IMPACT OF NEW PERSONALISED CANCER TREATMENTS



Impact of new personalised cancer treatments

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Executive summary

Introduction

- We are currently in a transition era towards personalised medicine. Biomarkers are being used to redefine cancer more precisely across several tumour groups, helping to improve patient outcomes by making more personalised cancer treatment selections. The number of markers has increased dramatically in the last decade.
- Advances in genomics, genetic tests and targeted drugs will enable increasing personalisation of cancer treatments. However, if a treatment is personalised this does not necessarily mean that it is accompanied with the complimentary personalised care.
- Immunotherapy is the newest wave of cancer treatment. The use of these drugs is still limited to specific indications and clinical trials, and they present different side effects and largely unknown long-term effects.
- A Genomics medicine service is being rolled out in England from October 2018 to April 2019 as a result of the 100,000 Genomes project.

Cancer treatment development and use

- There are an increasing number of targeted treatments in late stage development, at over 700 molecules by the end of 2017, an increase of 64% since 2007.
- Rates of chemotherapy, radiotherapy and surgery vary for different groups of patients in England. Factors including age, deprivation, ethnicity, stage of cancer and gender can influence treatments received by cancer patients.

Policy

- The main stages that lead to cancer patients using new drugs are Research, Authorisation, Recommendation and Use. The
 main bodies involved are the European Medicines Agency (EMA), Medicines and Healthcare Regulatory Agency (MHRA)
 and National Institute for Health and Clinical Excellence (NICE), with some variation in the devolved nations.
- Drug approval processes vary in the devolved nations, with all following NICE decisions to a degree, but also with Scotland and Wales having their own regulatory bodies and CDF equivalents. These differences can lead to variation in access to cancer treatments across the UK.
- Brexit has the potential to impact the delivery of new cancer treatments, from initial research to delivery in the NHS. Below is a summary of the current processes and the possible areas Brexit will impact.



Executive summary (cont.)

Clinical trials

- There is increasing **pre-selection on clinical trials based on biomarker status**. This, alongside an increased focus on research into rare cancers, has led to:
 - a decrease in late-stage trial duration;
 - a decline in average number of patients enrolled.
- Although the use of Patient Reported Outcome Measures (PROMs) in clinical trials is widespread, there is little published information available on Patient Reported Outcomes (PROs). There is existing research- based guidance on best practise and how to measure PROs.
- The increasing use of Progression Free Survival (PFS) as a surrogate marker for Overall Survival (OS- the 'gold standard') clinical effectiveness in trials has been challenged. The term PFS may also be poorly understood by patients and oncologists.
- There are a number of public misconceptions about clinical trials, including that 66% of the public think you have to be invited to participate in a clinical trials. This is a major misconception and could limit rates of enrolment in clinical trials, particularly as only 29% of cancer patients had researched discussed with them (England, 2016).

- There are also several other barriers in the decision making process to enrol in clinical trials, including structural, clinical, attitudinal and demographic factors. The main motivations for participation in clinical trials is for personal benefit and for altruistic reasons. Patients on early stage clinical trials may be motivated by tumour shrinkage or a cure, when the response rate for these early trials is typically very low.
- Treatments and clinical trials can cause further fear anxiety for cancer patients; this can act as a barrier to clinical trial participation. It is also possible that patients on clinical trials may not get the same level of support as on standard treatment.
- For clinical trials, there **tends to be a bias towards younger people, towards white people and towards richer people**. Apart from being potentially discriminatory, this means that we may be missing some of the impacts of new and personalised treatments on different groups.

Experience of people living with cancer (PWLC)

- There is very limited research that addresses the question of what PWLC understand of the concept of personalised medicine. However, this is a topic area that Macmillan's Research Grant Scheme is funding in 2018 in order to start to build a research base on this subject.
- The majority of patients **understand** the concept of **testing a tumour to inform treatment** decisions, however physicians over-estimate their willingness to delay treatment to allow for additional tumour testing.
- There are challenges for healthcare professionals (HCPs) in communicating complex subjects to PLWC, which can create a barrier in effective communication. One way to avoid this is to use simple language that patients are already familiar with. However, some experts are resistant to doing so.

- Personalised cancer medicine brings challenges in communicating treatment eligibility, as HCPs have to explain why a patient is 'eligible' for a certain treatment, but not another. Sensationalised headlines around immunotherapies present additional challenges for HCPs in explaining eligibility criteria.
- Patients must be well-informed and monitored in order to detect side effects early, so that they can be dealt with appropriately as early as possible.
 Patient Information Leaflets and Patient education are examples of how patients can learn more about their treatment.

Executive summary (cont.)

Information and Support

- Macmillan currently has some information on targeted treatments and immunotherapy, with limited in-depth information on immunotherapy, and on the genetics and cancer. However, there are future plans to create landing pages on personalised treatment, immunotherapy and genomics.
- Macmillan is currently collaborating with NHSE to co-create new information on genomics in cancer care and new education and training for HCPs, and should continue work with NHSE to engage the devolved nations in anticipation of the roll out of access to genomics medicines centres across the UK in 2019.
- Macmillan's **Online Community** facilitates discussion and support about all aspects of cancer experience. **Understanding of newer treatments by Online Community users varies**, and it is difficult to generalise their understanding as it has a very large and diverse usership.

Workforce implications

- New treatments, such as immunotherapy, create workforce implications for the ongoing and future use of cancer treatment services, which require estimates to be made on how many workforce and service configurations are needed to deliver best practice treatments to patients.
- A general education approach is required to upskill HCPs in new treatments such as immunotherapy. However, the level of upskilling required can be stratified by the level of their involvement in cancer care.
- There are challenges associated with implementing genomics services, around education and training, as well as in other areas such as lack of awareness and difficulties in engaging different groups.
- Further work is required to **understand whether core roles**, like chemotherapy nurses, are required to support the **increasing number of patients receiving immunotherapy**, or whether **upskilling** current workforce and looking at different ways of working would be a more appropriate approach.

