CLL	Phase II	Syk inhibitor
	Momelotinib	Myelofibrosis	Phase III	Momelotinib is a JAK inhibitor and it came to Gilead with the acquisition of YM BioSciences, Inc, in 2013

*NA: Not Avalilable

2.3.10 ABBOT

Following the divestment of AbbVie in 2011, Abbott has refashioned itself as pharmaceutical company focused largely on consumer healthcare and prescription medicines. Since 2011, Abbot's investment in R&D activities has fallen substantially.

Table xxxviii: ABBOT (US) Total Research and Development Investment

Mil USD	2014		2013		2012		2011	
Total R & D Expense	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales	Amount	% of Sales
	1345	6.6	1452	6.66	1544	7.18	1512	7.06
% Change	-7.37		-5.99		+2.12			

Abbot has a set of product for cancer in the pipeline in the different phase of research. Since 2011, the company's investment in R&D has substantially decreased, which is perhaps related to its divestment of AbbVie.

Table xxxix: ABBOT (US) Research Pipeline: Oncology

Year	Product Name	Indication	Phase	Comments
NA*	PARP-inhibitor Veliparib	Breast cancer and a number of additional	Phase III	Poly (ADP-ribose) polymerase inhibitor. In 2012 co-

		varieties of cancer		development with BMS.
		Colorectal Cancer	Phase I	
	Navitoclax ABT-263	CLL	Phase II	Bcl-2 proteins antagonist.
	Elotozumab (HuLuc63)	Multiple Myeloma	Phase III	It was acquired by AbbVie and BSM and Phase III studies are being done by them.
	Linifanib ABT-869	Liver Cancer	Phase III	Multi-targeted Kinase inhibitor
		NSCLC	Phase II	
	ABT-199 3/GDC-0199	Relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) and small lymphocytic Lymphoma (SLL)	Phase Ia	Next generation of Bcl-2 proteins antagonist. Co-developed by Genentech and Abbvie.

*NA: Not Avalilable

2.4.11. BIOGEN IDEC (US)

Biogen Idec is a global biotechnology company based in Cambridge, Massachusetts, that specializes in the development of treatments for neurodegenerative, hematologic and autoimmune diseases. Founded in Geneva in 1978, Biogen became the third largest biotechnology company in the world after merging with San Diego, California-based IDEC Pharmaceuticals in 2003. In terms of MHDs, Biogen Idec has focused its research exclusively on Alzheimer's disease.

Table xl: BIOGEN IDEC (US) Total Research and Development Investment

Mil USD	**2014**		**2013**		**2012**		**2011**	
Total R & D Expense	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**	**Amount**	**% of Sales**
	1893	19.50	1444	20.80	1335	24.20	1220	24.2
% Change	+31.0		+8.20		+9.4			

With its focus in other areas, BIOGEN does not have any Cancer relevant molecules under development. Since 2011, the company's investment in R&D has increased substantially, by almost 50%

2.5 Discussion: The Pharmaceutical Research Pipeline for Cancer

Overall, the European pharmaceutical sector has increased its commitment to R&D over the past four years. GSK is the only top 10 company to record a shrinking commitment to research investment. Some companies, like AstraZeneca, have recorded a massive increase in R&D spending. But most companies have recorded progressive of steady increases. By contrast, US levels of investment in R&D have been more mixed. Companies at the top of the scale, like Merck and Pfizer, have steady reduced their levels of investment. At the lower end of the scale, companies like Gilead and Celgene have massively increased their commitment.

Despite being the world leader for R&D investment in the pharmaceutical and biotechnology sector, major US companies have significantly less cancer molecules in their research pipelines than European based companies (116 v.53). In several cases, US firms were not at all active in developing new molecules for cancer. By contrast, European based pharmaceutical companies have a much greater commitment to cancer in terms of pipeline development. Certainly, the top 10 European companies seem to specialize in specific NCD categories, almost all the companies have molecules on development for cancer. However, compared with the US, other large European firms like GSK, Novartis and AstraZeneca have quite a number of products in development. Indeed, these three firms consolidate more molecules in their research pipelines than do the top ten US firms collectively. Where the number of molecules under development in the United States is set against broadly similar levels of patent need in the US and Europe, there are grounds for concluding that US R&D commitment to cancer is lacking and perhaps even broadly insufficient to tackle to scale of the problem that these diseases represent. These conclusions are similar to some other NCD categories, as CRDs.

These results are in contradiction of what is writing in previous analysis report where it has been found that in the US the R&D in pharmaceuticals has been higher than in the Europe, especially after 1992. In the analysis with found similar amount of money spent by companies in R&D (see table xli and xlii), but totally different amount of molecules in the pipeline for cancer (higher -almost the double- in Europe comparing in the US).

Table xli: Total Research and Development Investment (EUR)

MIL €	2014	2013	2012	2011
NOVARTIS (EUR)	8.118,000 €	6.940,800 €	6.840,000 €	7.114,800 €
ROCHE (EUR)	7.298,000 €	6.264,000 €	6.375,000 €	6.237,000 €
SANOFI-AVENTIS (EUR)	4.824,000 €	4.770,000 €	4.922,000 €	4.811,000 €
GLAXO (EUR)	3.968,000 €	4.080,000 €	4.305,000 €	4.800,000 €
BAYER (EUR)	3.574,000 €	3.406,000 €	3.013,000 €	2.932,000 €
ASTRAZENECA (EUR)	5.579,000 €	4.821,000 €	5.243,000 €	5.523,000 €
BOEHRINGER (EUR)	2.654,000 €	2.743,000 €	2.795,000 €	2.516,000 €
NOVO-NORDISK (EUR)	1.794,000 €	1.521,000 €	1.417,000 €	1.209,000 €
MERK & CO (EUR)	1.704,000 €	1.504,000 €	1.511,000 €	1.517,000 €
	39.513,000 €	36.049,800 €	36.421,000 €	36.659,800 €

Table xlii: Total Research and Development Investment (US)

MIL €	2014	2013	2012	2011
JOHNSON&JOHNSON (US)	5.169,600 €	5.400,000 €	6.150,000 €	6.545,000 €
MERCK (US)	6.115,680 €	5.891,760 €	5.748,750 €	5.811,960 €
PFIZER (US)	6.042,960 €	4.808,160 €	5.902,500 €	6.684,370 €
ELLI LILLY (US)	3.408,480 €	3.982,320 €	3.958,500 €	3.866,170 €
AMGEN (US)	3.093,840 €	2.952,000 €	2.550,000 €	2.464,000 €
BRISTOL MYERS (US)	3.264,480 €	2.686,320 €	2.928,000 €	2.956,030 €

ABBVIE (US)	2.373,840 €	2.055,600 €	2.083,500 €	2.015,860 €
CELGENE (US)	1.750,320 €	1.602,720 €	1.293,000 €	1.232,000 €
GILEAD (US)	2.054,880 €	1.526,400 €	1.320,000 €	947,100 €
ABBOT (US)	968,400 €	1.045,440 €	1.111,680 €	1.088,640 €
BIOGEN (US)	1.362,960 €	1.039,680 €	1.001,250 €	939,400 €
	35.605,440 €	32.990,400 €	34.047,180 €	34.550,530 €

2.6 Medical Devices Industry Investment in Cancer

A Medical Device (MD) is an instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,
- and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means (Council Directive 93/42/EEC on Medical Devices).

The objective of this section of the CA is to provide a detailed map of Cancer relevant outputs of the Medical Devices Industry across the EU. In order to map MDs industry R&D investments, we identified a list of top 16 medical device manufacturers worldwide ranked by total revenue (updated to October 9, 2014). Based on website interrogations and annual reports, general information and total R&D expenses for each MD company have been collected for the period 2011 to 2014.

Table xliii: Top 16 Medical Devices Companies by Research and Development Investment (2014)*

MD Co. Rank	World Co. Rank	Company	Country	Total revenues (Bil USD)	Total R&D Investment (Mil)
1	34	Johnson & Johnson	United States	28.7	8,494 (USD)
2	9	General Electric Co.	United States	18.1	4,233 (USD)
3	249	Medtronic Inc	United States	17.1	1,477 (USD)
4	54	Siemens AG	Germany	17.0	4,065 (EURO)
5	346	Baxter International Inc	United States	16.4	1,421 (USD)
6	283	Fresenius Medical Care AG & Co. KGAA	Germany	15.2	369 (EURO)

7	472	Koninklijke Philips NV http://blogs.terrapinn.com/total-biopharma/?s=glaxosmithkline	Netherlands	11.8	1,635 (EURO)
8	327	Cardinal Health Inc.	United States	11.0	NA**
9	52	Novartis AG (Alcon)http://blogs.terrapinn.com/total-biopharma/?s=astrazeneca	Switzerland	10.7	903 (USD)
10	349	Covidien plc[13]	Ireland	10.4	546 (USD)
11	719	Stryker Corp.	United States	9.3	614 (USD)
12	610	Becton, Dickinson and Co.	United States	8.3	550 (USD)
13	1047	Boston Scientific Corp.	United States	7.2	817 (USD)
14	732	Essilor International SA	France	7.2	188 (EURO)
15	753	Allergan Inc. (Actavis)[14]	Ireland	6.7	1,085.9 (USD)
16	957	St. Jude Medical Inc.	United States	5.6	692 (USD)

*http://www.mddionline.com/article/top-40-medical-device-companies; ** NA: Not Available

2.7 Search Methods

In order to identify new products associated with these companies, we under took three searches. In the first place, we searched a database of clinical studies (i.e. clinicaltrials.gov) for recently (≥2011) closed and ongoing clinical studies funded by each MD company identified above.

Secondly, we searched databases of new approved MDs (i.e. FDA premarket approval, de novo database, EuroScan) have been searched according to the same time frame (2011-2015).

Thirdly, at the European Level, we searched a database of CE marked products exists since 2009, called EUDAMED. This database is only accessible to government agencies in charge for the market surveillance in each country (e.g. Ministero della Salute in Italy). In the US, by contrast, the relevant authority, the Food and Drug Administration (FDA), has a whole section on the website with approval dossiers for all medical devices. Although there is not a direct link between technologies approved in the US and technologies licensed in the EU, knowledge of the most recent innovations overseas does provide some indication of the most up-to-date technologies that are available to improve clinical practice for the management for Cancer.

Therefore, the FDA premarket approval (PMA) and de novo databases have been searched for new approved products between 2011 and 2015. The 510(k) clearance has not been considered as this refers to products "substantially equivalent" to others already on the market. In this case, unlike the

[13] Medtronic plc (NYSE: MDT)) has completed the acquisition of Covidien plc (NYSE: COV) in 2015
[14] Actavis plc (NYSE: ACT) has completed the acquisition of Allergan, Inc. (NYSE: AGN) in 2015

previous steps, the search has been performed according to indication in cancer, respiratory disease, cardiovascular disease, diabetes, mental health.

In addition to the FDA databases, we also searched the EuroScan Database. In Europe there is not an equivalent of the FDA online databases for new approved devices. We therefore relied on the EuroScan database. EuroScan is the International Information Network on New and Emerging Health Technologies, a collaborative network of member HTA agencies for the exchange of information on important emerging new drugs, devices, procedures, programmes, and settings in health care. Many European HTA agencies are members of the network (e.g. Agenas from Italy, NIHR Horizon Scanning Centre from UK, Osteba from Spain, SBU from Sweden etc.). As for the FDA databases, the search has been performed according to indication in the five NCD areas.

Where results were generated, we report results in relation to the associated companies.

2.7.1. JOHNSON & JOHNSON (US)

Johnson & Johnson operates as an investment holding company with interests in health care products. It engages in research and development, manufacture and sale of personal care hygienic products, pharmaceuticals and surgical equipment. The company, through its subsidiaries operates in three business segments: Consumer, Pharmaceutical and Medical Devices and Diagnostics.

Table xliv: Johnson & Johnson (US)* Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	8,494	11.4	8,183	11.5	7,665	11.4	7,548	11.6
% Change	3.8		6.8		1.6			

* R&D expenses refer to all business segments of JOHNSON & JOHNSON (i.e. Consumer, Pharmaceutical, Medical Devices and Diagnostics)

Although J&J's commitment to R&D has been steadily increasing over the relevant period, searches did not reveal any results for the company in terms of Clinical Trials, FDA premarket approval (PMA), EUDAMED or the EuroScan Database.

2.7.2. GENERAL ELECTRIC CO (US)

General Electric Co. is a technology and financial services company that develops and manufactures products for the generation, transmission, distribution, control and utilization of electricity. Its products and services include aircraft engines, power generation, water processing, security technology, medical imaging, business and consumer financing, media content and industrial products. The company operates through eight segments: Power & Water, Oil & Gas, Energy Management, Aviation, Healthcare, Transportation, Home & Business Solutions and GE Capital. The Healthcare segment provides healthcare technologies such as medical imaging and information technologies, medical diagnostics, patient monitoring systems, disease research, drug discovery and biopharmaceutical manufacturing technologies. This segment predicts and detects disease earlier; monitoring its progress and informing physicians, and helping physicians tailor treatment for patients.

Table xlv: General Electric CO. (US) Total R&D Investment

R&D Investment	2014	2013	2012	2011

Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	4,233	2.8	4,750	3.3	4,520	3.1	4,601	3.1
% Change	-10.9		5.1		-1.8			

**R&D expenses refer to all business segments of General Electric Co, not only to the healthcare business area*

Searches did not reveal any results for the company in terms of Clinical Trials, FDA premarket approval (PMA), EUDAMED or the EuroScan Database. Since 2011, the company's commitment to R&D investments has decreased marginally.

2.7.3. MEDTRONIC INC (US)

Medtronic Plc was formerly known as Medtronic, Inc. The Group's principal activities are manufacturing, developing and marketing medical technology and providing device-based medical therapies. It operates in eight segments: Cardiac Rhythm Disease Management (CRDM), Spinal, CardioVascular, Neuromodulation, Diabetes, Surgical Technologies, Physio-Control. The company targets chronic diseases, providing therapeutic and diagnostic devices used for the treatment of diabetes, neurological, gastroenterological, urological, and movement disorders, spinal and neurosurgery, neurodegenerative disorders and ear, nose and throat (ENT) surgery. It also provides external and manual defibrillators.

Table xlvi: Medtronic INC (US) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	1,477	8.7	1,557	9.4	1,490	9.2	1,508	9.5
% Change	-5.1		4.5		-1.2			

The company's commitment to R&D investment has marginally decreased over the period. But searches revealed results for the company in terms of Clinical Trials. However, there were no results for FDA, EUDAMED or the EuroScan Database.

Table xlvii: Medtronic INC (US) Company Clinical Trials: Cancer*

Year	Device	Study Name	Application	Study Status
2010-2011	ENDO GIA™ Stapler with TRI-STAPLE™ Technology	A Prospective, Multi-Center Evaluation of the ENDO GIA™ Stapler With ENDO GIA™ Reload With Tri-Staple™ Technology in a Pulmonary Resection	Lung	Completed

*https://clinicaltrials.gov/ . For the search strategy see Appendix 1

2.7.4. SIEMENS AG (EUR)

Siemens AG is engaged in the electrical, engineering and electronics business. It operates through the following segments: Energy, Healthcare, Industry, Infrastructure and Cities, Equity Investments, and Siemens Financial Services (SFS). The Healthcare segment includes medical products such as medical imaging, in vitro diagnostics, interventional systems, and clinical information technology systems.

Table xlviii: Siemens AG (EUR)* Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales
	4,065	5.7	4,291	5.7	4,238	5.4	3,925	5.3
% Change	-5.3		1.3		8.0			

* *R&D expenses refer to Siemens group, not only to the Healthcare business area*

Despite a 5% reduction for 2014, the company's commitment to R&D has slightly increase since 2011. The searches revealed results for the company in terms of Clinical Trials and the EuroScan, however, there were no results for FDA, EUDAMED.

Table xlix: SIEMENS AG (EUR) Company Clinical Trials: Cancer*

Year	Device	Study Name	Application	Study Status
2011-2014	SIEMENS INSPIRATION DIGITAL BREAST TOMOSYNTHESIS (DBT) SYSTEM	Multi-center Case Collection Study to Create a Library of Images From Various Approved Full Field Digital Mammography (FFDM) Systems and 3D Images From Siemens Inspiration Digital Breast Tomosynthesis (DBT) System for Studies in Support of the Inspiration Digital Breast Tomosynthesis Approval	Breast	Completed

*https://clinicaltrials.gov/ . For the search strategy see Appendix 1

Table l: SIEMENS AG (EUR) EuroScan International Network: Cancer*

Year of Approval	Product Name	Application
2012	Biograph mMR (Simens) + Ingenuity TF PET-MRI (Philips) *(PET-MRI integrated hybrid scanners)*	Diagnosis

* http://euroscan.org.uk/technologies/public/search?advance-search=on. For the search strategy see Appendix 4

2.7.5. BAXTER INTERNATIONAL INC (US) Total R&D Investment

Baxter International, Inc. develops, manufactures and markets products for disease such as hemophilia, immune disorders, infectious diseases, kidney disease, trauma, and other chronic and acute medical conditions through its subsidiaries. It produces a combination of medical devices, pharmaceuticals and biotechnology products, operating through two divisions: BioScience and Medical Products.

Table li: BAXTER INTERNATIONAL INC (US) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	1,421	8.5	1,246	8.2	1,156	8.1	946	6.8
% Change	14.0		7.8		22.2			

Baxter's commitment to R&D has increased substantially over the relevant period, a gain of about 50% percent since 2011. However, searches did not reveal any results for the company in terms of Clinical Trials, FDA premarket approval (PMA), EUDAMED or the EuroScan Database

2.7.6. FRESENIUS MEDICAL CARE AG & CO. KGAA (EUR) Total R&D Investment

Fresenius SE & Co. KGaA engages in the provision of healthcare related products and services. It operates through the following divisions: Fresenius Medical Care, Fresenius Kabi, Fresenius Helios, Fresenius Vamed, and Corporate/Other. Fresenius Medical Care provides dialysis products and services for patients with chronic kidney failure. Fresenius Kabi offers IV drugs including intravenously administered generic anesthetics, anti-infectives, analgesics, and drugs for the treatment of oncological and other critical diseases; and infusion solutions and blood volume substitutes for infusion therapy. Fresenius Helios operates hospitals. The Fresenius Vamed manages projects and provides services for hospitals and other healthcare facilities. The Corporate/Other segment comprises holding activities of the company and the activities of the information technology service provider Fresenius Netcare.

Table lii: FRESENIUS MEDICAL CARE AG & CO. KGAA (EUR) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales
	369	1.6	348	1.7	305	1.6	267	1.6
% Change	6.0		14.1		14.2			

** R&D expenses refer to Fresenius group which includes Fresenius Medical Care business area*

The company's commitment to R&D investment has increased progressively over the period. However, searches did not reveal any results for the company in terms of Clinical Trials, FDA premarket approval (PMA), EUDAMED or the EuroScan Database.

2.7.7. KONINKLIJKE PHILIPS NV (EUR)

Koninklijke Philips NV is a technology company that is engaged in the healthcare, lighting and consumer well-being markets. It operates through the following divisions: Healthcare, Consumer Lifestyle, Lighting, and Innovation, Group and Services. The Healthcare division offers imaging systems, patient care and clinical informatics, home healthcare solutions, and customer services.

Table liii: KONINKLIJKE PHILIPS NV (EUR) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales
	1,635	7.6	1,733	7.4	1,810	7.3	1,610	7.1
% Change	-5.7		-4.3		12.4			

** R&D expenses refer to Philips group and not only to Philips Healthcare business area*

The company's levels of R&D investment have remained steady. Searches revealed several results for the company in terms of Clinical Trials. However, no results were found for FDA premarket approval (PMA), EUDAMED or the EuroScan Database.

Table liv: KONINKLIJKE PHILIPS NV (EUR) Company Clinical Trials: Cancer*

Year	Device	Study Name	Application	Study Status
2012-ongoing	MR-HIFU (Magnetic Resonance-guided High Intensity Focused Ultrasonid)	Magnetic Resonance-guided High Intensity Focused Ultrasound for Palliation of Painful Skeletal Metastases - a Multicenter Study	Bone	Ongoing
2011-2012	Philips MR-guided HIFU system	Magnetic Resonance-Guided High Intensity Focused Ultrasound for Palliation of Painful Skeletal Metastases - A Pilot Study	Bone	Completed
2010-2011	High Intensity Focused Ultrasonid	Pilot Study for the Treatment of Bone Metastases by High Intensity Focused Ultrasound Guided by MRI to Perform Pain Palliation	Bone	Completed

*https://clinicaltrials.gov/. For the search strategy see Appendix 1

2.7.8. CARDINAL HEALTH INC (US)

Cardinal Health, Inc. is a healthcare services company providing pharmaceutical and medical products and services for pharmacies, hospitals, surgery centers, physician offices and other healthcare providers, which focus on patient care, cost reduction, enhancing efficiency and improving quality. The company operates its business through two divisions: Pharmaceutical and Medical. The Pharmaceutical division distributes branded and generic pharmaceutical, over-the-counter healthcare and consumer products through its pharmaceutical distribution business to retailers, hospitals, and other healthcare providers. The Medical division distributes a broad range of medical, surgical and laboratory products to hospitals, surgery centers, laboratories, physician offices and other healthcare providers.

Table lv: CARDINAL HEALTH INC (US) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	NA		NA		NA		NA	
% Change								

Investment information was not available. And searches did not reveal any results for the company in terms of Clinical Trials, FDA premarket approval (PMA), EUDAMED or the EuroScan Database.

