

# From Patent to Patient

Analysing access to innovative cancer drugs



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### **Our mission is to make the discoveries that defeat cancer**

The Institute of Cancer Research, London, is one of the world's most influential cancer research organisations, with an outstanding record of achievement dating back more than 100 years.

Our research strategy focuses on unravelling cancer's complexity and creating smarter, kinder treatments that can overcome the disease's ability to adapt and evolve. We discover more new cancer drugs than any other academic centre in the world and help develop new treatments that have benefited countless patients in the UK and overseas.

# Creating tomorrow's cancer treatments

Our report asks how we can best harness advances in science to bring innovative drugs to patients. It is designed to help us reshape the landscape for drug discovery and development – and create tomorrow's cancer treatments.

**Cancer is one of our greatest medical challenges. It is the leading cause of disease worldwide, with more than 14 million new cases each year. And these numbers are increasing. In the UK, a child born today now has a one in two risk of developing cancer at some point in their lifetime.**

We are making good progress against cancer. Over the last decade the median survival time for people in the UK diagnosed with the disease has doubled from five years to 10 years.<sup>1</sup> Advances in technologies are driving rapid growth in our understanding of the genetic changes driving cancers, opening up new avenues for treatment. And we are reaping the rewards from this, in the form of a range of exciting new targeted drugs and immunotherapies for cancer.

But we are not yet where we want and need to be. We have seen dramatic improvements in survival for some cancer types, but much more modest progress against others. Many of the new-style targeted drugs are highly effective initially, only for cancer to develop resistance

and stop responding. Once cancer has begun to spread round the body, it is still extremely difficult to treat.

Cancer is enormously complex, and it can adapt and evolve in response to changes in its environment – including drug treatment. Only through radical innovation will we deliver the step-change improvements we need in cancer treatment, by attacking cancer in new ways that allow us to overcome or prevent drug resistance. We need to create a wider variety of targeted drugs and immunotherapies and find new treatment combinations that can block cancer's escape routes.

We set out in this report to understand the current landscape of drug discovery and development to assess what progress we are making in delivering the innovation that is needed. Our analysis finds some good news – rapid improvements in our understanding of cancer are leading to more cancer drugs than ever before being licensed. But we also uncover various areas of concern. People with certain cancer types, and especially children, are

missing out on new drugs. New treatments are taking even longer to reach cancer patients. And the system of drug appraisal still doesn't seem to encourage or reward the really ambitious innovation that will be necessary for the kind of progress against cancer that all of us want to see.

Our report provides a detailed picture of where we are today in the search for new cancer treatments – and vital pointers for reshaping the landscape of drug discovery and development in the future.



**Professor Paul Workman FRS**  
Chief Executive  
The Institute of Cancer Research, London

<sup>1</sup> Cancer Research UK statistics: <https://www.cancerresearchuk.org/health-professional/cancer-statistics-for-the-uk#heading-Two>



# About this report

We set out to assess the current landscape for drug discovery and development by analysing every cancer drug first licensed through the European Medicines Agency (EMA) from 2000 to 2016.

Our aim was to answer the following:



**What drugs are coming through the pipeline and for which types of cancer?**



**How long is it taking these to reach NHS patients?**



**Is the system set up in a way that encourages radical innovation?**

We identified all cancer drugs that were first licensed by the EMA and listed on its database from 1 January 2000 until 31 December 2016.<sup>2</sup>

We chose to look at licensing through the EMA because of its relevance to drug access in the UK. We recorded both the first drug authorisation and all subsequent licensed indications. To look for changing trends over time, we split the data into two consecutive time periods, from 2000 to 2008, and from 2009 to 2016, and then carried out comparative analyses.

We examined how quickly drugs are moving along the development pipeline from their initial discovery through clinical trials and on to EMA authorisation and then appraisal by NICE. We also assessed how innovative each drug was, in order to evaluate what difference this made to its chances of being successfully approved for NHS patients.

Nick Jones of BD Consulting conducted data collection and analysis with the Policy team at The Institute of Cancer Research (ICR), overseen by the ICR's scientific leadership.

## Our definitions

For consistency, we have used the following terms throughout this report:

### Licensing

The evaluation undertaken by the EMA leading to a drug receiving an authorisation.

### Drug authorisation

A licence from the EMA for use of a drug for a specific indication.

### Indication

A specific licensed use of a drug. One drug can receive multiple EMA authorisations for different indications – for example, different cancers.

### Appraisal

The evaluation process undertaken by NICE to decide whether a drug should be made available on the NHS.

### Approval

We have used approval within this report to indicate when a drug has received a positive appraisal from NICE. The word can also be used to mean drug authorisation but, to avoid confusion, we have not done so in this report.

<sup>2</sup> Drugs included in the study belong to the Anatomical Therapeutic Chemical (ATC) Classification System Code L: antineoplastic and immunomodulating agents and were included if they received their first indication after 1 January 2000. Supportive medicines, such as colony-stimulating factors, were excluded.

# 1 What drugs are being licensed for cancer?

We set out to understand how many cancer drugs are being licensed by the EMA over time and for which indications.

## Our approach

We identified all EMA authorisations for cancer indications of drugs that were first licensed between 2000 and 2016.

We categorised each drug authorisation by:

- its cancer type
- whether it covered use in paediatric populations – and if so, for what type of children's cancer.<sup>3</sup>

For each drug, we investigated whether the ICR was involved in its discovery or development or underpinning science (see Appendices for more detail).

## 1.1

### The EMA is licensing more cancer drugs

The number of cancer drugs being licensed by the EMA is increasing, as an explosion in our understanding of cancer fuels the discovery and development of new agents.

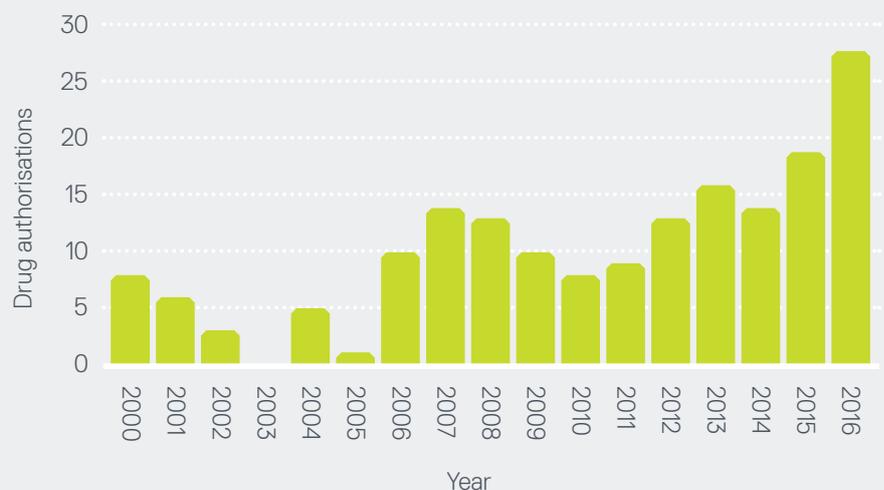
In total, the EMA licensed 97 cancer drugs across 177 indications from 2000 to 2016. The rate of authorisations has almost

doubled over that time period, with an average of 7.5 per year from 2000 to 2008 rising to 14.6 per year from 2009 to 2016.

In the first year covered by our analysis, in 2000, there were eight cancer drug authorisations by the EMA; in the last year of our analysis, in 2016, there were 28 (Figure 1).

**Figure 1**

Number of EMA drug authorisations for cancer indications from 2000 to 2016



<sup>3</sup> Authorisations for subsequent indications in drugs first licensed before 2000 were not included.

## 1.2

### But there are big variations between cancer types, with some missing out entirely

While it's good news that more cancer drugs are being authorised by the EMA, our analysis finds there are huge variations across cancer types in how many drugs are becoming available (Table 1).