Background, objectives, approach and acronyms

Background

The number of new cancer treatments has grown hugely over the past decade. Macmillan needs to better understand the issues relating to availability, access, development and dynamics of the market for new treatments.

- There are many potential benefits from personalised cancer treatment for patients and society, including increased efficacy of treatments. Macmillan needs to better understand the impact advancements in genomics and new personalised treatments is having on PLWC and the cancer workforce, and how this is likely to evolve.
- Treatment as a stage of the cancer journey, is one of Macmillan's focus areas; it is important for us to understand the impact of innovations in this area for PLWC (including those on clinical trials), and what this may mean for service development.
- Traditionally, Macmillan has not has not been seen as an organisation that is 'in the field of cancer drugs'. However, Macmillan contributes to the cancer drugs fund debates, provides information on drug treatment options in its patient information material, and advises patients on accessing clinical trials for new drugs. There is a need to understand our position and clarify this for strategic planning purposes.

Objectives

- To understand the size, historic and potential future growth for new personalised treatments for cancer, in particular the effect of genomics and new personalised treatments will have on PLWC and the cancer workforce.
- To identify the issues relating to funding of and access to new cancer treatments for PLWC.
- To identify the needs of patients who wish to access a new personalised treatments and the needs of those receiving such treatments.
- To identify gaps in knowledge for further exploration.

Approach

- a) Desk-based research and accessing market intelligence reports.
- b) Interviews with internal stakeholder.
- c) Interviews with external experts
- d) Write draft report and develop implications for Macmillan with internal stakeholders
- e) Finalise report and deliver findings
- f) Engagement and communication of findings (e.g. presentations, conferences)

Acronyms

HCP- health care professional

PWLC – person/people living with cancer

- QOL quality of life
- L&D learning and development

Introduction

Personalised treatments

Personalised cancer treatment is a move away from a 'one size fits all approach' to treatment, that is determined by the individual's tumour characteristics, in order to improve effectiveness, QOL, and potentially reduce side effects to normal cells.

Definition of personalised medicine

Personalised medicine is a **move away from a 'one size fits all'** approach to the treatment and care of patients with a particular condition, to one which uses new approaches to **better manage patients' health and targets therapies** to achieve the best outcomes in the management of a patient's disease or predisposition to disease.¹

What does this mean for cancer treatment?

Cancer treatment has seen increased focus on personalised medicine, leading to patient segmentation based on biomarker status.¹ Biomarker diagnostics have the potential to allow cancer patient's treatment to be tailored to the individual. This has the following potential benefits:²

- · Potentially less harmful to normal cells
- Potentially fewer side effects
- Improved effectiveness
- Improved quality of life

This approach delays or prevents the need to apply more severe treatments which are usually less tolerated and with increased quality of life and financial considerations.¹



Figure 1- Advantages of personalised cancer therapy³

Personalised treatments (cont.)

Advances in genomics, genetic tests and targeted drugs will enable increasing personalisation of cancer treatments. If a treatment is personalised this does not necessarily mean that it is accompanied with the complimentary personalised care.

Conditions for personalised treatment

Some cancer patients are already benefiting from personalised medicine. Whether a treatment regime can be personalised depends on whether:¹



a gene has been identified for the cancer type



• there is a **test available** for that gene

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1			
	\geq	96	86

• there is a treatment that targets that gene

If these are all present, it still does not guarantee that a treatment will work.

Even if all of these are present, the workforce and systems must be in place in order to deliver and interpret the tests, administer the treatment safely and ensure that the appropriate support is in place.

Is personalised care the right term?

Some believe the term 'personalised' is not appropriate as the defined 'personalised' medicine **does not necessarily mean that cancer care is tailored to the individual**, especially in terms of support, but perhaps '**precision' or 'targeted'** are more appropriate terms.

It does not reflect that a patient is supported to meet their personal, or holistic needs. Indeed, some argue that we shouldn't have 'personalised treatment' without the complimentary 'personalised care'

PERSONALISED TREATMENT PERSONALISED CARE

Personalised medicine is starting to impact the pathway of cancer patients, and it is expected to do so increasingly, thus we need to understand the possible impact on cancer patients of the coming advances as well as equip and plan for future workforce requirements. Macmillan must play a role in ensuring personalised treatment is accompanied by personalised care.

Transition to personalisation in cancer treatment

Personalised medicine has the potential to impact all aspects of cancer care, from screening to treatment. Currently we are in a transition era from the traditional population-based oncology.

Personalised medicine has the **potential to affect the care of PLWC at all stages** of their cancer experience, from screening and diagnosis, to clinical trials and treatments. It is evident that cancer treatments are now in a **transition period from 'population oncology' to 'personalised oncology'**, where ultimately every stage is determined by the profile of the individual.¹

	Population Oncology	Transitional Era	Personalised Oncology
Screening	population-wide risk reduction	population-wide approaches modified for at-risk sub-populations	individualized risk estimation & programs adapted to individual risk
Diagnosis	organ-of-origin/histology-based	organ-of-origin, histology, & some molecular markers	primarily molecular marker-based
Staging	anatomic extent of disease	anatomic extent with some molecular risk profiling	primarily molecular-risk based
Treatment Determination	typically organ-of-origin & stage- based	organ-of-origin & stage-based with some implementation of molecular markers	primarily molecular marker-based
Assessment Intervals	based on clinical evaluation/exam findings	based on routine interval imaging	early, frequent serial assessments by imaging, circulating tumour cells and other marker assessments
Early Phase Clinical Trials	oriented to maximum tolerated dose	oriented to "optimum biologic dose"	determine range of tolerable & active doses
Mid-Phase Clinical Trials	histology & prior treatment based eligibility; typically single arm non- comparator trials	histology & prior treatment based eligibility; some marker-based screening; some randomized, controlled trials	some trials histology & prior treatment based eligibility with rapid, serial assessments; many with eligibility restricted to tumour marker subsets

Examples of personalised oncology now

We are currently in a transition era towards personalised medicine, with some cancer patients benefiting from biomarker testing to optimise treatment regimes, such as ER/PR and HER2 tests to determine breast cancer treatment.