2.7.9. NOVARTIS AG (ALCON) (EUR)

Novartis AG develops, manufactures, and markets healthcare products. It operates through the following divisions: Pharmaceuticals, Alcon, Sandoz, Vaccines and Diagnostics, and Consumer Health. The Alcon segment offers surgical, ophthalmic pharmaceuticals, and vision care products.

Table lvi: NOVARTIS AG (ALCON) (EUR) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	903	8.3	939	8.9	950	9.3	869	8.7
% Change	-3.8		-1.2		9.3			

** R&D expenses refer to ALCON business area (and not to NOVARTIS group)*

Investment in R&D has remained steady over the period. Searches did not reveal any results for the company in terms of Clinical Trials, FDA premarket approval (PMA), EUDAMED or the EuroScan Database.

2.7.10. COVIDIEN PLC (EUR)

Covidien Plc engages in the development, manufacture and sale of healthcare products for use in clinical and home settings. It operates through three divisions: Medical Devices, Pharmaceuticals and Medical Supplies. The Medical Devices division includes the development, manufacture and sale of endomechanical instruments, energy devices, soft tissue repair products, vascular products, oximetry and monitoring products, airway and ventilation products, and other medical products. The company was founded in 2007 and was acquired by Medtronic in 2015.

Table lvii: COVIDIEN PLC (EUR) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	546	5.1	508	5.0	623	5.3	554	4.8
% Change	7.5		-18.5		12.5			

Investment in R&D remains steady. Searches revealed several results for the company in terms of Clinical Trials. However, no results were found for FDA premarket approval (PMA), EUDAMED or the EuroScan Database.

Table lviii: COVIDIEN PLC (EUR) Company Clinical Trials: Cancer*

Year	Device	Study Name	Application	Study Status
2014-ongoing	Radiofrequency Ablation (Barr ™)	A Safety and Tolerability Trial of Circumferential Anal Canal Radiofrequency Ablation For Anal Intraepithelial Neoplasia Using the Barrx™ Ablation System	Anal Canal	Ongoing

2009-ongoing	Radiofrequency Ablation	A Single-center Trial of Endoscopic Radiofrequency Ablation of Moderate and High-grade Intra-epithelial Squamous Neoplasia and Early Flat-type Squamous Cell Carcinoma Using the HALO Ablation System	Esophagus	Ongoing
2013-ongoing	Radiofrequency Ablation (RFA) using the HALO Ablation	A Trial of Radiofrequency Ablation for Anal Intraepithelial Neoplasia Using the HALO Ablation System	Anal Canal	Ongoing
2007-2014	Radiofrequency Ablation (HALO Ablation System)	HALO Patient Registry: Ablation of Barrett's Esophagus, A Multi-Center Patient Registry	Esophagus	Completed

*https://clinicaltrials.gov/. For the search strategy see Appendix 1

2.7.11. STRYKER CORP. (US)

Stryker Corp. engages in the provision of medical technology products and services. It operates through the following divisions: Orthopaedics, MedSurg, and Neurotechnology and Spine. The Orthopaedics division provides reconstructive and trauma implant systems. The Medsurg division deals with surgical instruments and equipment, endoscopy, patient handling, and reprocessed medical devices. The Neurotechnology and Spine division pertains to spinal implants and neurovascular products.

Table lix: STRYKER CORP. (US) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	614	6.3	536	5.9	471	5.4	462	5.6
% Change	14.6		13.8		1.9			

Investment in R&D has progressively increased since 2011. But searches did not reveal any results for the company in terms of Clinical Trials, FDA premarket approval (PMA), EUDAMED or the EuroScan Database.

2.7.12. BECTON DICKINSON AND CO. (US)

Becton, Dickinson & Co. is a global medical technology company. The company is engaged in the development, manufacture and sale of medical devices, instrument systems and reagents used by healthcare institutions, life science researchers, clinical laboratories, the pharmaceutical industry and the general public. The company operates through three worldwide business divisions: BD Medical, BD Diagnostics and BD Biosciences. The BD Medical division produces medical devices that are used in a wide range of healthcare settings.

Table lx: BECTON DICKINSON AND CO. (US) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	550	6.5	494	6.1	471.8	6.1	476.5	6.1

% Change	11.3	4.7	-1.0	

Investment in R&D has increased. Searches did not reveal any results for the company in terms of Clinical Trials, FDA premarket approval (PMA), EUDAMED or the EuroScan Database.

Table lxi: BECTON DICKINSON AND CO. (US) Company Clinical Trials: Cancer*

Year	Device	Study Name	Application	Study Status
2014-ongoing	BD HPV Assay on Viper LT	Longitudinal Clinical Evaluation of the HPV Assay on the BD VIPER LT System With Cervical Specimens	Cervix	Ongoing
2012-2013	BD HPV Assay on Viper LT	European Clinical Evaluation of the BD HPV Assay on the BD Viper LT System	Cervix	Completed

*https://clinicaltrials.gov/. For the search strategy see Appendix 1

2.7.13. BOSTON SCIENTIFIC CORP. (US)

Boston Scientific Corp. engages in the development, manufacture and marketing of medical devices that are used in a broad range of interventional medical specialties. The company's products and technologies are used to diagnose or treat a wide range of medical conditions, including heart, digestive, pulmonary, vascular, urological, women's health, and chronic pain conditions.

Table lxii: BOSTON SCIENTIFIC CORP. (US) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	817	11.1	861	12.1	886	12.2	895	11.7
% Change	-5.1		-2.8		-1.0			

Investment in R&D has decreased marginally since 2011. But searches revealed results for the company in terms of Clinical Trials, but Searches did not reveal any results for the FDA premarket approval (PMA), EUDAMED or the EuroScan Database.

Table lxiii: BOSTON SCIENTIFIC CORP. (US) Company Clinical Trials: Cancer*

Year	Device	Study Name	Application	Study Status
2006-2011	Contour SE ™ Microspheres/ Embospheres® Microspheres	A Prospective, Randomized, Single-Center Study Comparing Contour SE™ Microspheres to Embosphere® Microspheres for Treating Symptomatic Uterine Fibroids With Uterine Fibroid Embolization (UFE)	Uterus	Completed
2014-ongoing	WallFlex ™ Biliary RX Fully Covered/Uncovered Stent System	Randomized Controlled Trial Comparing Covered and Uncovered Biliary Self Expanding Metal Stents (SEMS) for Pre-operative Drainage During Neoadjuvant Therapy in Patients With Pancreatic Cancer	Pancreas	Ongoing
2013-	WallFlex ™ Biliary RX	Randomized Multi-Center Study	Pancreas	Ongoing

ongoing	Fully Covered/Uncovered Stent System	Comparing No Drainage to Preoperative Biliary Drainage Using Metal Stents in Patients With Resectable Pancreatic or Periampullary Cancer		

*https://clinicaltrials.gov/. For the search strategy see Appendix 1

2.7.14. ESSILOR INTERNATIONAL SA (EUR)

Essilor International SA designs, manufactures and sale of ophthalmic lenses and ophthalmic optical instruments. The company operates through three business divisions: Lenses & Optical Instruments, Equipment, and Sunglasses & Readers.

Table lxiv: ESSILOR INTERNATIONAL SA (EUR) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales
	188	3.3	164	3.2	161.9	3.2	151.5	3.6
% Change	14.6		1.3		6.9			

Investment in R&D is increasing. But searches did not reveal any results for the company in terms of Clinical Trials, FDA premarket approval (PMA), EUDAMED or the EuroScan Database.

2.7.15. ALLERGAN INC. (EUR)

Allergan, Inc. is a global healthcare engaged in the developing and commercializing pharmaceuticals, medical devices and over-the-counter products for the ophthalmic, neurological, medical aesthetics, medical dermatology, breast aesthetics, obesity intervention, urological and other specialty markets in more than 100 countries. The company operates through two business divisions: Specialty Pharmaceuticals and Medical Devices.

Tabla lxv: ALLERGAN INC. (EUR) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	1,085.9	8.4	616.9	7.2	401.8	6.9	227.7	6.9
% Change	76.0		53.5		76.5			

The company's commitment to R&D has increased massively since 2011, growing by over 375%. Searches revealed results for the company in terms of clinical trials and FDA premarket approval (PMA). But they did not yield results for EUDAMED or the EuroScan Database.

Table lxvi: ALLERGAN INC. (EUR) Company Clinical Trials: Cancer*

Year	Device	Study Name	Application	Study Status
2013-ongoing	SERI [R] Sugical Scaffold	SERI® Surgical Scaffold Postmarket Study of Soft Tissue Support and Repair in Breast Reconstruction	Breast	Ongoing

1997-2012	Natrelle (TM) Silicone-Filled Breast Implants	Adjunct Study of Natrelle(TM) Cohesive Round Silicone-Filled Breast Implants	Breast	Completed

*https://clinicaltrials.gov/. For the search strategy see Appendix 1

Table lxvii: ALLERGAN INC. (EUR) PMA Medical Devices: Cancer*

Year of Approval	Product Name	Application
2013	Natrelle Highly Cohesive Silicone-Filled Breast Implants	Breast

*http://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/. For the search strategy, see the Appendix 2

2.7.16. ST. JUDE MEDICAL INC. (US)

St. Jude Medical, Inc. develops, manufactures and distributes cardiovascular medical devices for the global cardiac rhythm management, cardiovascular and atrial fibrillation therapy areas and neurostimulation medical devices for the management of chronic pain. It operates through two divisions: Cardiovascular and Ablation Technologies and Implantable Electronic Systems Division.

Table lxviii: ST. JUDE MEDICAL INC. (US) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	692	12.6	691	12.6	676	12.3	705.1	12.6
% Change	0.1		2.2		-4.1			

Investment in R&D has remained steady over the relevant period. But they did not yield results for Clinical Trials, FDA premarket approval (PMA), EUDAMED or the EuroScan Database.

2.8 Medical Devices Industry Output Data: Bibliometric Evidence

Output data for the top medical devices companies were gathered from the Web of Science database. Table lxix presents information on research outputs funded by the MD companies in the areas Cancer for 2009-13. The search was performed on Web of Science (see **Appendix 5** for methodological details).

The search was performed under the bibliometric ONCOL filter. It must be noted that the aliases/ spelling errors in naming the RFOs by WoS means that not all them may have been captured or that other organizations may have accidentally also been captured due to the simplistic terms used. In cases where a company had only generic codes, the name was searched instead of the code. In ONCOL, only the funding data were searched. It should also be noted that some of the companies also make pharmaceutical drugs and the counts of papers may include them.

With the exception of Novartis, which seems to dominate Cancer research outputs, and is responsible for 65.3% of all scientific papers, we found limited scientific outputs for Cancer across the private sector.

Table lxix: Top Medical Devices Companies Bibliometric Output Data*

Company	Country	Code	Name of Alternative Code	Output Papers

				(ONCOL)
Johnson & Johnson	US	JJJ-IP-US	Johnson & Johnson	**135**
		AZC-IN-US	Alza Corporation (SUBSID)	**0**
		CDM-IN-US	Codman (SUBSID)	**0**
		DPY-IN-UK	DePuy International Healthcare (SUBSID)	**2**
		ETC-SP-US	Ethicon Inc (SUBSID)	**23**
		ETH-IN-AU	Ethnor (SUBSID)	**0**
		JJJ-IP-US	Cougar Biotechnology (SUBSID)	**18**
		LFD-IN-US	LifeScan (SUBSID)	**1**
		MNP-IN-US	McNeil Pharmaceutical (SUBSID)	**0**
		SJV-BT-US	Scios (SUBSID)	**1**
		VIO-BT-BE	Virco (Tibotec) (SUBSID)	**3**
		X15-IN-US	Neutrogena Corporation (SUBSID)	**0**
		JNA-SP-AU	Janssen Pharmaceutical / Cilag (SUBSID)	**170**
		JNS-SP-BE	Janssen Pharmaceutica N V, Beerse (SUBSID)	
		JNU-SP-UK	Janssen Pharmaceutical Ltd, Wantage, Oxon (SUBSID)	
		CCR-IN-NL	Centocor (SUBSID)	**28**
		CLG-IN-BE	Cilag Biotech (SUBSID)	**0**
		ORJ-BT-US	Ortho Biotech / Division (SUBSID)	**42**
General Electric Co.	US	XXG-IN-US	General Electric Co.	**5**
Medtronic Inc	US	MDI-BT-US	Medtronic Inc	**21**
Covidien plc	IE	Y1B-BT-IE	Covidien plc	**20**
		Y15-IN-IE	Covidien plc	
		HUF-IN-IE	Covidien	**0**
Siemens AG	DE	SMN-IN-DE	Siemens AG	**110**
Baxter International Inc	US	BXT-IN-US	Baxter International Inc	**47**
		BXW-SP-BE	Baxter Medical A B, Bromma, Sweden (SUBSID)	
		CLH-SN-UK	Clinitec, Nutrition Ltd (Baxter) (SUBSID)	
		BAX-SP-UK	Baxter Healthcare Ltd, Newbury, Berks (SUBSID)	

		BXR-SP-BE	Baxter R & D Europe, Nivelles (SUBSID)	
Fresenius Medical Care AG & Co. KGAA	DE	XFN-IP-DE	Fresenius Medical Care AG & Co. KGAA	**4**
		FRS-SP-UK	Fresenius Ltd (FHC Holdings Ltd), Runcorn, Cheshire (SUBSID)	
Koninklijke Philips NV	NL	PHG-IN-NL	Koninklijke Philips NV	**56**
Cardinal Health Inc.	US	X15-IN-US	Cardinal Health Inc.	**0**
		CJD-IN-US	Cordis (UK) Ltd, Brentford, Middx / Cardinal Health	
Novartis AG (Alcon)	CH	NVP-IP-CH	Novartis AG	**1380**
		ALC-IN-CH	Alcon Inc./Laboratories (SUBSID)	**2**
		CBP-FO-UK	Novartis Foundation (formerly Ciba Foundation), London	**2**
		CBG-IP-CH	CIBA-Geigy (SUBSID)	
		CBJ-SP-US	Ciba (now 'Novartis') Corporation, Summit NJ	
		CGP-SP-UK	CIBA-Geigy A G (Since 1996 'Novartis') , Basel, Switzerland	
		NGY-SP-NL	Ciba - Geigy B V, Arnhem, Netherlands	
		CIB-IP-JP	Japan: CIBA - Geigy Foundation, Takarazuka	
		CRN-BT-US	Chiron Corporation (SUBSID)	**2**
		SDZ-IP-CH	Sandoz Pharmaceuticals (SUBSID)	**13**
Stryker Corp.	US	X1B-BT-US	Stryker Corp.	**0**
Becton, Dickinson and Co.	US	X1B-BT-US	Becton, Dickinson and Co.	**6**
		BDC-IN-US	Beckton, Dickinson (BD), Franklin Lakes, NJ	
Boston Scientific Corp.	US	JBS-IN-US	Boston Scientific Corp.	**12**
Essilor International SA	FR	NO CODE	optical lenses	**Did not search**
Allergan Inc. (Actavis)	IE	ALL-IP-US	Allergan Inc. (Actavis)	**9**
		AVF-IP-US	Actavis Inc. / Aptalis	
		AZG-SP-UK	Allergan Therapeutics Ltd (UK), High Wycombe, Bucks (SUBSID)	
St. Jude Medical Inc.	US	NO CODE	CARDI	**Did not search**
TOTAL PAPERS (ONCOL)				**2112**

For the search strategy, see Appendix 5

2.9 Discussion and Conclusion

Of the 16 medical device manufacturers worldwide with higher income, only seven companies perform tests in cancer. Between 2011 and 2015, a total of 346 clinical trials have been conducted for NCD, for cancer corresponding to 4.62% of the total (16 clinical trials). The company Covidien has developed more clinical trials that are applied in breast cancer and bone cancer, both for diagnostic and therapeutic purposes. However, most companies in the sector had not developed any cancer relevant medical devices. Very few companies had produced research outputs in terms of scientific papers. Novartis was responsible for the overwhelming majority of papers (65.3%) with Jansen Pharmaceutical claiming a 8.0% share, Johnson and Johnson 6.4% and Siemens 5.2%.

Investment in research and development is a key industry activity across the pharmaceutical and biotechnology sector. Throughout the 20th century, the pharmaceutical industry has played a significant and indispensable role in the advancement of science through the production and publication of high quality research (Nairn and Rozek 1988, 139)[16].

Where conventional wisdom would suggest that pharmaceutical companies primarily invest in developmental and applied research in order to advance their economic interests; and where commonplace thinking would suggest that both the industry and wider society is dependent on blue sky scientific research undertaken in a predominantly academic environment; analysts have, and for some time, cast doubts on these ideas, finding that industry investments have contributed significantly to the vast body of scientific research in the public domain, which has guided and influenced researchers everywhere (Koenig 1983; Nairn and Rozek 1988)[15],[16]. Measuring the quality and quantity of industry published research in mainstream scientific journals, analysts have found that industry investment in R&D has contributed significantly to advancement of broad based scientific research and the general public welfare (Nairn and Rozek 1988, 139) [16].

Today, however, sentiments are changing. While investment in R&D remains a principal activity of industry, the larger scientific paradigms under which R&D activities are conducted has undergone a tectonic shift. In the 21st century, however, following the successful the mapping of the human genome, new pharmaceutical technologies are now created at the nexus of a number of intertwined disciplines: bio-pharmacology, chemistry, nanotechnology, and computational sciences (Allarakhia and Steven 2011, 105)[17]. Today, drug discovery is about managing complex information that derives from a variety of disciplines, all of which exist outside the walls of the traditional pharmaceutical firm. In the twenty-first century, large pharmaceutical companies are increasingly forming research consortia to manage and exploit new forms of data that have arisen from parallel advances in molecular biology, nanotechnology, super-computing, statistical analysis and data management (Allarakhia and Steven 2011, 105)[17].

Actually, drug research is a high-risk and time-consuming process. Only 1 out of every 5000-10,000 compounds screened becomes an approved drug. Today, it takes an average of 10 to 15 years at an average cost of more than US$1 billion to develop a successful medicine (Merck 2015)[6]. Significant can losses occur where outputs are dependent of research interaction at the interface of various disciplines, and where there is no guarantee that new compounds will advance to clinical trials.

[15] Koenig, Michael E.D. (1983) “A bibliometric analysis of pharmaceutical research”, Research Policy 12: 15-36

[16] Narin, Francis and Richard P. Rozek (1988) Bibliometric Analysis of the U.S. pharmaceutical industry research performance”, Research Policy 17: 139-154.

[17] Allarakhia, Minna and Steven Walsh (2011) “Managing knowledge assets under conditions of radical change: The case of the Pharmaceutical industry”, Technovation 31: 105–117.

Today, the increased possibility of R&D failure is one of the main factors in the raised estimates of the costs per new molecular entity (NME), on the basis which analysts now question whether industry is in the grip of an R&D productivity crisis (Cockburn, 2006, Pammolli et al., 2011)[4,,5]. In past, analysts lauded the contribution of industry to the advancement of science and medical technologies. Today, however, where they measure productivity in terms of the ratio of the "output" of a process to some measure of the "inputs", like rising R&D expenditures and falling or static counts of new drug approvals, they have identified a sharp decline in research productivity over the past decade (Cockburn 2007, 1)[7].

Today, the pharmaceutical industry is in the grip of major systematic change. In response to the rapidly changing environment, industry has implemented conservative management practices for the purpose of increasingly the predictability of drug discovery and the sustainability of returns on capital investment in R&D. A consequence, investments in R&D produce NMEs that are, at best, only marginally better than existing therapies, thereby stifling innovation and amplifying a sense of crisis across the industry (Munos and Chin 2011, 1)[18]. For the future, analysts fear that unless industry ceases to pursue “safe” risk-averse management strategies, unless it adopts more collaborative approaches to knowledge creation and costs sharing, few breakthroughs will reach patients and sufferers of disease (Munos and Chin 2011, 1)[18]. Indeed, analysts counsel that sustainability and risk aversion did not characterise the breadth of vision shown by the industry’s early pioneers. In the twenty first century, however, the entrepreneurial model is gone. The industry must find new means by which to respond to unmet need, particularly in the area of NCDs.

[18] Munos, Bernard H. and William W. Chin (2011) “How to Revive Breakthrough Innovation in the Pharmaceutical Industry”, Science Translation Medicine 3 (89): 1- 3

3 Stakeholder Interviews: Cancer

Cancer affects all of humankind, but there are marked differences across local, national, and regional boundaries, particularly when considering specific tumour types rather than cancer as a whole. Epidemiological data on incidence of cancer and deaths caused by cancer vary enormously in coverage and quality between countries and regions worldwide (IARC, 2014)[19].

The high-resource countries have the highest incidence of cancer and also provide the best services for detection, diagnosis, and treatment. The highest prevalence proportions of cancer also occur in these populations. The most common cancers include lung, breast, prostate, and colorectal cancers. In countries in epidemiological transition, these cancers are increasingly common but incidence of stomach, oesophageal, and liver cancers remains high. Data from low-resource countries show that cervical cancer is still often the most common cancer among women (IARC, 2014) [19].

In low-and-middle-resource countries, incidence of particular tumours may be relatively low, but corresponding mortality data often reflect late-stage diagnosis as the norm and consequently poor clinical outcomes. Worldwide, differences in cancer incidence have been recognized for more than half a century as indicating different causes and, by inference, different opportunities for prevention. For governments around the world, the prevention and management of Cancer is an important public health issue for the future (IARC, 2014)[19].