For many types of cancer, such as skin, breast, prostate and haematological cancers, we have seen dramatic advances in treatment over the last decade as cancer patients reap the rewards from progress in research. Over one-third of all authorisations were for haematological cancers (leukaemia, lymphoma and myeloma), with many individual drugs receiving authorisations for multiple indications which, in part, may reflect the diversity of this group of diseases.

Patients with other tumour types are not benefiting from such exciting progress, with many cancers seeing few or no drug authorisations over the time period. Some relatively common cancers affecting many thousands of people in the UK each year – including brain, oesophageal, bladder and womb cancer – saw no new drug authorisations at all. Many of the cancers missing out are diseases with an acute unmet need where survival rates remain low such as pancreatic, liver and ovarian cancers.

Table 1

Number of EMA drug authorisations from 2000 to 2016, categorised by cancer type

Cancer type	Authorisations (2000-2008)	Authorisations (2009-2016)	Total Authorisations (2000-2016) <sup>4</sup>	% Authorisations (2000-2016)
Haematological <sup>5</sup>	26	38	64	37%
Lung	4	19	23	13%
Breast	6	9	15	9%
Skin	1	11	12	7%
Bowel	6	5	11	6%
Kidney	4	6	10	6%
Stomach	3	5	8	5%
Prostate	0	6	6	3%
Sarcoma	1	4	5	3%
Thyroid	0	4	4	2%
Pancreatic	2	2	4	2%
Ovarian	0	3	3	2%
Head and neck	3	0	3	2%
Neuroendocrine	1	1	2	1%
Cervical	0	1	1	0.5%
Neuroblastoma (children)	0	1	1	0.5%
Liver	1	0	1	0.5%
Mesothelioma	1	0	1	0.5%
Urinary tract	0	1	1	0.5%
Brain <sup>6</sup>	0	0	0	0%
Womb	0	0	0	0%
Bladder	0	0	0	0%
Oesophageal	0	0	0	0%
Testicular	0	0	0	0%
<b>TOTAL</b>			<b>175</b>	

<sup>4</sup> Two agents were left out of this analysis as they couldn't be categorised into the standard cancer site/incidence groups (catumaxomab, which is used to treat ascites that result from certain cancers, and the HPV vaccine)

<sup>5</sup> Leukaemia, lymphoma and myeloma, and all subtypes.

<sup>6</sup> The brain cancer drug temozolomide was not included in our dataset as it received its first EMA authorisation in 1999.

## Some cancers are benefiting substantially from recent progress in research, including:

### Haematological (blood) cancers

Over one-third (37 per cent) of all authorisations were for haematological cancers. In total, the EMA licensed 34 new drugs across 64 different indications.

Five of the authorisations were for **imatinib** (also known as Glivec), which was one of the very first genetically targeted cancer drugs. It was first approved in 2001 to treat patients with chronic myeloid leukaemia with a specific cancer-causing genetic fault, with subsequent authorisations to treat patients with acute lymphoblastic leukaemia and rarer cancers. Another targeted drug is **idelalisib**, which works by blocking a protein called PI3K delta which can be overactive in cancer cells, driving cell growth. Blood cancers have also benefited from many new monoclonal antibody drugs, including **ibrutinomab**, which is approved to treat some types of non-Hodgkin lymphoma, and **elotuzumab** for multiple myeloma.

### Breast cancer

A total of 15 drugs were licensed for breast cancer from 2000 to 2016 – six from 2000 to 2008 and nine from 2009 to 2016.

A range of targeted drugs have been licensed including monoclonal antibodies such as **trastuzumab** (also known as Herceptin), **pertuzumab** and **bevacizumab**, and the small-molecule inhibitors **palbociclib** and **lapatinib**. Among the other authorisations, a new cytotoxic chemotherapy called **eribulin mesylate**, which is based on a substance derived from a marine sponge, was approved for women with advanced breast cancer.

### Skin cancer

There was a steep increase in the number of drug authorisations for skin cancers, rising from one from 2000 to 2008, to 11 from 2009 to 2016.

The authorisations over the most recent period include four new targeted drugs – **vemurafenib**, **dabrafenib**, **cobimetinib** and **trametinib** – for the treatment of advanced malignant melanoma. Two of these target a common fault in the BRAF gene jointly discovered by scientists at the ICR and the Sanger Institute.

Patients with skin cancer are also benefiting from recent progress in immunotherapy. The first success story came in 2011, when the monoclonal antibody **ipilimumab** was licensed for patients with advanced melanoma,

followed a few years later by the similar drugs **nivolumab** and **pembrolizumab**. These drugs, called T-cell checkpoint inhibitors, work by releasing the brakes on immune cells so they can target cancer cells more effectively.

**Talimogene laherparepvec** (known as **T-Vec**), a genetically modified form of herpes simplex virus type 1, was the first viral immunotherapy to be licensed as a cancer treatment. In 2015, a landmark clinical trial led by researchers at the ICR and The Royal Marsden NHS Foundation Trust was the first to definitively demonstrate that viral immunotherapy can have benefits for patients with cancer, showing it can halt progression of melanoma by killing cancer cells and sparking the immune system into action against tumours.



“In my previous role at GlaxoSmithKline I was a member of the team that discovered the skin cancer drug dabrafenib. The success of this project was underpinned by great work from scientists at the ICR who did crucial research on the BRAF mutation and determined the structure of the faulty protein.”

#### Dr Olivia Rossanese

Head of Biology in the Cancer Research UK Cancer Therapeutics Unit at the ICR



### Changing lives

Debbie Keynes is 51 and lives in Gosport. She was diagnosed with malignant melanoma in April 2016 after discovering a suspicious mole on her scalp. Her tumour was removed by surgery, but later that year she found out her disease had spread, with lumps found on her head and in her liver. She has been doing well on dabrafenib and trametinib since June 2017.

“At the last scan they were struggling to see anything – it worked really quickly which was great. In the first year of being diagnosed I was very much living scan to scan. I was worried I would get ill if I travelled. But I have just come back from Crete. I have things to look forward to, things that I thought I would never do again.”

**Debbie Keynes**  
Cancer patient advocate

### Lung cancer

Authorisations for lung cancer drugs sharply increased, with four from 2000 to 2008 rising to 19 from 2009 to 2016. This is encouraging since there is a major need for more treatment options for lung cancer – there are more than 46,000 new cases in the UK each year and only 5 per cent of patients currently survive 10 years after their diagnosis.<sup>7</sup>

The licensed drugs include several small-molecule inhibitors that target specific faulty molecules helping drive cancer growth, such as **ceritinib** and **crizotinib** (ALK inhibitors) and **gefitinib** (an EGFR inhibitor). There are also several monoclonal antibodies, including immunotherapies such as **nivolumab** and **pembrolizumab**.



<sup>7</sup> Cancer Research UK statistics: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer>

## The story of abiraterone

In the 1990s, scientists at the ICR started to look for ways to shut off production of male androgen sex hormones to treat prostate cancer.

They began with an existing antifungal drug called ketoconazole which inhibits an enzyme called CYP17, and showed it could prevent the growth of prostate cancer cells in the lab. But ketoconazole wasn't potent or specific enough and was quickly broken down by the body. So the ICR team, with funding from Cancer Research UK, designed other prototype drug molecules that inhibited CYP17. The researchers discovered one – abiraterone – that was really good at switching off testosterone production in both cancer cells and in mice. The ICR further progressed abiraterone

in collaboration with several commercial partners: the British Technology Group, Cougar Biotechnology and Johnson & Johnson.

Abiraterone was developed in clinical trials led by the ICR and The Royal Marsden. Early-phase studies showed that it was safe and effective with impressive and durable anti-tumour activity, leading to a larger phase III trial involving just under 1,200 men at 128 different sites worldwide. In 2010, the first results showed that men with prostate cancer who took abiraterone lived on average for 15.8 months, compared with 11.2 months for men taking a placebo. Follow-up studies showed that the drug also has quality of life benefits over other treatments.

