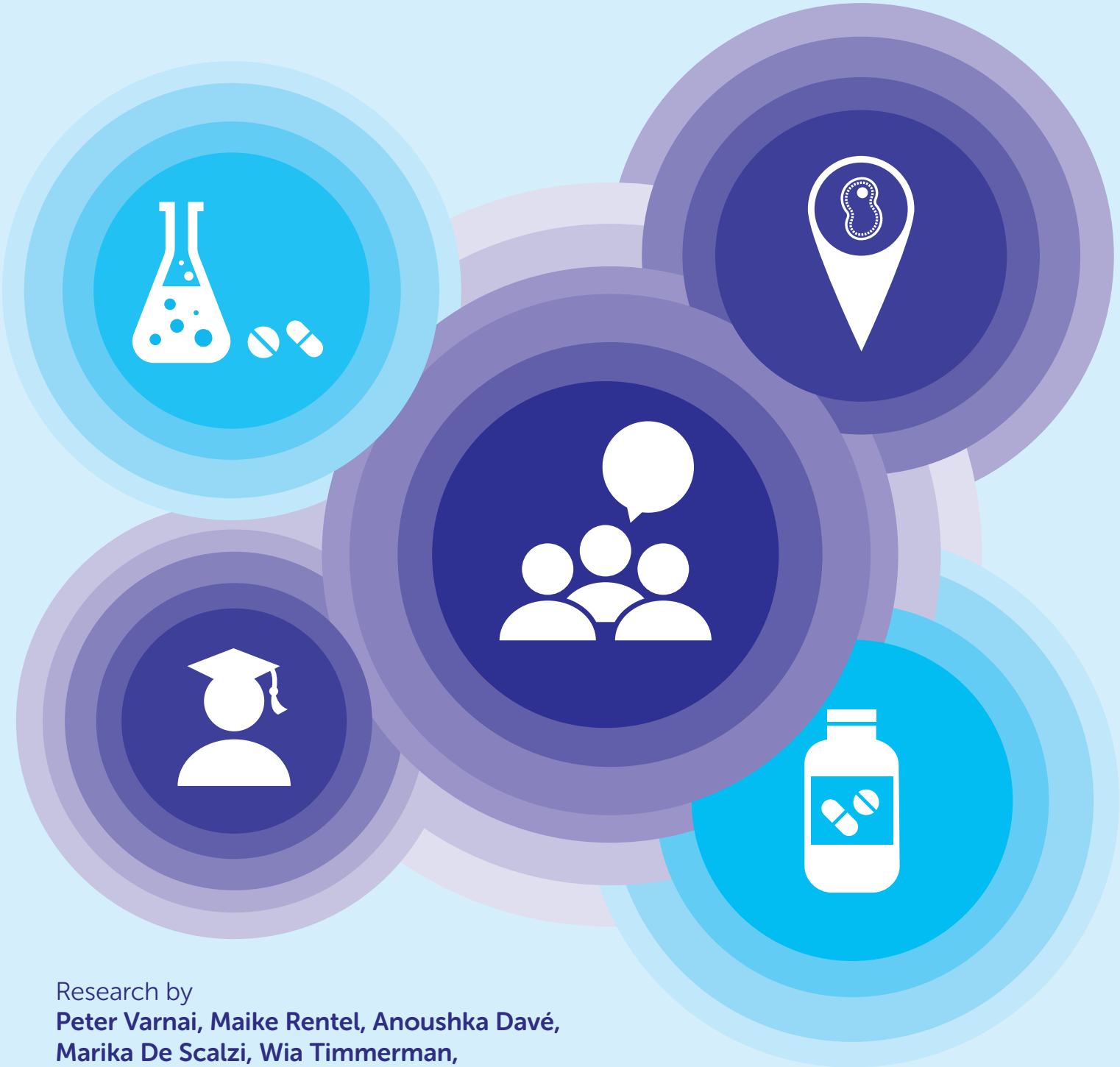
# THE IMPACT OF COLLABORATION:
## THE VALUE OF UK MEDICAL RESEARCH TO EU SCIENCE AND HEALTH

**CASE STUDIES**



Research by
**Peter Varnai, Maike Rentel, Anoushka Davé, Marika De Scalzi, Wia Timmerman, Cristina Rosemberg-Montes, Paul Simmonds**
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# CONTENTS

# 1 LEADERSHIP IN RARE DISEASE RESEARCH: NEWCASTLE

Researchers in Newcastle, from both the NHS and academia, have played a central role in many European (and global) efforts to progress research into rare diseases, and lead several large-scale initiatives in this field.

The European Union defines rare diseases as those that affect no more than 5 per 10,000 persons [1]. While the number of individuals suffering from each rare disease is (by definition) low, there are between 6,000 and 8,000 separate conditions that are considered rare. This means that in total, rare diseases are estimated to affect more than 30 million EU citizens –in other words, "rare diseases are rare, but rare disease patients are numerous". The socio-economic burden of illness is therefore substantial. For example, an estimated 500,000 patients are directly affected by neuromuscular disease (NMD) across Europe. For one NMD, Duchenne muscular dystrophy (DMD), the annual direct cost of illness is estimated at US$24,000-$54,000, with an overall societal cost of US$80,000-$121,000 per patient [2]. With around 26,000 patients in the EU [3], this suggests a societal cost of €2.4 billion per year - as a result of DMD alone.

Rare diseases are often not considered a public health priority and there are few experts conducting research on each condition. In addition, since the market for each disease is so narrow, investment from the pharmaceutical industry tends to be low [4]. Research collaboration across borders is therefore particularly important, as this allows pooling of limited resources, data and patient networks. The UK has been an important leader and convening power, building and managing networks and collaboration structures for research and patient care in rare diseases.

**"The infrastructure of the UK rare disease community is outstanding, and the UK is powerful in building and managing networks and collaboration structures in the area of rare diseases. TREAT-NMD & RD-Connect are prime examples of how networks can be managed very well. It would be a loss to the research community and patients if the UK were not able to participate in the future."**

Professor Leena Bruckner-Tuderman, Vice President of the Deutsche Forschungsgemeinschaft (DFG) and Professor of Dermatology, Albert-Ludwigs-University of Freiburg, Germany

## 1.1 Cross-border collaboration on neuromuscular disease research – TREAT-NMD

Ten years ago, a team of researchers at Newcastle University recognised that in certain NMDs, long-hoped-for therapies were at last on the horizon. However, even the largest countries did not have enough affected patients to rigorously assess novel therapies, unravel complex genetic risk factors, and determine patient outcomes; there was a notable lack of infrastructure and networking in place to support the translation of potential therapies into clinical trials and practice.

To address this gap, Newcastle University coordinated TREAT-NMD [5], a five-year 'network of excellence' (2007-2012) funded through the European Commission's FP6, with the aim of 'reshaping the research environment' in the neuromuscular field [6]. The €20 million initiative included 26 participants from 11 countries.

Following the FP6 cycle, the network expanded its formal collaboration to engage in additional strategic partnerships with universities, patient organisations and pharmaceutical companies across the world, with continued coordination through the secretariat at Newcastle. Now a globally-reaching alliance, TREAT-NMD focuses on the development of tools needed to bring

novel therapeutic approaches into the clinic, and on establishing best practice in care for neuromuscular patients.

For example, TREAT-NMD offers infrastructure to support industry and researchers, such as the care and trial site registry - which identifies centres with capacity and experience to conduct NMD trials - and the international patient registry platform for recruitment of patients. Its DMD registries comprise more than 13,500 patients from 31 different countries [7].

Newcastle's leadership has helped to grow the EU's NMD research community: Collaborations under TREAT-NMD seeded at least 16 successful funding applications in FP7, H2020, the Health Programme, COST and EU Joint Actions, with many of these led from Newcastle.

## 1.2 Research infrastructure for the global research community – RD-Connect

The limited number of patients, experts, and resources in the rare disease field means that coordination and pooling of knowledge is crucial to accelerate progress in the development of treatments for rare disease patients. Newcastle University is at the centre of these efforts by providing coordination for RD-Connect [8], a global rare disease research platform, capable of linking often disparate data sources for rare disease patients, from databases, registries, biobanks, and bioinformatics resources. Funded through FP7 with a budget of more than €17 million over a six-year period, this central resource is available to rare disease researchers worldwide. RD-Connect comprises 28 full partners, from 11 EU countries as well as Switzerland, the USA and Australia.

## 1.3 Key input to EU policy development - EUCERD Joint Action and RD-Action

Newcastle coordinated the EUCERD Joint Action (JA) [9], a 3-year, €5.5 million initiative to support the activities of the EU Committee of Experts on Rare Diseases (EUCERD; 2012-2014). The JA helped the Commission to formulate and implement the EU's activities in the rare disease field [10], for example by facilitating the exchange of policies and practices between all stakeholders and Member States.

The achievements of the EUCERD JA were expanded in the subsequent Rare Diseases Joint Action initiative (RD-Action; 2014-2018) [11]. RD-Action's principal objective is to help EU Member States implement the recommended measures adopted by the European Commission Expert Group on Rare Diseases (CEGRD), and to produce the data necessary for countries to advance and improve their rare disease programmes. Newcastle University still continues to lead the Policy Development and Integration work-stream, working with the Orphanet team in Paris who coordinate the project overall.

### 1.4 At the heart of patient care – European Reference Networks (ERNs)

A major focus of Newcastle's activities in both EUCERD and RD-Action was to support the development of pan-European expert networks, and assist the rare disease research community in Europe in organising itself into 'European Reference Networks' (ERNs) [12]. The first 24 ERNs were launched in February 2017, creating a clear governance structure for knowledge sharing and care coordination across the EU[i]. They will facilitate patient referrals to specialists located in other EU Member States and ensure the availability of subsequent treatment facilities where

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i ERNs are expected to involve at least 10 hospitals/specialised centres from at least 8 EU Member States. Information from NHS European Office ERN briefing, 2015.

necessary, regardless of where patients live. By pooling of expertise and resources, ERNs will boost rare disease research throughout the EU.