Across Europe, policy-makers are engaged in funding research for developing interventions and prevention strategies to mitigate the impact of Cancer before they require a public health response. There are a total of 136 Research Funding Organizations (RFOs) investing in Cancer research. These RFOs display major divergences. Indeed, despite the majority of public funding in cancer research being concentrated in public funding organizations (41% public and 7% private-public sectors), each country has its own funding system. Research systems are generally complex, with some common features depending on the European area: Eastern Europe is characterized by a single funding source (100% of the RFOs are from the public sector; other sectors do not exist), while in Northern Europe charitable and voluntary sectors are the main active funders of cancer research. A more balanced situation is observed in Southern and Central Europe, where all types or funding organizations and funding sources are active.

The Problem for Policy Makers

EU MSs face diverse challenges with regard to Cancer: the prevalence of NCD risk factors varies considerably across Europe and national policy agendas and research activities also vary. As a result, MAPPING_NCDs aims to map current Cancer research funding and impact across the EU with a view to improving returns on investment. Mapping Cancer research investment and associated research impacts holds a potential to identify overlaps, synergies, gaps and also opportunities for policy learning, exchange and collaboration across the EU.
This mapping exercise is complicated and involves the use of multifarious research techniques and databases, from the direct survey of RFOs to web based queries, literature review and bibliometric analysis. Indeed, responding to the challenge Cancer present, European policy makers will need to consider a number of means and strategies to redress their impact. For example, effective medical devices and pharmaceuticals are essential for treatment and diagnosis. Financial incentives are also a means for improving the management of NCDs by targeting certain goals, processes and

[19] International Agency for Research on Cancer (IARC). World Cancer Report 2014. Lyon, 2014. IARC/WHO

outcomes. Moreover, Cancer patients often suffer from multiple co-morbidities. The management and treatment of Cancer requires multi-provider settings and integrated strategies. Policymakers need to consider improved information technology for the purposes of sharing data and information between care settings and to ensure quality control. In addition, they might also consider developing mechanisms for evaluating NCD management, and using health technology assessment (HTA) institutions to supporting policy-making and decision-making. In addition, however, policy makers need to consider stakeholder motivation to improve outcomes for patients with Cancer. New strategies and funding initiatives must, to some extent, align with the scientific, clinical and economic priorities and interests of leaders in the field of Cancer research.

Semi-Structured Interviews

While accurate mapping of Cancer research via surveys and bibliometrics can assist government in identifying the most fruitful approaches to making research investments; policy makers must also take account of the often strong visions and firm priorities of leaders in the field of Cancer research. To this end, MAPPING_NCDS involves the conduct of semi-structured interviews as a means for eliciting the preferences and opinions of key Cancer stakeholders. The project opens a dialogue with Cancer researchers on the basis that qualitative interviews hold the potential to develop wider theory for mapping of Cancer research funding with a view to improving the relevance, efficiency and impact of Cancer research (Wright et al 2014)[20].

Stakeholders are located at various points of the Cancer research funding process. As a result, MAPPING_NCDs opens a dialogue at these manifold points. Typically, Cancer funding originates from a variety of sources: national governments (European Union Member States), international organizations with regional or global reach (OECD, WHO Regional Office for Europe, World Bank, International Monetary Fund, United Nations), the private sector (pharmaceutical, biotechnology and medical device industry), charities (European Diabetes Foundation, Macmillan Cancer, World Cancer Research Fund), non-governmental organizations (United Nations Children's Fund, Global Fund to Fight AIDS, Tuberculosis and Malaria) and, importantly, supranational organizations (European Investment Bank, Council of Europe, The European Commission) as well as public-private partnerships (e.g. the Innovative Medicines Initiative). Funding can either be directly associated with NCD research or flow indirectly into NCD research via overall budgets (i.e. hospital budgets). In this way, national governments play an important role in encouraging and fostering research in innovation, including direct governance for key research areas and indirect mechanisms for incentivizing NCD research. At each of these points, the project makes contact with stakeholders, seeking their views on both the current and future state of funding for Cancer research.

Interviews provide opportunity to develop hypotheses about the future shape of Cancer research funding. Enabling close collaboration between the researchers and stakeholders, interviews allow stakeholders to describe their views of the current state of Cancer research and to improve researcher's understandings of the key factors influencing the shape of Cancer research. Interviews hold the capacity to answer the 'how' and 'why' of Cancer research funding, allowing researchers to understand how funding activities are influenced by the contexts in which they are embedded (Baxter and Jack, 2008)[21]. Interviews improve the quality of the mapping exercise providing

[20] John S.F. Wright, Paul G. Dempster, Justin Keen, Pauline Allen & Andrew Hutchings (2014) How should we evaluate the impacts of policy? The case of Payment by Results and the 18 Week Patient Pathway in English hospitals, Policy Studies, 35:1, 59-78, DOI: 10.1080/01442872.2013.875139

[21] Baxter, P., and S. Jack. 2008. "Qualitative Case Study Methodology: Study Design and Implementation for Novice Researchers." The Qualitative Report 134: 544–559

researchers with more complete understandings of causes and effects, enabling researchers to develop better ideas for future funding strategies that target more relevant disease factors. Ultimately, the purpose of the stakeholder interviews is to open a sophisticated and collaborative dialogue between policy makers and key personnel involved in the conduct of Cancer research with a view to producing a more nuanced map of Cancer research funding and heightening the potential for improving the state of Cancer research funding in the future.

3.1 Methods

The aim to be achieved with the interviews is to gather opinions and information of the major policy makers, researchers, leaders of the past, present and future strategies in cancer research funding. For this purpose, a systematic process is followed for selecting interviewed (Researchers/ stakeholders), conducting the interview, and subsequent qualitative analysis of the data obtained. The methods used have been described elsewhere (Allen et al. 2010[22]; Dempster, Woods, and Wright 2013[23]).

Stakeholders were purposively selected to reflect a range of factors including: expertise in cancer research, geographic location and expertise in awarding research funding. For all stakeholders, interview questions explored (1)current threads of research; (2) future research areas; (3) types of collaborations; (4) working with collaborators; (5) working with the private sector ; (6) types of funding organizations; (7) working with funding organizations; (8) future strategies for funding NCD research.

We identified 57 experts, outstanding in the field of cancer research in their origin countries (Austria, France, Luxembourg, Belgium, Germany, Netherlands, Denmark, Greece, Norwey, Bulgary, Hungary, Poland, Croatia, Ireland, Portugal, Cyprus, Italy, Romania, Czech Republic, Slovenia, Spain, Finland, Lithuania, Swiss). Besides to researchers from international level organizations (WHO, IARC, WCRF). Finally, nine leading experts agreed to participate and conduct interviews (Table lxx), seven of them preferred to answer by telephone, except two who chose to answer the questions written.

Table lxx: Interviews (Stakeholder/researcher)

	Stakeholder/researcher	Country	Time
1	FC (researcher)	Portugal	38´20´´
2	JMB (stakeholder)	Spain	19´15´´
3	SK (stakeholder)	Germany	35´13´´
4	GC (researcher)	Italy	11´30´´
5	MC (researcher)	UK	40´54´´
6	WCRF (RFO)	International	11´74´´
7	DCRC (RFO)	Denmark	*
8	GF (researcher)	France	25´54´´
9	SK (stakeholder)	Finland	*

* They answer a written questionnaire

[22] Allen, P., J. S. F. Wright, J. Keen, P. G. Dempster, A. Hutchings, and J. Townsend. 2010. "Investigating the Governance of NHS Foundation Trusts." Final Report. London: NIHR Service Delivery and Organisation Programme.

[23] Dempster, P. G., D. K. Woods, and J. S. F. Wright. 2013. "Using CAQDAS in the Analysis of Foundation Trust Hospitals in the National Health Service: Mustard Seed Searches as an Aid to Analytic Efficiency." Forum: Qualitative Social Research 14 (2): Article 3

The interviews were conducted by two EASP technicians, an English native-speaker (BM), responsible for conducting the interviews and a responsible for overseeing the recording and solve potential setbacks (MR, EM). The total duration was 3h 1min 6s, with an average of 26 minutes per interview. All interviews were recorded and transcribed. Consent was gained for all interview subjects and their anonymity.

3.2 Results

3.2.1. Impacts of funding strategies for cancer

This study analyses the effects that funding strategies on cancer have on the society and knowledge in an effort to improve research programmes on cancer and enhance cancer control.

In the main, researchers find funding very complex and limited. They hold that most funding focuses on basic research which although it has an impact in the academic research of Europe, it also limits "our capacity to compete with US where money from government and other sources is available for conducting academic clinical trials trying to answer strategic questions, instead of questions linked to drugs". Researchers are concerned about lack of funding for independent clinical studies.

They also resent the lack of funding for multi-national projects. On one hand, it is difficult to conduct a trial with subjects from just one country, and yet funding possibilities are mainly national and employ no money for central coordination. "They are usually ok for giving money for national patients involved in the study but not for patients outside their country and not to central coordination".

Researchers demand easing the heavy administrative burden. They defend the simplicity and political support of *Europe Against Cancer Programme* (including publication *Europe Code Against Cancer*), late 1990s, perceived as the most effective programme in "raising public consciousness and making research money available to help control cancer", whilst they are critical about the avoidable cumbersome and complicated procedures they need to go through when applying for funding on cancer research, not always balanced and sometimes leading to a waste of effort since "the investment of your effort, against the probability of success is too disproportionate to make it valuable".

Whilst they are pleased to learn that the EU is willing to improve cancer control, they question whether "the mechanisms that the European Union uses are necessarily the most efficient or the most effective" to achieve this goal. In addition, they hold that the European multi-centred approach of cancer research efforts imposes too much bureaucratic work on the coordination team and "take up a lot of time of researchers that could be better spent doing research".

For some researchers, impact of research is difficult to quantify, especially for fundamental research, and are currently trying to move towards clinical research. "One of the difficulties is usually funding research with multiple grounds and so it's difficult to measure the impact of our findings amongst lots of different findings, but in clinical trials we usually have much bigger impacts in terms of findings so it's easier". Whereas for others, quantifying impact is relatively easy. Clinical trials are registered under the *EU Clinical Trials Register* which allows you to search for protocol and results information, not only for interventional clinical trials that are conducted in the European Union and the European Economic Area but also for those conducted outside this area that are linked to European paediatric-medicine development. In addition, impact and relevance of scientific research can be measured by the number of published issues. Yet, they hold "since the first publication of the

Clinical Trials Directive, there have been several publications showing the enormous decrease of academic clinical trials or academic studies all over Europe".

According to one of the researchers, significant funding has been put on cancer programmes in Europe over the past decade, both at European level and at the national level and has had a positive impact on therapeutic cancer. "The impact has definitely gone towards the direction of personalised therapy for cancer, towards the genetic and epigenetic characterisation of cancer".

Stakeholders believe that the major contribution has been promoting international research network structures. "Building real networks of different researchers of different countries and different situations, as well as making possible to build research infrastructure at the European level". Assessing different countries from different settings, at different risks for papillomavirus, for example,
on a more effective use of the vaccination is a very positive impact of the strategies for cancer. Translational research is an important re-structuring effort "delivering the results of research faster to the clinic".

Besides the classic "it's usually too short" or "the continuity of the programmes receiving funding could sometimes be threatened by the fact that programmes are for two years, three years..." stakeholders do not think that research funding programmes can have a negative impact.

RFOs report huge positive impacts "in terms of understanding the cell biology of cancer and of tumours", whereas they consider that care must be taken to make sure that programmes implemented are effective and carried out for the direct benefit of patients, holding "there has been an increased potential to identify markers of cancer with pressure to develop screening programmes that may be premature" which sometimes leads to a negative impact since the benefits of screening not always outweigh the risks.

3.2.2 Challenges

Indeed, one of the basic problems researchers state to be facing is the lack of funding. Thus, one of the main challenges for them is "to maintain the same level of funding or increase it" which seems very hard to achieve in this difficult economic climate.

Similarly, there is a concern for the lack of dedicated calls for cancer research. "Current call topics are very broad... There is going to be a tremendous competition between cancer and other therapeutic areas with no anticipated, expected, dedicated funding for cancer research".

One researcher was critical that the European Union priorities for funding research initiatives "are not necessarily correct", claiming that the billion Euros spent on the Innovative Medicines Initiative (Europe's largest public-private initiative between the European Union and the European Federation of the Pharmaceutical Industries and Associations, aiming to speed up better medicines to patients) "could have been spent more wisely in other forms of research, not necessarily cancer but including cancer... I think the pharmaceutical industry was perfectly able to deliver their drugs on their own", on the grounds of the huge profits the pharmaceutical industry makes.

The need for independent sources of funding is always a cause of concern. "We had to go to the industry to be able to actually complete the project... And when you are in a consortium that has several commercial partners, then of course you will get into difficult intellectual property rights discussions and also you will necessarily have to do some compromise... It is not the best way we wanted but it was the only way to finish the project"

Information is crucial in cancer control and data resources are therefore considered by all researchers interviewed to be one of the biggest challenges to cancer research in Europe, and also a serious threat to medical research in general if amendments proposed to the European General Data Protection Regulation (which include a requirement for specific consent for the use and storage of personal data) become law. “It would disable cancer research, it would disable public health research, and I cannot understand how the EU can let this happen, unless it is blind”. Cancer regulation is the first essential element for improving cancer control. “We know how many cases there are each year of each type of cancer across Europe, what the mortality is, what the levels of survival are and how they are changing with time, between cancers, between sexes, between countries and over time. All of that comes from cancer registration, yet the current draft regulation would disable cancer registries”. Just the EUROCARE-6 study, call for data, would require seeking the consent of 10 million cancer patients across Europe. “I just don’t understand how the European Union can be so dissociated that it sets up a cancer information centre in Italy, at the Joint Research Centre, to collect all this information from cancer registries and to use it productively to drive European cancer policies, yet, at the same time as passing - by 621 votes to 10 - a regulation that would make that very data collection impossible. Does that make any sense? I don’t think so”.

Whilst researchers believe that a multidisciplinary and multinational approach in cancer is vital, they report a need for harmonisation of procedures among European countries for the storage of human material for research since each country has its own regulations. “Very frequently we need collection of biological material... The possibility to transport tumour samples from one country to the other is very different from country to country. So, you can imagine the complexity of organising such a study”.

Another key issue is handling the Big Data, i.e. storing, analysing, sharing and understanding the huge quantities of data collected. “A lot of efforts have been made to sequence lots of tumour genomes so research all over the world has obtained a huge amount of genetic data”. The main concern is “how to manipulate all these data coming from the sequencing of the tons and tons of genomes”. There is a real need for IT professionals and specifically in bio-informatics.

Challenges identified by stakeholders are similar to those from researchers. An important asset for cancer research is counting on reliable data on cancer incidence. “Linking bio-bank data with cancer registry data creates new possibilities for translational research”. They, too, are concerned that the new Data Protection legislation will seriously endanger research. “Especially for rare diseases, cross-border research is very important... Too strict data protection regulation may even endanger this”.

Stakeholders also state the need for more funding. “It is more difficult to convince Research Councils of the governments that we need more resources for cancer research... Getting funding for clinical research, especially for clinical trials, has become more difficult”. In addition, they highlight the need for making a more efficient use of the research funding available, “trying to focus the funding on really excellent groups”, asserting that a reasonable strategy would be “to fund on a long-term basis research infrastructure on a wider perspective... some good research... to offer good advanced statistical support in terms of the development of new techniques”.

There is also a need to exert more efforts to conduct translational research in cancer genetics, to move research from the bench to the bedside, to move genome discoveries into health practice and disease prevention, and to improve early cancer detection. Genetic signature improves the understanding of tumour biology and the development of personalised therapies. “We are really more at the beginning of this process, of understanding the interaction, so, personalised medicine, personalised cancer research and personalised cancer medicine should be the programme of the future”. For this “we need epidemiological studies which are also joined up at the European level...

Different population groups have different characteristics and it would provide a lot more insights... In the biomedical research you have to think much more long-term... European level is much too focused on short-term innovations and I would like to see a more holistic approach". This challenge is also common to researchers, as one stated, "have a comprehensive description of the genetic and epigenetic heterogeneity and how this impacts on the response and, in particular, resistance to therapies… necessary to work through collaborative programmes with a considerable amount of allocation since it would require genetic and epigenetic characterisation".

Building a European solid collaboration for research at different levels is another major challenge for stakeholders, although sometimes difficult "to go beyond the borders of your own institution, your own group".

Improving cross-border collaboration is also a major challenge of RFOs. Small national studies have their limitations. "Instead of organising one big European trial, we initiated seven smaller trials, each with too small statistical power to detect a survival advantage... The seven European trials have their own individual design in regard to inclusion criteria and criteria for abnormal findings, which makes it difficult to do a metanalysis".

RFOs also resented the lack of a "funding organisation for researcher initiated cancer research".

Finally, two broad areas identified by RFOs as challenges for future cancer research are to do with prevention. The first one refers to the implementation of effective policies to promote behaviours "to create an environment that is conductive to health... not just permissive but positively conductive". The second alludes to the identification of key characteristics of tumours "to allow appropriate and different interventions for their management and prevention. However, funding challenges for prevention are perceived as being problematic since "there isn't and needn't be a pharmacological model and the industrial input into cancer research is not available for prevention research".

3.2.3 Recommendations

Some of the current gaps identified by the researchers are detailed in the foregoing section since what is lacking is perceived as an objective to be achieved in the future. In the main, gaps include mostly: cross-border collaboration, no link between basic and clinical researchers and the patient, gap in translational and clinical research due to lack of independent sources of funding, gap in the validation and clinical implementation of basic research, gap in the regulation in terms of homogeneous validation for new health technologies (diagnostic tools, predictive tests, biomarkers…); lack of central coordination for cancer registries, lack of quality of data in some cancer registries, no cancer relapses and metastasis registration ("how can we allocate resources and define the needs of those patients if we don't know how many they are?"), lack of epidemiological studies in cancer, gap in rare cancers and in child cancers ("because they don't concern that many people although we have many different rare cancers").

On the basis of the gaps and challenges mentioned throughout the report, researchers, stakeholders and RFOs interviewed for the purpose of this study suggest the following issues as recommendations for future EC activity on cancer:

- Prioritise personal cancer medicine ("We need to understand the tumour microenvironment... understand therapy resistance and the processes around metastasis... will involve developing new tools such as whole-genome sequencing... develop new biomarkers... new imaging techniques").

- There is a need for independent research on all the new technologies on radiotherapy, surgery and, in particular, in the area of molecular biology. “Almost every week there are studies published of a new biomarker and of a new test that is developed but we have no idea on the clinical application”. “More research is required on new surgical techniques or new methods of delivering radiation”.
- Provide more funding for academic independent research in general.
- Establish networks of comprehensive cancer centres throughout Europe.
- Finance projects in which participation from several countries is encouraged.
- Invest on multinational research infrastructures “funding the foundation and implementation phase”.
- Potentiate strategies such as ERANet programmes, effective to synergise co-funding programmes between the European Commission and the different countries.
- Promote transnational programmes for the translational and clinical areas of research.
- Encourage cooperation between basic translational and clinical researchers. “I think projects that would give priority to that cooperation should be favoured in terms of funding”.
- Promote larger population-based, observational studies, as opposed to intervention studies.
- The Council of Europe should “produce a summary of the risks to cancer information in Europe if the current draft Regulation on Data Transfer is not suitably modified”.
- Raise awareness to conduct research not for the sake of just publishing but for the impact that research will have on the treatment and management of cancer.
- Cooperation with patient advocacy groups (listen to them to understand and address their needs).
- Develop Europe-wide (not just in the EU) strategies on cancer.
- Promote NCD research programmes “to identify new strategies for NCD prevention”. “It is just a staggering disparity in vision and commitment between communicable and non-communicable disease”, even though communicable disease is responsible for around 1% deaths in Europe, whilst cancer for 20-29%.
- Invest more on prevention research rather than at the interface between pharmacological research, cell-based research and health system delivery.
- Striking a balance between basic science intervention and prevention research “changing the behaviours that lead to the risk factors... promoting healthy behaviours”.
- Improve cancer registries (“there should be a central coordination of all cancer registries, and they should be homogenous on what we collect).
- Allocate funding on a European level to enable sharing useful data from national cancer registries databases. “Most European countries have excellent health registers... diagnostic information linked to hospital admissions and outpatient visits, registration of use of prescribed pharmaceuticals”. “Link data from registries with valuable biobank data”.
- Promote the conduction of more epidemiological studies “but I would say not just any kind of epidemiological studies but a correct registry of all cancers, the important data coming from those cancers and the particular case of breast cancer”.
- Cancer continues to need new treatments. “I would like to see more funding dedicated to advanced cancer… since it stills kills 100% of cases”.
- Prioritise child cancers
- Promote a better use of in vitro and animal models to ensure that every piece of research is relevant to human cancer
- Devote efforts to identify the mechanisms through which normal cells become abnormal.
- Support cross-disciplinary research involving basic researchers in epidemiology and cancer biology and in cancer prevention and clinical treatment and care.
- Ease the heavy administrative burden of procedures for applying for funding for cancer research.
- Develop and recognise “health services” as a field of research.

- Promote discussions on ethical implication of research.

Basically, most interviewees believe that funded research in cancer is not always delivering the best possible results. Partly due to the lack of knowledge ("Our inability to truly understand the complexity of a cancer cell and how we can overcome the problem of resistance") which could be improved by investing more efforts on conducting research that has a clinical application, the bottom-up approach (researcher initiated research) and rigorous peer review for best science.

A special mention, not on financing itself but on procedures, is made by one researcher with regards to applications to specific call topics, in particular the previous FP7 but also the current Horizon 2020. Applicants do not receive basically any or not enough feedback on the outcome, and specifically "the negative outcome of the first stage proposal", which is perceived as unmotivated.