Based on these results, the drug received authorisation from the EMA in 2011 for men with advanced metastatic prostate cancer. In 2012, NICE announced that it would be made available on the NHS for men who had received chemotherapy for their disease, and it is now also available for patients earlier in the course of their treatment. So far, more than 400,000 men worldwide have received abiraterone to treat their cancer.

### Hope for patients

At the age of 55, Rob Lester, a retired GP, was diagnosed with advanced prostate cancer that had spread to his spine. In 2012, he was given the opportunity to receive abiraterone through taking part in the STAMPEDE clinical trial.

“I would call myself a lucky man. My doctor examined me six months after starting abiraterone and saw that the tumour in my prostate had shrunk incredibly, which was a great sign that it was working well. When I was first diagnosed I had hoped I would survive five years. I've done that now – it's been six years. And not only that, I've been living and enjoying life – I actually feel better now than I did 10 years ago!”

**Rob Lester**  
Cancer patient advocate





### Prostate cancer

There was a striking increase in the number of prostate cancer drug authorisations, which increased from zero from 2000 to 2008, to six from 2009 to 2016.

These include two authorisations for **abiraterone**, an innovative new therapy discovered by the ICR and developed in clinical trials by researchers at the ICR and The Royal Marsden – for treating men with advanced prostate cancer before and after chemotherapy (see box).

Researchers at the ICR and The Royal Marsden also led key clinical trials that brought drug authorisations for **enzalutamide**, a hormone treatment for advanced prostate cancer, and a new non-targeted cytotoxic chemotherapy called **cabazitaxel**. In addition, the EMA licensed another hormone therapy called **degarelix**.

### Cancers with few or no authorisations

For many other cancer types, including brain, oesophageal, womb, bladder, pancreatic and liver cancer, there were few or no authorisations between 2000 and 2016.

Notably, the diseases with no new licensed drugs include brain cancer, which is a disease with an acute unmet need. It is the ninth most common type of cancer in the UK, with around 11,500 people diagnosed every year.<sup>8</sup> And these numbers are rising – since the early 1990s, rates have increased by around one-third in the UK. Survival rates from brain cancer remain very low with only 14 per cent of people living for 10 years or more.

Earlier this year, brain cancer was thrust into the spotlight thanks to campaigning by former cabinet minister Dame Tessa Jowell before she sadly lost her life to the brain cancer glioblastoma. During a moving speech to the House of Lords that she gave shortly before her death, she called for more NHS patients to be given the opportunity to take part in clinical trials that have been designed with a more flexible and innovative approach.



Dame Tessa Jowell

Image attributed to Willwal, Wikimedia Commons.  
Licensed under CC-BY-SA 4.0

These include adaptive trials in which patients can be switched between different treatment arms, and basket or umbrella trials, where patients are given treatments according to their specific tumour profile rather than disease type.

Oesophageal cancer and pancreatic cancer are two other tumour types that have an acute unmet clinical need. There were no new authorisations from 2000 to 2016 for oesophageal cancer, which affects around 9,000 people every year in the UK and has a 10-year survival rate of only 12 per cent. Pancreatic cancer received only four drug authorisations. This is a disease that devastates lives – 9,800 people are diagnosed every year in the UK and only 1 per cent will survive for 10 years or more.

Other cancer types receiving no authorisations include womb cancer, which is the fourth most common cancer in women, and bladder cancer, which is the tenth most common cancer in the UK. And there was only a single authorisation for liver cancer – for the tyrosine kinase inhibitor sorafenib. Liver cancer affects around 5,700 people every year in the UK, and over the last decade incidence rates have increased by almost two-thirds.

8 Cancer Research UK cancer incidence statistics: <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type>

## 1.3

### Children are missing out on the advances seen in adult treatments

Children are seeing far slower progress in access to promising new treatments than adults.

Around 8 per cent of drugs were licensed for use in children's cancer (only eight of the total 97 drugs).<sup>9</sup> Among the 177 drug authorisations, the proportion licensed for children was even smaller – with just 10 of these, or 6 per cent, including a paediatric indication (Figure 2a).

Children's cancer survival in the UK has more than doubled in the last 40 years.<sup>10</sup> In the 1970s, a little over one-third of children survived their disease beyond 10 years, but now it's around three-quarters. Although these

dramatic improvements are welcome, those who survive are often left with serious adverse effects that can have a long-term impact on their quality of life. There is therefore an urgent need to develop new, better and kinder treatments. Survival rates in children greatly depend on tumour type. For example, 99 per cent of children with retinoblastoma and over 80 per cent of children with blood cancers will survive beyond 10 years, but this figure drops to only just over 60 per cent for children who are diagnosed with a brain tumour<sup>11,12</sup> and only 57 per cent for children with bone sarcomas.

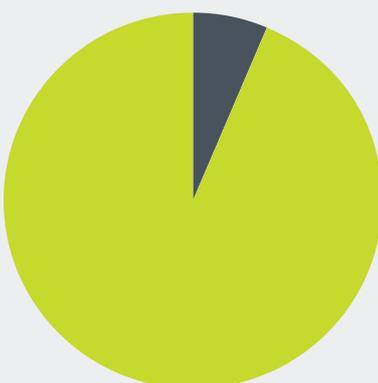
Leukaemia is the most commonly diagnosed cancer in children in the UK,

accounting for nearly one-third of all cases. These cancers were by far the most common focus for new drugs, with eight out of 10 (80 per cent) of new authorisations for either acute lymphoblastic leukaemia or chronic myeloid leukaemia (Figure 2b).

Only two paediatric cancer drugs were licensed for non-leukaemia indications. There were no drug authorisations at all for lymphomas or brain tumours – which are the second and third most common groups of cancers in children, together accounting for over one-third of all cases. New treatments are desperately needed; brain tumours, for example, are the most common cause of children's cancer death in the UK.

**Figure 2a**

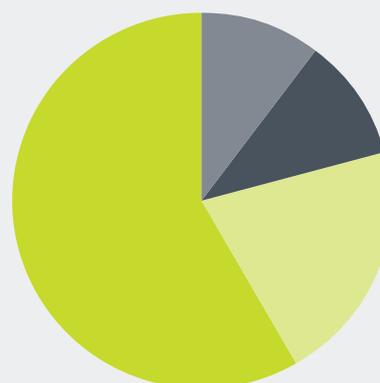
Drug authorisations for paediatric indications from 2000 to 2016



● Drug authorisations without a paediatric indication  
● Drug authorisations with a paediatric indication

**Figure 2b**

Paediatric drug authorisations by cancer type



**Haematological cancers:** ● Acute lymphoblastic leukaemia (ALL)  
● Chronic myeloid leukaemia (CML)  
**Solid tumours:** ● Osteosarcoma  
● Neuroblastoma

<sup>9</sup> We excluded the HPV vaccine which, although licensed for use in children, is designed to prevent cancers in adulthood rather than for treating paediatric cancers

<sup>10</sup> Cancer Research UK children's cancer survival statistics: <http://www.cancerresearchuk.org/health-professional/cancer-statistics/childrens-cancers#heading-Two>

<sup>11</sup> Cancer Research UK's children's cancer survival statistics: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/childrens-cancers/survival#heading-Zero>

<sup>12</sup> Statistics based on children diagnosed with brain, other CNS or intracranial tumours



### Fighting children's cancers

Lynn Lucas and her husband, also called Lynn, tragically lost their son to a rare form of cancer, rhabdomyosarcoma, in July 2000. Diagnosed at only 15 years of age, he died just three years later. The pair have since channelled their energy into creating a charity, the Chris Lucas Trust, for which they have raised more than £2.4 million to fund research at the ICR to help discover new targeted therapies for children.

"It's incredibly frustrating that children are still missing out on progress in developing new cancer drugs since we lost our son in 2000. New therapies are desperately needed to help more children and young adults with cancer survive, sparing families from experiencing the same heartbreaking loss as us."