Newcastle upon Tyne/NUTH will coordinate for three ERNs, with focus on NMDs, rare liver diseases, and rare immunological and auto-inflammatory diseases [13] . The UK clearly plays a key role in the care of rare disease patients in the EU: NHS institutions coordinate a quarter of all ERNs (6 of 24), more than any other Member State[ii].

ii France and the Netherlands coordinate five ERNs each, Germany four, Italy two, and Spain and Austria one each.

# 2 IMPORTANCE OF THE UK FOR PAN-EU TRIALS

The UK is regarded as one of the best clinical trial markets in Europe by key stakeholder groups, it utilises specialised and high quality clinical trials expertise and infrastructure, and makes valuable contributions to health impacts in EU countries through the provision of better drugs and treatment guidelines.

## 2.1 The UK is a popular destination for clinical trials

**"The UK is one of the major clinical research contributors in the world"** according to Professor Piotr Rutkowski from the Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology in Poland. Likewise, the UK is rated one of the best clinical trial markets in Europe by key stakeholder groups, such as the BioPharma industry, medical device manufacturers, clinical research organisations and clinical trial units [14].

Evidence shows that UK is a leading participant in pan-EU clinical trials: data cited by the Association of the British Pharmaceutical Industry (ABPI) for 2015 show that within the EU, the UK conducted the highest number of phase I trials and the second highest number (after Germany) of phase II and III trials [15]. Indeed, our analysis of the European Clinical Trials database (EudraCT) [16] shows that apart from having the highest number of country-specific clinical trials in the database, the UK also has the third highest number of shared trials with other EU countries behind only Germany and Spain.

Interestingly, the UK also has the highest participation in clinical trials for rare diseases and paediatric patients, compared to other EU member states (see Section 4.4.1). In these areas, the UK often leads on coordinating Europe-wide initiatives. One such example is the DevelopAKUre programme [17], a series of major clinical trials run by a consortium of 12 European partners and led by the UK's Royal Liverpool University Hospital (funded by the European Comission and a European consortium). UK research expertise and patient participation is vital for these trials which aim to determine if a potential new drug, nitisinone, can reduce the symptoms of alkaptonuria, a rare disease that affects one in every 250,000 people worldwide.

## 2.2 The UK has specialised and high quality clinical trials expertise and infrastructure

The UK adds significant value to pan-EU clinical trials through provision of patients, high-quality clinical research expertise and a well-organised clinical research system.

The UK's reputation as a desirable clinical trials venue is down to **"a well-structured clinical trials community with very knowledgeable clinical researchers and strong research support, e.g. good infrastructure and good biostatisticians"**, according to Dr Hubert Misslisch, Coordinator "International Cooperations", DLR Project Management Agency, Health Research, on behalf of the Federal Ministry of Education and Research (BMBF), Germany.

Additional reasons for the UK's appeal could include its greater patient recruitment potential because of the large population, and the large market size [18]. Positive attitudes towards collaborating with the UK also stem from its proven track record in efficiently delivering results, the presence of specialised clinical research centres, and the ability of clinical trial sponsors and organisers to access comprehensive information quickly and effectively.

In fact, several European interviewees mentioned the Medicines and Healthcare Products Regulatory Agency (MHRA) as an institution that is respected among industry and peer

institutions across Europe as a source of knowledge and advice on conducting clinical trials. In addition, interviewees commended the UK's network of stably funded specialised clinical trial units (CTUs) that provide high quality expertise in clinical trial coordination (also across multiple centres), design, data management, and analysis.

The benefit of a robust infrastructure is illustrated by the Alder Hey Children's NHS Foundation Trust's participation in the international paediatric trials of tocilizumab (Roche) for systemic juvenile arthritis patients [19]. Despite the challenges of very specific eligibility criteria and a smaller recruitment window compared to other trial centres (17 countries including the UK and 10 other EU countries [20]), the required number of patients were recruited to the study.

Another contributing factor is that patient groups are often integrated into clinical trials. Among our interviewees, awareness about clinical trials was also perceived to be high among the UK population, and UK patient registries were seen to be more advanced than in many other EU countries. In fact, in the case of DevelopAKUre, the UK-based AKU Society and the French ALCAP patient groups play a major role in patient recruitment and public communication. A study on symptom development is also being conducted in parallel at the Royal Liverpool University Hospital with alkaptonuria patients of all ages participating from all over Europe [21].

## 2.3 UK contributions to clinical trials have potential impacts on the health of EU citizens

Clinical trials conducted in the UK contribute to health impacts in EU countries through the provision of better drugs and treatment guidelines. Better population health translates into a better quality of life and a better economy. Here, we present three examples of EU impact from UK clinical trials.

(1) The first of the three planned DevelopAKUre trials has ascertained the correct and most effective amount of nitisinone that alkaptonuria patients should take. The next trial, also with the UK as a partner, will look at the safety and the ability of nitisinone to reduce symptoms, with potentially life-changing results for alkaptonuria patients [22].

(2) Research done at the University of Glasgow led to clinical trials of a combination therapy of two drugs, capecitabine and oxaliplatin (known together as XELOX or CAPOX), for bowel cancer treatment [23]. The phase I trials were conducted in the UK and Spain, and helped to determine the optimum doses and administration schedule of XELOX [24]. Phase II and III trials were conducted internationally [25, 26]. XELOX is now recommended for patients with advanced bowel cancer in the European Society for Medical Oncology clinical guidelines based on the positive findings from these trials [27, 28].

The XELOX regimen requires only one clinic visit every 3 weeks for a 2-hour infusion of oxaliplatin, and is £947 cheaper per patient than the previously recommended treatment [29]. Thus, XELOX has a potential impact not only on patient survival and cancer recurrence, it has potential economic impact for EU member state health providers.

(3) The previously mentioned tocilizumab trial was instrumental in the drug being licensed by the European Medicines Agency for use in children with systematic juvenile idiopathic arthritis [30]. In addition, this led to tocilizumab becoming the standard of care in the EU for patients in whom methotrexate or non-steroidal anti-inflammatory drugs do not work [31, 32]. Projections based on current evidence suggest that this development will have a sustained impact on the long-term health of patients.

# 3 UK RESEARCH ON STATINS CONTRIBUTES TO CARDIOVASCULAR DISEASE PREVENTION IN THE EU

Cardiovascular disease (CVD) accounts for approximately one-third of deaths worldwide [33]. A high level of cholesterol in the blood has been linked to a higher risk of developing CVD [34]. A class of drugs called statins are known to lower cholesterol levels, and are routinely prescribed to patients with high cholesterol levels to reduce the risk of developing CVD or having a heart attack or stroke. UK research has provided important evidence that this strategy works, thus influencing the evidence base for EU clinical guidelines on the use of statins for prevention of CVD.

Here we outline five influential studies based in the UK that have contributed significantly to the widespread adoption of statins, saving thousands of lives across the EU each year.

## 3.1 University of Glasgow research showed that regular use of statins can reduce CVD risk

In 1995, Professor James Shepherd and his team from the University of Glasgow (UK) produced the first evidence that statins could prevent the development of heart disease in apparently healthy individuals [35]. The study, conducted in 6,595 men aged 45–64 years with no history of heart problems, but high cholesterol levels, showed that after 5 years of treatment, the risk of a heart attack was reduced by 31% in the group that had taken pravastatin. This study - the West of Scotland Coronary Prevention Study (WOSCOPS) –concluded that statins were a safe preventative measure for CVD.

## 3.2 WOSCOPS follow-up study confirms pravastatin legacy effect

A 20-year follow-up study of the WOSCOPS showed that treatment with pravastatin for 5 years provides long-term benefits to individuals at high-risk of CVD. This unprecedented length of follow up and detailed reporting allowed Shepherd's team to demonstrate the lifetime benefit of long-term statin therapy also known as 'legacy effect', while also confirming that statins are effective, safe and well tolerated [36].

Benefits include a persistent reduction in adverse cardiovascular outcomes - such as coronary heart disease, heart attacks, and strokes - and similar improvements were shown to accrue beyond the initial 5 years of statin use [37].

Importantly, the WOSCOPS 20-year follow-up study also showed that lowering blood cholesterol levels using statins is cost-effective [38, 39], and hence the use of the drug also has a significant positive economic impact.

## 3.3 The benefits of statins are extended to other population groups

The University of Glasgow also led a collaborative randomised controlled trial (PROSPER 2002) to test pravastatin in older adults at a high-risk of CVD who had either undergone a cardiovascular event (such as heart attack, stroke or related surgery), or who had raised cholesterol levels. This study involved nearly 6,000 participants, both women and men aged 70-82. Pravastatin was found to reduce the incidence of death from coronary heart disease, non-fatal heart attacks and strokes by 15% compared to that in the control group, who received a placebo [40].

Another clinical trial (ASCOT-LLA 2003), conducted collaboratively by UK and Scandinavian researchers, tested the effect of a different statin - atorvastatin - in people with high blood pressure and average cholesterol levels, which showed a 36% reduction in the number of coronary heart disease deaths and non-fatal heart attacks in the atorvastatin-treated group [41].

Professor Shepherd and his team also investigated the effect of statins in people with elevated C-reactive protein - a marker linked to the inflammation of the arteries and heart disease - and no history of heart disease (JUPITER trial 2008). They found that treatment with the statin, rosuvastatin, reduced the incidence of heart attacks and death (from any cause) by 54% and 20% respectively [42].

## 3.4 European guidelines recommend statin therapy for CVD prevention

UK contribution to statin research has driven the global adoption of statins to prevent CVD. Statin therapy has become a worldwide gold standard for CVD prevention [43]. In 2003, atorvastatin became the best-selling pharmaceutical in history [44], and in the last few years many statins have become available as generic formulations, making them even more cost-effective [45]. Moreover, new drug options for CVD prevention are now tested against existing statins rather than a placebo, ensuring they are improvements on the gold standard, according to Dr D'Addato, a specialist with over thirty years' experience at Sant'Orsola University Hospital, Bologna, Italy[iii].