The areas beyond financing in which the EU should be looking at, according to interviewees, include:

- Engagement of the Patient Organisation, increasing awareness of cancer patients towards new therapies and personalised medicine.
- Revision of the proposed amendments to Data Protection Regulation because it will have a tremendous negative impact on research.
- Harmonisation of laws and regulations that affect multinational trials in terms of the transport of tumour and biological samples.
- Investment of further efforts on the validation of quality of care and even accreditation.
- Establish networking among foundations and a platform for charities to encourage cross-border collaboration.
- EU should take a leading role to help raise awareness about the importance of supporting cancer research.

As for ways in which cancer research may be suffering from a certain degree of duplication there is a variety of opinions. Whilst some researchers believe that there is indeed duplication due to the complexity of procedures and different regulations among countries ("it's a nightmare to run multinational projects, people just give up and run smaller projects inside their own country… so you have duplication instead of one large European project") which could be avoided by enhancing multinational cooperation, by making unified programmes "to bring together all different actors to walk in the same direction", by establishing a sort of a "high level policy funding board" to encompass funders; others think that duplication is not always a bad thing since research needs to be re-demonstrated "Sometimes it is important to illustrate that a finding is replicable", and since "duplication may and should also lead to collaboration between researchers who are interested in the same scientific problem area".

3.3 Discussion and Conclusion

This analysis provides a view about the impact of research funding activities of cancer in the Europe while identifying areas of unmet needs to gain deeper insight of the main challenges that, as suggested by respondents, should be addressed for the future research in this area.

With regards to intervention programmes and impacts, it outlines that while significant funding has been devoted to cancer programmes in the last decade, with major contributions made to cancer control, most efforts have been directed towards basic research and to interventions at a national level, as opposed to applied research and multinational interventions. It also reveals that several publications show a decrease of academic clinical trials all over Europe. In addition, and despite the

many positive impacts reported in the area of cancer in general and specifically in innovative fields such as tumour biology, it is suggested that care should be taken to ensure that benefits outweigh the risks of the screening procedures and invasive tests.

A current issue which according to respondents needs to be addressed urgently, since it seems to constitute a major threat for the continuity of research, is the issue of the specific consent requirement proposed as an amendment to the European General Data Protection Regulation which may apparently disable cancer registries and cancer research if approved. Indeed, information is key to cancer research and the raised concerns do seem to have a point there if researchers are to fall inside the duties of this regulation.

Another issue that strikes from the interviews is the apparent disparity in allocations between communicable and non-communicable disease, with non-communicable diseases receiving a tiny percentage of funding compared with their burden, taking into account that cancer on its own accounts for 20-29% of deaths in Europe *vs*. 1% of deaths from communicable diseases, according to data provided by a senior research interviewed.

Cancer continues to be a leading cause of death and, consequently, respondents suggest there is a need for increasing funding for cancer research and prevention programmes in an effort to contribute to an overall reduction in cancer incidence and mortality. More specifically, this analysis demonstrates the need for more independent research since, amongst other consequences, commercial partnerships compromise intellectual property rights.

Certainly, there has been a generalised recognition of the growing importance of personalised cancer medicine which several respondents considered to be the future of cancer research and, therefore, urge the European Union to prioritise.

In conclusion, this analysis reveals the need for strengthening and implementing policies that enhance cancer control efforts across the European Union. Cancer is a non-communicable disease which encompasses multiple diseases in one and requires data from different population groups with different characteristics to gain a deeper insight and determine the patterns and trends that affect cancer incidence. Cancer requires a multinational and multidisciplinary approach, in particular with regards to rare cancers. To this end, this analysis suggests that the European Union should prioritise research on personalised cancer medicine and direct more efforts towards the establishment of networks or programmes that encourage solid cross-border collaboration for research at different levels, provide more funding opportunities for independent academic research and for translational research to place latest discoveries into health practice and disease prevention, implement effective policies that promote behaviours that are conductive to health, and, last but not least, implement priorities to protect personal data whilst not hampering research.

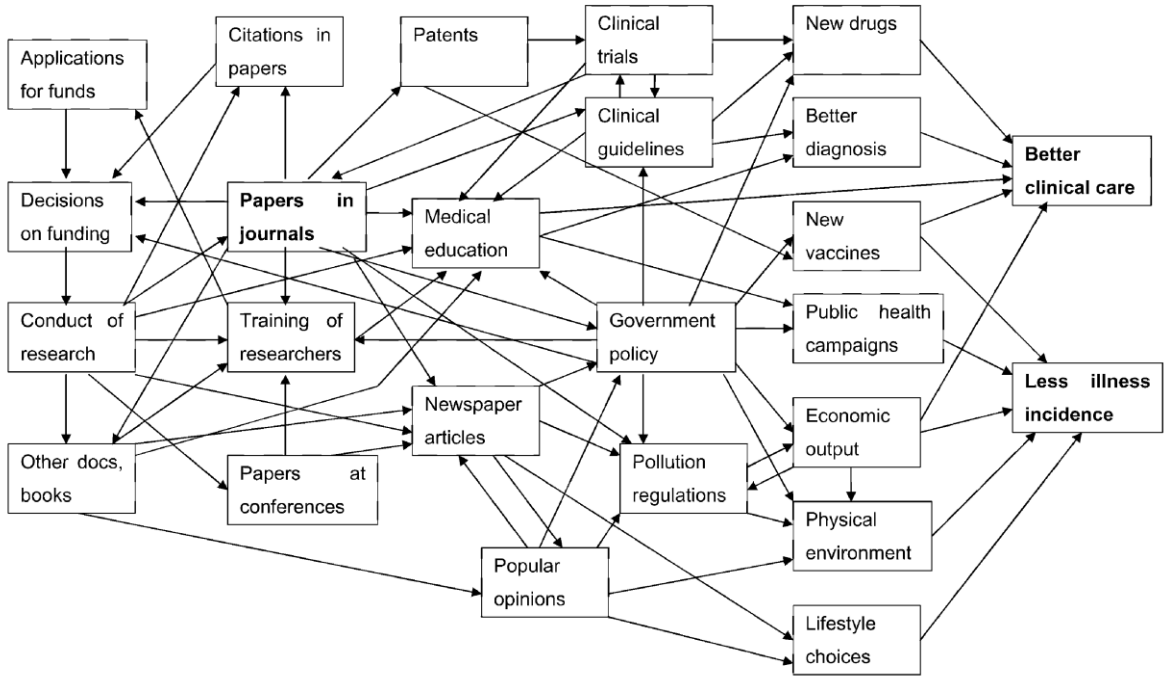
4 Bibliometrics: Impact of Cancer Research Funding

A key aim of MAPPING_NCDs is to establish the impact of funding investment across five key NCD areas: cardiovascular disease, chronic respiratory diseases, diabetes, cancer and mental health. In this aim, MAPPING_NCD moves beyond the state of the art in the research area by pursuing bibliometric mapping and analysis of the volume of research outputs in the EU and MSs relevant to these disease areas. Bibliometrics establishes the impact of funding investments by mapping and analyzing of the volume, citations, funding sources, influence on clinical guidelines and newspaper stories of research papers and reviews in the Web of Science (WoS) published in EU MSs during the last ten years (2002-12). Where funded research produces scientific papers, funding is considered to have had 'impact'. Bibliometrics identifies specific impacts associated with individual research papers through citations in other relevant papers. Bibliometrics also checks funding acknowledgments in relevant papers. It considers the extent to which they have provided the evidence base for clinical guidelines relevant to various NCDs. And, it also considers the extent to which they are cited in stories about NCD research in newspapers and the broadcast media in MS. In this way, the impact of the paper is associated with the relative values that papers achieve against these measures.

4.1 What is Research Impact?

Measuring the impact of research is a complex task. Often, health improvements depend on a host of different research discoveries, which are made at different times and in different places. The pathway from the conduct and publication of research to better health is usually indirect. In addition, the results of research contribute to better health in different ways, from the improved diagnosis and treatment of patients to the prevention of illness or the reduction incidence. Figure iv details the manifold linkages between research funding and health impacts.

Figure iv: Some of the links between research and healthcare improvement



Among these many nodes and linkages, 'government policy' occupies a central position and has a several linkages to other nodes. Moreover, the 'reduction of illness incidence' also depends on a large number of inputs, including: environmental pollution, individual health behaviours, wealth,

education and the effectiveness of public health campaigns. Thus, it can be observed that research impacts upon all these nodes, many of which are not specific to individual disease areas. Similarly, different types of research can also deliver advances in individual disease areas. And for these reasons, the norms for measuring both the effectiveness of research and its quality can also differ.

Nevertheless, all of these nodes are inter-connected. And at connection points, hard evidence of research impact necessarily accumulates. In the main, the evidence of research impact manifests itself in the paper trails that flow between one node and another. For example, research funding produces research, which produces papers in scientific journals, which in turn lead to citations in other journals, decision making influence, policy, media stories and even the allocation of additional research grants. Tracking and analyzing these paper trails, using them as a proxy for research impact, is the fundamental business of bibliometic research.

In this section of the paper, we utilize bibliometric methods to analyses data that accumulates at five of these nodes along the many paths to research impact for Cancer. These nodes are:

- Scientific research papers
- Funding sources (decisions on funding)
- Citations
- The evidence base of clinical guidelines;
- The stories in newspapers and the research papers that they cite.

4.2 Scientific Research Papers: Cancer

The first means by which bibliometric analysis establishes funding impacts is by the number of published scientific papers. This section of the report details the number of downloads papers for Cancer whose details are in the Web of Science (WoS) from 31 European countries (the 28 EU Member States, plus Iceland, Norway and Switzerland) in the 12 years 2002-13. To this end, bibliometric analysis utilizes two overlapping databases, the Science Citation Index Expanded (SCI) and also the Social Sciences Citation Index (SSCI), for the provision of knowledge on socio-economic impact and behavioral interventions associated with Cancer.

The report identifies by means of a “filter” whose precision and recall was determined by means of experts in the subject area marking sets of papers as relevant or not. Filters were developed for each of the five disease areas:

- Cancer research (oncology): ONCOL
- Cardiovascular research, including stroke: CARDI
- Diabetes research: DIABE
- Mental disorders research: MENTH, and
- Respiratory disease research: RESPI

Details for each filter were written to five Excel spreadsheets for analysis, which are explained in each of the five relevant Critical Appraisal documents. The main analyses were of country outputs, their research levels (from clinical to basic) and for some subject areas, the type of research or disease. Each filter was applied to the Web of Science for the Science Citation Index (extended) – SCI – and for the Social Sciences Citation Index(SSCI), for the twelve years 2002-13, and articles and reviews only were identified. The papers were also limited to those with at least one address in one or more of the following 31 countries – the 28 Member States of the European Union plus Iceland, Norway and Switzerland. Table lxxi lists the countries with their digraph ISO codes.

Table lxxi: List of 31 countries used to limit the downloaded papers

ISO	*Country*	ISO	*Country*	ISO	*Country*	ISO	*Country*
AT	*Austria*	**EE**	*Estonia*	**IS**	*Iceland*	**PL**	*Poland*
BE	*Belgium*	**ES**	*Spain*	**IT**	*Italy*	**PT**	*Portugal*
BG	*Bulgaria*	**FI**	*Finland*	**LT**	*Lithuania*	**RO**	*Romania*
CH	*Switzerland*	**FR**	*France*	**LU**	*Luxembourg*	**SE**	*Sweden*
CY	*Cyprus*	**GR**	*Greece*	**LV**	*Latvia*	**SI**	*Slovenia*
CZ	*Czech Rep.*	**HR**	*Croatia*	**MT**	*Malta*	**SK**	*Slovakia*
DE	*Germany*	**HU**	*Hungary*	**NL**	*Netherlands*	**UK**	*United Kingdom*
DK	*Denmark*	**IE**	*Ireland*	**NO**	*Norway*		

The "full record", which includes all addresses, e-mails and funding details (where given) were then downloaded to a series of 12 "year" files, 500 papers at a time These were then processed by a special macro to produce one combined Excel spreadsheet. The 12 separate spreadsheets were then combined together to make a single sheet. This contained 282,055 papers.

Each paper in the combined sheet was given an individual index number, and the following parameters were recorded:

- Names of all authors, in the format SMITH-AB
- Paper title
- Source (journal name, year, volume, issue, pages)
- Journal name
- Document type (article or review)
- Addresses (all in upper case, separated by a forward slash). Note: in the WoS UK papers are attributed separately to ENGLAND, WALES, SCOTLAND or NORTH-IRELAND.
- Country of publication
- Year of publication
- Month of publication (for most papers where the date of the journal was given)
- Language (almost all were in English)
- E-mail address(es) of corresponding author, sometimes others
- Funders, FU (for late 2008 papers and subsequently)
- Funding acknowledgement text, FX
- Composite list of authors and their individual addresses (from 2008)
- Authors' full names (where given), in the format Wilhelm, Hans; Wanke, Isabel; Hirche, Herbert (this allows the sex of most of the authors to be determined)
- Whether in the SCI or SSCI only

Although most papers in the WoS have their chosen keywords and formal abstracts, these were not recorded in the main spreadsheet as they would have made it far too cumbersome. From the paper title, a macro was applied to determine if the paper could be classed as "clinical " or "basic" or "both", according to the presence of one or more words on two lists, see Lewison and Paraje, 2004[24]. The research level of the journal in which the paper was published was also determined

[24] Lewison, G & Paraje, G (2004) The classification of biomedical journals by research level. Scientometrics,60(2) , 145-157.

from a master list, based on the same scheme; clinical journals were classed as RL = 1 and basic ones as RL = 4, and ones in between were given an RL value as a decimal number between 1.0 and 4.0. These RL values were determined for groups of five years, 2000-04, 2005-09 and 2010-14.

In order to measure the impact of Cancer, a specialized ONCOL filter was created. This filter, consisted of two main parts: a list of specialist journals and another list of title words. The filter was first developed in consultation with Cancer Research UK, a leading charity, for the Science Citation Index on CD-ROM. It has since been extensively modified to make it apply to the Web of Science (WoS) with its different interface and software, and to take account of the additional journals covered by the WoS, and ones added recently. It has also been amended to include newly-discovered genes that predispose a person to cancer, and new medicines. The list of title words also includes the names of a large number of cancers.

The filter was calibrated with reference to three sets of papers taken from the WoS: ones captured by the filter (or not) and ones whose addresses included (or did not include) department names (and their contracted forms) characteristic of cancer such as CANC, ONCOL, ONKOL, and TUMOR.

- Set A were papers identified by the filter AND having one or more cancer words in their address field;
- Set B were papers out with the filter but with one or more cancer words in their address field;
- Set C were papers identified by the filter but without a cancer address word.

The number of papers in each of these three sets in a given year in the WoS was then designated as N. Samples of all three sets of paper details were downloaded to a spreadsheet and presented to one of the NCD mapping partners to mark as relevant to cancer research (1) or not relevant (0). Shading of the marks with a decimal between 0 and 1 was also possible. These markings were used to determine the numbers of papers retrieved by the filter that were deemed to be relevant, and by rule-of-three, the estimated number in set D (not found by the filter and without a cancer address word). Table lxxii, below, shows the calculations.

Table lxxii. Example of calculations used to determine the precision (p) and recall (r) of the ONCOL filter.

Set	*N (WoS)*	*n (sample)*	*n* (relevant)*	*precision = p*	*N* (relevant)*
A	32670	200	190	0.950	31037
B	17316	500	22.5	0.045	779
C	42697	500	402	0.804	34328
D					862
Total					67006
Found	75367	= (32670+42697)		(31037+34328) =	65365
Precision		**p =**	**0.867**	= (65365/75367)	
Recall		**r =**	**0.976**	= (65365/67006)	

If the precision and/or recall were insufficient, then the titles of the papers causing problems were examined in detail with a view to the addition of extra title words to the filter (for papers marked “1” in set B) or their removal, or the addition of “no” words to the filter (for papers marked “0” in sets A and C). This was an iterative process, and several rounds were needed, with successive sets of papers being marked by the Andalusian School of Public Health. The final values of precision and recall were **p = 0.95 and r = 0.98**.

Cancer is one of the biggest NCD research areas. By comparison with other disease areas, the ONCOL generated the biggest of the five NCD files, with just 282055 papers.

Table lxxiii: Outputs and Parameters of the five NCDs by size

Subject	World output*	EUR31 output*		% world	% BIOMED
BIOMED	6075502	2442063		40	
ONCOL	748724	282055		38	11.5
CARDI	508611	211507		42	8.7
MENTH	349027	138666		40	5.7
DIABE	103792	40550		35	1.7
RESPI	33629	18822		56	0.8

**indicates the number of research papers published in the disease area*

ONCOL research was divided into 11 defined research types, listed in Table lxxiv.

Table lxxiv. List of research types in cancer research defined by sub-filters.

Research type	*Code*	*Research type*	*Code*	*Research type*	*Code*
Chemotherapy	CHEM	Palliative care	PALL	Radiotherapy	RADI
Diagnosis	DIAG	Pathology	PATH	Screening	SCRE
Epidemiology	EPID	Prognosis	PROG	Surgery	SURG
Genetics	GENE	Quality of life	QUAL		

Each of these was defined by means of title words and journal name strings, selected by Professor Richard Sullivan of KCL. They generated different numbers of papers, as described in the first report, with genetics giving the most (48,259 or 17.1%), followed by chemotherapy (28,240 papers or 10.0%), prognosis (27,189 papers or 9.6%) and surgery (26,585 papers or 9.4%). Figure v shows the distribution of research levels on the same basis as Table lxxiv and Figure vi shows the mean number of five-year cites to papers of the different research types.

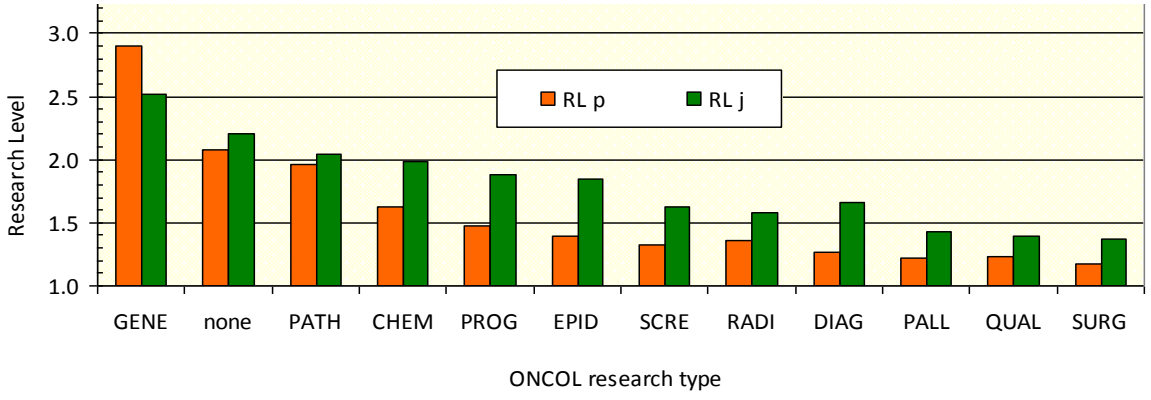


Figure v. Chart of mean Research Level of papers and of journals in which they were published for ONCOL papers of 11 research types. ***RL = 1.0 is clinical observation; RL = 4.0 is basic research.***

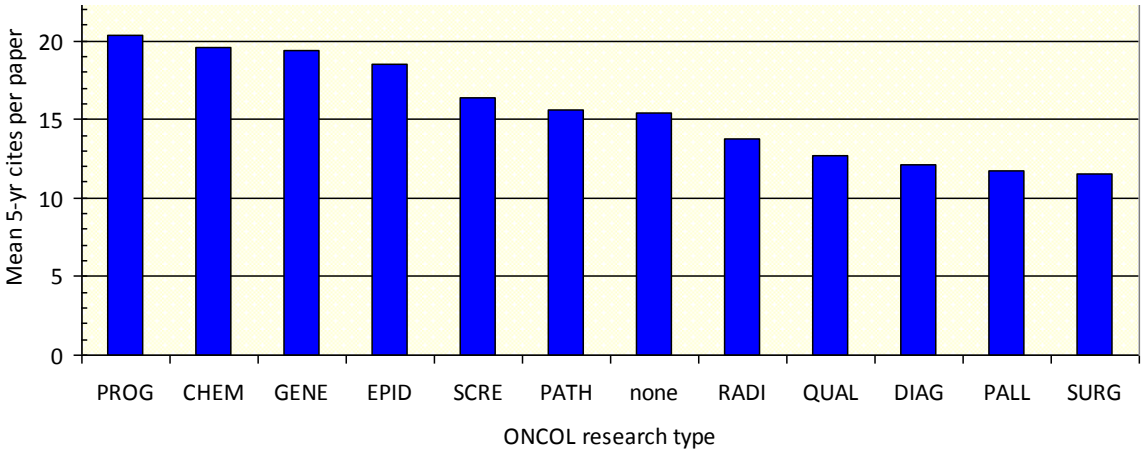


Figure vi. Chart of mean five-year cites for ONCOL papers of 11 research types published in 2002-09.

It´s has been examined the outputs for 22 different cancer sites, and they were as shown in Table lxxv.

Table lxxv. List of 22 cancer manifestations (body sites) for which sub-filters were developed to identify relevant ONCOL papers.

Site	*Code*	*Site*	*Code*	*Site*	*Code*
bladder	BLA	liver	LIV	pancreas	PAN
bone	BON	lung, trachea, bronchus	LUN	prostate	PRO
brain	BRA	lymphoma	LYM	stomach	STO
cervix	CER	breast	MAM	testicles	TES
colon / rectum	COL	melanoma	MEL	thyroid	THY
gallbladder	GAL	mouth (head & neck)	MOU	uterus	UTE
kidney	KID	oesophagus	OES		
leukaemia	LEU	ovaries	OVA		

The numbers of papers on each cancer site are shown in Table lxxvi as numbers and percentages of the European contributions to the ONCOL papers (which totalled 252718 out of the 282555 ONCOL papers).