**Lynn Lucas**  
Parent

Read about the ICR's pioneering research into children's cancers on our website:  
[www.icr.ac.uk/childhoodcancers](http://www.icr.ac.uk/childhoodcancers)

## 1.4

### The ICR is playing a prominent role in the discovery and development of new cancer drugs

The analysis reveals the major role played by the ICR in the discovery or development of many of the cancer drugs which have been licensed for use in patients since 2000.

The ICR has been directly involved in 17 of the 97 drugs licensed since 2000 – a total of 18 per cent. Our researchers were involved in different ways along the journey from the lab bench to the bedside – ranging from identifying drug targets, to creating new drugs and learning how best to use them, to leading the evaluation of drugs in clinical trials with our colleagues at The Royal Marsden. When we add in drugs developed in clinical trials led by close colleagues at The Royal Marsden with academic positions at the ICR, we have collectively been involved in 22 of the 97 drugs – or nearly one-quarter of all cancer drugs licensed since 2000.

The ICR has been involved in some of the most innovative and exciting advances in treatment in the last two decades, often working with commercial partners to take treatments to patients. As well as discovering **abiraterone** and developing it for patients with The Royal Marsden (see box on page 10), we pioneered the genetic targeting of the ovarian cancer drug **olaparib**, which became the first ever cancer drug to be approved for patients that exploits an inherited genetic fault.

## Examples of ICR involvement

### PARP inhibitors

Scientists at the ICR demonstrated that drugs called PARP inhibitors could be particularly effective in cancers with BRCA mutations. Our researchers then ran clinical trials with The Royal Marsden which led to the first PARP inhibitor, **olaparib**, receiving authorisation in 2014, transforming the outlook for ovarian cancer patients with BRCA mutations.

Our science underpinned the development of olaparib. The story began back in the 1990s, when a team of scientists at the ICR identified the BRCA2 gene – which along with BRCA1 is mutated in many inherited breast and ovarian cancers. ICR researchers then worked with biotechnology company KuDOS to show that targeting a DNA repair protein called PARP was a highly effective way to kill cancer cells with a faulty BRCA gene.

The ICR team continued to contribute to the refinement of PARP inhibitors, working with The Royal Marsden and manufacturer AstraZeneca on early clinical trials of olaparib, with subsequent larger trials leading to the drug's authorisation. So far, more than 20,000 women around the world have received this drug to treat their cancer. Three other PARP inhibitors have also now been licensed.

### BRAF inhibitors

The ICR played a major role in characterising the BRAF protein and its role in cancer, with our work underpinning the discovery of BRAF inhibitors. In 2001, ICR scientists co-discovered that the BRAF gene is mutated in several cancer types, including approximately 50 per cent of malignant melanomas.

This discovery was followed by ICR scientists revealing the detailed molecular structure and function of the mutant protein, leading onto the design and development of inhibitors of mutated BRAF. Between 2000 and 2016, **vemurafenib** and **dabrafenib** both received authorisation for treating melanoma.

### Abiraterone

One of our biggest success stories is with the prostate cancer drug **abiraterone**, which now benefits hundreds of thousands of men worldwide. It was discovered by scientists at the ICR and developed in clinical trials led by researchers at the ICR and The Royal Marsden (see box on page 10 for full story).

### Palbociclib

A phase III clinical trial led by researchers at the ICR and The Royal Marsden found that novel cancer drug **palbociclib** in conjunction with hormone treatment could delay the onset of advanced breast cancer and substantially extend the lives of patients. This is a 'first in class' drug because of its novel mechanism of action, blocking two proteins – CDK4 and CDK6 – that help cancer cells divide. The drug received authorisation in 2016 for the treatment of women with advanced breast cancer alongside hormone therapy.

### Other small-molecule drugs

Many of the medicines that ICR scientists have been involved with are drugs that are cleverly designed to target specific genetic faults within cancer cells. As well as those mentioned above, these include **afatinib** (an EGFR/multi tyrosine kinase inhibitor), **idelalisib** (a PI3K inhibitor) and **sorafenib** (a multi tyrosine kinase inhibitor).

The anti-angiogenic drug **sunitinib** is designed to target several protein kinases involved in tumour blood vessel growth, receiving authorisations for treating patients with stomach, pancreatic and kidney cancers.

## Extending lives

Anne Goward, 54, is from Canvey Island. In 2015, she was diagnosed with ovarian cancer. Sadly, following surgery and chemotherapy, her disease returned two years later. With genetic testing identifying that she carried a BRCA1 mutation, she started taking olaparib in March 2018.

"Olaparib worked amazingly for me, and really quickly. The fact it worked immediately put my mind at rest that it will extend my life. I'm hopeful that I'll have a few years chemo free and feeling good with fewer side-effects. I am so thankful the drug exists and feel very lucky to have been able to get it."

### Anne Goward

Cancer patient advocate





## Discussion: What drugs are being licensed for cancer?

Our analysis finds that rapid advances in cancer research are driving a big increase in the numbers of new cancer drugs that are being approved, often with the involvement of the ICR's world-leading cancer biology, drug discovery and drug development teams. But we also identify stark differences in the rate of development of new cancer drugs between different tumour types, with cancers of high unmet need and children's cancers among those missing out.

We could and should be doing better. We may be seeing more cancer drugs coming through, but the rate of discovery of genuinely innovative treatments still lags behind the unprecedented advances we have seen over the last decade in our understanding of the genetics and biology of cancer. That is especially the case for hard-to-treat cancers, such as brain, pancreatic and oesophageal cancer – all relatively common forms of the disease that continue to claim far too many lives.

There are a range of reasons why we are seeing relatively little progress in cancers like these. Historically, there has been less funding available for research in these cancers, and even where this is getting better it takes a long time for the research to catch up. Some researchers may also be attracted to cancer types where there is a track record of success, where they can be confident of being able to make a difference for patients. There may also be inherent difficulties in studying some hard-to-treat cancers, such as access to tumour material where cancers are often inoperable, or potentially greater challenges in running clinical trials. Drug companies may prefer to focus on the most common



cancer types because of the higher potential rewards and lower risk of failure.

Tackling these issues won't be easy but it must be done. It will be critical for academic organisations, which can afford to take greater risks than industry and are less driven by the need for financial return, to play a more active role in leading the search for innovative new drugs for these hard-to-treat cancers. Although there are challenges, there are also unexploited opportunities. Current estimates reveal that approved drugs are available for only around 5 per cent of the 500 or so known cancer-causing genes. If we want to make big advances in treating cancers that are not currently treatable, drug discovery research will need to look beyond the low hanging fruit to focus on new and potentially challenging drug targets.

For paediatric cancers, far too few drugs are being developed. It is uncommon for cancer drugs to be created specifically for children since paediatric cancers are rare and do not offer pharmaceutical companies the kind of return they see

with many adult cancers. And neither are children benefiting from drugs originally developed for adult cancers. The lack of paediatric cancer trials restricts or delays access for children to the latest cancer treatments, some of which could be of significant benefit to them.

To improve the situation so children can gain the same kind of access to cancer treatments as adults do, there need to be improved financial incentives for creating drugs specifically for children, and new collaborative models of funding involving government, academia, charities and industry for taking these treatments forward into clinical trials. In addition, we need to ensure that pharmaceutical companies that have developed drugs for adults also evaluate them for treating children where the mechanism of action is relevant. At the moment, a loophole in European drug regulations means it is too easy for pharmaceutical companies to opt out of running clinical trials in children, even where there is evidence that a drug could benefit them.

# 2 How long does it take for patients to get new cancer drugs?

We examined the data to find out how quickly patented discoveries for cancer are moving through the drug development pipeline, EMA authorisation and the NICE appraisal process.

## 2.1

### It is taking longer to get drugs to patients

The time it is taking to evaluate drugs in clinical trials and make them available for NHS patients is increasing.

Between 2000 and 2008, it took an average of **12.7 years** to take a patented discovery through drug development and licensing to final NICE approval. Between 2009 and 2016, the time to final NICE approval increased to **14.1 years** (Figure 3).