From 2011 onwards, the European Society of Cardiology and European Atherosclerosis Society guidelines have supported the use of statins as the preferred preventive drugs for adults with a 20% risk of developing CVD within 10 years (primary prevention), as well as for high-risk individuals, such as those who have already experienced a cardiovascular event (secondary prevention) [46].

The 2016 European guidelines for the management of dyslipidaemia - a medical condition characterised by an abnormal amount of lipids, e.g. cholesterol, in the blood - state that statins substantially reduce the incidence of CVD and associated deaths in both genders and all age groups, and that they also slow the progression or even reduce the narrowing of the arteries (atherosclerosis) [47].

## 3.5 Statins can help to reduce the economic burden of CVD across EU

More than 1.8 million people die from CVD across the EU every year (37% of all deaths) [48], with more than 440,000 dying before the age of 75 years [49]. An ageing population, together with the increasing prevalence of major CVD risk factors, notably type 2 diabetes and obesity, make CVD prevention important for EU [50]. The total cost of CVD, estimated to be as high as €210bn per year, puts a heavy burden on the economy of the EU [51]. The costs include health care, informal care and losses in productivity due to disease and death. There are also wide inequalities across the EU in terms of CVD burden: Eastern Europe has higher levels compared to the longest standing (EU-15) member states [52].

UK research has played a key role in the development and adoption of statins as a preventative treatment across the EU. Their adoption continues to offer enormous benefits, not only in terms of economic impact but, importantly, for the health and well-being of patients living throughout the EU.

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iii Personal communication, 25 January 2017.

# 4 UK RESEARCHERS ARE LEADING THE WAY IN BREAST CANCER

Over the past 40 years, substantial advances in cancer treatment have led to valuable health gains, and cancer survival rates have doubled [53]. Research conducted in the UK has provided crucial findings and tools that contributed to this remarkable achievement, benefitting patients in the EU and beyond.

The UK public have spent more than £15 billion on cancer research since the 1970s, through both direct charitable donations and taxes [54]. This research, which has resulted in improvements in interventions such as cancer screening, better organised healthcare services and new drug treatments, is estimated to have resulted in £124 billion worth of health benefits to the UK alone over the 1991-2010 period[iv]. Nevertheless, the economic costs of breast cancer in the EU remain high [55].

## 4.1 The burden and economic cost of breast cancer

Breast cancer is the most common cancer in the EU, with an estimated 364,000 patients newly diagnosed in 2012 (14% of all cancer cases and 30% of cancer cases in women) [56]. 92,000 women died of the disease that year, making it the leading cause of death from cancer in women. However, substantial progress has been made in the fight against breast cancer: today women with breast cancer have a 78% chance of surviving at least 10 years, compared to only 40% in the 1970s. Patients now have a wider range of treatment options, from surgery and radiotherapy to new cytotoxic, hormonal and biological therapies.

Researchers at the University of Oxford and King's College London estimated that the economic cost[v] of breast cancer in the EU was €15.0 billion in 2009 - and this estimate was considered conservative, as some categories of healthcare costs, such as screening programmes, were not included [57]. Healthcare costs were highest for breast cancer at €6.7 billion per year, largely due to high rates of spending on drugs for this illness.

A recent study determined the total direct medical costs of breast cancer in the Province of Milan, Italy, to amount to approximately €10,970 per patient for the 6-month period before the diagnosis of breast cancer and the first two years after diagnosis [58]. In addition, cancer also causes physical and emotional suffering in caregivers: People who cared for cancer patients reported worse physical and mental health, were more 50% more likely to be diagnosed with depression, and had twice the odds of anxiety and insomnia [59].

## 4.2 Break-through discoveries into the genetic causes and potential new treatments of breast cancer – BRCA 1, BRCA 2, and PARP inhibitors

Faulty genes are the underlying cause for about 3% of breast cancers. While this figure seems small, women with a genetic fault have a substantially increased risk of developing the disease. For example, between 45 and 90% of women with a fault in the BRCA1 (Breast Cancer-Associated 1) and BRCA2 (Breast Cancer-Associated 2) genes go on to develop breast cancer during their lifetime [60]. Today, genetic tests and regular surveillance of women can reduce the

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iv Breast cancer treatments made up 10% of this net monetary benefit (with smoking reduction and cervical screening representing 65% and 24%, respectively).

v The term economic costs includes direct costs for healthcare, i.e. costs in addressing the illness, as well as indirect costs to the economy, e.g. for productivity loss, premature mortality, and burden for caregivers

risk of dying from breast cancer by 20 per cent [61]. It took researchers nearly five decades to identify these genes, with many of the important discoveries taking place in the UK.

The first study showing that breast cancer could run in families, with several relatives being affected by the disease across the generations, was undertaken in the 1940s by Sir David Smithers from the Royal Free Cancer Hospital in London [62]. At the time, researchers did not yet fully understand how genes and DNA work.

Over the following decades, scientists developed a clearer picture: that these hereditary cases of breast cancer were caused by faulty genes. By the late 1980s, researchers were scouring the human genome, searching for a gene they called "Breast Cancer 1" [63].

A major breakthrough came in 1993 when a Cancer Research UK team (then The Cancer Research Campaign) at the Institute of Cancer Research in London, led by Professor Doug Easton, analysed the combined data from more than 200 families affected by breast and ovarian cancer. The search culminated in a 'race' between research groups in the US and UK. In October 1994, a US group revealed the identity of the gene now known as BRCA1, which, when mutated, confers a higher, heritable risk of breast cancer. The following year, a CRUK team at the Institute of Cancer Research in London identified a second gene, identified in breast cancer risk, BRCA2 [64].

UK researchers have also made key discoveries in finding treatments for breast cancers caused by mutations in these genes: In 2005, teams led by researchers at the University of Sheffield, and the Institute for Cancer Research in London demonstrated that cells with faults in BRCA1 and BRCA2 were extremely sensitive to a class of compounds called PARP inhibitors [65, 66].

In 2014, the PARP inhibitor olaparib, developed by AstraZeneca, was approved by the European Medicines Agency for treatment of women with BRCA1/2 mutations who had developed ovarian[vi] cancer. Several other PARP inhibitors for treatment of breast and ovarian cancer are in late phase development [67].

## 4.3 Developing tools to identify women with elevated risk of developing breast cancer – the BOADICEA algorithm

Women with a family history of breast and ovarian cancer may want to know their risk of developing cancer themselves. If they are found to carry a faulty version of the BRCA1 or BRCA2 gene, they may wish to seek advice from healthcare professionals on breast screening, risk-reducing surgery to remove their breasts or ovaries, or drugs to help reduce their chances of getting cancer. However, screening women for BRCA1 and BRCA2 mutations can be associated with adverse psychosocial effects, such as permanent anxiety, and increased costs for the health system [68]. Therefore, it is important that healthcare professionals can assess risks to patients to ensure that genetic testing is targeted toward those individuals most likely to be carriers.

In 2004, Professor Easton and Dr Antoniou at the University of Cambridge developed a web-based tool to do just that - the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) [69]. BOADICEA can be used to determine the probability that a woman carries a cancer-associated mutation in the BRCA1 or BRCA2 gene, and calculate their risk of breast and ovarian cancer based on their family history. The algorithm draws on the work of colleagues at Cambridge, where 60 of the 67 known breast cancer alleles (different versions of the faulty genes) have been identified [70].

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vi Mutations in BRCA1 and BRCA2 can also cause ovarian cancer.

BOADICEA was the first algorithm to comprehensively model genetic susceptibility to breast cancer, based on the largest available data resources worldwide [71]. The web-interface of BOADICEA was made available to the broader healthcare community in November 2007, and the current version was released in February 2014. The BOADICEA model takes into account a range of factors, such as the family history of breast, ovarian, and pancreatic cancer, Ashkenazi Jewish ancestry, population specific cancer incidence rates, year of birth, breast tumour pathology in affected relatives, and mutation carrier status .

To date, more than 6,800 healthcare professionals have registered to use the latest version of BOADICEA, based in more than 100 countries worldwide. The model remains the only breast cancer risk model that takes into account multiple genes involved in determining risk, and it is widely used in Europe: since December 2014, 1,453 users from the EU have registered, with 673 located in Great Britain and 780 in other member states (e.g. 168 in Germany, 103 in France, 101 in Spain, 93 in Italy, 73 in the Netherlands, and 42 in Denmark)[vii]. EU users include general practitioners, researchers, clinical geneticists, surgeons, oncologists and genetic counsellors.

## 4.4 A global effort to optimise breast cancer treatment – the EBCTCG

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview is a major collaborative endeavour that investigates the treatment of women with early (or operable) breast cancer by combining and analysing data from clinical trials conducted around the world.

In high-income countries, most women diagnosed with breast cancer tend to be diagnosed when the disease is still at an early stage [72]. The primary treatment for most of these women is surgery. However, the extent of surgery considered necessary has varied substantially, and a wide variety of additional treatments are given, such as radiotherapy and the anti-oestrogen agent tamoxifen. Different treatments and combinations of treatments have been compared in many hundreds of individual trials. By combining data from multiple trials that address similar questions, it is possible to analyse and reliably assess even moderate treatment effects, giving much more precise results than any individual trial. For such a common disease, even moderate effects on long-term survival can result in the avoidance of many thousands of deaths each year.

The EBCTCG was officially established in 1985, with UK scientists among the key drivers of the initiative. Over the decades, the collaboration has grown and essentially involves all groups currently conducting relevant clinical trials. The UK acts as a major convening force, with the EBCTCG Secretariat coordinating this immense global effort from the Clinical Trial Service Unit (CTSU) within the Nuffield Department of Population Health at the University of Oxford. CTSU also houses the central database where trial data are collected and prepared for analysis, funded through the long-term support of the CTSU by the UK Medical Research Council and Cancer Research UK. The database holds data from several hundred research groups who have shared individual patient data on more than 450,000 women in 400 trials. The UK continues to contribute strongly to the EBCTCG; for example, of nearly 200 collaborating groups listed on the EBCTCG website, the largest number are based in the UK (34 groups; for comparison, the list includes 20 groups in Italy, 19 in the USA, 18 in Germany, 12 in France, and 5 in the Netherlands) [73].

vii Personal communication, Dr Alex Cunningham, 20 Feb 2017.