Table lxxvi. Numbers and percentages of cancer papers on each of 22 sites (for codes, see Table lxxiii).

Site	*N*	*%*		*Site*	*N*	*%*		*Site*	*N*	*%*		*Site*	*N*	*%*
MAM	25805	10.2		LIV	9746	3.9		OVA	5457	2.2		THY	2996	1.2
COL	17389	6.9		STO	9601	3.8		PAN	4523	1.8		BON	2673	1.1
LEU	14838	5.9		BRA	9560	3.8		CER	4032	1.6		OES	1802	0.7
LYM	11903	4.7		MEL	9247	3.7		BLA	3567	1.4		TES	1465	0.6
PRO	11399	4.5		MOU	6578	2.6		UTE	3136	1.2		GAL	200	0.1
LUN	10392	4.1		KID	5510	2.2								

The research levels of the papers on the different cancer sites are shown as two separate charts, Figures vii and viii; and the mean five-year citation scores in Figures ix and x

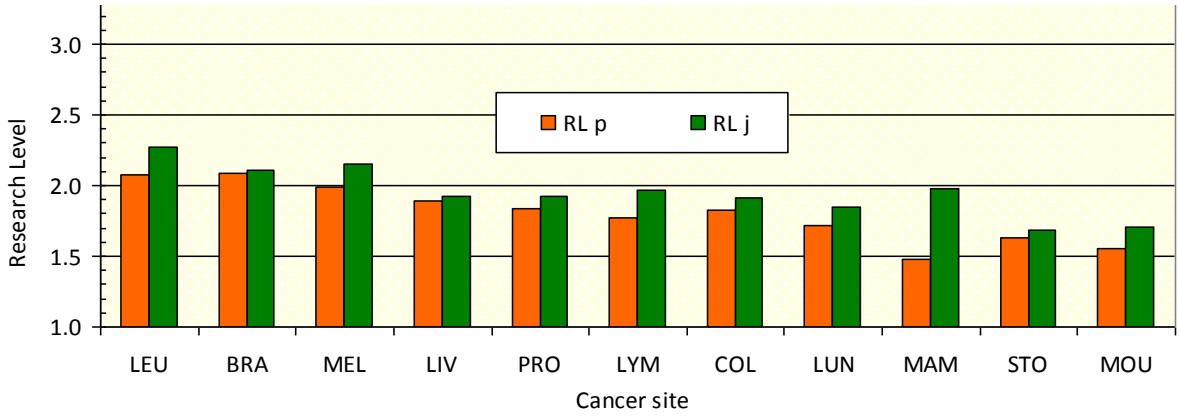


Figure vii. Chart of mean Research Level of papers and of journals in which they were published for ONCOL papers on 11 leading cancer sites with > 2.5% of papers. RL = 1.0 is clinical observation; RL = 4.0 is basic research.

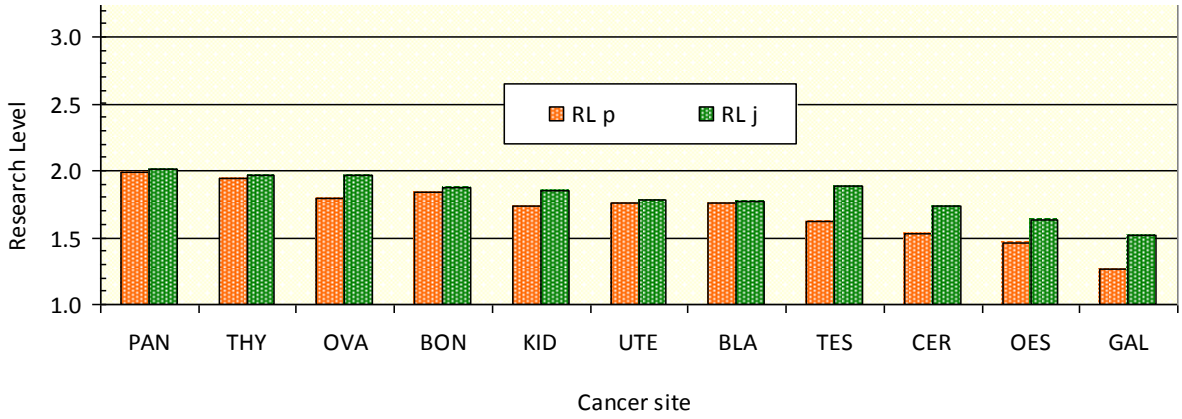


Figure viii. Chart of mean Research Level of papers and of journals in which they were published for ONCOL papers on 11 other cancer sites with < 2.5% of papers. RL = 1.0 is clinical observation; RL = 4.0 is basic research.

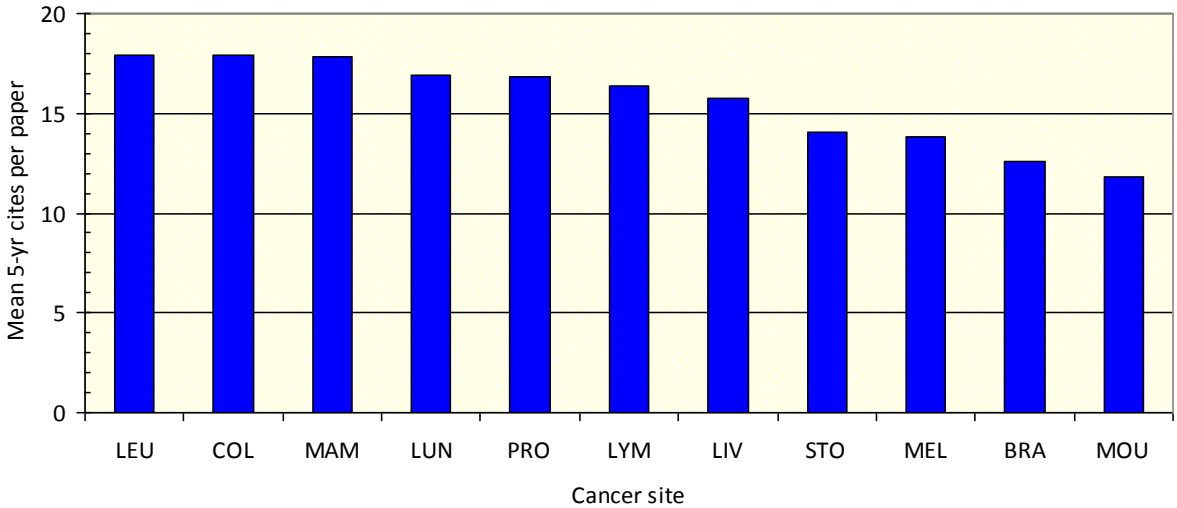


Figure ix. Chart of mean five-year cites for ONCOL papers on 11 leading cancer sites with > 2.5% of papers published in 2002-09.

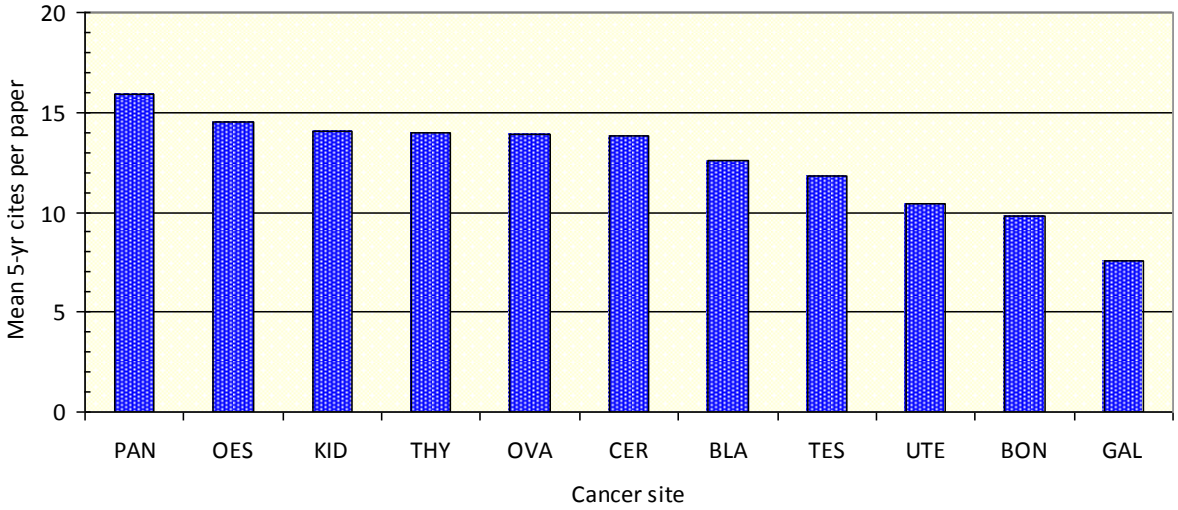


Figure x. Chart of mean five-year cites for ONCOL papers on 11 other cancer sites with < 2.5% of papers published in 2002-09.

The mean citation score varies by a factor of more than two for the extremes of the cancer sites (leukaemia, colorectal, breast = 17.9; gallbladder = 7.6) and by almost two for the extremes of the types of research (prognosis = 20.3; surgery = 11.5). In fact, the ACI value is positively correlated with the size of the research community, or at least the number of papers, with $r^2 = 0.56$ for the 22 cancer sites, and $r^2 = 0.33$ for the 11 types of research.

The analysis began with a comparison of the European and world outputs in cancer research, and the determination of how much biomedical research was accounted for by oncology. For this purpose, It has been used a previously-developed filter based on biomedical address words, such as: an*esthe*, biophys, Cilag, dermatol*, epidem*, family, Genentech, hlth*, IRCCS*, Janssen which was found to give good discrimination between biomedical and non-biomedical papers in journals such as Nature and Science, and to provide virtually complete coverage of most biomedical journals. Table lxxvii shows the world outputs of biomedical research papers and ones in oncology, with the output of the 31 European countries as a group (integer counts) in biomedical research.

Table lxxvii: Biomedical research outputs from the world and from the EUR31 country group (integer count), and the corresponding outputs in oncology.

	BIOMED			ONCOL			ONCOL/BIOMED, %	
Year	**World**	**EUR31**	**EUR %**	**World**	**EUR31**	**EUR %**	**World**	**EUR31**
2002	372134	158121	42.5	43473	17857	41.1	11.7	11.3
2003	387844	163324	42.1	46098	18908	41.0	11.9	11.6
2004	405565	168608	41.6	48023	19159	39.9	11.8	11.4
2005	425313	176562	41.5	51027	20550	40.3	12.0	11.6
2006	450141	185422	41.2	53941	21486	39.8	12.0	11.6
2007	484370	198119	40.9	58964	23334	39.6	12.2	11.8
2008	521430	209200	40.1	63670	24608	38.6	12.2	11.8
2009	545028	216739	39.8	66477	25110	37.8	12.2	11.6
2010	571067	225649	39.5	71168	26182	36.8	12.5	11.6
2011	605770	235267	38.8	74890	26862	35.9	12.4	11.4
2012	641615	248188	38.7	83025	28584	34.4	12.9	11.5

2013	665225	256864	38.6	87968	29414	33.4	13.2	11.5

So the European group of nations has diminished its presence more in cancer research (from 41% of the world to 33%) than in biomedical research overall (from 43% to 39%). The reduction is primarily because of the rise in output of China and other Asian nations such as South Korea, Taiwan and India. Cancer research represents just over one ninth of all European biomedical research output, but one eighth of world biomedical output.

The addresses on each of the 282,055 ONCOL papers were analysed by means of a special macro to give both the integer and the fractional count of countries on each. For example, a paper with two French and one German address would be classed as FR = 1 and DE = 1 on an integer count basis, and as FR = 0.67 and DE = 0.33 on a fractional count basis. The latter was used for most of the analysis as it gives a much better impression of the amount of effort contributed by each country, particularly to highly collaborative international papers where the contribution of a given country may be quite small.

Since we wished to investigate the extent and nature of international collaboration, we recorded not only the presence of the 31 countries in Table lxxi as fractional counts, but also that of 11 other major countries with who European countries may be expected to collaborate. They were among those with the largest foreign contributions to the fractional count totals, but this ranking varied somewhat by year (and by subject area). The additional countries were as in Table lxxviii.

Table lxxviii. List of 11 countries whose fractional contribution to each paper was also recorded.

ISO	*Country*	*ISO*	*Country*	*ISO*	*Country*	*ISO*	*Country*
AU	Australia	CN	China (P.R.)	JP	Japan	TW	Taiwan
BR	Brazil	IL	Israel	KR	Korea (South)	US	United States
CA	Canada	IN	India	TR	Turkey		

The outputs of these 11 countries were, of course, only a small part of their total output. For each of the original 31 countries, it has been determined the integer and fractional count totals, and the numbers in each of the 12 years; and also has been determined the annual average percentage growth rate (AAPG) based on fractional counts. [This was obtained from a plot of the logarithm of the number of papers each year.] Table lxxv lists the results for ONCOL papers, with the total integer and fractional counts, the percentage of the foreign contribution and the annual average percentage growth rate. Since research output tends to be correlated with Gross National Product (rather than simply with population), we have plotted the countries' fractional paper counts against GDP for a representative year (Figure xi).

Table lxxix. Outputs of 31 European countries in cancer research (ONCOL), 2002-13 (12 years) in both the SCI and SSCI. Integer and fractional counts, the percent foreign contribution and the annual growth rate. ***The countries are ranked by their fractional count outputs. For codes see Table lxxi.***

Country	*Int cts*	*Frac cts*	*% Int*	*AAPG*		*Country*	*Int cts*	*Frac cts*	*% Int*	*AAPG*
DE	60456	45436	24.8	2.6		IE	3367	2247	33.3	9.3
IT	48499	37876	21.9	4.8		PT	3136	2079	33.7	13.3
UK	52465	37541	28.4	2.4		HU	2855	1897	33.6	3.2
FR	40329	30127	25.3	4.1		HR	1720	1429	16.9	9.7
NL	23572	16068	31.8	4.5		RO	1748	1248	28.6	35.7
ES	21453	15654	27.0	7.6		SI	1298	898	30.8	10.6

SE	14881	9205	38.1	2.0		SK	1196	755	36.9	6.6
PL	9699	7543	22.2	10.0		BG	673	453	32.6	10.4
GR	9513	7243	23.9	3.8		LT	396	265	33.0	16.4
CH	12827	6837	46.7	4.1		IS	509	208	59.1	3.7
BE	10891	6253	42.6	2.9		LU	259	116	55.3	14.6
AT	8971	5563	38.0	1.1		EE	208	97	53.2	4.0
DK	7692	4713	38.7	8.0		LV	191	86	55.2	7.3
NO	6650	4054	39.0	6.2		CY	198	79	60.1	18.0
FI	6015	3721	38.1	0.0		MT	51	22	56.5	12.1
CZ	4422	3005	32.0	9.2						

This table shows that there are big differences in output, with more than three orders of magnitude between the largest (Germany) and the smallest (Malta). However, some of the smaller countries are expanding their output rapidly – notably Romania, whose fractional count output rose from only 7 papers in 2002 to over 250 in 2013.

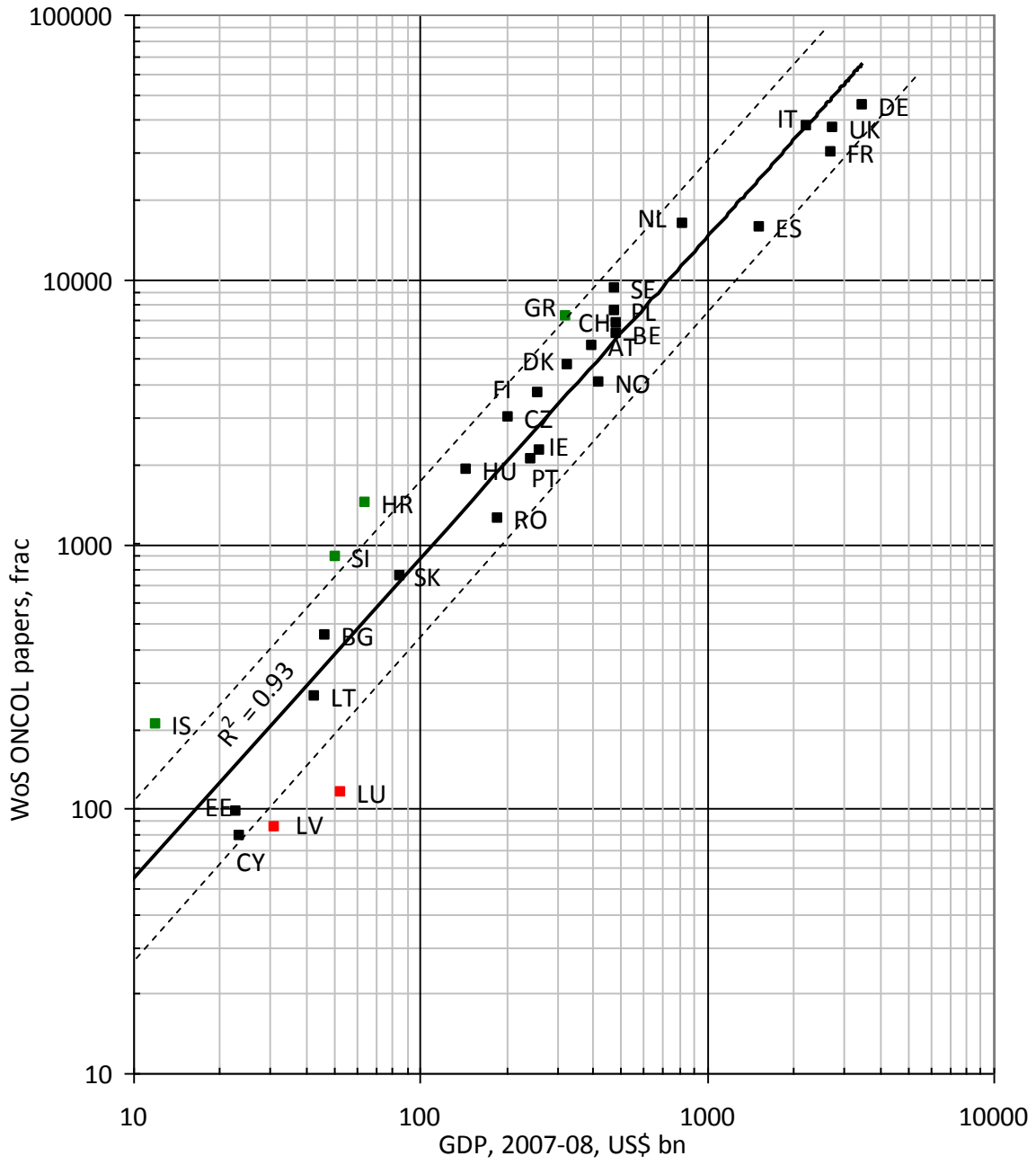


Figure xi. Plot of ONCOL paper output, 2002-13, against GDP for European countries. Note: MT omitted. Dashed lines show values x2 or x0.5 relative to power trend-line. For codes, see Table lxxi.

It is also expected that researchers in the scientifically larger countries (e.g., UK, Germany) would find it easier to work with a partner within the country that provided complementary expertise than researchers from small countries (e.g., Estonia, Ireland) and would therefore tend to collaborate less internationally. However it might expect that international transnational links would be much weaker for the Member States in eastern Europe, and so Figure xi has been plotted to show if this is the case. The figure shows that these "accession" Member States do indeed collaborate less than expected, whereas the five Scandinavian countries, with Belgium, Luxembourg and Switzerland, collaborate internationally more than the trend-line would suggest.

Table lxxx. Outputs of the 11 internationally collaborating countries, with fractional counts for three four-year periods (2002-05, 2006-09 and 2010-13) and annual average percentage growth for papers co-authored with the European countries. *For codes, see Table lxxviii*.

ISO	*2002-05*	*2006-09*	*2010-13*	*AAPG*		*ISO*	*2002-05*	*2006-09*	*2010-13*	*AAPG*
US	4491	5715	7515	6.5		IL	130	161	217	6.5
CA	483	707	1031	9.5		IN	57.1	114	187	16.7
CN	223	428	809	16.3		KR	63.0	72.3	151	11.5
AU	305	495	730	11.0		RU	102	90.4	123	2.0
JP	380	385	474	2.5		TR	49.9	85.4	107	10.3
BR	72.4	189	307	18.3						

The countries whose European collaborations are expanding most rapidly are Brazil, India and China, followed by South Korea and Australia. However there is little expansion in collaboration with Russia and Japan during the period 2002-13.