So despite a range of initiatives to speed up drug development, licensing and NICE evaluation, it is taking a year and a half longer to get drugs to NHS patients now than it was a decade ago.

We next examined each stage in detail to identify at which points during drug development, licensing and appraisal the delays were occurring.

#### Our approach

For each cancer drug licensed by the EMA, we calculated the average time in years (to the nearest year) between:

- the filing of the patent and it entering phase I clinical trials.<sup>13</sup>

For cancer drug authorisations, we calculated the average time in years (to the nearest year) between it:

- entering phase I clinical trials and receiving its first EMA authorisation.

For each of the drug authorisations that had undergone a **full NICE appraisal**<sup>14</sup> at the time of our analysis, we calculated:

- the average time in years (to the nearest year) between the drug's patent filing date and NICE finishing its appraisal
- how many months after a drug received EMA authorisation that NICE began its appraisal (counting negative numbers as zero)
- how long it took NICE to complete the appraisal, counting this from the start date of the final scoping document to the date of the Final Appraisal Determination.

<sup>13</sup> We carried out analysis on each drug, excluding those with no publicly available phase I data or other anomalies (for example, if the phase I trial was completed before the patent was issued or where a drug had been repurposed as a cancer medicine many years after its initial licensing).

<sup>14</sup> We included all indications that had a Final Appraisal Determination issued by NICE at the time of our analysis.

## 2.2

### It is getting no faster to take drugs from patent to phase I trial

There has been no real change in the time it takes to progress drugs from the filing of patents through preclinical development and to the initiation of phase I trials. The time from the patent to the start of the phase I trial rose only very slightly from **3.5 years** from 2000 to 2008 to **3.6 years** from 2009 to 2016.

## 2.3

### Developing drugs in clinical trials is getting slower

The average time from the start of a phase I trial to EMA authorisation is increasing – going up from **7.8 years** between 2000 to 2008 to **9.1 years** from 2009 to 2016 (Figure 4). That suggests that there are delays arising in setting up and running clinical trials, progressing from one trial to the next, and gaining authorisation based on the findings. This is worrying, since clinical trials should be getting faster as targeted cancer drugs can be assessed in smaller, smarter trials, and the EMA has committed to licensing drugs earlier in their clinical development.



Figure 3

Average time from patented discovery to NICE Final Appraisal Determination for all 107 drug authorisations that had undergone full NICE appraisal (36 from 2000 to 2008; 71 from 2009 to 2016)

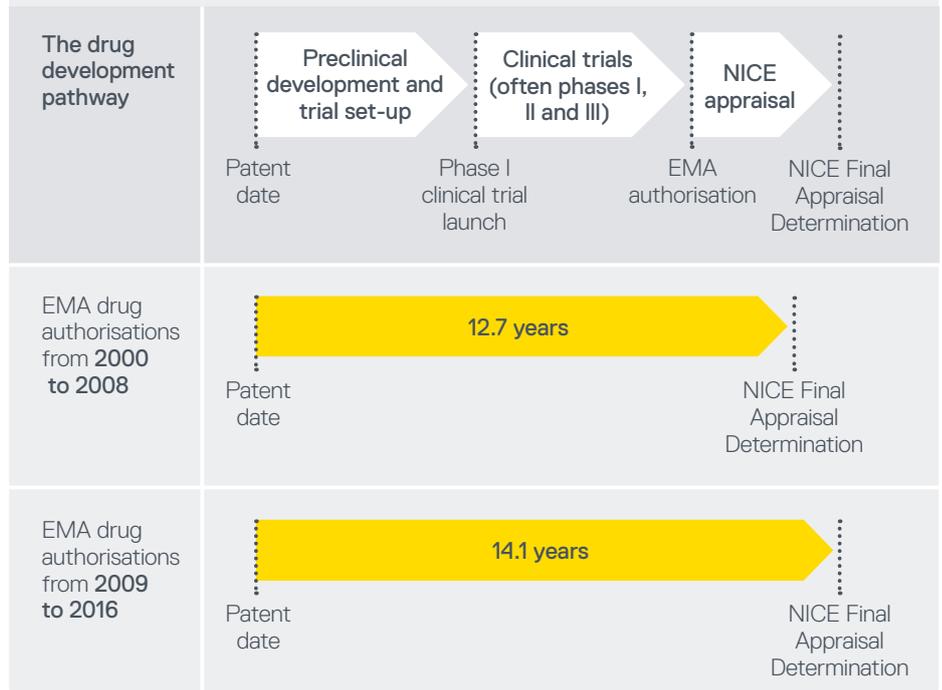


Figure 4

Average time for all 177 drug authorisations from phase I trial launch to receiving an EMA authorisation.



## 2.4

### NICE is starting its appraisals sooner, but they are still taking too long

NICE is now starting its appraisals for new cancer drugs much sooner after EMA authorisation – often even before the licensing process is complete. But unfortunately, NICE is still taking too long to carry out its appraisals of new drugs.

Since 2009, NICE has successfully reduced the lag time between EMA authorisation and the beginning of its appraisal from a mean of **21 months** to **6.5 months**. When we examined the median length of time, we found that this has decreased from **13 months** from 2000 to 2008 down to **zero** from 2009 to 2016, as NICE is often beginning its appraisal before the EMA has licensed a drug.

However, although NICE is off the mark more quickly in starting evaluations, it is not meeting its commitment to speed up the time it takes to evaluate drugs. It took an average of **16.0 months** to get a drug through NICE approval from 2009 to 2016, which is barely shorter than the **16.7 months** from 2000 to 2008.



## 2.5

### Delays in clinical trials seem to be responsible for drugs taking longer to reach patients

The substantial increase in the average time taken from when a drug is patented to gaining approval by NICE appears to be mainly as a result of delays in taking drugs through clinical trials and licensing. This is despite a range of initiatives that were supposed to speed up the time it takes to gain access to new cancer drugs – such as allowing drugs to be licensed based on data from smaller, more targeted phase II trials.

Some drugs did progress from patenting through trials to licensing and NICE approval more quickly. For example, the drug **nivolumab** is a highly innovative immunotherapy that blocks a protein called PD-1 on the surface of certain immune

cells. Patented in 2007, it received its first licence in 2015 – to treat patients with advanced melanoma – and was approved by NICE in 2016 for use on the NHS. This was helped by its inclusion in the early access to medicines scheme (EAMS), which was introduced to accelerate drug approvals based on more flexible standards of evidence.

But other drugs took much longer to reach patients. For example, **mifamurtide** took 20 years from the time a patent was filed to approval by NICE for treating osteosarcoma. And it took 22 years from the patent filing date for **trabectedin** to be licensed and approved by NICE for treating patients with advanced soft tissue carcinoma.



## Discussion: How long is it taking to get drugs to patients?

There is a consensus among the public, politicians, policy makers and cancer researchers that it is taking too long to get innovative new cancer drugs to patients. Unfortunately, our analysis finds that despite the introduction of various initiatives aiming to accelerate drug development, licensing and appraisal – such as the UK's early access to medicines scheme (EAMS) and the EU's adaptive pathways – cancer drugs are still getting to patients too slowly. Indeed, our report finds that it is now taking longer to get drugs through clinical trials and into the NHS than it was a decade ago.

We are concerned that at least part of the reason for the increase in the time taken to get drugs to patients is that researchers are facing excessive bureaucracy in setting up and gaining approval for clinical trials. The regulation of clinical trials is governed by the EU Clinical Trials Directive, although a new EU Clinical Trials Regulation will shortly be coming into force. The current directive has proved highly controversial, with many organisations insisting that it has made clinical trials more expensive and bureaucratic. It is essential that the new regulation is monitored closely when it is implemented to ensure it doesn't prove similarly onerous.

New targeted treatments usually work in subsets of patients rather than everyone with a particular cancer type. So in theory, precision medicine should allow for smaller, more focused trials, making drug development faster and cheaper. But we are failing to see the faster trials we would expect if drug companies were adopting a smarter, more streamlined approach.