The 19 reports published by the EBCTCG since its establishment have accumulated more than 20,000 citations in the medical literature. Its findings have been embedded into clinical practice and guidelines for treatment of women with early breast cancer across the world, and have informed the design of planned clinical trials. For example, a 2011 study on radiotherapy was cited extensively in a practical guideline update by the breast cancer expert panel of the German Society for Radio-oncology (Deutsche Gesellschaft für Radioonkologie, DEGRO) [74] . The panel concluded that "this (the EBCTCG's) important large-scale meta-analysis impressively confirmed that prevention of locoregional recurrences by postoperative radiotherapy translates into improved survival", and that "no subgroup even in low risk patients has yet been identified for whom radiotherapy can be safely omitted without compromising local control and, hence, cancer-specific survival". Since its publication, the EBCTCG's report on radiotherapy [75] has been cited 847 times, indicating extensive use of the findings[viii].

viii Personal communication, EBCTCG Secretariat, 1 Feb 2017.

# 5 GLOBAL IMPACT OF UK'S DISCOVERY OF MONOCLONAL ANTIBODIES FOR TREATMENT OF RHEUMATOID ARTHRITIS

Over the past 50 years, UK researchers have played a crucial role in the development of monoclonal antibodies and therapies against inflammatory diseases such as rheumatoid arthritis (RA). In the mid-1980s, researchers from the Kennedy Institute of Rheumatology, at the time part of Imperial College London, demonstrated unprecedented improvements by treating RA patients with antibodies directed against Tumour Necrosis Factor (TNF), a molecule which occurs naturally in the body and plays a key role in inflammation. The introduction of this new class of therapies in the early 2000s has revolutionised the treatment of RA and other inflammatory diseases.

## 5.1 Rheumatoid arthritis in the EU

Rheumatoid arthritis (RA) is an autoimmune disease that causes inflammation in the joints. The main symptoms are chronic joint pain and swelling due to inflammation and degradation of the synovial membrane. Untreated, the deterioration of joint structures leads to deformations and disability. As the disease progresses, patients require more frequent invasive procedures (e.g. joint injections, synovectomy) as well as the eventual replacement of affected joints. RA is also associated with higher mortality, likely due to an increased risk from cardiovascular, infectious, hematologic, gastrointestinal, and respiratory diseases among RA patients [76].

RA is estimated to affect approximately 0.5% of the EU's adult population (between 2 and 9 in 1000 adults) [77]. The incidence of RA is typically two to three times higher in women than men (1-6 per 1000 for men and 3-12 per 1000 for women). In both women and men, the onset of RA is highest among those in their sixties. Due to its ageing population, the number of RA patients in the EU can therefore be expected to increase in the coming years.

RA represents a significant economic cost to the EU (and globally), both in direct costs for healthcare and indirect costs (i.e. productivity loss, premature mortality, and burden for caregivers). A 2008 study estimated the annual economic burden to be more than €45 billion in Europe [78]. A 2014 study estimated that RA resulted in a total social cost of €3.5 billion per year in Italy alone [79]. While direct medical costs accounted for 21%, the remaining 79% were non-medical costs – predominantly to households, for informal care, and to the economy, due to absence from work of patients and caregivers.

## 5.2 Discovery of monoclonal antibody therapies

In the 1970s, working at the University of Cambridge, Cesar Milstein and Georges Köhler developed a reliable technique for the production of monoclonal antibodies [80]. This discovery was a major breakthrough, recognised by a Nobel Prize for Physiology or Medicine in 1984, and led to an enormous expansion in the exploitation of antibodies in science and medicine[ix].

Initially, monoclonal antibodies were developed from mice. Treating patients with these 'non-human' molecules could trigger severe immune responses. In the 1980s, looking for ways to

ix After this post-doctoral training period in Cambridge, Köhler, a German national, continued his research career on the European continent: He first worked in Switzerland before becoming Director of the Max Planck Institute of Immunobiology in Freiburg, where he worked until his death in 1995. Information available from The American Association of Immunologists. Georges Jean Franz Köhler, Ph.D. (1946–1995). **http://www.aai.org/about/History/Notable_Members/Nobel/Kohler_Georges.html** [Accessed 23 March 2017]

minimise these adverse reactions, another Cambridge researcher, Greg Winter and his team, worked on techniques to 'humanise' these antibodies, by introducing modifications that would increase their similarity to antibodies produced naturally in humans. Winter pioneered a technique to fully 'humanise' antibodies for therapeutic use in 1986.

In 1989, Winter founded one of the first commercial biotech companies involved in antibody engineering, Cambridge Antibody Technology (CAT). CAT discovered and developed the technology for production of what later became one of the most successful antibody drugs ever developed: Adalimumab, known by its trade name Humira®, the world's first fully human antibody [81].

Today, monoclonal antibodies are being used, or are in development, for treatment of a broad spectrum of diseases including cancer, multiple sclerosis, allergic asthma, and Alzheimer's Disease.

## 5.3 Monoclonal antibody therapy for treatment of rheumatoid arthritis

In the late 1980s, researchers from the Kennedy Institute of Rheumatology, an institute of Imperial College London at the time, under the supervision of Marc Feldmann and Ravinder Maini, discovered that drugs directed against TNF (anti-TNF) had a therapeutic effect on RA in tissue culture and animal models [82, 83, 84]. This was a unique finding: up to this point, research on anti-TNF therapies had almost entirely focussed on anti-tumour activity.

The first evaluation of TNF as a key target for treatment of RA in patients took place at the Charing Cross Hospital in London in 1992, in a study led by Feldmann and Maini. Twenty patients whose RA had not responded to any of the existing drugs were given a single infusion of infliximab, a monoclonal antibody against TNF. There was a large (79%) response rate at four weeks (for the highest dose of infliximab), compared to 8% with the placebo treatment [85].

Subsequent clinical trials demonstrated that a combination therapy of infliximab and methotrexate, a drug that was known to slow RA, significantly improved disease symptoms and at the same time reduced the incidence of joint damage [86]. This was a welcome surprise, since it was thought at that time that the damage was progressive and unstoppable.

Together, these key findings have informed guidelines for treating RA world-wide. In Europe, the European League Against Rheumatism (EULAR) recommends the use of anti-TNF treatment for people with RA who showed insufficient response to other disease-slowing treatments [87].

## 5.4 Commercial impacts

These key discoveries by researchers working at UK universities have transformed the treatment of RA and other inflammatory diseases and improved the quality of life for many patients. Since 1998, infliximab, also known by its trade name Remicade®, has been used to treat over 2.6 million patients worldwide with inflammatory conditions such as RA, plaque psoriasis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and ankylosing spondylitis [88]. In 2015, three of the five top-selling drugs globally were biological molecules blocking the action of TNF (Humira®, Enbrel® and Remicade®) [89].

The success of anti-TNF therapy has led to the development of a broader field of antibody therapies, which target or mimic the action of biological molecules, including in the treatment of cancer, Multiple Sclerosis, and Alzheimer 's disease. The Antibody Society expects that the annual number of first approvals for new antibody therapeutics will reach a record in 2017. Monoclonal antibody therapies are hence set to grow their impact on the lives of many patients in Europe and worldwide.

# 6 THE PERSON-CENTRED UK MODEL OF DEMENTIA CARE ADOPTED THROUGHOUT THE EU

In 1997 Professor Thomas Kitwood from Bradford University (UK), proposed that the concept of 'well-being' should be a key indicator for successful care for people living with dementia, creating a truly innovative model of dementia care. It was centred on a deeper understanding of the experience of patients living with dementia, but was also designed to be easily observed, measured and assessed. The Person-Centred Care (PCC) and the Dementia Care Mapping (DCM) from the Bradford Dementia Group [90] (BDG) have transformed policy and practice in dementia care in the EU and beyond. In the last twenty years, the BDG have been at work not only been honing their model - incorporating new evidence, and incorporating know-how from other approaches - but also training practitioners in Europe.

## 6.1 Person-Centred Care

Professor Dawn Brooker, a clinical psychologist who took part in the first PCC training session in Bradford, explained that **"Kitwood's initial theories around the maintenance of personhood in relation to people living with dementia came at a time when there was no theory supporting what care for people with dementia should be like and why. The focus of care, before PCC was introduced, was simply on minimising the symptoms of the disease, thus the person experiencing those symptoms was totally undermined"**. Brooker co-authored a vast number of publications on PCC and DCM as part of the Kitwood group, and was responsible for structuring the training in DCM overseas. Brooker is now affiliated to Worcester University (UK), but her research focus on PCC remains unchanged.

Kitwood proposed that high levels of challenging behaviour, distress, or apathy in people living with dementia would occur more commonly in care situations that were not supportive of personhood [91]. Therefore, as Dr Silvia Vettor, a geriatric psychologist in Italy, explains: **"[under Kitwood's model of care,] everyone who comes into contact with a person living with dementia - from senior geriatricians and directors of Dementia Care Homes to physiotherapists, social workers nursing staff and cleaners - is trained in PCC and assessed through the DCM. This is an integral part of the model, as it is the only way a fully protected environment for the people living with dementia can be provided"**.

## 6.2 Dementia Care Mapping

DCM was developed as an observational tool to empirically test PCC - as well as other approaches - and assess the impact of the social and psychological environment for people living with dementia. The method and coding system for DCM were developed through many hours of ethological observations in nursing homes, hospital facilities, and memory clinics.

Kitwood described DCM as **"a serious attempt to take the standpoint of the person with dementia, using a combination of empathy and observational skill"** [92]. DCM represented and still represents a unique tool for monitoring the interaction between carers and people living with dementia, no other attempt to systematically record and analyse these interactions was ever made before, and DCM is widely used both at the level of the individual, and 'to rate the quality of a care environment' [93] in general.