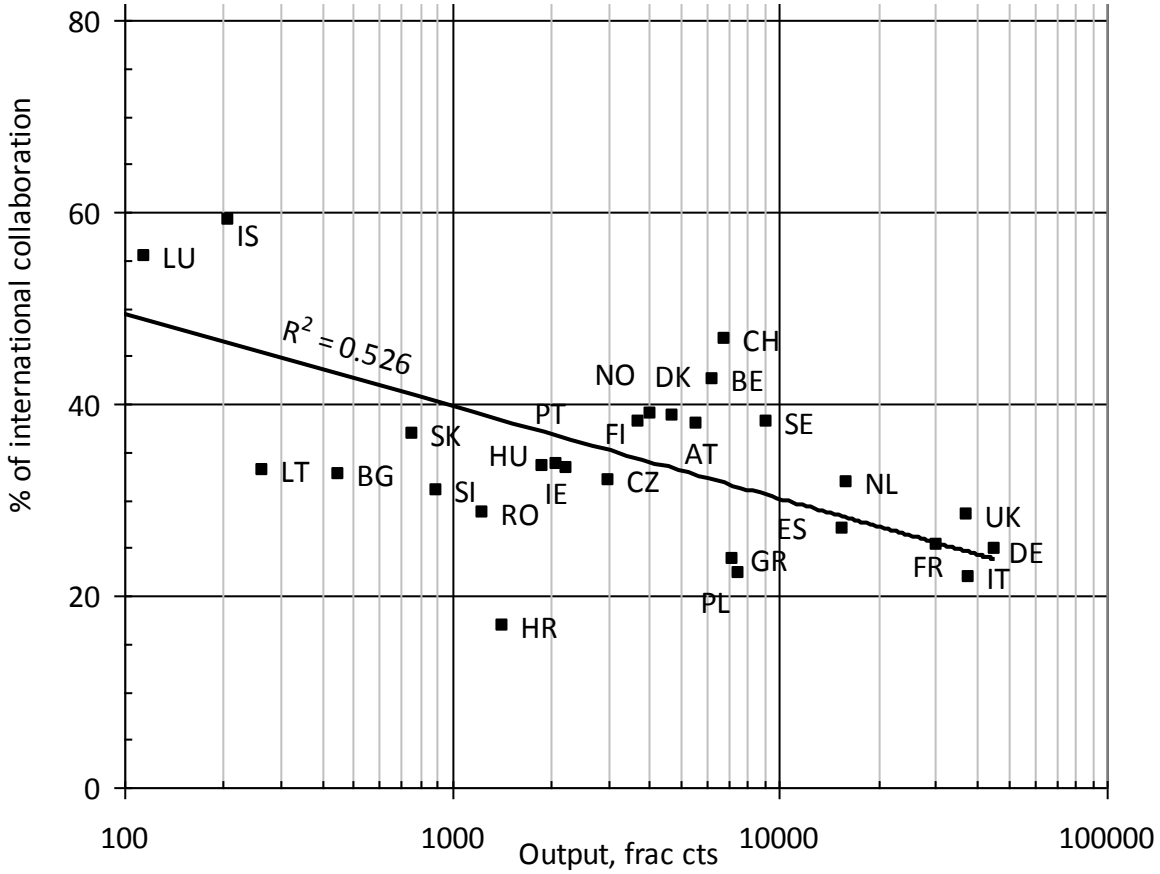


Figure xii. Percentages of international collaboration in cancer research (ONCOL), 2002-13, by European countries plotted against their output (fractional counts of papers). For codes, see Table lxxi.

The research level of the papers decreased over the years from 2.05 to 1.87 (*i.e.*, they became more clinical). However the mean RLs of the journals in which the papers were published were rather more basic, with a mean of 2.1 on the scale 1 = clinical to 4 = basic research. This feature, that the European NCD research papers were more clinical than the mean for the journals in which they appeared, occurred in the other four NCD study areas.

A similar set of sub-filters was created to identify ONCOL papers where the focus was on the cancer site of concern – again, some papers mentioned several sites and many more made no mention of any site. Table lxxxi lists the cancer sites, with their assigned trigraph codes.

Table lxxxi. List of 22 cancer manifestations (body sites) for which sub-filters were developed to identify relevant ONCOL papers.

Site	*Code*	*Site*	*Code*	*Site*	*Code*
bladder	BLA	liver	LIV	pancreas	PAN
bone	BON	lung, trachea, bronchus	LUN	prostate	PRO
brain	BRA	lymphoma	LYM	stomach	STO
cervix	CER	breast	MAM	testicles	TES
colon / rectum	COL	melanoma	MEL	thyroid	THY
gallbladder	GAL	mouth (head & neck)	MOU	uterus	UTE
kidney	KID	oesophagus	OES		
leukaemia	LEU	ovaries	OVA		

Table lxxxii. Ratio of observed to expected numbers of papers relevant to 13 main cancer sites for the leading 18 European countries, 2002-13, with > 2000 papers. Countries are ranked by total output, fractional counts.

Cancer sites ranked from left to right by amount of research output, based on integer counts. *Values > 2 tinted bright green; values > 1.41 tinted pale green; values < 0.71 tinted orange; values < 0.5 tinted pink*.

	MAM	*COL*	*LEU*	*LYM*	*PRO*	*LUN*	*LIV*	*STO*	*BRA*	*MEL*	*MOU*	*KID*	*OVA*
DE	0.75	0.85	1.07	1.05	1.06	0.81	1.16	1.19	1.24	1.12	1.04	1.22	0.78
IT	0.92	0.93	1.08	1.09	0.89	1.15	1.34	1.03	1.10	1.04	0.82	0.90	1.06
UK	1.19	1.15	0.92	0.87	1.09	0.80	0.68	0.77	0.83	0.85	1.23	0.83	1.08
FR	0.92	0.89	1.00	1.14	0.99	1.14	1.24	0.92	0.99	0.89	0.61	1.35	0.85
NL	1.09	1.33	0.81	0.75	1.10	1.20	0.80	1.03	0.80	1.00	1.52	0.86	0.84
ES	0.99	1.10	0.99	1.25	0.78	1.24	1.18	0.97	1.00	0.95	1.19	1.05	0.69
SE	1.17	1.14	1.07	0.87	1.61	0.67	0.52	0.83	1.12	0.85	0.71	0.74	0.96
PL	1.01	0.93	1.43	0.71	0.47	1.19	0.62	1.16	0.83	1.07	0.64	0.96	1.93
GR	1.23	1.07	0.88	1.25	0.82	1.56	1.03	1.40	0.71	0.67	1.15	0.85	1.64
CH	0.84	0.72	0.73	1.20	0.90	1.01	0.94	0.65	1.22	1.38	1.28	0.81	0.63
BE	1.11	0.74	0.88	0.79	0.97	1.26	1.04	0.96	0.92	0.94	1.19	0.77	0.99
AT	1.00	0.75	1.26	1.06	1.28	0.67	1.03	0.66	1.12	1.39	0.92	1.33	1.19
DK	1.41	1.49	0.89	1.02	0.70	1.12	0.40	0.75	0.71	1.17	0.96	0.51	1.85
NO	1.32	1.42	0.89	0.86	1.07	0.92	0.47	0.86	1.08	0.94	0.83	0.33	1.84
FI	1.48	0.94	0.70	0.66	1.96	0.70	0.36	1.09	0.76	0.91	1.70	0.90	1.67
CZ	0.66	1.01	2.00	1.37	0.62	0.66	1.10	0.80	0.87	0.82	0.65	1.31	0.86
IE	1.59	1.35	0.51	0.57	1.37	1.03	0.54	1.08	0.66	0.76	0.90	1.30	0.67
PT	1.39	0.86	0.56	0.60	0.92	0.83	0.61	2.22	0.64	0.76	0.52	0.77	0.61

A recent publication by the World Health Organization (Murray *et al.*, 2012)[25] provides detailed estimates of the burden of disease (both deaths and Disability-Adjusted Life Years, DALYs) for each

[25] Murray, CJL, Ezzati, M, Flaxman, AD, Lim, S, Lozano, R, Michaud, C et.al. (2012) GBD 2010: design, definitions and metrics The Lancet, 380 (9859) 2063-2066.

country and for many individual diseases for the year 2010. The data are provided both as different-sized rectangles within a square representing a country's (or region's, or the whole world's) total disease burden, and they can also be downloaded to file. This has been done for the 31 countries of the European region, and for the disease areas relevant to this study; the data selected were for all ages and both sexes. They are in the form of percent of total DALYs for the country, and were then multiplied by the DALY total to give the DALYs for each disease and country. These could then be added to give the total for the EUR31 region, and the pattern of disease burden for each country compared with the European average. For some diseases, the differences were not great, but for others there were big variations in relative burden between countries. For cancer, data were provided on some 24 different manifestations, not all of which corresponded to our analysis of sites (see Table lxxxi above). However DALYs were given for all 13 of the sites listed in the columns of Table lxxxi, and the percentages of total DALYs (all disease areas) for the 18 countries are shown in Table lxxxii.

4.3 Funding Sources

The funding of research is now recognised as an important source of information for its evaluation (Lewison & Dawson, 1998[26]; Lewison & Devey, 1999[27]; Lewison & van Rooyen, 1999[28]; Lewison, Grant & Jansen[29], 2001; Roe et al., 2010[30]; Rigby, 2013[31]). At its simplest, the acknowledgement of a funding source on a paper indicates that an agency, usually an external one, has reviewed the research project and judged that it is worthy of support. Multiple funding sources would indicate that the project has found favour in several places.

In the past, the recording of the funding sources on a paper was a labour-intensive task as each paper needed to be inspected individually, usually in a big library. It was, however, worthwhile if the work could serve to provide many different funding bodies with a tally of papers that they had supported. This was the principle behind the creation of the Wellcome Trust's Research Outputs Database (Jeschin et al, 1995[32]; Dawson et al., 1998[33]; Webster, 2005[34]). This covered all UK biomedical papers over the 14 years, 1988-2001, and was based on the papers in the Science Citation Index on CD-ROM, which was purchased from the Institute for Scientific Information in Philadelphia (now Thomson Reuters) and operated under license from them. The data were made available to members of the "ROD club", who paid a graduated annual fee and in return received a list of their papers, together with access to consultancy advice.

[26] Lewison G, Dawson G. The effect of funding on the outputs of biomedical research. Scientometrics. 1998;41(1–2):17–27. doi: 10.1007/BF02457963.

[27] Lewison, G., & Devey, M. E. (1999). Bibliometric methods for the evaluation of arthritis research. Rheumatology, 38(1), 13–20

[28] Lewison G & van Rooyen S (1999) Reviewers' and ediotrs' perceptions of submitted manuscripts with dirrerent numbers of authors, addresses and funding sources. Journal of Information Science 25(6),509-511

[29] Lewison G, Grant J & Jansen P (2001) International gastroenterology research: subject areas, impact, and funding Gut 49(2), 295-302

[30] Roe PE, Wentworth A, Sullivan R & Lewison G (2010) The anatomy of citations to UK cancer research papers. Proceedings of 11th conference on S&T Indicators, Leiden, The Netherlands, 225-226. Available at http://www.cwts.nl/pdf/BookofAbstracts2010_version_15072010.pdf

[31] Rigby J (2013) Looking for the impact of peer review: does count of funding acknowledgements really predict research impact? Scientometrics 94(1) 57-73

[32] Jeschin D, Lewison G & Anderson J (1995) A bibliometric database for tracking acknowledgements of research funding. Proceedings of the 5th International Conference on Scientometrics and Informetrics, River Forest, IL, USA; Medford, NJ: Learned Information Inc.; 235-244. ISBN 1-57387-010-2

[33] Dawson G, Lucocq B, Cottrell R & Lewison G (1998) Mapping the Landscape: National Biomedical Research Outputs, 1988-95. London: The Wellcome Trust; Policy Report no 9. ISBN 1869835-95-6

[34] Webster B (2005) International presence and impact of the UK biomedical research, 1989-2000. Aslib Proceedings, 57(1), 22-47.

Since the introduction of the Science Citation Index, the facilities available for searching and for retrieving data have been steadily enhanced. During 2008, Thomson Reuters started to provide details of funding for individual papers – quite likely stimulated by the earlier existence of the ROD! There are two individually searchable fields, FO = funding organization and FT = funding text. The FO field lists the names of the acknowledged funders and FT gives the full text of the acknowledgement, including recognition of individuals who have helped with the research. For some funding bodies, the FO field also lists the grant numbers, although they are often absent and have not been considered in this analysis.

Authors of papers record their funding acknowledgements in a wide variety of ways. Many papers had multiple funding acknowledgements[35]. In order to determine the funding sources for RESPI and the four other disease areas, it was therefore decided to use a coding system, with four parts:

- a trigraph (three character) code designating the individual funding body;
- a single letter code showing the form of support (no longer used);
- a digraph (two character) code designating the sector and sub-sector of the funder;
- and another digraph showing the country of the funder based on the ISO codes.

The trigraphs were designed to be easily memorable, *e.g.*, MRC = UK Medical Research Council; BHF = British Heart Foundation, although it turned out that there were so many different funders of UK research papers that many had to be given odd combinations of letters[36].

It also became apparent that some papers did not carry an acknowledgement because they had been supported internally – in a government lab (such as one supported by a research council or Government department), by a collecting charity, or by a commercial company. So the decision was made to include these "implicit" acknowledgements along with the "explicit" ones in the acknowledgement paragraph to form a composite acknowledgement[37].

In principle, the research described in all published papers has to be paid for in some way. In practice, however, there are many papers (especially ones describing clinical work) that do not contain any formal acknowledgement.

In any case, most of their authors would be academics or medical personnel working in a hospital or clinic, supported by general university funds or by salary support from the health service. But such support would not be peer-reviewed, and so such papers would perhaps be of a lower standard. For these reasons, it did not seem appropriate to record this nominal support, and the ROD was set up to record such papers as "unfunded", and the hospital or university or research institute address was not given a code. However, if a specific acknowledgement appeared to a university or department, or to a hospital, then it was presumed that some system of grants was in place and the contribution of the employing organisation WAS recorded with a code. This gave rise to three sub-sectors of the private-non-profit sector, namely HT = hospital trustees, MI = academic[38] and NP = other non-profit. The other two were CH = collecting charity and FO = endowed foundation.

The methodology used to extract funding information for papers whose details were downloaded from the Web of Science (WoS) was the same across the five disease areas. The basic principle used was to assign a three-part code to each funding body, with a three-letter code to identify it uniquely,

[35] There are also acknowledgements to individuals who have provided help or advice. These are not considered further in this report.

[36] Initially, every UK research funder was given an individual trigraph in order to cater for the possibility that it would become a ROD member, although membership seldom rose above 30.

[37] Several of the ROD members maintained their own labs and also gave external research grants and this system allowed them to compare their respective outputs.

[38] This term was used because many universities and colleges are both endowed with capital and are still collecting money (*e.g.*, from their alumni).

a two-character code to identify the sector and sub-sector, and another two-character code to identify the ISO designation. Codes were assigned to each funding body listed in the FO = funding organisation section of the WoS, subject to redaction if they were mentioned in a conflict of interest statement only as having paid for unrelated work. Codes were also assigned where there was an acknowledgement implicit from one (or more) of the addresses - a government department or agency, the laboratory of a collecting charity, or of an industrial company.

Once codes were assigned to each funding body, they were collected and written to two thesauruses for future use. The spreadsheet of papers was then completed with the explicit and implicit codes by means of a special macro, which also combined the codes into a single column. Another macro determined the division of funders by main sector for each European country (own government including local and regional authorities; own private-non-profit (PNP), industry, international, and other). These were doubly fractionated: to allow for the fractional presence of the target country on each paper, and to allow for the total number of funders on a paper.

The commercial sector was divided up into five sub-sectors, with companies divided into three: pharmaceutical, biotech and industrial. The first and third of these were further divided into independent and subsidiary. The purpose was to distinguish between the research activities of UK subsidiaries of large multi-national companies which might be relatively independent of the parent, e.g., the Merck Neuroscience Park in Harlow, which did its own research and also gave funding to universities. However there were many takeovers of small biotech (and not so small pharma) companies and it seemed appropriate to regard the takeover as a way in which the new parent company would thereby gain the intellectual property of the new acquisition. This meant that many of the commercial codes became out-of-date. This had two consequences for the analysis of funding sources. First, the country of a company was effectively undefined, and second, the sub-sector could change when a biotech company had brought a new drug to market and had so become a pharma company.

The public sector was divided into three sub-sectors: government department (controlled by ministers), government agency (nominally independent of ministerial directives) and local authorities (including regions, counties and cities). They were given sectoral codes: GD, GA and LA, respectively. Although the latter form of support hardly exists in the UK, it is becoming increasingly common in several continental European countries (Länder in Germany, régions in France, provinces in Spain) and also in North America (provinces in Canada and states in the USA) and in Australia (states and territories). Most of these regions have been given their own trigraphs, although some smaller regions have generic codes, see below.

Because of international collaboration on biomedical research papers, many of the UK papers covered in the ROD also had foreign partners and acknowledgements to foreign funding sources. The thesaurus soon began to run out of trigraph codes, and we started to use "generic" codes for the smaller organisations (in terms of their biomedical research spend). These consisted of a single letter (X, Y or Z) followed by one digit (to designate the country) and another to designate the sector and sub-sector. Individual countries that supported a lot of biomedical research were given their own digraph (e.g, X1 = USA); others were given one that showed their continent. There is, of course, some redundancy as the country and sector/sub-sector are also given by the second and third digraphs, but these are needed for the main analyses. For example, X1B-BT-US indicates a US biotechnology company in two ways. Generic codes for the UK were not used initially, but have been introduced to cater for the large number of new British funding bodies, and codes UK1, UK2 etc. are employed.

Table lxxxiii: Digraphs for countries with generic codes and designated sector or sub-sector

Digits 1 & 2	ISO	Country		Digit 3	Code	Category

X0	NL	Netherlands		1	CH	Charity
X1	US	USA		2	FO	Foundation
X2	DE	Germany		3	GD/GA	Government
X3	JP	Japan		4	HT	Hosp. Trustees
X4	SE	Sweden		5	IN	Industry (non-pharma)
X5	NZ	New Zealand		6	IP	Pharma industry
X6	CA	Canada		7	LA	Local/regional authority
X7	FR	France		8	MI	Mixed (i.e., academic)
X8	ZA	South Africa		9	NP	Non-profit (e.g., professional body)
X9	IT	Italy		B	BT	Biotech company
Y0	BR	Brazil		Z0	EU	Europe
Y1	IE	Ireland		Z1	CN	China
Y2	CH	Switzerland		Z2	HU	Hungary
Y3	DK	Denmark		Z3	AT	Austria
Y4	NO	Norway		Z4	HK	Hong Kong
Y5	ES	Spain		Z5	AU	Australia
Y6	FI	Finland		Z6	XX	not known
Y7	BE	Belgium		Z7	AF	Africa
Y8	IL	Israel		Z8	AS	Asia
Y9	IN	India		Z9	LA	Latin America

The code "Z4" for Hong Kong is still used, although the country digraph of CN for China shows that this is now part of the People's Republic.

These trigraphs, and the associated sectoral and country codes, were assembled into a large thesaurus of funding bodies. The thesaurus is structured so that the different names and formats given to a funding body (and in some cases its dependent agencies, bodies or companies) are all listed to facilitate the allocation of codes. At the time of writing, there were 17,485 entries and 10,045 (out of a possible 17,576) individual letter trigraphs. This suggests that there is still plenty of opportunity for new codes, but it is often difficult to find appropriate letter combinations for new organisations with many funded papers. These are appearing in continental European countries as work on the project develops, because the thesaurus was originally developed mainly for UK funding bodies.

4.4 Cancer: Funding Sources

Not information from KINGS College until the end of July.

4.5 Citations of Research Papers

Bibliometric analysis uses citation scores to measure of the impact of research papers. For most NCDs, European research was better cited than the world average, although there was much variation between countries. Interestingly, there was generally poor correlation between the burden from particular diseases and the amount of research. In this case, there may be grounds for re-balancing some national research portfolios.

The 11 defined research types, listed in Table lxxiv was defined by means of title words and journal name strings, selected by Professor Richard Sullivan of KCL. They generated different numbers of papers, as described in the first report, with genetics giving the most (48,259 or 17.1%), followed by chemotherapy (28,240 papers or 10.0%), prognosis (27,189 papers or 9.6%) and surgery (26,585 papers or 9.4%). Figure xiii shows the distribution of research levels on the same basis as Figure xiv.

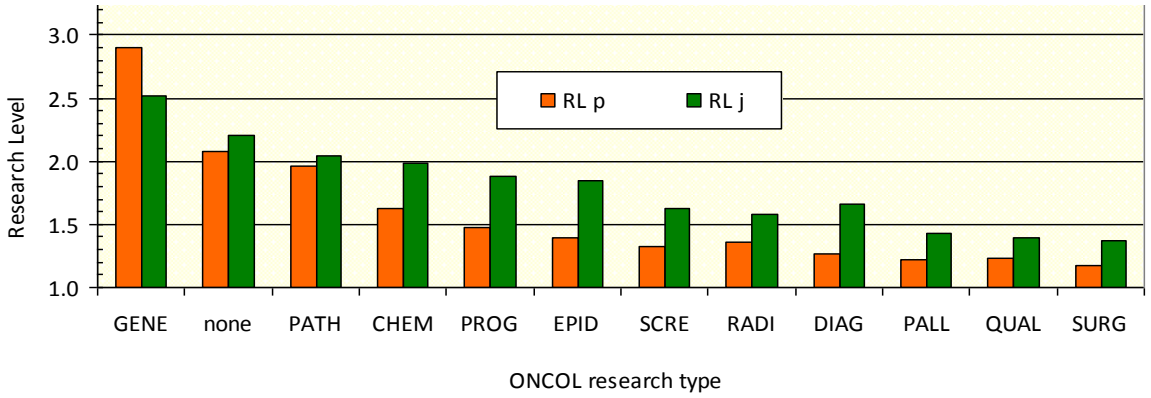


Figure xiii: Chart of mean Research Level of papers and of journals in which they were published for ONCOL papers of 11 research types. RL = 1.0 is clinical observation; RL = 4.0 is basic research.