Some personalisation of treatment is already available to cancer patients. Below are some example of where this is already seen.

Example: personalised treatment in breast cancer

For breast cancer there are some tests that can be used to determine treatment regimes, by testing for the presence or absence of biomarkers:^{1,2}

- HER2+ if overexpressed, patients are offered trastuzamab (Herceptin)
- **ER+ or PR+** more likely to respond to hormone therapies
- **Triple negative** don't express ER, PR or HER2 receptors. Hormone therapies and targeted cancer drugs don't work as well for these breast cancers, so chemotherapy is more likely to be used.



Other examples of personalised treatments⁴

- Bcr/Abl a change in this gene is common in chronic myeloid leukaemia. If a tumour tests positive, you are likely to respond to a drug called imatinib (Glivec).
- **EGFR-TK** this is over-expressed in some lung cancers. If a tumour tests positive, then the cancer may respond to the drugs afatinib, erlotinib, and gefitinib.
- **ALK** this is an overactive enzyme in some lung cancers. The drugs crizotinib and ceritinib only work in cancer cells with an overactive version of ALK.
- K-RAS some bowel cancers have an altered K-RAS gene. The drugs cetuximab (Erbitux) and panitumumab (Vectibix) only work for cancers that have the normal version of the gene.
- PD-1/L1 some non-small cell lung cancers (among others) can be positive for surface PD-L1 expression. There is a lot of research in this area, and it can mean that patients who test positive are more likely to respond to certain immunotherapies.

(1) Trastuzamab (Herceptin ®). Macmillan Cancer Support. Available from: https://www.macmillan.org.uk/information-and-support/treating/targeted-biological-therapies/find-your-therapy/trastuzumab.html#319776 (2) Tests on your breast cancer cells. CRUK. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer (3) Overview of Breast Cancer. Project Breast Cancer. Available from: https://www.cancerresearchuk.org/about-cancer/cancer (4) Personalised medicine. CRUK. Available from: https://www.cancerresearchuk.org/about-cancer/cancer.org/typesofbreastcancer.html (4) Personalised medicine. CRUK. Available from: https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/personalised-medicine.

Immunotherapy

responders

Immunotherapy is the newest wave of cancer treatment. The use of these drugs is still limited to specific indications and clinical trials, and they present different side effects and largely unknown long term effects.

Immunotherapy is activation of a person's own immune system to identify and target their cancer.¹ Some types of immunotherapy are also called *targeted* treatments or *biological therapies*. There are several different types of immunotherapy, and these include monoclonal antibodies, checkpoint inhibitors, cytokines, vaccines to treat cancer and adoptive cell transfer.²

Immunotherapies are a 'new wave' of treatment, which at this point are showing improved survival in select cancer types, most notably in metastatic melanoma, lung and urethral cancer, but hold promise for other malignancies. They are more commonly used for patients with **metastatic disease**, **however their use is expanding**. Many oncologists, scientists, medical professional associations, and advocates agree that no recent cancer advance has been as **successful**, **transformative**, **and potentially paradigm-shifting** as immunotherapy.³

Patients' **outcomes vary considerably**, with some individuals showing marked improvement, in terms of tumour shrinkage and longer survival (**responder**), while others show no response (**non-responder**).⁴ There is great challenge in understanding why immunotherapies work for only a subset of patients who receive it, which itself depends on the cancer type and particular drug.⁵

By interfering with the immune system, **these treatments generate immune-related adverse effects (iRAEs)**, that mainly involve the gut, skin, endocrine, liver and lung.⁵ These side effects are notably different from chemotherapy as they are **less predictable and can range from mild** (e.g. rash) **to severe** (e.g. pneumonitisinflammation in the lungs). The long-term effects are still largely unknown because many of the treatments are so new.

(1) What's new in cancer. Presentation by Dr Anna Olsson-Brown and Ms Joanne Upton, The Clatterbridge Cancer Centre. Macmillan Primary Care Conference 2017. Not widely available – please ask to view (2) Types of immunotherapy. CRUK. Available from: https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/immunotherapy/types (accessed July 2016) (3) D.LMadden. From a Patient Advocate's Perspective: Does Cancer Immunotherapy Represent a Paradigm Shift? Current Oncology Report. 2018.20:8. (4) Image from: G Varricchi, et al. Cardiotoxicity of immune checkpoint inhibitors. ESMO Open (2017); 2(4). (5) Blood Will Tell: Scientists Find Clues to Immunotherapy Responders. Available from: <u>https://www.mskcc.org/blog/blood-will-tell-scientists-find-clues-immunotherapy-responders-and-non-</u>

Immune-related adverse effects (immunotherapy side-effects/toxicities)



Figure 1⁴- diverse side effects of immunotherapy

Immunotherapy is a growing treatment area, which will increasingly impact on the treatment regimes of PLWC. Therefore, it is vital that Macmillan understands the clinical and non-clinical effects on PLWC, and their needs as a result.

Genomics

Genomic medicine has the potential to save costs and improve quality of care by personalising cancer treatment, thus maximising benefit and reducing side effects.

Genomic medicine is the study of all DNA in the genome together with the technologies that allow it to be sequenced, analysed and interpreted.¹

Genomic medicine has the potential to save costs and improve quality of care by personalising cancer treatment, thus maximising benefit and reducing side effects. It will bring improvement in the care of cancer patients, including identifying the most effective drugs, drugs which will cause fewer side effects, seeking new drugs and treatments, and moving to personalised prevention. In addition to this, there will also be further applications, many of which we are not aware of.¹

We already know that mutations in DNA are responsible for cancer, but we do not always know what these mutations are. Some are inherited (e.g. BRCA) whilst others occur by change or due to environmental exposure (e.g. tobacco smoke or UV radiation).¹ The use of genomic testing to determine cancer treatment is therefore limited by the known mutations which are linked to effectiveness of specific cancer treatments.

However, there are ambitions to accelerate the UK's position in the use of genomics to personalise cancer treatments to the individual (see slide 18).

Your genome

is found in almost every cell of your body and it is the instructions for making you.