According to Professor Brooker, **"PCC stood the test of time, as Kitwood's initial theories around the maintenance of personhood still endure today: they resonate across country boundaries and across the experience of professionals, families and people living with**

**dementia. DCM, however, has been through a number of changes since its inception: its emphasis on observation without communicating directly with the person living with dementia make it seem out of step with current inclusive practice. It is a complex tool that requires specialist training and is seen as being expensive to implement"**.

Today, the School of Dementia Studies at Bradford University, the Association for Dementia Studies at Worcester University and other dementia research groups in the UK continue to be committed to complement and update Kitwood's theories, just as UK researchers in numerous other disease areas continue to utilise their expertise to update models of care that are applied right across the EU.

## 6.3 Training of European professionals

What is most impressive about the researchers who belonged to the BDG is their commitment to the dissemination of Kitwood's theories. The worldwide spread of DCM has been remarkable: the DCM tool and training materials have been translated into ten different languages, and it is estimated that up to 12,000 practitioners have been trained in DCM across Europe since the early 1990s [94] .

To maintain high quality, formalised structures for DCM were created by the University of Bradford, who hold the copyright of the method[x]. Experts from the UK provide training sessions for members of the first institution expressing an interest in PCC in any given country; when the training is complete, that organisation becomes responsible for training similar institutions in the same country; they also organise translations, updating, data gathering and dissemination of the care model. Directors of these 'local strategic lead organisations', become part of the International DCM Implementation Group.

Germany was one of the first European countries to adopt PCC in the early 2000s, followed by Denmark, the Netherlands, Norway, Belgium, Spain, Portugal, Italy, France Sweden and Iceland [95] . **"In the '90s, there were no guidelines to support care-givers in the dementia area in Germany, this is why Kitwood's work was ground-breaking. Furthermore, the fact that his theories are still applied today are indicative of the quality of his research and of its subsequent body of work"**, says Dr Christian Mueller-Hergl, University of Witten, Germany.

In Norway, Sweden and the Netherlands, the PCC and DCM have already become national strategy. In Germany, PCC and DCM became policy, and care providers embraced the new model and its methodology in 2004-05. Dr Mueller-Hergl is a qualified DCM trainer with twenty years of experience and describes PCC as **"working well both at a practical level, because it allows the integration of other techniques; and at a psychiatric level, because it is in line with the concept that mental illness implies inter-personal readjustments, or re-learning of relationship building"**.

x Personal Communication with Professor Brooker on 8th February 2017.

## 6.4 PCC continues to influence the quality of dementia care in Europe

In 2006, PCC and DCM were included in the British National Institute of Health and Care Excellence (NICE) guidelines and, soon after, an abridged version of the DCM was recommended by the National Audit Office [96]. The NICE guidelines on dementia care were regarded as a point of reference for the drafting of the European guidelines for psycho-social interventions in dementia care in 2014 [97]. For the development of these guidelines and quality indicators related to dementia care, 'Alzheimer Europe' brought together a number of pan-European organisations, European projects and informal collaborations, such as the Cochrane Dementia and Cognitive Improvement Group, the European Alzheimer's Disease Consortium, the European Association of Geriatric Psychiatry, the dementia panel of the European Federation of Neurological Societies, the INTERDEM (Early detection and timely intervention in dementia) group, the International Association of Gerontology (European region) and the North Sea Dementia Research Group. Some of the quality indicators in their report are clearly inspired by PCC, for example: 'actual care delivered to and negotiated with people living with dementia and their care givers need to elicit the views of people with dementia (including those with a relatively high degree of cognitive impairment) to inform care planning' [98].

# 7 UK RESEARCH FINDINGS UNDERPIN EU POLICIES AIMED AT REDUCING SMOKING

Before the advent of mass-marketed cigarettes, lung cancer was a rare disease. As cigarette smoking increased, so did lung cancer – accounting for 20% of all cancer deaths in Europe today [99]. Since the 1950s, UK medical research has provided clear evidence that cigarette smoking is damaging to people's health. This scientific work provided strong support for campaigns and health warnings and, importantly, influenced changes in policies in the EU throughout the last decades. From a peak in the 1970s, the number of smokers has dropped by more than one third in the EU, bringing with it substantial gains - both in terms of human lives and lower health care costs.

## 7.1 The impact of smoking on the health of EU citizens

Tobacco consumption is the single largest avoidable health risk in the EU [100]. Smoking tobacco causes cancer, cardiovascular disease and other illnesses. More than a quarter of Europeans smoke tobacco [101], and 700,000 adults aged 30-69 die from smoking-related causes every year [102]. Around 50% of smokers die prematurely - on average 14 years earlier – and smokers spend more life years in poor health [103]. The economic burden of smoking to EU society is staggering, and has been estimated at 2.5% of Europe's (2017) [104] and 4.6% of the EU27's (2009) [105] annual GDP - more than €500 billion.

While this situation is serious, it has markedly improved over the past decades. Between 1979 and 2010, smoking rates in the EU dropped by around 35%, supported by policies aimed at reducing tobacco consumption [106]. UK researchers provided some of the key evidence on which these policies are based.

## 7.2 UK researchers make the link between smoking and disease

In 1950, a seminal study by UK doctors Sir Richard Doll and Sir Austin Bradford Hill definitively proved the link between smoking and lung cancer, demonstrating that smoking causes damage to cells lining the lungs and turns them into cancer cells [107]. The following year, Doll and Hill enrolled 40,000 participants into a new study, which recorded their smoking habits and eventual causes of death [108]. This study continued for 50 years, and showed that half of all smokers are eventually killed by their habit, that smoking was also associated with heart disease, and that stopping smoking is remarkably effective in decreasing these risks again [109].

Other UK research subsequently provided crucial evidence for public health actions to reduce the level of smoking. This included the first smoking-related risk predictions [110], life expectancy predictions related to the age at which smokers quit [111], and the association between smoking rates and cigarette advertising [112], including the link between different packaging and increased consumption [113].

UK experts have also been at the forefront of research on the tobacco industry itself, which has re-shaped approaches to tobacco control globally. For example, research findings from the University of Bath on how the tobacco industry exerts political influence has informed legal judgements that ultimately led to tobacco control legislation being upheld when it was challenged by the tobacco industry [114]. The university's knowledge exchange platform, www.TobaccoTactics.org, is used by members of the European Parliament and more widely as a model for international tobacco industry observatories [115, xi].

xi Personal Communication, Professor Anna Gilmore, University of Bath, 16 February, 2017

## 7.3 Early action on anti-smoking policies in the UK

Following Doll and Hill's studies in the 1950s, doctors in the UK were the first in the world to call for concerted action to combat smoking, such as providing support for smokers in quitting and national health education campaigns [116]. This early anti-smoking advocacy by the UK medical profession was helped by the fact that the 40,000 participants in Doll and Hill's long-term study were all doctors - two thirds of all doctors in the UK at the time [117]. As part of their anti-smoking activities, the Royal College of Physicians (RCP) launched its 'Smoking and Health' report in 1962, at its first ever press conference [118]. The report created a media storm at the time, and by the autumn of 1963, it had sold 33,000 copies. In 1971, the RCP created 'Action on Smoking and Health' (ASH), with the aim of raising public awareness of the health risks of tobacco, and promoting policy measures that eliminate the harm caused by tobacco [119]. ASH continues this work today, including at EU level, as members of the European Smoke Free Partnership (alongside Cancer Research UK, the European Heart Network, and the Dutch Cancer Society) [120].

**"In public health, the UK has had a tremendously important role in pinpointing the relationship between smoking and cancer and cardiovascular disease. British doctors were among the first to act on abandoning tobacco, and played a leading role in [promoting] stopping smoking as a health guidance."**

Professor Liselotte Højgaard, Chair of the Advisory Group on Health for H2020; Former Chair of the European Medical Research Council; University of Copenhagen, Denmark

## 7.4 UK research contributes important evidence to EU anti-smoking policies

Over the past 40 years, the EU and individual Member States have implemented a range of policies to control smoking [121]. This includes regulation of tobacco products on the EU market (e.g. by regulation of packaging, labelling and ingredients), advertising restrictions for tobacco products, the creation of smoke-free environments, tax measures, and anti-smoking campaigns. Several key reports underpinning these policies originated in the UK.

In 1988, the 4th report of the UK's Independent Scientific Committee on Smoking and Health [122], also known as the Hunter Committee, presented all the scientific evidence in this area gathered throughout the 1980s. It concluded that 'environmental tobacco smoke', better known as 'passive smoking', was the cause of lung cancer in 10-30% of cases. The review fed into a growing body of data on the implications of environmental tobacco smoke. Based on this evidence, the European Council and the Ministers for Health of the Member States passed a resolution to ban smoking in places open to the public in 1989 [123], inviting Member States to adopt measures banning smoking in public places and on all forms of public transportation.

More recently, a 2012 review conducted by the University of Stirling on the promotional impact of tobacco packaging found strong evidence that plain packaging would reduce the attractiveness and appeal of tobacco products, and potentially dissuade people from smoking [124]. These findings informed consultations on tobacco product packaging in the EU and Member States. In May 2016, a revised EU Tobacco Products Directive tightened the rules on cigarette packaging and labelling [125], and France and Ireland (along with the UK) banned branded packaging [126]. A similar EU-wide ban on branded packaging, which is currently under discussion, would be estimated to reduce the number of smokers by 2.4 million over a five year period, resulting in annual healthcare savings of €506 million [127].

Researchers in the UK have made important contributions to the fight against smoking. UK scientific findings and engagement in policy development in the EU have contributed to a reduction in the number of smokers in the EU by more than a third over the past 40 years, and will continue to contribute to the ultimate aim of a smoke-free future.

# 8 LINKS IN TRAINING AND RESEARCH: THE MAX PLANCK SOCIETY

Institutions in Europe need highly-skilled staff to drive forward their research. The UK provides one of the world's best training environments for researchers – and European institutions, such as Germany's Max Planck Society, are benefitting from the talent emerging from its universities.