The pharmaceutical industry has preferred to stick to tried and tested ways of steering a new drug through to the market, perhaps because they believe the regulatory environment does not support a change in approach. Indeed, we are concerned that pharmaceutical companies are becoming more risk averse and taking longer to make decisions over which drugs to progress.

Academic organisations need to play a leadership role in encouraging industry to adopt more innovative approaches. We should be using innovative clinical trial designs to generate findings more quickly and cheaply, and routinely using 'biomarker' tests to select patients for treatment based on the genetics and biology of their tumours. And we should be assessing new cancer drugs at an earlier stage in a patient's cancer, rather than as currently in late-stage disease which is often already drug resistant. As drugs are increasingly assessed in patients who have been selected because they are most likely to respond, it should be possible to demonstrate benefit in smaller, faster clinical trials, since the expected effect size will be much greater.

It is also essential that the EMA and NICE play their part in speeding up the path of new drugs onto the market and into the NHS. We need to see the EMA learn from best practice at bodies elsewhere in the world – such as the Food and Drug Administration in the US – in taking a faster, more flexible approach to assessing evidence. The EMA and NICE should increase the variety of measures they use to judge a drug's effectiveness such as by

including evidence gathered in early-phase trials and placing more weight on measures such as patients' health-related quality of life and progression-free survival. NICE could approve drugs based on measures such as these – allowing treatments to become available to patients much more quickly after the completion of smaller phase II trials.

NICE also needs to do more to meet its commitment to approve medicines more quickly. There has been some progress – NICE is now beginning its appraisals much earlier, in many cases before a drug has been licensed by the EMA. But the process of evaluation itself is still taking too long. The average length of time for NICE to complete an appraisal has barely fallen over the time period of our analysis – it was 16.7 months from 2000 to 2008, and 16.0 months from 2009 to 2016. NICE needs to dedicate the resources required to take drugs through appraisal much more quickly. In particular, it needs to review whether it is possible to hold price negotiations earlier in the evaluation, since discussions over price are routinely causing delays between NICE's draft and final decisions.



# 3 Are cancer drugs being made available to NHS patients?

We set out to find out whether drugs licensed through the EMA are receiving NICE approval for use on the NHS, and whether a drug's degree of innovation has any impact on the outcome.

## Our approach

For each of the drug authorisations that had undergone a full NICE appraisal at the time of our analysis, we assessed:

- whether the drug received a positive recommendation by NICE
- whether its degree of innovation (see Appendices for definitions) has an impact on the outcome of its appraisal.

We also analysed the drug authorisations that had not undergone a full NICE appraisal at the time of our analysis, assessing the degree of innovation and availability to patients of these drugs.

## 3.1

### Less than half of licensed drug indications have been approved by NICE for patients

At the time of our analysis, NICE had completed its appraisal for 107 of the total of 177 drug authorisations. Of these, 71 received a positive recommendation. So overall, from 2000 to 2016, less than half (40 per cent) were recommended for NHS use.

Among the drugs which had not been approved, some were turned down, some had never been assessed, and for others their assessment was not complete at the time of our analysis. In the following sections, we explore these issues in more depth.





## 3.2

### Of the drugs NICE has assessed, two-thirds were approved

NICE recommended around two-thirds (66 per cent) of all the cancer drugs that it appraised. This proportion has remained consistent over the analysis period, at 67 per cent between 2000 and 2008, and 66 per cent between 2009 and 2016 (Table 2). In 2011, the Cancer Drugs Fund (CDF) was set up to provide access to some additional cancer drugs that had not been approved by NICE.

Table 2

Outcome of completed NICE appraisals for drugs licensed by the EMA from 2000 to 2008, and from 2009 to 2016. In the latter period, the CDF was launched, enabling more drugs to become accessible to NHS patients.

#### Outcome of NICE appraisal

	2000-08		2009-16		TOTAL	
Recommended	24	67%	47	66%	71	66%
Not recommended	12	33%	19	27%	31	29%
CDF	–	0%	5	7%	5	5%
<b>TOTAL</b>	<b>36</b>		<b>71</b>		<b>107</b>	

### 3.3

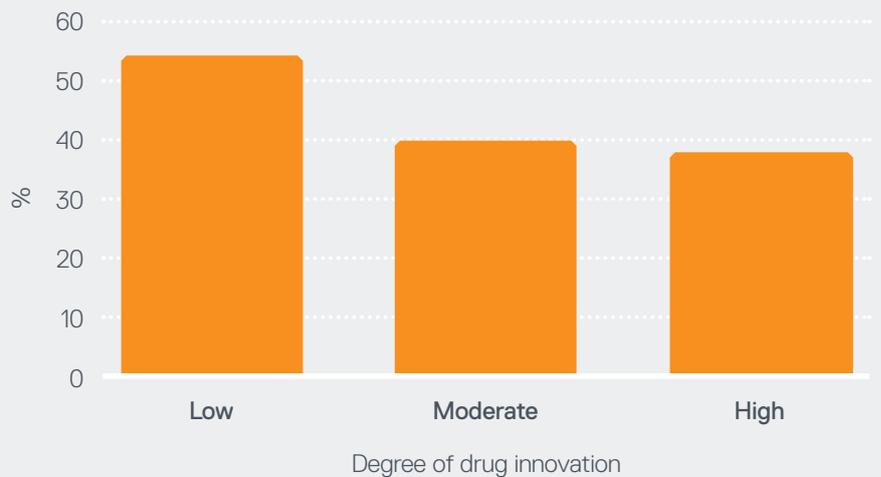
#### A highly innovative drug is less likely to have been approved by NICE than a low-innovation drug

Highly innovative drugs, which attack cancers in new ways, were less likely to have been approved by NICE for use in the NHS than lower-innovation medicines. Only 38 per cent of authorisations for highly innovative cancer drugs – defined as those with a novel mechanism of action or a new class of chemical structure offering clear benefits over what existed before – had received a positive recommendation from NICE at the time of our analysis (Figure 5). That compares with 40 per cent of drugs classed as moderately innovative – which includes many ‘me too’ drugs with similar mechanisms of action to others already on the market – and 53 per cent of low-innovation drugs.

Once NICE evaluates a drug, the chance that it will say yes is essentially the same whether it is highly innovative or not. NICE approved 69 per cent of highly innovative drugs it appraised, compared with 63 per cent of moderately innovative drugs and 67 per cent of low-innovation drugs. But only 68 per cent of authorisations for highly innovative drugs had been assessed by NICE, compared with 73 per cent of moderately innovative authorisations and 87 per cent of low-innovation authorisations (Figure 6).

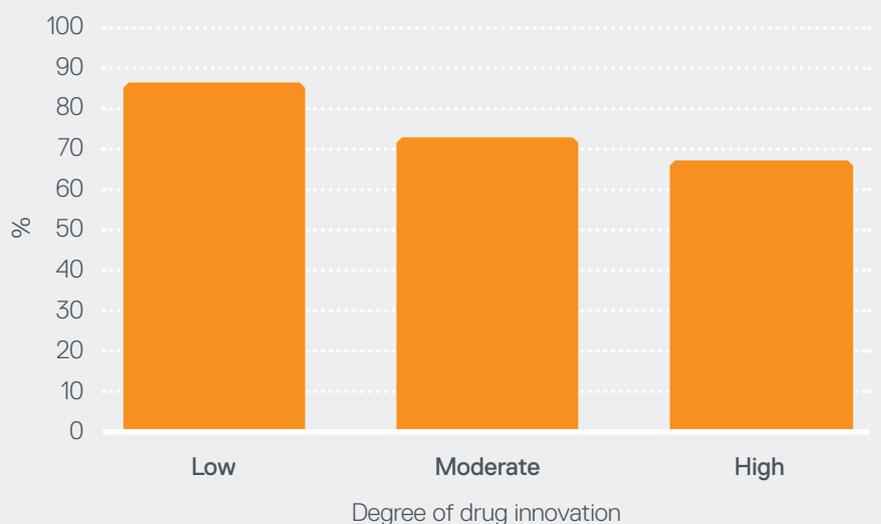
**Figure 5**

The proportion of 107 drug authorisations from 2000 to 2016 that had received a positive recommendation from NICE after undergoing a full appraisal – categorised by their degree of innovation.