It contains all your 20,000 genes

It is all 3.2 billion letters of your DNA

Source Genomics England

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1 genome = 3.2 billion letters of DNA. If it was printed, your genome would fill a stack of paperback books 61m high or fill 200 telephone directories!

1 sequenced genome equals 2 billion bytes or 200 GB. That's enough to fill the memory of an average laptop.

100,000 Genomes Project

The 100,000 genomes project aims to sequence 100,000 whole genomes from patients with rare diseases and cancer. This research has the potential to increase the personalisation of treatment for cancer patients by using genomic information to select treatments and predict response.

The 100,000 Genomes Project was launched in late 2012, aiming to **sequence 100,000 whole genomes** from NHS patients, with a focus on those with **rare diseases and cancer**.¹ Primarily samples were from patients in England, but each of the devolved nations has since joined, with Wales being the final nation to join in early 2018.² It is likely that around 50,000 genomes will be sequenced from cancer patients. As of **August 2018**, there were **75,552 genomes sequenced** in total (cancer and rare diseases), with the full 100,000 genomes expected to be sequenced by March 2019. This genomics research could ultimately be used to **predict how well a person will respond** to a treatment or **find one that will work best for them**.



Figure 11- 100,000 genomes project

Mainstreaming genomics in cancer care in England

On the back of the work from the 100,000 Genomes Project, NHS England is aiming to set up a full Genomics medicine service from October 2018 to April 2019. However, this presents many challenges.

NHS-England mainstreaming

The project is currently a research database, but the programme is looking at how to act upon the results. Early analysis finding that **65% of project cancer cases have variants in actionable genes**.³ However, even if a result is theoretically actionable this does not mean that there are the systems in place (e.g. laboratories, services, workforce etc.) to go forward, so **may not be truly actionable**.

The aim now is to mainstream the 100,000 genomes project, setting up a **Genomic Medicine Service in England from October 2018 to April 2019**.³ This presents several challenges including:

- Ethics (e.g. consent, disclosure of information)
- Workforce (e.g. education, shortages, funding, wider engagement)
- Systems (e.g. laboratories in place, procedures adapted)

There are also plans to explore access to the genomics medicine centres in the devolved nations in 2019.

Moreover, the potential to impact treatment is also limited (see slide 12).

NHS Genomic Medicine Service:

A national genomic medicine service driving personalised treatments and interventions with consistent & equitable access across the country

Focus on improving quality and reducing variability, setting standards and driving consistency, economies of scale and affordability

Routine care and treatment will be closely linked through to clinical research, academia and industry to support ongoing learning from genomics and promote the development of new treatments and interventions

What we can do now: actionable information for cancer patients

Early analysis found 65% of Project cancer cases have variants in actionable genes



Figure 1- NHS England slides on mainstreaming 100,000 Genomes Project³

(1)100,000 Genomes Project. Genomics England. Available from: https://www.genomicsengland.co.uk/the-100000-genomes-project/ (2) Wales joins the 100,000 Genomes Project. Genomics England. Available from: https://www.genomicsengland.co.uk/wales-joins-the-100000-genomes-project/ (3) Early results shared from NHS-E, not widely available – please ask to view.

NHS

England

Cancer treatment development and use

New cancer drugs

In the last five years 78 new indications have been approved in oncology, covering multiple tumours, with the most new therapies approved for lymphoma, leukaemia and lung cancers.

New treatments in cancer care have continued to develop across many different cancer types (see figure 1). This includes:¹

68

New Active Substances (NAS) approved in oncology, with some treating multiple tumour types.

78

New indication (NASs for a specific tumour types) approvals for New Active Substances in oncology in 2013-2017 .

Lymphoma, leukaemia and lung cancers

Have had the most NAS approved 2013-2017. In 2017 alone lymphoma had nine NASs approved, leukaemia had nine, lung had 11 as well as six in melanoma.

75%

of all targeted treatments in oncology are used in multiple indications (tumour types).



New Active Substance Approvals in Oncology by Indication, 2013–2017

Source: IQVIA, ARK R&D Intelligence, Apr 2018; IQVIA Institute, Apr 2018

Notes: Includes initial and subsequent indications. Excludes supportive care. GIST = gastrointestinal stromal tumor. ALL = acute myeloid leukemia; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; FL = follicular lymphoma; MCL = mantle cell lymphoma; DLBCL = Diffuse large B-cell lymphoma; PTCL = peripheral T-cell lymphoma; WM = Waldenstrom macroglobulinemia; SLL = small lymphocytic lymphoma. Report: Global Oncology Trends 2018: Innovation, Expansion and Disruption. IQVIA Institute for Human Data Science, May 2018

Figure 1¹

Biomarker targeting

Biomarkers are being used to redefine cancer more precisely across several tumour groups, and this improves patient outcomes by making more personalised cancer treatment selections. The number of markers has increased dramatically in the last decade.

The use of **biomarkers to target drugs enables the personalisation of cancer treatment**. Over the last decade the number of markers has dramatically increased. Even in the early 2000s, breast cancer was highly segmented (see slide 14 for further information), but more recently there have been further biomarker identified for breast cancer and across different cancer types. In particular, the addition of **PD-L1 expression across a range of tumour types** has enabled identification of sub-populations who are more likely to respond to certain treatments.

The increase in the number of identified biomarkers can mean that HCPs need to run **multiple tests**, which can add further delays to starting cancer treatment and require specialist expertise, but there is **clear clinical benefit** in doing so.