The Max Planck Society is Germany's most successful research organisation, attracting leading scientists from across the globe [128] . The 83 Max Planck Institutes (MPIs) and facilities conduct basic research in the natural sciences, life sciences, social sciences, and the humanities. Since its establishment in 1948, it has produced 18 Nobel laureates, and the society's researchers publish more than 15,000 publications each year in internationally renowned scientific journals.

The Society defines itself as a person-centred research organisation. Its focus is solely on attracting the world's leading talent. Once hired, the society provides prime working conditions and gives its researchers complete freedom in selecting research topics and staff.

A total of 27 MPIs make up the society's Biology and Medicine Section (BMS), working across the entire breadth of the life sciences. The section is headed by Professor Bill Hansson, who is originally from Sweden.

Professor Hansson explains that the UK has contributed significantly to the training and education of researchers in biomedicine:

**"The strong educational system [in the UK] produces opportunities for others to go and learn at those sites. There is no doubt that the UK tradition of science and education produces excellent people and expertise that we [the Society] draw on as well - individuals that are extremely well educated. Our impression is extremely positive. Britain produces most of the top talent [in the biomedical area]. It is extremely strong."**

The relationship between the Max Planck society and UK bioscience is enhanced through an extensive network of collaborations. There are more than 500 collaborations between MPIs and UK researchers, and even a joint MP-UK centre: the Max Planck-UCL Centre for Computational Psychiatry and Ageing Research.

In addition, UK scientists are strongly involved in supporting the Society's work. For example, of the 277 members of the Scientific Advisory Boards of MPIs in the biomedical section, 17% are UK nationals, second only to the US (41%) and ahead of Germany (11%), Switzerland (8%), France (6%), and the Netherlands (3%)[xii].

Professor Hansson highlighted that the Society has benefitted from the world-class talent emerging from UK universities: several directors of Max Planck Institutes having spent a training period in the UK. For example, two directors, Professor Dr Werner Kühlbrandt and Professor Dr Ralf Adams, started their education in Germany, then worked at UK institutions for a number of years before returning to Germany. Here they reflect on their experience in the UK and the impact this has had – and continues to have - on their research.

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xii Personal communication, MPG office, 30 Jan 2017.

## 8.1 Prof. Dr. Werner Kühlbrandt, Max-Planck Institute of Biophysics, Frankfurt

Professor Werner Kühlbrandt is Director and Scientific Member of the Department of Structural Biology at the Max Planck Institute of Biophysics in Frankfurt, Germany. He is an associate professor at the Goethe University Frankfurt, a member of European Molecular Biology Organisation (EMBO) and the German National Academy of Science Leopoldina. From 2006-2009, Professor Kühlbrandt was Chair and Vice-Chair of the European Molecular Biology Laboratory (EMBL) scientific advisory committee.

Following undergraduate studies in Chemistry at the Free University in Berlin, Professor Kühlbrandt began his research career in the UK: first as a PhD student at the MRC Laboratory of Molecular Biology (LMB) in Cambridge (1977-1981), and later again as a postdoctoral researcher at Imperial College London (1984–1987). He then returned to Germany in 1987, where he became group leader at the EMBL in Heidelberg. In 1997, Professor Kühlbrandt joined the MPI of Biophysics, where he continues his research on the structure and mechanisms of membrane proteins.

Of his time in the UK, Professor Kühlbrandt says:

**"I acquired knowledge and skills in my area of science that at the time were not available anywhere in Germany, or indeed in the world. [...] I was most impressed with the scintillating scientific atmosphere at the MRC LMB, which has been, and continues to be, the most important hub of innovation and one of the most successful research laboratories anywhere, ever (it has produced 12 Nobel prize winners in 40 years). I still profit daily from my time in the UK and am in close contact with colleagues at the LMB and other institutions on a regular basis.**

**The UK continues to be an invaluable source of training and inspiration, especially in the life and medical sciences today, through its unique international outlook. It is hard to estimate numbers outside my department/group, but I would say that 5-10% of my best colleagues have spent or continue to spend formative periods in UK laboratories. I may be biased, but I cannot think of another country (except the US) that has been or is more influential."**

## 8.2 Professor Ralf Adams, Max Planck Institute for Molecular Biomedicine, Münster

Professor Adams is Director of the Max Planck Institute for Molecular Biomedicine, in addition to his role as Head of the Department of Tissue Morphogenesis.

Following his undergraduate degree in biochemistry at the University of Bayreuth, Prof Adams completed a doctorate at the Max Planck Institute for Brain Research in Frankfurt/Main (1996) and conducted postdoctoral work at the European Molecular Biology Laboratory (EMBL) in Heidelberg. In 2000, he moved to the Cancer Research UK London Research Institute (LRI) in the UK, first as a research group leader and, later, a tenured senior scientist.

He spent the next 8 years at the LRI, conducting research on the molecular regulation of blood vessel growth. This process plays a critical role in the repair of damaged blood vessels, for example after a heart attack. It is also a crucial factor in tumour growth, as blood supply to the cancerous cells allows tumours to grow bigger and grow more quickly. Professor Adams continues to work on the interaction of different cells and cell types during the formation of new blood vessels at the MPI and the Westphalian Wilhelms-University in Münster.

Of his time in the UK, Professor Adams says:

**"The time at the LRI and in London was a great experience, which has greatly influenced my career afterwards. First of all, it was fantastic to work in a cutting edge scientific environment and contribute to the success of an institute. Thanks to its international character, the LRI was buzzing with excellent scientists from all over the world. The many interactions with these colleagues were very stimulating for our research.**

**The LRI was also a great place to improve leadership and people management skills. Here, I learned to appreciate the benefits of a flat hierarchy, an open-minded attitude, tolerance, and other things that are 'a bit special' in British culture and science. One thing that impressed me very much was the generosity of the public and the scale of the donations given to the many charities. I do not think that this is matched by any other European country.**

**In my time in the UK, I also learned a lot about my own culture and was able to combine my German background with the new experiences made in the UK. This has greatly influenced my management and communication style. It is fair to say that I would not be the same person and scientist today without the positive influence of the time in the UK. This may also explain why I still feel very much attached to the UK, have come to London as a tourist numerous times, and actively collaborate with various scientists and institutes."**

# ENDNOTES


1 EURORDIS. About Rare Diseases. Available from **http://www.eurordis.org/about-rare-diseases** [Accessed 13 Jan 2017]

2 Landfeldt, E et al. The burden of Duchenne muscular dystrophy: an international, cross-sectional study. Neurology. 2014; 83(6):529-36

3 European Medicines Agency. EU/3/15/1478 Orphan designation. Available from **http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/orphans/2015/05/human_orphan_001571.jsp&mid=WC0b01ac058001d12b** [Accessed 6 March 2017]

4 EURORDIS. About Rare Diseases. Available from **http://www.eurordis.org/about-rare-diseases** [Accessed 13 Jan 2017]

5 TREAT-NMD Neuromuscular Network. Available from **http://www.treat-nmd.eu** [Accessed 13 Jan 2017]

6 European Commission. Community Research and Development Information Service. Translational Research in Europe – Assessment and treatment of neuromuscular diseases. Available from **http://cordis.europa.eu/project/rcn/84926_en.html** [Accessed 2 Feb 2017]

7 Bladen, CL et al. The TREAT-NMD Duchenne muscular dystrophy registries: conception, design, and utilisation by industry and academia. Human Mutat. 2013; 34(11):1449-57

8 RD-Connect. Available from **http://rd-connect.eu/** [Accessed 17 Jan 2017]

9 EUCERD Joint Action. Available from **http://www.eucerd.eu/?page_id=54** [Accessed 17 Jan 2017]

10 Lynn, S et al. How the EUCERD Joint Action supported initiatives on rare diseases. Eur. J. Med. Genet. 2017; 60(3):185-189

11 RD-Connect. Available from **http://rd-connect.eu/** [Accessed 17 Jan 2017]

12 RD-Connect. Coordination of European Reference Networks. Available form **http://www.rd-action.eu/european-reference-networks-erns/coordination-of-rare-disease-erns/** [Accessed 7 March 2017]

13 European Commission, Public Health. European Reference Networks. Available from **http://ec.europa.eu/health/ern/networks_en** [Accessed 7 March 2017]

14 Gehring M, Taylor RS, Mellody M, Casteels B, Piazzi A, Gensini G, Ambrosio G. Factors influencing clinical trial site selection in Europe: the Survey of Attitudes towards Trial sites in Europe (the SAT-EU Study). BMJ open. 2013;3(11):e002957.

15 Clarivate Analytics. Open for innovation: UK Biopharma R&D Sourcebook 2016. London: Association of the British Pharmaceutical Industry; 2016.

16 EU Clinical Trials Register. Website. Available from: **https://www.clinicaltrialsregister.eu** [Accessed 18 January 2017]

17 Alkaptonuria Society. Clinical trials. Website. Available from: **http://www.akusociety.org/aku-clinical-trials.html** [Accessed 20 February 2017]**.**

18 Clarivate Analytics. Open for innovation: UK Biopharma R&D Sourcebook 2016. London: Association of the British Pharmaceutical Industry; 2016.

19 National Institute for Health Research. MCRN helps deliver new treatment option for Juvenile Arthritis patients. Webpage. Available from: **http://www.nihr.ac.uk/nihr-in-your-area/musculoskeletal/documents/Insight%20articles/New%20treatment%20options%20for%20young%20arthritis%20patients.pdf** [Accessed 20 February 2017]

20 EU Clinical Trials Register. Website. Available from: **https://www.clinicaltrialsregister.eu** [Accessed 18 January 2017]

21 Alkaptonuria Society. Website. Available from: **http://www.akusociety.org/aku-clinical-trials.html** [Accessed 20 February 2017]

**22** Alkaptonuria Society. Website. Available from: **http://www.akusociety.org/aku-clinical-trials.html** [Accessed 20 February 2017]

**23** Research Excellence Framework 2014 impact case studies. Improving tolerability, convenience and cost of bowel cancer chemotherapy. Webpage. Available from: **http://impact.ref.ac.uk/CaseStudies/CaseStudy.aspx?Id=40439** [Accessed 20 February 2017]**.**

**24** Diaz-Rubio E, Evans TR, Tabernero J, Cassidy J, Sastre J, Eatock M, Bisset D, Regueiro P, Baselga J. Capecitabine (Xeloda®) in combination with oxaliplatin: a phase I, dose-escalation study in patients with advanced or metastatic solid tumors. Annals of Oncology. 2002;13(4):558-565.