**Figure 6**

The proportion of 177 drug authorisations from 2000 to 2016 that had started a NICE evaluation at the time of our analysis, categorised by their degree of innovation.



### 3.4

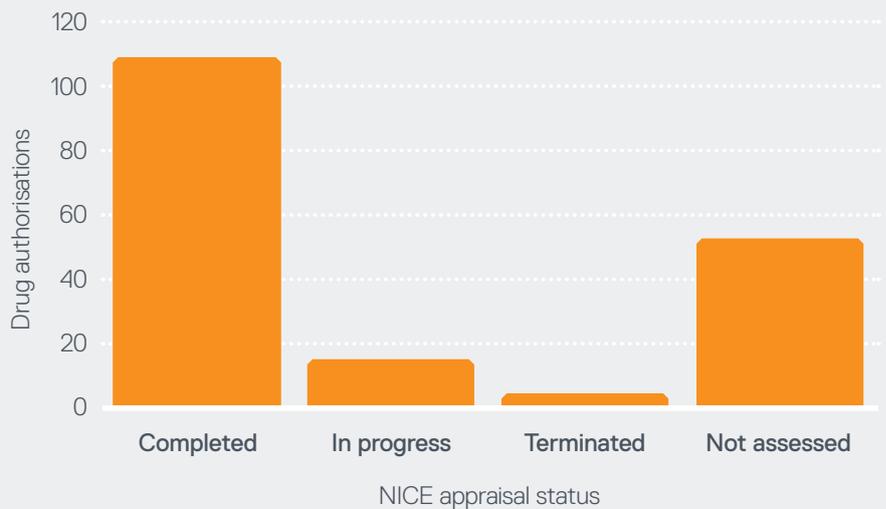
#### Some drugs have ‘fallen through the gaps’ and missed out on a NICE appraisal

In 2016, NICE committed to appraise all new cancer drugs when it took over responsibility for the Cancer Drugs Fund (CDF). However, at our point of analysis, until the end of 2016, we found that a worrying proportion of drug authorisations had not been appraised by NICE at all, meaning that patients were missing out on potentially effective new treatments.

NICE had completed appraisals for 107 of the 177 drug authorisations at the time of our analysis. Of the remaining 70 that had not yet had an appraisal completed, 16 appraisals were still in progress at the time of analysis and three had been terminated early.<sup>15</sup> Some 51 drug authorisations (29 per cent) had not been appraised at all by NICE at the time of our analysis, meaning that a significant number of new treatments may have either missed out on appraisal altogether or been subjected to substantial delays before reaching patients (Figure 7).

Figure 7

NICE appraisal status reached by the 177 cancer drug authorisations from 2000 to 2016, at the point of our analysis.



<sup>15</sup> For example, the appraisal of bevacizumab for the treatment of non-small-cell lung cancer was terminated due to no evidence being submitted from the manufacturer or sponsor of the technology.

## 3.5

### Although some drugs were accessible through the CDF, the majority were unavailable for patients

At the time of our analysis, the CDF was available to provide access to some of the drugs which had missed out on an NICE appraisal. Of the 51 drug authorisations not appraised by NICE, 10 were funded for NHS use through the CDF.<sup>16</sup> However, drugs were not available on the NHS for the remaining 41 authorisations, raising the prospect that patients might either miss out on the treatments entirely, or experience substantial delays in doing so.

Among the 51 drug authorisations not appraised by NICE, 32 – or 63 per cent – were for highly innovative medicines. Examples of drugs which cannot be accessed by NHS patients, or where there have been major delays, include:

- **pazopanib**, a tyrosine kinase inhibitor that was licensed in 2012 for treating patients with soft tissue sarcomas which has still not been appraised by NICE
- **bevacizumab**, a monoclonal antibody that received authorisation for use as a treatment for cervical cancer in 2015 but has not been appraised by NICE
- **lapatinib**, a small-molecule HER2 inhibitor that was licensed in 2008 for the treatment of patients with advanced metastatic breast cancer in combination with trastuzumab (Herceptin) but has still not been appraised by NICE for this indication.

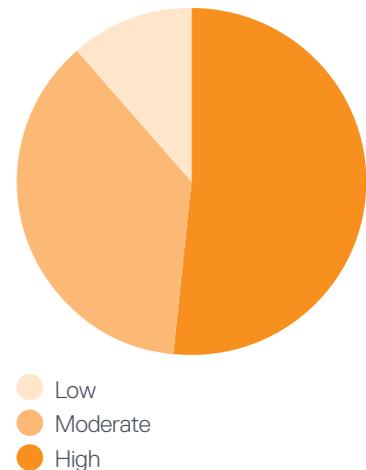
#### Innovation in new cancer drugs

Of all the cancer drugs licensed by the EMA from 2000 to 2016, over half – 50 out of 97 (51 per cent) – were classed as highly innovative (see Appendices for criteria).

The proportion of drugs with the highest degree of innovation is increasing over time. Drugs that are categorised with the highest degree of innovation (defined as having a novel mechanism of action or a new class of chemical structure offering clear benefits over what existed before) have increased from eight of the 30 drugs (27 per cent) authorised by the EMA from 2000 to 2008, to 22 of the 66 drugs (33 per cent) authorised from 2009 to 2016.

Figure 8

Drugs licensed by the EMA from 2000 to 2016 categorised by their degree of innovation.



<sup>16</sup> The NHS England website was used as the source for a drug's inclusion into the Cancer Drugs Fund.



## Discussion: Are new cancer drugs reaching NHS patients?

At the ICR, we believe the NICE drug evaluation system should provide NHS patients with the fastest possible access to the most exciting new treatments – drugs that are not only cost-effective, but also highly innovative. By supporting innovation, NICE can give patients treated on the NHS the best possible chance of a good outcome from their disease. And in addition, it can reward pharmaceutical companies for the risk taking required to deliver step-change improvements in treatment, encouraging the creation of the next generation of novel drugs.

The ICR supports the role of NICE in ensuring public resources are spent on treatments that are good value for money. We do however believe its systems are in urgent need of reform.

Our analysis finds that NICE could be doing more to bring the best, most innovative treatments to patients. NICE committed in 2016, when it took over responsibility for the CDF, that it would appraise all new licenced indications for cancer drugs. But our findings raise concerns that a significant proportion of treatments from before this date may have slipped through the net or suffered significant delays in their appraisal. Only 60 per cent of cancer drug authorisations had been fully evaluated by NICE at the point of our analysis. In part, this will be a product of the way we conducted the analysis – assessing the progress of drugs at a particular point in time (until the end of 2016) when some will only recently have been licensed.



However, it still suggests that NICE needs to dedicate the resources required to clear the backlog of cancer drugs that have been waiting for appraisal since its job expanded when it took over the CDF. It is important that NICE meets its commitment to evaluate all new cancer drugs as quickly as possible.

Our analysis also finds that highly innovative treatments are particularly likely to have missed out on a NICE appraisal. This suggests that the NICE appraisal system, rather than encouraging innovation, is not doing enough to expedite the progress of the most highly innovative drugs.

Innovation is vital to deliver step-change improvements in patient care, by attacking cancer in brand new ways that can overcome cancer evolution and drug resistance. In order to encourage innovation, the concept needs to be embedded at every stage of drug discovery, development, licensing and appraisal. There is a clear need for NICE to fast track appraisals of the most

innovative cancer drugs and to take into account their degree of innovation in making a decision on whether they should be approved for patients on the NHS. Otherwise, we will continue to see 'me too' drugs approved ahead of genuinely pioneering ones. Once a drug has been turned down it becomes very difficult to find out what it might be capable of when used in combination or earlier in the course of disease, so getting a new drug approved is a really important first step.