Chart 7: Patient Incidence of Positive Biomarker Results Per Cancer by Biomarker Availability, 2017

Source: FDA.gov and Drugs@FDA, Apr 2018; IQVIA, ARK R&D Intelligence, Apr 2018; IQVIA Institute, Apr 2018

Availability of new cancer medicines globally

The availability of new oncology medicines varies globally, with UK having access to over 40 of the 55 new medicines launched in 2012-2016, but does however lag behind in the supply of specific innovative immunotherapies (PD-1/PD-L1).¹



Source: IQVIA MIDAS, Dec 2017

Notes: Includes therapeutic new active substances (NAS) in oncology (excluding supportive care medicines) first launched globally between 2012 and 2016. Availability is based on sales appearing in IQVIA market audits in the period from launch to the end of 2017, regardless of reimbursement status. By assessing country availability at least a year after the last drug's first launch, the analysis highlights differences that would not be present if filings had occurred simultaneously in all countries, if reviews were largely similar duration with the same results, and reimbursement or commercial considerations and incentives were similar across country availability at least a very file of both retail pharmacy and hospital settings to ensure comparable availability assessment for oncology products. Report: Global Oncology Trends 2018: Innovation, Expansion and Diaruption. IQVA Institute for Human Data Science, May 2018

Figure 1¹

The uptake of innovative PD-1/PD-L1 immunotherapies varies significantly globally, with the uptake in the UK at a third of that of the US in 2017 (see slide 14 for details on PD-1/PD-L1).

Variation in usage can be for multiple reasons, including differences in reimbursement schemes as well as difference in how drugs are approved for tumour groups.

Countries that determine reimbursement and recommended use through health technology assessments, as in EU markets, generally have lower usage than the United States.

The UK has access to 41 of the 55 new medicines launched globally in 2012-2016, behind US (47) and Germany (42).

For those countries under the European Medicines Agency, Germany has the most of the medicines available (42). Other countries under the EMA (including the UK), have lower availability, due to either pending reimbursement reviews and negotiations or due to a company's decision not to market an approved medicine in that country.



Source: IQVIA, MIDAS, Economist Intelligence Unit, Dec 2017

Notes: I/O drugs included were pembrolizumab, nivolumab, atezolizumab, avelumab and durvalumab. Report: Global Oncology Trends 2018: Innovation, Expansion and Disruption. IQVIA Institute for Human Data Science, May 2018

Figure 2¹

Composition of the new medicines pipeline

There are an increasing number of targeted treatments in late stage development, at over 700 molecules by the end of 2017, an increase of 64% since 2007.

64%

Increase in the number of late phase (Phase II or higher) molecules in development from 2007 (434) to 2017 (710).

The Pipeline of Late Phase Oncology Molecules, 2007-2017

90%

Of the pipeline is made up of targeted treatments, which has largely driven the increase in molecules in late phase development



2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017

Source: IQVIA, ARK R&D Intelligence, Dec 2017; IQVIA Institute, Mar 2018

Notes: Late phase pipeline includes trials in Phase II or higher for the most advanced indication. Phase I/II trials are included as Phase II. Report: Global Oncology Trends 2018: Innovation, Expansion and Disruption. IQVIA Institute for Human Data Science, May 2018

Figure 1¹

Global spending forecast

Spending globally on oncology medicines has continued to grow since 2013, and is forecast to continue to grow into 2022, but with the EU5 (includes UK) increasing at a slowing rate.

Growth globally is led by the US, with global growth in oncology spending reaching nearly \$200 billion (approx. £151billion) by 2022, with average growth of 10-13%.

The EU5 (includes UK) growth is expected to slow, due to budget pressures and wider use of Health Technology Assessments limiting oncology spending.



Growth Rates for Global Oncology Therapeutic Medicines, Constant US\$, 2013–2022

Source: IQVIA Institute, Dec 2017

Notes: Spending Growth in Constant US\$.

Global Oncology Trends 2018: Innovation, Expansion and Disruption. IQVIA Institute for Human Data Science, May 2018

Figure 1¹ N.B EU5 = Spain, Germany, Italy, France & UK,

*Pharmerging= developing countries where the pharmaceutical industry is growing

Future trends

Five major trends are predicted to hit oncology, some of which we are already seeing, including smaller patient populations, shorter product life cycles, new age of combination therapies, a significant shift in value across healthcare and a new wave of technologies.

Looking at the trends seen across the industry already, there are five major areas that are predicted/forecast to shape the future of oncology.

Smaller patient populations

due either to a focus on niche tumors or narrower stratification of subpopulations in more common tumor types.

2 Shorter product life cycles

reduced by almost fivefold since the 1990s because of a more competitive landscape and faster innovation cycles.

5

3New age of combination therapy

and sources of innovation triggered by a recent wave of immuno-oncology launches. These have served to increase the level of external sourcing of innovation and collaboration, especially among pharmaceutical and biotechnology companies.

Significant shift in value across healthcare

partly driven and informed by big data, which in turn will enable more innovative access models

New wave of technologies

providing tools to address a broader set of indications and offering greater promise of personalized therapies

Variation in access to current treatments

Rates of chemotherapy, radiotherapy and surgery vary for different groups of patients in England. Factors including age, deprivation, ethnicity, stage of cancer and gender can influence treatments received by cancer patients.

Rates of chemotherapy, radiotherapy and surgery vary for different groups of patients in England.¹ Public Health England (PHE) identifies seven key differences:

I. Fewer older patients receive chemotherapy, radiotherapy and surgery for their tumour

Across all cancer sites combined, the proportion of patients treated with chemotherapy, radiotherapy and surgery falls as the patients get older. As an example, the proportion with chemotherapy falls from 34% among patients diagnosed aged 60-69 years to 9% among those diagnosed aged 80+.

2. Fewer patients living in more deprived areas receive surgery for their tumour

To understand how treatment changes by deprivation, PHE divided the population into five groups, or quintiles, using a measure of income based on where the person lives.

This analysis showed that patients in more deprived areas have substantially less surgery (40% of patients in the most deprived quintile receive surgery, compared to 48% of those in the least deprived quintile). It was found that this variation does depend on the type of cancer that the patient is diagnosed with, for example, it appears to be more influential among patients with rectal cancer.

3. Fewer females receive chemotherapy, radiotherapy and surgery for their tumour than males

Certain cancer types occur more commonly or exclusively in the different sexes, for example breast and prostate cancers. These drive differences in treatments overall, making all three treatments appear less common in males. After excluding these cancers (breast, cervical, ovary, prostate, uterine, vulva), females in fact receive less radiotherapy, chemotherapy and surgery overall than males.