**25** Cassidy J, Tabernero J, Twelves C, Brunet R, Butts C, Conroy T, Debraud F, Figer A, Grossmann J, Sawada N, Schöffski P. XELOX (capecitabine plus oxaliplatin): active first-line therapy for patients with metastatic colorectal cancer. Journal of Clinical Oncology. 2004;22(11):2084-2091.

**26** Cassidy J, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. Journal of Clinical Oncology. 2008;26(12):2006-2012.

**27** Labianca R, Nordlinger B, Beretta GD, Brouquet A, Cervantes A, ESMO Guidelines Working Group. Primary colon cancer: ESMO Clinical Practice Guidelines for diagnosis, adjuvant treatment and follow-up. Annals of Oncology. 2010;21(suppl 5):v70-v77.

**28** Van Cutsem E, Nordlinger B, Cervantes A, ESMO Guidelines Working Group. Advanced colorectal cancer: ESMO Clinical Practice Guidelines for treatment. Annals of Oncology. 2010;21(suppl 5):v93-v97

**29** National Institute for health and Clinical Excellence. Colorectal cancer costing report – Implementing NICE guidance. NICE clinical guideline 131. London: National Institute for health and Clinical Excellence; 2011.

**30** European Medicines Agency. Summary of the European Public Assessment Report for RoActemra (tocilizumab). Webpage. Available from: **http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000955/human_med_001042.jsp&mid=WC0b01ac058001d124** [Accessed 2 March 2017]**.**

**31** Dueckers G, Guellac N, Arbogast M, Dannecker G, Foeldvari I, Frosch M, Ganser G, Heiligenhaus A, Horneff G, Illhardt A, Kopp I. Evidence and consensus based GKJR guidelines for the treatment of juvenile idiopathic arthritis. Clinical immunology. 2012;142(2):176-193.

**32** University College London. Tocilizumab – a new treatment for severe juvenile idiopathic arthritis in children. Webpage. Available from: **https://www.ucl.ac.uk/impact/case-study-repository/new-treatment-for-severe-juvenile-idiopathic-arthritis-in-children** [Accessed 2 March 2017]**.**

**33** European Heart Network. 2017 European Cardiovascular Disease Statistics. Available from: **http://www.ehnheart.org/cvd-statistics.html** [Accessed 31 March 2017]**.**

**34** European Association of Preventive Cardiology. Website. Available from: **www.escardio.org** [Accessed 31 March 2017].

**35** Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, Macfarlane PW, McKillop JH, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. New England Journal of Medicine. 1995;333(20):1301-1308.

**36** REF 2014 Impact Case Studies. Global adoption of statins for cardiovascular disease prevention. Webpage. Available from: **http://impact.ref.ac.uk/CaseStudies/CaseStudy.aspx?Id=41155.** [Accessed 31 March 2017]**.**

**37** Packard CJ, Ford I, Murray H, McCowan C. Lifetime clinical and economic benefits of statin-based LDL lowering in the 20-year follow-up of the West of Scotland Coronary Prevention Study. Circulation. 2014;130:2105-2126.

**38** McConnachie A, Walker A, Robertson M, Marchbank L, Peacock J, Packard CJ, Cobbe SM, Ford I. Long-term impact on healthcare resource utilization of statin treatment, and its cost effectiveness in the primary prevention of cardiovascular disease: a record linkage study. European heart journal. 2014;35(5):290-298.

**39** Ward S, Jones ML, Pandor A, Holmes M, Ara R, Ryan A, Yeo W, Payne N. A systematic review and economic evaluation of statins for the prevention of coronary events. Health Technology Assessment 11. 2007

**40** Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. The Lancet. 2002;360(9346):1623-1630.

**41** Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. The Lancet. 2003;361(9364):1149-1158.

**42** Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto Jr AM, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. New England Journal of Medicine. 2008;359(21):2195.

**43** REF 2014 Impact Case Studies. Global adoption of statins for cardiovascular disease prevention. Webpage. Available from **http://impact.ref.ac.uk/CaseStudies/CaseStudy.aspx?Id=41155.** [Accessed 31 March 2017]**.**

**44** Taylor D. The Pharmaceutical Industry and the Future of Drug Development. In: Pharmaceuticals in the Environment. 2015, pp. 1-33.

**45** REF 2014 Impact Case Studies. Global adoption of statins for cardiovascular disease prevention. Webpage. Available from **http://impact.ref.ac.uk/CaseStudies/CaseStudy.aspx?Id=41155.** [Accessed 31 March 2017]**.**

**46** REF 2014 Impact Case Studies. Global adoption of statins for cardiovascular disease prevention. Webpage. Available from **http://impact.ref.ac.uk/CaseStudies/CaseStudy.aspx?Id=41155.** [Accessed 31 March 2017]**.**

**47** Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Ž. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. European Heart Journal. 2016;37(39):2999-3058.

**48** European Heart Network. European Cardiovascular Disease Statistics 2017. Available from: **http://www.ehnheart.org/cvd-statistics.html** [Accessed 31 March 2017]

**49** Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M. (2016) Cardiovascular disease in Europe: epidemiological update 2016. European Heart Journal. 2016;37, 3232-3245.

**50** European Association of Preventive Cardiology. Website. Available from: www.escardio.org [Accessed 31 March 2017].

**51** European Heart Network. 2017 European Cardiovascular Disease Statistics. Available from: **http://www.ehnheart.org/cvd-statistics.html** [Accessed 31 March 2017]**.**

**52** Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M. (2016) Cardiovascular disease in Europe: epidemiological update 2016. European Heart Journal. 2016;37, 3232-3245.

**53** Cancer Research UK. Half of all cancer patients now survive at least 10 years. 2014. Available from **http://www.cancerresearchuk.org/about-us/cancer-news/press-release/2014-04-29-half-of-all-cancer-patients-now-survive-at-least-10-years?_ga=1.27964476.1899612207.1476955237** [Accessed 8 Feb 2017]

**54** Glover, M et al. Estimating the returns to UK publicly funded cancer-related research in terms of the net value of improved health outcomes. BMC Medicine. 2014; 12:99

**55** Luengo-Fernandez, R et al. Economic burden of cancer across the European Union: a population-based cost analysis. Lancet Oncology. 2013; 14: 1165-1174

**56** Ferlay, J et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. Eur. J. Cancer. 2013; 49:1374-403

**57** Luengo-Fernandez, R et al. Economic burden of cancer across the European Union: a population-based cost analysis. Lancet Oncology. 2013; 14: 1165-1174

**58** Capri, S & Russo, A. Cost of breast cancer based on real-world data: a cancer registry study in Italy. BMC Health Services Research. 2017; 17:84

**59** Mori, A et al. Quantifying the Burden of Caregiving for Patients With Cancer in Europe. 2013. Available from **http://www.kantarhealth.com/docs/publications-citations/quantifying-the-burden-of-caregiving-for-patients-with-cancer-in-europe.pdf?sfvrsn=20** [Accessed 02 Feb 2017]

**60** Cancer Research UK. Inherited genes and cancer types. Available from **http://www.cancerresearchuk.org/about-cancer/causes-of-cancer/inherited-cancer-genes-and-increased-cancer-risk/inherited-genes-and-cancer-types#inherited_genes1** [Accessed 2 Feb 2017]

**61** The Independent UK Panel on Breast Cancer Screening. The Benefits and Harms of Breast Cancer Screening: An Independent Review. 2012. Commissioned by Cancer Research UK and the Department of Health (England)

**62** Cancer Research UK. Tracking down the BRCA genes. Available from **http://scienceblog.cancerresearchuk.org/2012/02/28/high-impact-science-tracking-down-the-brca-genes-part-1/ [Accessed 2 Feb 2017**

**63** Cancer Research UK. Tracking down the BRCA genes. Available from **http://scienceblog.cancerresearchuk.org/2012/02/28/high-impact-science-tracking-down-the-brca-genes-part-1/ [Accessed 2 Feb 2017**

**64** Cancer Research UK. Tracking down the BRCA genes. Available from **http://scienceblog.cancerresearchuk.org/2012/02/28/high-impact-science-tracking-down-the-brca-genes-part-1/ [Accessed 2 Feb 2017**

**65** Bryant, HE et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature. 2005; 434: 913-917

**66** Farmer, H et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005; 434: 917-921

**67** Brown, JS et al. PARP inhibitors: the race is on. British Journal of Cancer. 2016; 114: 713–715

**68** REF 2014 Impact Case Studies. Development of risk prediction algorithms for familial breast and ovarian cancer and their use for genetic counselling purposes-Ponder. Available from **http://impact.ref.ac.uk/CaseStudies/CaseStudy.aspx?Id=29694** [Accessed 1 Feb 2017]

**69** University of Cambridge Centre for Cancer Genetic Epidemiology. BOADICEA. Available from **http://ccge.medschl.cam.ac.uk/boadicea/** [Accessed 1 Feb 2017]

**70** REF 2014 Impact Case Studies. Development of risk prediction algorithms for familial breast and ovarian cancer. Available from **http://impact.ref.ac.uk/CaseStudies/CaseStudy.aspx?Id=21201** [Accessed 1 Feb 2017]

**71** REF 2014 Impact Case Studies. Development of risk prediction algorithms for familial breast and ovarian cancer and their use for genetic counselling purposes-Ponder. Available from **http://impact.ref.ac.uk/CaseStudies/CaseStudy.aspx?Id=29694** [Accessed 1 Feb 2017]

**72** Darby, S. et al. The Early Breast Cancer Trialists' Collaborative Group: a brief history of results to date. from 'Celebrating Statistics'. In AC Davison, Y Dodge, N Wermuth (eds). Oxford University Press, Oxford, 2005.