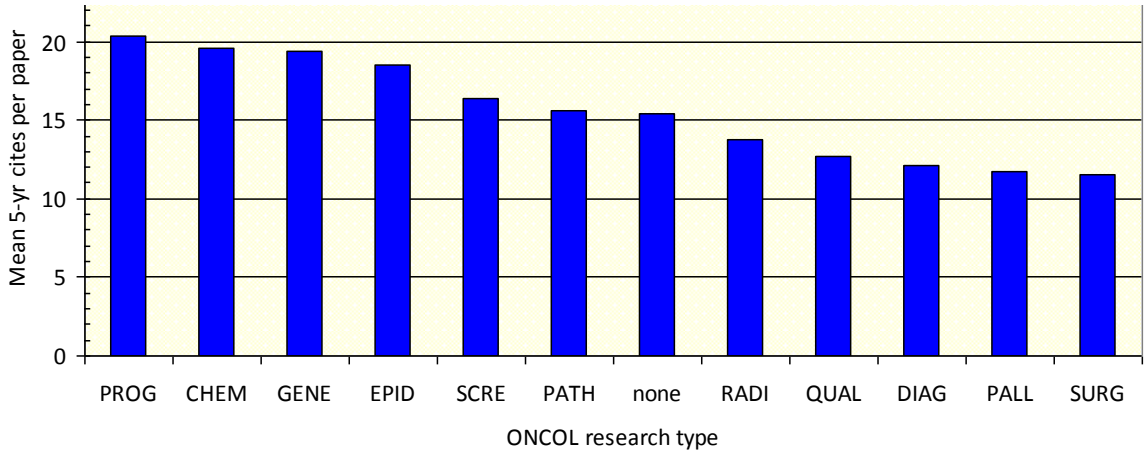


Figure xiv: Chart of mean five-year cites for ONCOL papers of 11 research types published in 2002-09.

As the ONCOL papers for each of the first eight years were identified, their citation scores were found on the WoS and downloaded as a series of Excel files. These were then concatenated and modified by means of another special macro so that the source was in exactly the same format as the one used for the preparation of the papers spreadsheet. The five-year citation count

(designated as Actual Citation Impact, ACI) for each paper was calculated (beginning with the year of publication), and this value was then carried across to the papers spreadsheet by means of a look-up function based on paper titles. A few citation scores could not be determined either because the paper title was too long (> 255 characters) or contained quote marks. For these papers, the source was used as the look-up field.

In order to determine the mean citation score for each country and other citation statistics, the spreadsheet was annotated with 31 additional columns each of which contained the product of the paper's citation score, ACI, with the fractional presence of each country among its addresses. The sum of these products, divided by the fractional count of the country for the relevant years (in the first instance, the eight years 2002-09), then gave the country's citation score on a fractional count basis, which is more appropriate than the score based on integer counts.

These individual country scores could then be compared with the ACI values for the EUR31 countries as a group and those for the world. These were obtained for each year's ONCOL publications directly from the WoS, although the sets of papers needed to be divided into sub-sets, based on journal initial letters, in order that each one should have no more than 10,000 papers, as this is the limit in the WoS for citation reports.

Citation scores have been increasing slowly with time, in part because the WoS now covers more journals than previously, and also because authors are expected to be more punctilious in their acknowledgement of earlier work. Figure v shows the progression in ONCOL ACI scores from 2002 to 2009; the values for intermediate years (2003-08) for Europe are shown as three-year moving averages in order to smooth out annual fluctuations. The mean score for Europe was slightly below the world average in 2002-03, but since 2006 it has been slightly higher, probably because of the greatly increased world presence of China, whose papers tend to be less well cited than average.

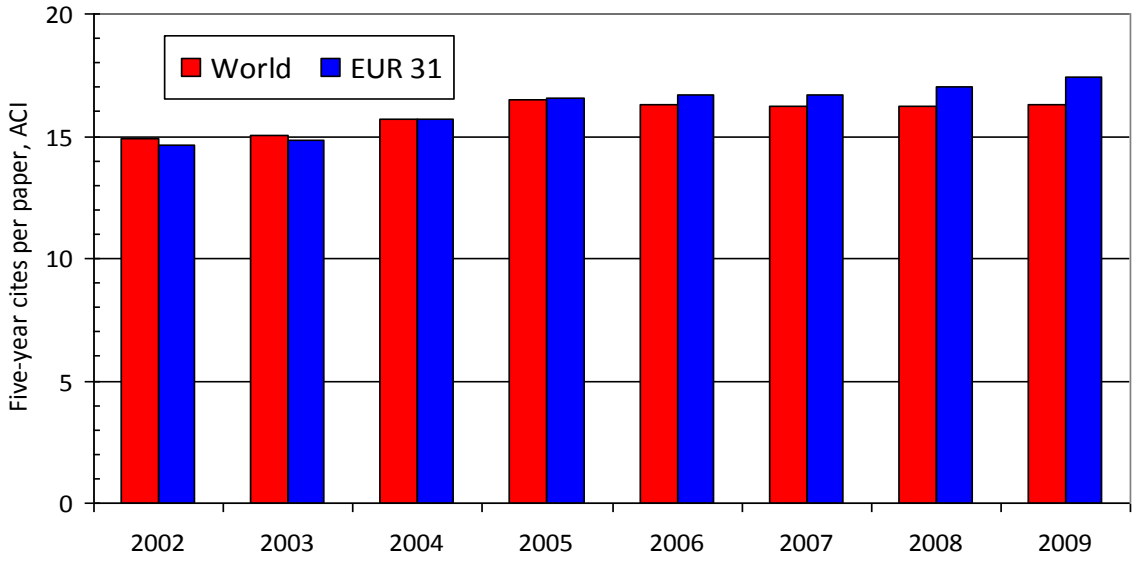


Figure xv. Chart showing the increase in mean citations per ONCOL paper with publication year, 2002-09, for world and for EUR31 papers.

The mean citations per paper for the EUR31 countries are shown in Table lxxvii. This also shows how many of a country's papers received enough cites to put them in the top 5% of EUR31 papers in the eight-year period, for which the qualification was 53 cites. [There were actually 5.15% of European papers that achieved this number of citations.] This may be a better measure of how effective a

country's research output is because it is normally the most influential papers that are really important to the development of a field.

Table lxxxiv. Citation performance of EUR31 countries in ONCOL in 2002-09, ranked by the percent with 53 or more cites in the five years following publication (ACI) (Top 5%) rather than the mean value.

ISO	*Mean*	*Top 5%*	*%*		*ISO*	*Mean*	*Top 5%*	*%*		*ISO*	*Mean*	*Top 5%*	*%*
CH	19.1	280.1	6.67		FR	14.1	763.0	4.12		CZ	9.5	27.4	1.66
NL	19.4	603.1	6.17		ES	14.2	366.3	4.11		BG	6.3	3.3	1.27
UK	18.0	1469.1	6.14		IT	14.3	905.5	3.96		PL	7.9	50.9	1.25
IS	19.3	6.9	5.83		IE	13.8	47.0	3.74		RO	6.0	4.3	1.05
BE	17.2	216.6	5.44		NO	15.0	86.3	3.61		LT	5.8	1.2	1.05
DK	17.5	139.2	5.30		LV	9.4	1.5	3.25		SI	7.3	4.1	0.83
FI	16.6	117.4	4.74		PT	12.6	30.9	3.17		EE	8.5	0.3	0.60
SE	15.6	267.7	4.51		GR	9.5	89.9	1.93		MT	3.9	0.1	0.50
AT	15.0	158.0	4.37		CY	9.3	0.7	1.89		HR	5.1	3.7	0.47
LU	16.7	2.4	4.26		HU	9.3	21.7	1.81					
DE	14.3	1211.5	4.22		SK	8.9	7.7	1.75					

The mean ACI and percentage of citable papers in the top 5% are closely correlated (r^2 = 0.94) but they are different indicators of citation impact.

Figure xvi shows the effects of co-authorship with extra-European countries for ten leading European countries. For each non-European country, the effects are quite striking. The biggest positive effect overall is seen for Australia, followed by Canada. Somewhat surprisingly, the effect of the USA being a partner was not as positive as might have been supposed, and for the 10 countries examined and taken as a group, the mean ACI value (30.5 cites per paper) was only slightly above the values for China and Japan, and well below the values for Canada (36.6) and Australia (44.2).

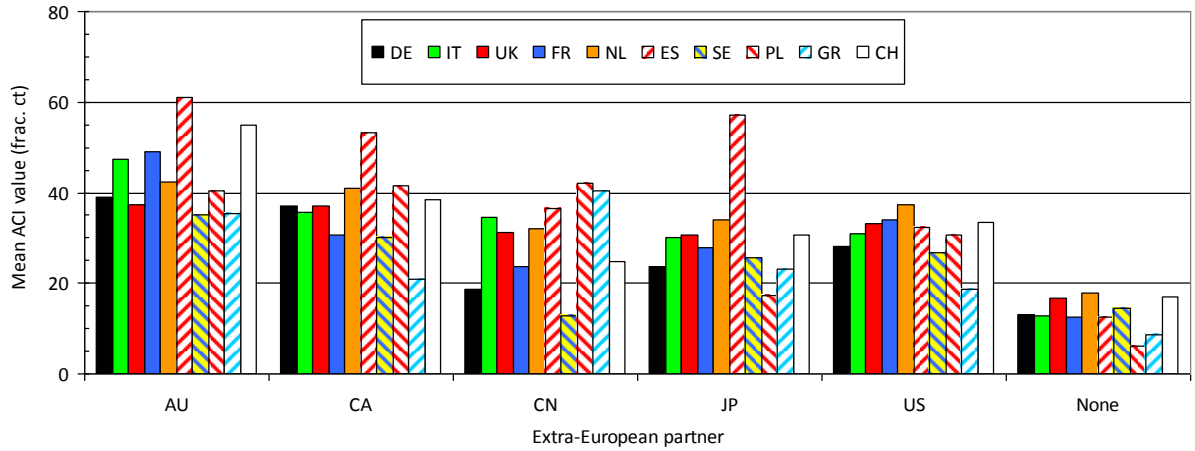


Figure xvi. Mean ACI values for 10 leading European countries in cancer research, 2002-09, for their papers co-authored with a researcher from the five specified countries, or from none of the 11 extra-European prospective partners.

Another indicator of "quality", or more accurately the esteem with which a country's researchers are held, is the percentage of reviews (Lewison, 2009)[39] which are usually invited by journal editors from senior scientists. Figure xvii shows this percentage, with the bars coloured according to the number of reviews published by the country in the 12-year period.

[39] Lewison G (2009) The percentage of reviews in research output: a simple measure of research esteem. Research Evaluation, 18 (1), 25-37.

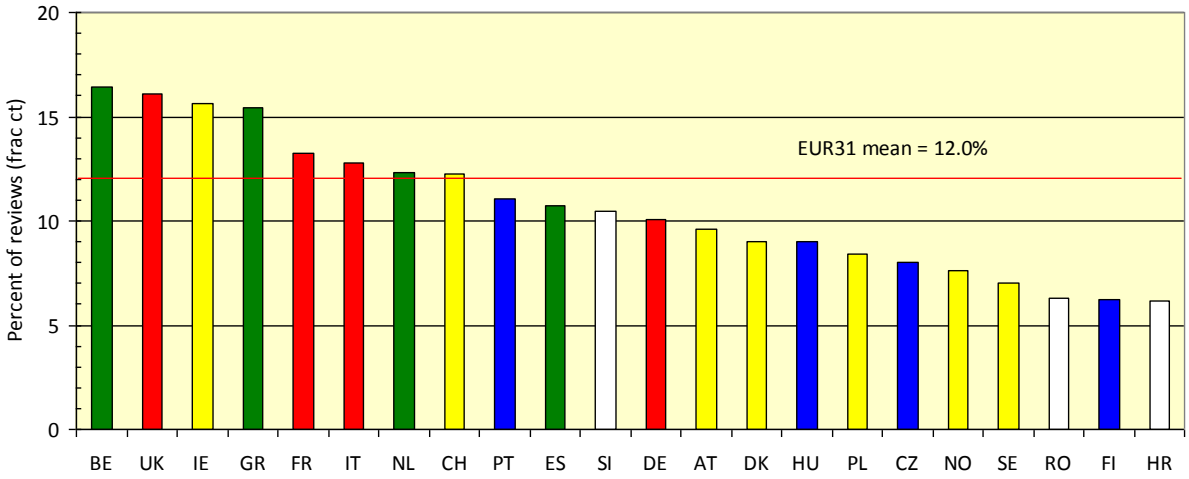


Figure xvii. Chart showing the percentage of ONCOL reviews by 22 European countries with at least 50 papers classed as "reviews" in the WoS during 2002-13. Red bars: > 3000 reviews (frac. cts); green bars: > 1000 reviews; yellow bars: > 300 reviews; blue bars: > 100 reviews; white bars: < 100 reviews.

It is perhaps surprising that the five Scandinavian countries score relatively low on this indicator, whereas Greece performs highly and is in the top group, with > 15% of its papers classed as reviews.

4.6 Clinical Guidelines

This measure of impact has been used previously both to evaluate the research being cited, and to describe the evidence base for recommendations regarding clinical practice. However, the mere presence of such guidelines is no guarantee that they will be effective at improving healthcare (Schrader et al., 2006)[40]. The first study, on a small scale, examined the cited papers on a sample of 15 UK clinical guidelines (Grant et al., 2000)[41]. It found that they were very clinical and that UK research was over-cited by 2.5 times. A subsequent study of 43 cancer clinical guidelines in the UK (Lewison et al., 2008)[42] reached similar conclusions, and showed that they could also be used as a means to evaluate research in other countries, for example six Swedish universities. This work was subsequently updated (Pallari and Lewison, 2014)[43] and showed that surgery featured strongly among the cited references (over 25% of the total). It also showed a big variation in whether a country's papers were over- or under-cited relative to its presence in cancer research. Thus UK research was over-cited by almost four, Danish, Dutch and Swedish research by more than two, but that from the "accession" Member States (Poland, Czech Republic and Romania) by half or less.

We investigated the clinical guidelines currently available in the different European Member States in order to extend the work to other countries. Although many countries had a set of national guidelines, some had regional ones as well, and there were yet others published by European societies of professionals in various branches of medicine. We even learned that in Sweden, each of

[40] Schrader M, Weissbach L, Weikert S, Schostak M and Miller K (2006) Paper tigers - Do clinical guidelines improve health care quality in patients with testicular germ cell tumors in Germany? *Health Policy*, vol 75 (3), pp 338-346.

[41] Grant J, Cottrell R, Cluzeau F and Fawcett G (2000) Evaluating "payback" on biomedical research from papers cited in clinical guidelines: applied bibliometric study *BMJ*, vol 320, pp 1107-1111.

[42] Lewison G, Tootell S, Roe P & Sullivan R (2008) How do the media report cancer research? A study of the UK's BBC website. *British Journal of Cancer* 99, 569-576

[43] Pallari E and Lewison G (2014) Papers cited by cancer clinical guidelines. Poster presented at the 15th COLLNET meeting, Ilmenau, Germany.

the 21 counties had their own clinical guidelines. Clearly, it would have been impossible for us to collect the references on all of these, and so we decided to limit the study to national guidelines.

In the earlier studies on UK guidelines, the identification of the references with papers processed for the Web of Science involved much labour as each one had to be sought individually. It would not have been practical in the scope of this project to continue in this way for guidelines for the other NCDs and for all the other European countries, but we were able to semi-automate the process by means of a visual basic macro, written by Dr Philip Roe of Evaluametrics Ltd. This worked as follows: first, the references section of a guideline in PDF format were copied and pasted to an Excel spreadsheet; second, these were slightly tidied by removal of page numbers, document running heads, etc; and thirdly, the macro was then operated, and it generated sets of search statements, eight at a time, ready for copying and pasting into the search panel of the WoS. An example is given below:

((AU=(Anderson AND Pottier AND Strachan) AND TI=concurrent AND SO=(T*) AND PY=1992) OR (AU=(Heaney AND Conway AND Kelly AND Johnston AND English AND Stevenson) AND TI=Predictors AND SO=(T*) AND PY=2003) OR (AU=(Martin AND McLennan AND Landau AND Phelan) AND TI=childhood AND SO=(B*) AND PY=1980) OR (AU=Roorda,R AND TI=adolescence AND SO=(T*) AND PY=1996) OR (AU=(Remes AND Pekkanen AND Remes AND Salonen AND Korppi) AND TI=hyperresponsiveness AND SO=(T*) AND PY=2002) OR (AU=(Brouwer AND Roorda AND Brand) AND TI=spirometry AND SO=(E*) AND PY=2006) OR (AU=(Pellegrino AND Viegi AND Brusasco AND Crapo AND Burgos AND Casaburi) AND TI=Interpretative AND SO=(E*) AND PY=2005) OR (AU=(Dundas AND Chan AND Bridge AND McKenzie) AND TI=bronchodilator AND SO=(T*) AND PY=2005))

The limit of eight individual papers was set so as to keep within the limits for the number of terms allowed by the WoS. Author names (AU) up to six in number were given without initials as sometimes they were given incorrectly by the guideline although if there was only one author the first initial was given. [In the WoS, Jones or Jones, A will find papers by Jones, AT but Jones,PR will NOT find papers by Jones, PRT.] The title word (TI) was selected to be the longest in the paper title. The journal name (source, SO) was given by just its initial letter as the guidelines usually gave an abbreviated name and this would have needed to be substituted by its full name, which would have had to be researched and entered into the macro. Finally, the publication year (PY) was given for completeness.

This process worked well, and even though the search statements needed to be inspected individually (to remove author names with non-Roman characters which are not recognized by the WoS and to delete any punctuation marks attached to title words), it was possible to identify and download over 860 references from one guideline in about 3 1/2 hours. The macro also listed references that did not satisfy its specific requirements so that any errors could be corrected manually and the macro then run again.

4.7 Clinical Guidelines: Cancer

The example chosen here is the set of 17 guidelines for lung cancer (almost always the most burdensome form of the disease) in five countries: France, Germany, Italy, Spain and the UK. There were a total of 3232 references, but only 2512 of them could be identified as papers in the WoS, and their parameters determined. Some of the papers were cited on more than one of the 17 guidelines, with one being cited on seven of them. Although the guidelines were all published in the years 2008-14, some of the cited papers appeared as long ago as the 1960s, and the inter-quartile range was from 1998 to 2006. As expected, the large majority (78%) of the cited papers were in the sub-field of lung cancer research, and they were very clinical in character. Figure xviii shows that papers from European countries, and Canada, are relatively over-cited compared with their

presence in lung cancer research, but research from east Asian countries (China, South Korea and to a lesser extent, Japan) is almost ignored. This was found previously in a study of 43 UK cancer clinical guidelines (Lewison & Sullivan, 2008)[44].

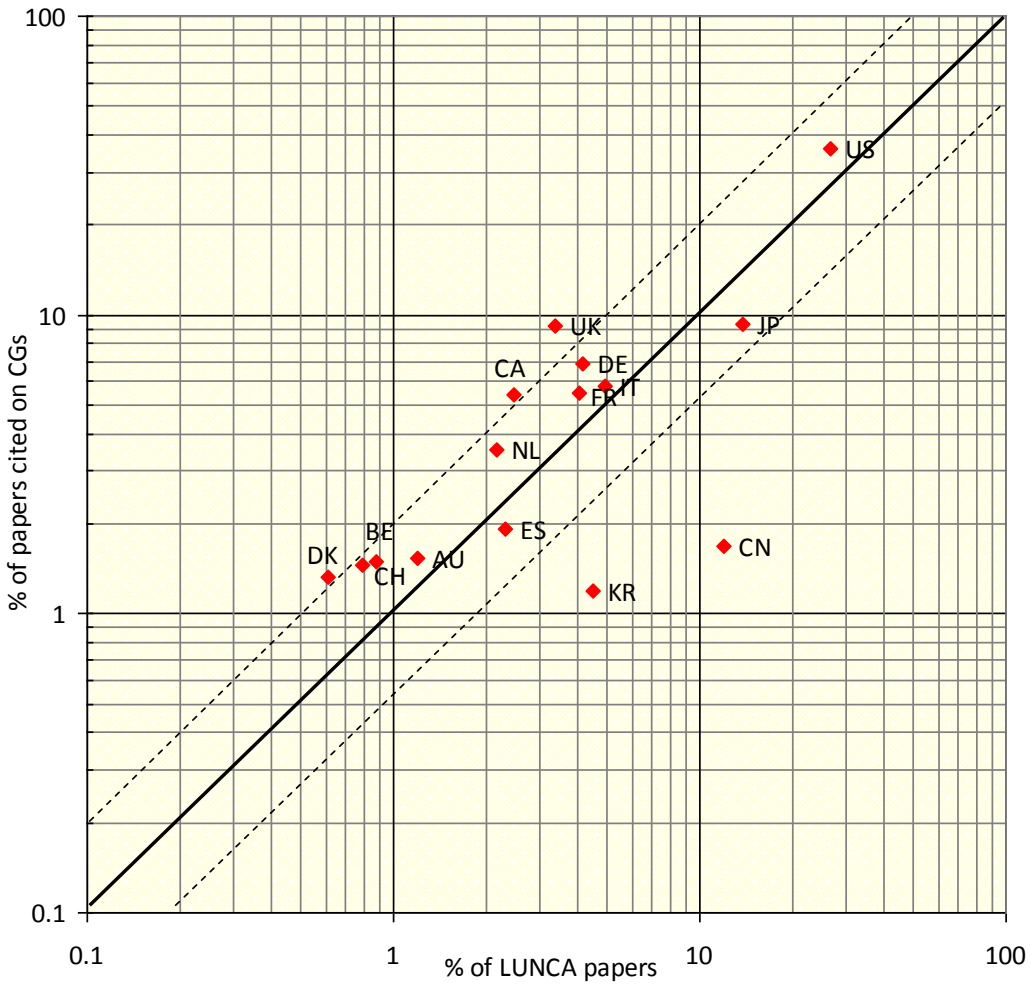


Figure xviii. Comparison between presence of leading countries in the papers cited on 17 European clinical guidelines on lung cancer and their presence in lung cancer research, 2004-13, fractional counts. (Dashed lines indicate a factor of two, up or down.)