4. More non-White patients have chemotherapy and surgery than White patients

Chemotherapy and surgery were more common among non-White patients than White patients, although more research is needed to understand why. Treatment rates were lower for patients whose ethnicities were unknown, and this group may actually include a large proportion of non-White patients.

If a true difference exists between White and non-White patients, it could be driven by differing age distributions, whereby the non-White population is generally younger. For certain sites, such as breast cancer, differences may also be driven by cancer biology.

(1) Seven things we learned from our latest treatment data. PHE (July 2018). Available from: <u>https://publichealthmatters.blog.gov.uk/2018/07/17/seven-things-we-learned-from-our-latest-cancer-treatment-data/</u>

Variation in access to current treatments (cont.)

Rates of chemotherapy, radiotherapy and surgery vary for different groups of patients in England. Factors including age, deprivation, ethnicity, stage of cancer and gender can influence treatments received by cancer patients.

5. Fewer patients with multiple comorbidities have chemotherapy, radiotherapy and surgery PHE used a measure called the Charlson comorbidity index. It is a measure of the presence and severity of diseases that a patient has prior to their cancer being diagnosed.

It was found that for patients with a higher index, fewer received treatment, particularly chemotherapy and surgery. Overall across the sites, a substantial higher proportion of those with no comorbidities receive chemotherapy, radiotherapy and surgery (31%, 29% and 48% respectively) compared to those with one comorbidity (22%, 23%, 36%).

6. Compared to patients diagnosed with late stage cancer, fewer patients diagnosed with early stage cancer have chemotherapy, and higher proportions have surgery

Stage at diagnosis is a very important factor affecting the treatment options available to the patient. More than double the proportion of patients with early stage disease had surgery (68%) compared to patients with late stage disease (28%), and half the proportion were treated with chemotherapy (20%) compared to patients with late stage tumours (42%).

7. Across England, there are differences in the proportion of patients receiving cancer treatments, and the reasons for this are complex

In order to support local provision of services in the NHS one must understand the local picture. PHE have published these results at a subnational geography which we call *Cancer Alliances*. These *Cancer Alliances* bring together those leading the local delivery of improving cancer service, including local senior clinical and managerial leaders, to represent the whole cancer patient pathway across that specific geographic area. In doing this it can be see that the proportion of patients receiving the three treatments types varies across the country.

There are a number of possible reasons for this variation. For example, the characteristics of the Cancer Alliance's population could be different to England overall, the sample size could be small meaning figures are affected by random variation, or there could be more or less missing data for that Cancer Alliance compared to England overall.

In order to take action Macmillan needs to better understand the drivers behind these inequalities in access to treatments, which are likely multi-layered and complex.

Clinical trials

Rate of success of clinical trials

The rate of successful transitions between phase of trials has generally increased for Phase I and III, reaching 66% and 73% respectively in 2016.

The **rate of success of oncology clinical trials has increased** from 2012-2016, particularly for Phases I and III. This could be due to Phase I trials increasingly being used to test the efficacy and dosing, and not just the safety, which as a result would have a positive knock on effect on the success rate of later phase trials.

It is also estimated that clinical success rate for drug development **could continue to increase** by selecting targets for development that have supportive genetic evidence.



Oncology Trial Phase Transition Success Rate by Phase, 2012–2016

Source: IQVIA ARK R&D Intelligence, IQVIA Institute, Apr 2018

Figure 1¹

Notes: Phase II includes phases I/II, II, IIa, IIb. Phase III includes Phase II/III and III. Success rate based on 1,727 records. A successful outcome to a trial is defined as the commencement of a subsequent phase, or regulatory approval. Rates of successful phase shifts were calculated by dividing the number of phase advances by the total number of status changes including those which were discontinued, suspended, withdrawn or have had no active update to the records for more than three years. Trials were industry sponsored and interventional. Diagnostics, behavioral therapies, supplements, devices, and medical procedures were excluded. Report: Global Oncology Trends 2018: Innovation, Expansion and Disruption. IQVIA Institute for Human Data Science, May 2018

The fluctuating rates of success of Phase II trials may be down to the introduction of new Breakthrough designations in the US in 2015, which accelerated the development of promising drugs, by submitting to the FDA earlier (Phase II or as early Phase I/II).

Trial duration and patient enrolment

As late-stage trial duration has declined, so has the average number of enrolled patients. This can be attributed to segmentation based on biomarker status allowing for pre-screening, as well as increased research in rarer cancers, which typically requires enrolment of fewer patients.

The average number of patients enrolled in Phase II and III clinical trials has marginally decreased in the last five years (2013-2017).

The reduction of patients in these late stage trials can be attributed to two main factors:

- 1. Segmentation based on biomarker status allowing for pre-screening for potential trial inclusion
- 2. Increasing research in rarer cancers, which typically recruit fewer patients.

Conversely, the average enrolment to Phase I trials has increased. The growing number of targeted therapies in oncology and the increasing availability of predictive biomarkers is changing the clinical development pathway for Phase I oncology trials. Phase I trials have a greater focus on efficacy and an increased emphasis on pre-screening patients using pharmacogenomic testing for potential trial inclusion.



Mean Trial Duration and Patient Enrollment Shifts in Phase I and Phase III Trials (2013–2017)

Source: Clarivate Analytics Cortellis, Jan 2018; IQVIA Institute, Apr 2018

Notes: Average is reported as the mean. Phase II includes phases I/II, II, IIa, IIb. Phase III includes Phase II/III and III. Data for duration includes 3,341trials; date for number of subjects includes 3,896 trials. Terminated and withdrawn trials were excluded from the analysis. Trials were industry sponsored and interventional. Diagnostics, behavioral therapies, supplements, devices, and medical procedures were excluded.

Report: Global Oncology Trends 2018: Innovation, Expansion and Disruption. IQVIA Institute for Human Data Science, May 2018

Figure 1¹

Trial duration and patient enrolment (cont.)

Increased pre-selection based on biomarker status slows recruitment to clinical trials by 20% (2016), meaning it is more challenging than traditional population oncology. This is due to it being more difficult to find patients and the patient pool available is much smaller.

Increased pre-selection based on biomarker status also brings with it its own enrolment challenges.