**73** Clinical Trial Service Unit at Nuffield Department of Population Health, University of Oxford. EBCTCG: Early Breast Cancer Trialists' Collaborative Group. Available from **https://www.ctsu.ox.ac.uk/research/ebctcg** [Accessed 20 Jan 2017]

**74** Sedlmayer, F. et al. DEGRO practical guidelines: radiotherapy of breast cancer I: radiotherapy following breast conserving therapy for invasive breast cancer. Strahlenther Onkol. 2013; 189:825-33.

**75** Early Breast Cancer Trialists' Collaborative Group (EBCTCG) et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials. Lancet. 2011; 378: 1707–1716

**76** Gabriel, SE & Michaud, K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. Arthritis Research & Therapy. 2009; 11: 229

**77** European Commission. Public Health: Musculoskeletal Conditions. Available from **http://ec.europa.eu/health/major_chronic_diseases/diseases/musculoskeletal_en#fragment3** [Accessed 8 March 2017]

**78** Lundkvist, J et al The burden of rheumatoid arthritis and access to treatment: health burden and costs. Eur J Health Econ 2008; 8 (Suppl. 2): S49-60

**79** Turchetti G, et al. The social cost of rheumatoid arthritis in Italy: the results of an estimation exercise. Reumatismo. 2014; 65: 271–277

**80** MRC Laboratory of Molecular Biology: Therapeutic antibodies and the LMB. Available from **http://www2.mrc-lmb.cam.ac.uk/research/technology-transfer/recent-technology-transfer-initiatives/therapeutic-antibodies/** [Accessed 8 March 2017]

**81** Lawrence, S. Billion dollar babies—biotech drugs as blockbusters. Nature Biotechnology. 2007; 25 (4): 380–2

**82** Feldmann, M et al. Role of cytokines in rheumatoid arthritis. Annu. Rev. Immunol. 1996; 14: 397–440.

**83** Feldmann, M & Maini, RN. TNF defined as a therapeutic target for rheumatoid arthritis and other autoimmune diseases. Nat. Med. 2003; 9: 1245–1250

**84** Williams, RO et al. Anti-tumor necrosis factor ameliorates joint disease in murine collagen-induced arthritis. Proc. Natl. Acad. Sci. USA. 1992; 89: 9784–9788

**85** Elliott, MJ et al. Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrosis factor alpha. Arthritis Rheum. 1993; 36: 1681–1690

**86** Maini, RN et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum. 1998; 41: 1552–1563

**87** Smolen, JS et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis. Published Online First: 25 October 2013. doi: 10.1136/annrheumdis-2013-204573

**88** Janssen Immunolog.: Remicade (Infliximab). Available from **http://www.remicade.com.** [Accessed 8 Feb 2017]

**89** PharmaCompass – Global Pharmaceutical Intelligence. Available from **http://www.pharmacompass.com.** [Accessed 8 Feb 2017]

**90** Available from: **http://www.brad.ac.uk/health/dementia/dementia-care-mapping** [Accessed 9 January 2017]

**91** Brooker, D & Surr, C. Person-centred care and dementia care mapping, in N.A. Pachana (ed.) Encyclopaedia of Geropsychology, 2016

**92** Kitwood T M. Dementia reconsidered: the person comes first (Rethinking ageing), Buckingham, Open University Press, 1997, p. 4.

**93** The NICE – SCIE Guidelines on Supporting People with Dementia and their Carers, 2006 (Ballard et al. 2001), p. 271.

**94** Brooker, D & Surr, C. Person-centred care and dementia care mapping, in N.A. Pachana (ed.) Encyclopaedia of Geropsychology, 2016

**95** Brooker, D & Surr, C. Person-centred care and dementia care mapping, in N.A. Pachana (ed.) Encyclopaedia of Geropsychology, 2016

**96** University of Bradford, Improving Care for people with dementia, 2014, Available from: www.impact.ref.ac.uk/CaseStudies/CaseStudy.aspx?Id=43368 [Accessed 20 February 2017]

**97** Vasse E, Vernooij-Dassen et al. Guidelines for psychosocial interventions in dementia care: a European survey and comparison, Int J Geriatr Psychiatry, 2012, 27: 40-48.

**98** EuroCOllaboration on Dementia – EUROCODE. Alzheimer Europe is a project aimed at developing a European network of players active in the area of dementia to jointly develop consensual indicators of quality of care. Available from: www.alzheimer-europe.org [Accessed 2 March 2017].

**99** European Lung Foundation. Lung health in Europe – Facts and Figures. 2013. Available from: **http://www.europeanlung.org/assets/files/publications/lung_health_in_europe_facts_and_figures_web.pdf** [Accessed 29 March 2017]

**100** European Commission. Public Health – Tobacco. Available from: **http://ec.europa.eu/health/tobacco/policy_en** [Accessed 30 March 2017]

**101** World Health Organisation. Tobacco data and statistics. Available from: **http://www.euro.who.int/en/health-topics/disease-prevention/tobacco/data-and-statistics** [Accessed 27 March 2017]

**102** Goodchild, M et al. Global economic cost of smoking-attributable diseases. Tob Control. 2017;0: 1–7

**103** European Commission. Public Health – Tobacco. Available from: **http://ec.europa.eu/health/tobacco/policy_en** [Accessed 30 March 2017]

**104** Goodchild, M et al. Global economic cost of smoking-attributable diseases. Tob Control. 2017;0: 1–7

**105** DG SANCO. A study on liability and the health costs of smoking. 2009. Available from: European Commission. Public Health – EU anti-tobacco campaigns

**106** European Respiratory Society. European Lung White Book. Available from: **http://www.erswhitebook.org/chapters/tobacco-smoking/** [Accessed 30 March 2017]

**107** Doll, R & Hill, AB. Smoking and carcinoma of the lung; Preliminary report. Br Med J. 1950;2 (4682): 739-48.

**108** Peto, R & Beral V. Sir Richard Doll CH OBE. Biogr. Mems Fell. R. Soc. 2010; 56: 63-83 Available from: **http://rsbm.royalsocietypublishing.org/content/roybiogmem/56/63.full.pdf** [Accessed 31 March 2017]

**109** Doll R & Hill AB. The mortality of doctors in relation to their smoking habits. Br Med J. 1954; 1 (4877): 1451–1455.

**110** Doll R & Peto R. Mortality in relation to smoking: 20 years' observations on male British doctors. Br Med J. 1976;2(6051):1525-36; Doll R et al. Mortality in relation to smoking: 40 years' observations on male British doctors. Br Med J. 1994;309 (6959): 901-11.

**111** Doll R et al. Quitting cigarette smoking at age 30, 40, 50, 60 increases life expectancy by 10, 9, 6 and 3 years. In: Mortality in relation to smoking: 50 years' observation on male British doctors. Br Med J. 2004; 328 (7455): 1519

**112** Smee C. Effect of tobacco advertising on tobacco consumption: a discussion document reviewing the evidence. Department of Health, UK; 1992

**113** Moodie C et al. Stirling Review Plain Tobacco Packaging: A Systematic Review. UK Centre for Tobacco Control. Public Health Research Consortium. 2012.

**114** Gilmore A et al. Understanding tobacco industry pricing strategy and whether it undermines tobacco tax policy: the example of the British cigarette market. Addiction. 2013, 108 (7): 1317-26.

**115** Tobacco Tactics. Available from: **http://www.tobaccotactics.org/index.php/About_Us** [Accessed 24 May 2017]

**116** World Health Organization. WHO European strategy for smoking cessation policy. 2004. Available from: **http://www.euro.who.int/__data/assets/pdf_file/0017/68111/E80056.pdf** [Accessed 9 Feb 2017]

**117** Doll, R & Hill, AB. Smoking and carcinoma of the lung. Br Med J. 1950;2 (4682): 739-48.

**118** Royal College of Physicians. Smoking and Health (1962). Available from: **https://www.rcplondon.ac.uk/projects/outputs/smoking-and-health-1962** [Accessed 31 March 2017]

**119** Action on Smoking and Health. **http://ash.org.uk/** [Accessed 31 March 2017]

**120** Smoke Free Partnership. Available from: **https://smokefreepartnership.eu** [Accessed 31 March 2017]

**121** The ASPECT Consortium for the European Commission. Tobacco or Health in the European Union: Past, Present and Future. 2004. Available from: **http://ec.europa.eu/health/archive/ph_determinants/life_style/tobacco/documents/tobacco_fr_en.pdf** [Accessed 31 March 2017]

**122** Independent Scientific Committee on Smoking and Health (Hunter Committee): Second Report 'Developments in Tobacco Products and the Possibility of Low Risk Cigarettes'; drafts, comments and amendments. 1978.

**123** Council of 18 July 1989 on banning smoking in places open to the public. Resolution of the Council and the Ministers for Health of the member states, meeting within the Official Journal 26/07/1989; C 189: p. 1.

**124** Moodie C et al. Plain Tobacco Packaging: A Systematic Review. Plain Tobacco Packaging: A Systematic Review. 2012. Available from: **https://www.stir.ac.uk/research/hub/publication/22535** [Accessed 30 March 2017]

**125** European Commission. Press release: 10 key changes for tobacco products in Europe. 2016. Available from: **http://europa.eu/rapid/press-release_IP-16-1762_en.htm** [Accessed 29 March 2017]

**126** Forster, K. 'World's ugliest colour' used on cigarette packets to put smokers off. The Independent. 11/06/2016. Available from: **http://www.independent.co.uk/news/world/australasia/worlds-ugliest-colour-revealed-pantone-448c-a7076446.html** [Accessed 30 March 2017]

**127** European Commission. Memo - Questions & Answers: New rules for tobacco products. 2014. Available from: **http://europa.eu/rapid/press-release_MEMO-14-134_en.htm** [Accessed 30 March 2017]

**128** Max Planck Gesellschaft. A portrait of the Max Planck Society. Available form **https://www.mpg.de/short-portrait** [Accessed 3 Feb 2017]

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