We believe NICE's limited definition of innovation, which is based on effectiveness in areas of unmet need rather than scientific innovation, fails to encourage the development of genuinely innovative drugs that could help combat drug resistance. We agree that meeting unmet need is vital, but believe the evaluation process must also assess whether a cancer drug is novel in its design or its drug target, unique in a rare disease, or innovative in the way it's used or delivered. If the answer is yes, a drug should be prioritised by NICE for rapid evaluation and its level of innovation taken into account.

# Conclusions

Our report highlights the progress that is being made with discovering exciting new cancer medicines. But it also draws attention to key challenges that will need to be overcome to ensure more patients can benefit from these advances.

Overall, our analysis finds that huge advances in cancer research are helping to fuel the discovery and development of increased numbers of cancer treatments. Drugs like abiraterone for men with prostate cancer, olaparib for a subset of ovarian cancers and nivolumab for melanoma are giving patients with advanced cancer new treatment options, which are not only extending survival but also greatly improving quality of life. However, we also found that there are substantial barriers to taking innovative new drugs and combination treatments to patients, and that not enough is being done to encourage radical innovation in drug discovery, development and approval.

We face some major challenges:



## Many cancer patients are missing out on new drugs

Survival remains poor for many cancer types, and our analysis finds that cancers of high unmet need are missing out on the rush of new cancer drugs seen in other tumour types. We need to do more to ensure that patients with cancers of high unmet need benefit from the same kind of concerted research efforts that have delivered such progress in other cancer types such as breast, skin and blood cancers.



## More drugs are needed for children's cancers

In paediatric cancers, very few targeted drugs are coming through to the clinic – and there is an urgent need to ensure children with cancer begin benefiting from advances in research in the same way that adult patients already are.

We need stronger incentives for pharmaceutical companies to develop new treatments specifically for children, and updated regulations to ensure that many more adult cancer drugs are evaluated in paediatric clinical trials.



## It is taking far too long to deliver new cancer drugs to patients

It is essential to get cancer drugs to patients more quickly. However, despite a range of new initiatives aimed at speeding up drug development, our report shows that the situation is getting worse rather than better. We need to combat excessive bureaucracy in setting up and running clinical trials and to take a more flexible approach to drug licensing. We also need to encourage the pharmaceutical industry to be less risk averse in its decision making, and to embrace the use of smarter, faster trials.



**We need to do more to encourage radical innovation**

The biggest challenge we face in defeating cancer is the fact we are up against a moving target – cancer is genetically diverse, adaptable and adept at evolving resistance to treatment. If we are to overcome cancer’s ability to adapt and evolve, we need real innovation – drugs with new mechanisms of action which can deliver step changes in cancer outcomes, rather than simply ‘me too’ treatments which provide only incremental gains. But the drug discovery and development ecosystem does not sufficiently support the high-risk research that is required for true innovation. We need to encourage innovation at every stage, including in the design and regulation of clinical trials, and in drug licensing and evaluation by NICE, to give much greater priority to innovative drugs.

The progress needed to deliver big improvements in cancer survival is eminently achievable, but it will rely on creative risk taking in drug discovery and development. We need to find ways of encouraging this radical innovation, and ensuring that the advances it produces reach patients as quickly as possible – so that more people with cancer live longer, healthier lives.



“Big leaps forward in cancer survival are achievable, but only if we find ways to better harness our increased scientific knowledge of cancer and accelerate the delivery of innovative new drugs to patients.”

**Professor Raj Chopra**  
 Head of the Division of Cancer Therapeutics and Director of the Cancer Research UK Cancer Therapeutics Unit at the ICR

# Appendices

## – methods and resources

### Innovation criteria

Our innovation matrix (Table 3) is an adapted version of one previously published in the *BMJ Open*.<sup>17</sup> We developed the matrix in consultation with scientific experts at the ICR. We then performed a thorough literature search to establish if each drug had any characteristics considered innovative under our criteria.<sup>18</sup> We applied the innovation matrix to each drug and a level of innovation was assigned based on a drug's most innovative property.

**Table 3**  
The ICR's innovation matrix

Degree of innovation	Category	Type of innovation	Example
High	H1	New target or novel mechanism	Palbociclib
	H2	Novel application	Thalidomide
	H3	Improved identification of those who are likely to benefit or be harmed (pharmacogenetics, biomarkers)	Cetuximab
	H4	Novel class of compounds (in an area of high unmet need)	Nivolumab
Moderate	M1	Fewer adverse effects or interactions	
	M2	Improved delivery or formulation	Afatinib
	M3	Improved pharmacokinetics	Tegafur
	M4	Novel class of compounds (not in an area of high unmet need)	Cabazitaxel
Low (health related)	L1	Novel structure (if it confers a therapeutic advantage)	Pomalidomide
	L2	Improved production	
Low (non-health related)	L3	Novel structures that do not confer a clinical benefit e.g. stereoisomers	Afibercept
	L4	Improved delivery or formulation	Capecitabine

<sup>17</sup> Ward DJ, Slade A, Genus T, et al How innovative are new drugs launched in the UK? A retrospective study of new drugs listed in the British National Formulary (BNF) 2001–2012 *BMJ Open* 2014;4:e006235.

<sup>18</sup> Sources include the European Public Assessment Reports, NICE technology appraisal documents, ASCO clinical guidelines, FDA breakthrough therapy approval and scientific literature.

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## Patent date

We sourced patent data for each drug through the European Patent Office and the US Food and Drug Administration's (FDA's) Orange Book, recording the patent priority date, the date a patent was filed. Where multiple patents were filed, we used the first one.

## Licensing

We sourced information about a drug's initial authorisation and subsequent licensed indications from the EMA medicines database.

## Clinical development

We searched the European Public Assessment Report and the FDA licensing dossier for details of registration trials and cross-referenced these with clinicaltrials.gov. Where details of trials were not publicly available, we searched individual drug company registers of clinical trials and the SciFinder database for conference abstracts and unpublished trials. The drug's registered name was cross-referenced with any previously used names and synonyms.

## Paediatric indications

We used the European Public Assessment Reports from the EMA website as the source of any paediatric investigation plans and whether the drug was licensed for use in children. We carried out a search of the clinical trials registry (clinicaltrials.gov) to determine whether a drug was tested for paediatric use.

## NICE appraisal

We used a drug's appraisal documents on the NICE website to determine whether a drug had been appraised by NICE and its outcome. We defined the start date as the date of the Final Scope and the end date as the date of the Final Appraisal Determination.

## CDF

We used the NHS England and NICE websites as the source for a drug's inclusion on the Cancer Drugs Fund.

## ICR involvement

We carried out a literature search to determine if the ICR was instrumental in the discovery of a drug – or for an underlying advance in scientific understanding that led to the drug being discovered and developed, for example leading a study that identified the target for the drug or revealing the protein structure to allow for structure-based drug discovery. We also examined drug patents to determine whether a member of ICR staff was listed as an inventor, the ICR was listed as an applicant, or whether the organisation was cited on the patent as having carried out supporting research.

To identify the ICR's involvement in clinical trials, we searched the EMA's European Public Assessment Report to find details of clinical trials cited in a drug's registration to find whether these were led by researchers at the ICR or The Royal Marsden. We included trials where a member of staff at the ICR or The Royal Marsden led the trial for any of the approved indications included in the data. We did not include drugs where we led trials in indications which were not yet licensed at the time of analysis.

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CANCER  
RESEARCH  
UK

breast cancer  
**now**



The ICR is grateful to its clinical partner The Royal Marsden, with which it has worked on the development of many innovative cancer drugs.

*The* ROYAL MARSDEN  
NHS Foundation Trust

We also extend our gratitude to everyone else who has supported this project.

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## Declaration of interests

The ICR works with a wide range of commercial partners on drug discovery and development, and in some cases benefits from collaboration and invention income.

## Find out more

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