Chart 1 shows the median patient enrolment/site/month. When this is higher, it indicates that more patients were recruited per month. From 2012-2016, recruitment rates increased, suggesting that there were fewer constraints in recruiting. However, Chart 2 shows that patients stratification based on pharmacogenomics (PGX- based on biomarker status), enrolment rates were 20% lower in 2016 compared with without PGX patient stratification.

This means that **due to pre-selection**, **patients may be more difficult to find and the patient pool available is much smaller**. Therefore, with personalisation of clinical trials it may become more challenging to recruit patients than in traditional population oncology.

If systems are put in place to ensure patients with appropriate biomarkers can be identified and linked to relevant clinical trials, this risk could potentially be mitigated.

For example, with increasing use of genomic testing in the NHS, in the future there may be potential to link patient genomics data-bases with clinical trial databased, enabling automatic identification of patients eligibility for clinical trials based on their test results. However, this has the potential to increase inequity in access to clinical trials if access to Genomics Medicines Services varies across the UK.



Median Patient Enrollment Rates (Patients/Site/Month) for Phase I-III Oncology Trials



Increased pre-selection of patients has the potential to improve the experience of PLWC on clinical trials. However, if challenges in identifying eligible patients are not addressed then inequity in access to clinical trials could worsen.

Chart 1¹

Biomarker segregation in clinical trials

Biomarker segregation has been seen to decrease duration of late stage trials, but also presents further benefits as well as challenges for clinical trials.

There are further benefits and challenges of biomarker segregation, which are summarised below:

Benefits

Increased success rate of trials

Patients can preselect patients for studies who are more likely to respond to the new treatment.

Smaller patient cohort

Patients included in the clinical trials are more likely to be 'responders', so fewer patients are required to show a response. This can also be as a result of more clinical trials for rarer cancer, which typically recruit fewer patients.

Shorter trial duration

More likely to early success, thus shortening trial duration.

More cost effective

This is mainly as a result of the increased success rate of trials, smaller patient cohorts and shorter trial duration.

Reduced unpleasant side effects

Drugs are more likely to be effective, and less likely to produce unpleasant side effects.

Increase in compliance

It is possible that patient compliance may increase, and patients may be more likely to adhere to the treatment regime if they don't suffer from side effects.

Challenges

Slower enrolment

Patients may be more difficult to find and the patient pool available is much smaller, making average enrolment speeds shorter. Patients need to be identified and linked up to relevant clinical trials in order to mitigate this risk.

Technology

If genetic data is used in clinical trials, there must be systems in place to collect, store and track the samples. Where there are a large number of patients, there must be the IT infrastructure in place to store and access the genetic data, and to carry out complex analysis.

Regulation

As new technologies offer better tools for analysing and delivering more effective safer medicines, regulators (including the FDA and EMA) will need to adapt, provide and help to set up new rules for the incorporation of pharmacogenetic data within the submission process leading to a successful Marketing Approval for new products. This is analogous to their gradual acceptance of image data in support of license applications. (direct copy and paste)

Ethics

Ethical issues around consent to store and share personal and sensitive data. There is also potential danger in 'cherry picking' of more 'valuable' subsets of the population for clinical trials (i.e. more likely to respond and have fewer side effects), so other subsets of the population may be neglected and left with fewer treatments.

(1) How Will Personalised Medicine Have an Impact on Clinical Trials? Abel Ureta-Vidal, Eagle Genomics Ltd. Available from: http://www.hartengroup.co.uk/resources/files/PersonalisedMedicine.pdf 32

Clinical trials – design

Overall survival is the gold standard for demonstrating clinical benefit, but can require large trial populations and lengthy follow-up. The surrogate marker Progression Free Survival (PFS) is often used instead. However, the meaning of PFS can be misunderstood by both patients and oncologists.

The table below describes the two clinical endpoints, Overall Survival (OS) and Progression Free Survival (PFS), as well as their **advantages** and **disadvantages**:²

Endpoints	Definition	Advantages	Limitations
Overall survival (OS)	Time from randomization* until death from any cause	 Universally accepted measure of direct benefit Easily and precisely measured 	 May require a larger trial population and longer follow-up to show statistical difference between groups May be affected by crossover or subsequent therapies Includes deaths unrelated to cancer
Progression-free survival (PFS)	Time from randomization* until disease progression or death	 Requires small sample size and shorter follow-up time compared with OS Includes measurement of stable disease (SD) Not affected by crossover or subsequent therapies Generally based on objective and quantitative assessment 	 Validation as a surrogate for survival can be difficult in some treatment settings Not precisely measured (ie, measurement may be subject to bias) Definition may vary among trials Requires frequent radiologic or other assessments Requires balanced timing of assessment among treatment arms

Overall survival (OS) is the internationally recognised gold standard for the demonstration of clinical benefit.¹ However, measuring OS may require a **very large trial population and long follow-up**, which can incur considerable costs and delay patients' access to new cancer drugs. **Surrogate markers** which correlate with OS are often used; **progression free survival (PFS)** is commonly used. PFS requires a smaller sample and shorter follow up.

One study showed that the **phrase PFS** is rarely used in consultations and when asked, **most patients were unclear of its meaning**. PFS can be a **confusing** term for patients, as the word 'survival may imply that the extension of life, where in fact it means slowing or stopping of cancer growth. It is suggested that progression-free interval might be a more helpful phrase to use when discussing drugs with PFS or modest OS benefits. Therapeutic aims of drugs offering only progression-free survival are misunderstood by patients, and **oncologists may be overly optimistic** about likely benefits.³.

New 'fast-tracked' **drug approvals are based increasingly upon surrogate end points** with an expectation that post-marketing studies (i.e. Phase IV) will later demonstrate other benefits such as OS. Completion of such studies is patchy and can demonstrate that PFS is not necessarily a reliable surrogate for OS (see slide 45 for further explanation of study phases).³

New OHE Research Paper: Extrapolation from Progression Free Survival to Overall Survival in Oncology. Available from: <u>https://www.ohe.org/news/new-ohe-research-paper-extrapolation-progression-free-survival-oncology</u> (2) Efficacy Endpoints in Oncology Clinical Trials. Biooncology. Available from: <u>https://www.biooncology.com/clinical-trials/efficacy-endpoints.html</u>
 (3) Therapeutic aims of drugs offering only progression-free survival are misunderstood by patients, and oncologists may be overly optimistic about likely benefits. Supportive Care in Cancer (2017); 33 25(1): 237-244.