There is a big difference between the types of research cited on the 17 clinical guidelines and those forming the lung cancer *oeuvre*. This is shown in Figure xix. The evidence base for the clinical guidelines depends much more on the three treatment options (surgery, SURG; chemotherapy, CHEM; and radiotherapy, RADI) and much less on genetics (GENE). There is a contrast here, because papers of the different research types achieve very different levels of academic citations, with the most highly cited (genetics) obtaining more than twice the citation score of one of the least cited (surgery), see Figure xix. But as Figure xx shows, surgery papers have the most influence on patient treatment, whereas genetics papers have very little. Genetics papers in lung cancer may obtain the most citations, and so may impress grant-giving bodies, but it is lung cancer surgery research that may actually benefit patients through its effect on clinical guidelines.

[44] Lewison G and Sullivan R (2008) The impact of cancer research: how publications influence UK cancer clinical guidelines British Journal of Cancer, vol 98, pp 1944-1950

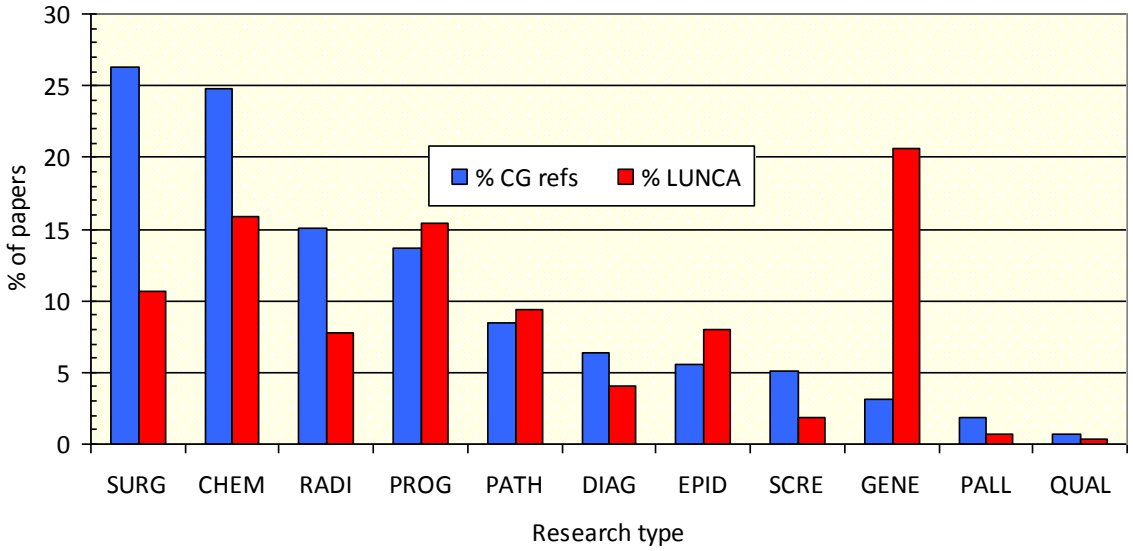


Figure xix. Chart showing the different types of research found in lung cancer, 2004-08, and in the papers cited on 17 European lung cancer clinical guidelines. (For codes see Table lxxi)

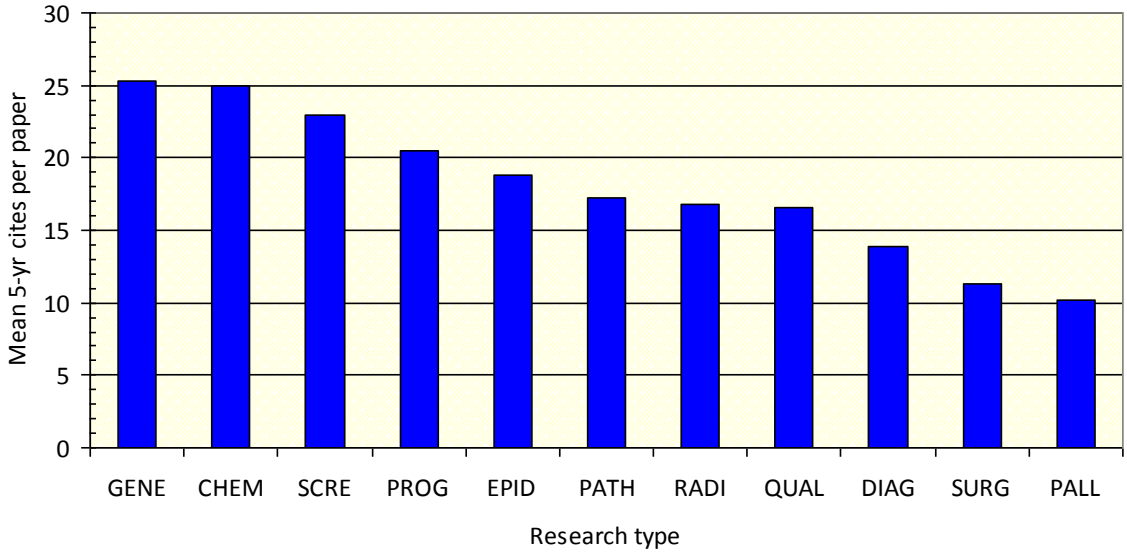


Figure xx. Mean five-year citation scores for European lung cancer papers, 2004-09, of different research types (for codes, see Table lxxi)

4.8 Newspaper Stories

There is abundant evidence that politicians are unduly sensitive to stories in the media. Some of these are based on individual cases, in which it is reported that named patients do not have access to particular means of therapy (expensive drugs, for example). Ministers react by making special provision for them, but this can distort the overall health-care system as with the Cancer Drugs Fund in the UK (Thornton, 2011; Knapton, 2014)[45],[46]. Senior officials can use the stories to bring news of research to their ministers; most will not have the time to read the literature extensively and need

[45] Thornton S (2011) Cancer Drugs Fund is not a fair allocation of NHS resources. *BMJ* 342, d621

[46] Knapton S (2014) Cancer Drugs Fund makes no sense, says head of drugs rationing body NICE. Daily Telegraph, 2 September.

help to learn about interesting developments. The same is true for health-care administrators in hospitals and clinics, who may learn about new methods of health-care delivery that offer potential cost savings. Medical personnel will also benefit, though the media can also provide misinformation that can cause doctors to misdiagnose (Schmidt *et al.*, 2014)[47]. They can also influence researchers, and there is evidence that media coverage increases modestly the numbers of citations (Phillips *et al*., 1991; Lewison *et al*., 2008)[48],[49]. The print media may even be a source in their own right (Hicks & Wang, 2013)[50]. The biggest influence may be on ordinary people, and could assist the public to choose healthier life styles (Nishtar *et al*., 2004; Caburnay *et al*., 2008; Hellyer & Haddock-Fraser, 2011)[51],[52],[53] including enrolment for vaccinations (Olufowote, 2011; Robbins, Pang & Leask, 2012)[54],[55] although sensational press coverage of supposed links between MMR (measles, mumps, rubella) vaccination and autism has had a negative effect (Holton *et al*., 2012)[56].

They may also add to the political pressure for public investment in medical research, particularly if own-country papers are well-cited. In some countries, commentators on the significance of the research often come from medical research charities, which thereby gain exposure (Lewison et al., 2012)[57]. Print newspapers are in decline in many countries, but many have a strong web presence and are still important despite the growing influence of social websites such as Twitter and Facebook.

This part of the project was intended to show the effects of European NCD research on six groups of people:

- politicians and other decision-makers;
- senior officials and advisers;
- health-care administrators;
- medical personnel (doctors, other professionals);

[47] Schmidt HG, Mamede S, van den Berge K, van Gog T, van Saase JLCM and Rikers RMJP (2014) Exposure to media information about a disease can cause doctors to misdiagnose similar-looking clinical cases. *Academic Medicine*, vol 89 (2), pp 285-291

[48] Phillips DP, Kanter EJ, Bednarczyk B & Tastad PL (1991) Importance of the lay press in the transmission of medical knowledge to the scientific community. *New England Journal of Medicine* 325, 1180-1183

[49] Lewison G, Tootell S, Roe P & Sullivan R (2008) How do the media report cancer research? A study of the UK's BBC website. *British Journal of Cancer* 99, 569-576

[50] Hicks D & Wang J (2013) The *New York Times* as a resource for Mode 2. *Science Technology & Human Values* 38 (6), 851-877

[51] Nishtar S, Mirza YA,Jehan S *et al*. (2004) Newspaper articles as a tool for cardiovascular prevention programs in a developing country. *Journal of Health Communication* 9 (4), 355-369

[52] Caburnay CA, Kreuter MW, Cameron G et al. (2008) Black newspapers as a tool for cancer education in African American communities. *Ethnicity & Disease* 18 (4), 488-495

[53] Hellyer NE & Haddock-Fraser J (2011) Reporting diet-related health issues through newspapers: portrayal of cardiovascular disease and Type 2 diabetes. *Health Education Research* 26 (1), 13-25

[54] Olufowote JO (2011) Local resistance to the global eradication of polio: newspaper coverage of the 2003-2004 vaccination stoppage in northern Nigeria. *Health Communication* 26 (8), 743-753

[55] Robbins SCC, Pang C & Leask J (2012) Australian newspaper coverage of Human Papillomavirus Vaccination, October 2006 - December 2009. *Journal of Health Communication* 17 (2), 149-159

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- researchers;
- the general public.

It embarked on an ambitious programme of study on the coverage of research in the five NCDs during the 12-year period, 2002-13, in a large number of European newspapers. Some of these have their own searchable websites; others can be searched through full-text databases such as Factiva ©Dow Jones, to which KCL subscribes.

The results of this element of the project span the five NCD disease areas. For this reason, they will be reported in the Bibliometrics Work Package of Mapping NCDS.

4.9 Discussion and Conclusion

The complexity of investments streams and differences between the countries may make the development of common cancer funding policies very difficult and measuring the impact research investments is a complex task. Indeed, health improvements stem from a wide variety of interrelated research discoveries, made at different times and in different places. Other factors such as environmental, lifestyle, or behavioral exposures also have an important bearing on the incidence of illness and further complicate the task of measuring research impact. For this reason, research impacts are evident at a variety of nodes along the pathway, many of which are not specific to individual disease areas. Bibliometrics has the capacity to quantitative measure impact at several of these nodes, including: scientific research papers, funding sources (decisions on funding), citations, evidence base of clinical guidelines; and newspapers stories regarding research papers.

In terms of the number of published scientific papers, Cancer generated the biggest of the five results for NCDs worldwide, with just 282055 papers. However, by comparison with the other NCDs, published research for Cancer shows a significant European presence, among the top three with an average of 38% of paper published, behind RESPI (56%) and CARDI (42%) and followed by 40% for DIABE and 35% for MENTH.

According to the results in Europe, Cancer is a big subject area, averaging 11.5 % of the papers in biomedicine overall. Cancer research represents just over one ninth of all European biomedical research output, but one eighth of world biomedical output.

In terms of individual European countries, there are big differences in output, with more than three orders of magnitude between the largest (Germany) and the smallest (Malta). However, some of the smaller countries are expanding their output rapidly – notably Romania, whose fractional count output rose from only 7 papers in 2002 to over 250 in 2013.

Regarding collaboration it is expected that researchers in the scientifically larger countries (e.g., UK, Germany) would find it easier to work with a partner within the country that provided complementary expertise than researchers from small countries (e.g., Estonia, Ireland) and would therefore tend to collaborate less internationally. However, we might expect that international transnational links would be much weaker for the Member States in Eastern Europe. These “accession” Member States do indeed collaborate less than expected, whereas the five Scandinavian countries, with Belgium, Luxembourg and Switzerland, collaborate internationally more than the trend-line would suggest.

According to the results, the countries whose European collaborations are expanding most rapidly are Brazil, India and China, followed by South Korea and Australia. Nevertheless, there is little expansion in collaboration with Russia and Japan during the period 2002-13.

Within the area of Cancer, the impact of European research is defined first of all into 11 research types, generating different numbers of papers, with genetics giving the most (48,259 or 17.1%),

followed by chemotherapy (28,240 papers or 10.0%), prognosis (27,189 papers or 9.6%) and surgery (26,585 papers or 9.4%). Second by 22 different cancer sites, with breast giving the most of cancer papers (25805 or 10.2 %), followed by colon/rectum (17389 or 6.9%), leukaemia (14838 or 5.9%) and lymphoma (11903 or 4.7%).

The mean citation score varies by a factor of more than two for the extremes of the cancer sites (leukaemia, colorectal, breast = 17.9; gallbladder = 7.6) and by almost two for the extremes of the types of research (prognosis = 20.3; surgery = 11.5). In fact, the ACI value is positively correlated with the size of the research community, or at least the number of papers, with r2 = 0.56 for the 22 cancer sites, and r2 = 0.33 for the 11 types of research.

5 Conclusion

Cancer is among the leading causes of morbidity and mortality in Europe, with an estimated 3.45 million new cancer cases (excluding non-melanoma skin cancer) and 1.75 million deaths from cancer in 2012. In the future, the burden of cancer will become higher. Today, Europe as a whole is working together in the area of cancer policy initiatives and research in order to understand the underlying causes of cancer, to ensure the improved management of this disease and to study its social impact.

Across Europe, the EU and its MS have mainly supported research on dissecting the causes and mechanism of cancer, translating this basic knowledge into clinical applications and supporting clinical research on new and improved interventions. Other issues related to cancer have been also covered, but have received a considerably lower attention (e.g. cancer control, prevention, patient care, etc.). Thus, room is left for cancer research aimed at improving existing treatments as well as studies of the organization of care, and methods to enhance quality of life and prevention.

The major US companies that are the world leaders for R&D investment in the pharmaceutical and biotechnology sector have significantly less cancer molecules in their research pipelines than European based companies. In several cases, US firms were not at all active in developing new molecules for cancer. By contrast, European based pharmaceutical companies have a much greater commitment to cancer in terms of pipeline development. Certainly, the top 10 European companies seem to specialize in specific NCD categories, almost all the companies have molecules on development for cancer. However, compared with the US, other large European firms like GSK, Novartis and AstraZeneca have quite a number of products in development. Indeed, these three firms consolidate more molecules in their research pipelines than do the top ten US firms collectively. These conclusions are similar to some other NCD categories, as CRDs.

The analysis interviews reveals the need for strengthening and implementing policies that enhance cancer control efforts across the European Union. Cancer is a non-communicable disease which encompasses multiple diseases in one and requires data from different population groups with different characteristics to gain a deeper insight and determine the patterns and trends that affect cancer incidence. Cancer requires a multinational and multidisciplinary approach, in particular with regards to rare cancers. To this end, this analysis suggests that the European Union should prioritise research on personalised cancer medicine and direct more efforts towards the establishment of networks or programmes that encourage solid cross-border collaboration for research at different levels, provide more funding opportunities for independent academic research and for translational research to place latest discoveries into health practice and disease prevention, implement effective policies that promote behaviours that are conductive to health, and, last but not least, implement priorities to protect personal data whilst not hampering research.

Cancer is the first leading cause of lost DALYs across Europe in terms of NCDs (17,68%). Otherwise, in case of cancer papers, relevant to 13 main cancer sites for the leading 18 European countries from 2002 to 2013, the differences for some diseases were not great, but for others there were big variations in relative burden between countries. Breaking down the category into its major diseases, Leukaemia is the largest cause of lost DALYs by comparison with Kidney. In the past few years, research investment in Cancer was well adjusted to reflect their relative burden.
According to the results for numbers of papers of 11 research types from each of 31 European countries in ONCOL, we can note that Germany (45436) has a greater total number of papers, followed by Italy (37876) and UK (37541), highlighting that genetics is the dominant research type, followed by chemotherapy, prognosis and surgery. Very little research attention is evidently paid to quality of life, palliative care or screening. Therefore the overall situation, with a positive but rather

small correlation between disease burden and research output it is apparent that lung cancer is under-researched and perhaps breast cancer over-researched.

On the other hand, Malta is publishing very little, and Germany, Italy and UK are the ones most publishing in cancer research, being correlative within is level of GDP. However, some of the smaller countries are expanding their output rapidly – notably Romania, whose fractional count output rose from only 7 papers in 2002 to over 250 in 2013, and followed by Cyprus Lithuania and Luxemburg.

Appendix 1

Search strategy for MDs' clinical trials from www.clinicaltrials.gov

The search was performed according to top MD companies.

Search strategy:

1. Interventions: device
2. Sponsor (lead):
    - Johnson & Johnson
    - General Electric Co.
    - Medtronic Inc
    - Siemens AG
    - Baxter International Inc
    - Fresenius Medical Care AG & Co. KGAA
    - Koninklijke Philips NV
    - Cardinal Health Inc.
    - Novartis AG (Alcon)
    - Covidien plc
    - Stryker Corp.
    - Becton, Dickinson and Co.
    - Boston Scientific Corp.
    - Essilor International SA
    - Allergan Inc. (Actavis)
    - St. Jude Medical Inc.

Only ongoing/completed clinical trials between 2011 and 2015 have been considered. Moreover only MDs for non-communicable diseases have been included.

We excluded terminated clinical trials and those with unknown/not verified status.

Appendix 2

Search strategy for PMA (Premarket Approval) of medical devices at FDA

Premarket approval (PMA) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. Due to the level of risk associated with Class III devices, FDA has determined that a PMA is needed in order to obtain marketing clearance. PMA is the most stringent type of device marketing application required by FDA.

The search was performed according to indication in the five NCD areas (cancer, respiratory disease, cardiovascular disease, diabetes, mental health) and not according to top MD companies.

Search strategy:

3. Date: 01/01/2011 – current date (June 2015)
4. Keywords:
    - ONCOL:
        - cancer
    - CARDI:
        - cardiovascular
        - stroke
    - DIABE:
        - diabetes
    - RESPI:
        - respiratory
        - pulmonary
        - pneumonia
        - pharyngitis
        - rhinitis
        - bronchitis
        - asthma
        - allergy
        - COPD
        - emphysema
        - lung
        - apnea

- MENTH:
    - mental
    - depression
    - schizophrenia
    - dementia
    - alzheimer
    - brain
    - pain
    - epilepsy
    - addiction
    - smoke/smoking
    - behavior/behavioral
    - anxiety
    - eating disorder
    - sleep

Appendix 3

Search strategy for de novo medical devices at FDA

The FDA added the de novo classification option as an alternate pathway to classify novel devices of low to moderate risk that had automatically been placed in Class III after receiving a "not substantially equivalent" (NSE) determination in response to a premarket notification [510(k)] submission. Devices that are classified through the de novo process may be marketed and used as predicates for future 510(k) submissions.

The search was performed first according to top MD companies, but we did not find any result. The search strategy adopted was the following:

1. Decision date: 01/01/2011 – current date (June 2015)
2. Requester name:
    - Johnson & Johnson
    - General Electric Co.
    - Medtronic Inc
    - Covidien plc
    - Siemens AG
    - Baxter International Inc
    - Fresenius Medical Care AG & Co. KGAA
    - Koninklijke Philips NV
    - Cardinal Health Inc.
    - Novartis AG (Alcon)
    - Stryker Corp.
    - Becton, Dickinson and Co.
    - Boston Scientific Corp.
    - Essilor International SA
    - Allergan Inc. (Actavis)
    - St. Jude Medical Inc.

Then, we performed a second search using as filter only the decision date (from 01/01/2011 to June 2015). We included only MDs for non-communicable diseases and MDs which have not received 510(k) clearance yet.

Appendix 4

Search strategy for EuroScan medical devices

The search was performed according to indication in the five NCD areas (cancer, respiratory disease, cardiovascular disease, diabetes, mental health) and not according to top MD companies.

Search strategy:

1. Technology–type: device
2. Specialty:
    - ONCOL: Oncology & radiotherapy
    - CARDI: Cardiovascular disease & vascular surgery
    - DIABE: Endocrine, nutritional and metabolic
    - RESPI: Respiratory disease & thoracic surgery
    - MENTH: Mental health, addiction & learning difficulties

Only MDs approved between 2011 and 2015 have been considered.

Appendix 5

Search strategy for top MD companies research outputs

The search was performed on Web of Science database. As ONCOL, MENTH and CARDI have yet to be coded, specific search terms were used to filter the RFOs. It must be noted that the aliases/ spelling errors in naming the RFOs by WoS means that not all them may have been captured or that other organizations may have accidentally also been captured due to the simplistic terms used. In cases where a company had only generic codes, the name was searched instead of the code. In RESPI and DIABE the funding data that were searched also include papers where the company was listed among the addresses; for the three other NCDs only the funding data were searched. It has to be noted that some of the companies also make pharmaceutical drugs and the counts of papers may include them.

Appendix 6

Table lxxxv: Semi Structured Interview Questionnaire

Name: **Organization:** **Date:**
Past and Existing Funding Strategies and Programmes for Cancer: ➢ Can you describe some of the impacts of these programmes and strategies? ➢ In what ways have the impacts been positive? ➢ In what ways have the impacts been negative?
The Challenges for the Future: ➢ Can you describe some of the challenges for future Cancer research? ➢ Can you describe some of the funding challenges for Cancer research?
Recommendations for Future EC Activity on Cancer: ➢ How would you describe the current research gaps for Cancer? ➢ How would you describe the future priorities for Cancer research funding? ➢ How can the EC position itself to address the gaps and priorities? ➢ What do you think the EU should be doing with regard to Cancer funding and research?
Any other Relevant Information: ➢ Can you recommend any other key stake holder to who we should speak?