Clinical trials – design (cont.) PFS has increasingly been used as a surrogate for OS in drug authorisation, although there are limitations to the assumed correlation between the two. The use of PFS has been challenged, as it may not best meet the needs of the patients, clinicians and healthcare systems.^{1,2}

A study, looking at cancer drugs approved by the European Medicines Agency (EMA) from 2009 to 2013, found 48 cancer drugs had been approved for 68 uses. The study found only half of drug approvals had clear evidence showing they either prolonged people's lives, or improved their quality of life. The study raised questions about whether medicine regulators should be stricter in the evidence they accept for market authorisation.*

The researchers say that their findings show that:

"European regulators commonly accept the use of surrogate measures of drug benefit as primary endpoints in pivotal trials for both conditional and regular pathways to market authorisation"

They argue that

"these standards are failing to incentivise drug development that best meets the needs of patients, clinicians, and healthcare systems"

They say their analysis shows that

"critical information about the outcomes that matter most to patients" might never be gathered, once a drug is approved for use. This may mean that insufficient Phase 4 clinical trials are carried out post-authorisation.*

*See policy and new treatment approval section (p44-5) for further explanation of these processes

(1) Many new cancer drugs so 'no clear benefit', argues review. NHS choices. October 2017. Available from: https://www.nhs.uk/news/cancer/many-new-cancer-drugs-show-no-clear-benefit-arguesreview/ (2) C Davis, et al. Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009-13. BMJ (2017); 359: j4530.

Clinical trials - design (cont.)

Although the use of Patient Reported Outcome Measures (PROMs) in clinical trials is widespread, there is little published information available on Patient Reported Outcomes (PROs). There is existing research- based guidance on best practise and how to measure PROs.

The issue

The use of PROMs in clinical trials is widely spread, as it can help researchers, clinicians and patients understand the impact of treatments and medication on different aspects of people's live, beyond the purely medical.

However, evidence shows that, although widely used and recommended in best practice publications and guidelines, there is little information available on PROMs in clinical trials. This is likely because:

- **PRO information is often omitted from protocols**, leading to impaired data collection
- PRO results are poorly reported in trial publications, or may not be reported at all.¹

A further issue identified with cancer clinical trials is **the lack of information on PROMs and new treatments, such as immunotherapy**, where the link between treatment and non-clinical outcomes is still to be fully explored.²

Best practice

Information on best practice around the use and measurement of PROMs in cancer clinical trials is lacking. The **EPiC study** is looking at addressing some of these gaps. This research is in progress and findings should start to be available in 2019.¹

Beyond cancer, examples of best practice on the use of PROMs in clinical trials exist.

How to measure

An example of a common research-based validated tool available is the **PRO Checklist**. This outlines the key factors to take into consideration when developing a plan to include PROMs in clinical trials. This tool can help researchers set up a methodologically solid and comparable process to include PROMs in their research.³

What to measure

A 2014 study also looked at PROMs in clinical trials. Out of a total of **251 PROMs used**, the research identifies the most commonly used as:

- The five dimension European Quality of Life instrument (EQ-5D)
- The Short-Form Health Survey 12-item (SF-12) and 36-item (SF-36) questionnaires
- The Hospital Anxiety and Depression Scale (HADS).4

CREW

Macmillan already has examples of successful use of PROMs in research studies. In particular, the **CREW study looked at PROMs in the context of PLWC**. Therefore, methods and measures used in the study can provide a good example of existing best practice in the use of PROMs in cancer research.⁴

PROMS and capturing outcomes via digital and in published research is a key area Macmillan can influence and is pivotal going forward in comparing the impact new of treatments to current treatments.

(1) A Retzer, et al. Evaluation of patient-reported outcome protocol content and reporting in UK cancer clinical trials: the EPiC study qualitative protocol. BMJ Open (2018); 8(2). (2) P Cubi-Molla, et al. Quality of Life in Long-term Cancer Survivors: Implications for Future Health Technology Assessments in Oncology. Office of Health Economics (June 2018). (3) D Kyte, et al. Systematic Evaluation of the Patient-Reported Outcome (PRO) Content of Clinical Trial Protocols. PLoS ONE (2014); 9(10) – see Appendix 2 in the paper for the full list. (4) CREW variables.

Clinical trials – perceptions

There are a number of public misconceptions about clinical trials, which may act as barriers to participation. Research also revealed regional variation in clinical trial enrolment.

Recent survey work by NIHR reveal a number of **public misconceptions** about clinical research, as well a revealing **regional variation in clinical trial participation**. However, these perceptions are of the general public and it is possible that the perspective of PLWC may differ.



Figure 1¹

66% think you have to be invited to participate in a clinical trial. This is a major misconception and could limit rates of enrolment in clinical trials, particularly as only 29% of cancer patients had had research discussed with them (England, 2016).²

Over half (56%) of adults said concerns about getting a treatment that was not safe or had side effects would stop them from volunteering. But separate data indicates that the overwhelming majority of patients who participate in research have a positive experience (87%) and would be happy to take part in another study (83%).

A combination of these misconceptions, disparity between expectations and experiences of clinical research and lack of discussion about research opportunities could be leading to fewer people having the opportunity to participate in clinical research.

(1) Public urged to take part in clinical research to find new NHS treatments. NIHR article based on survey of 2,000 UK adults. Available from : <u>https://www.nihr.ac.uk/news/public-urged-to-take-part-</u> 36 in-clinical-research-to-find-new-nhs-treatments/8549 (2) England National Cancer Patient Experience Survey 2016. Quality health. Don't know./don't remember responses excluded in calculations.
Clinical trials – fear and anxiety

Treatments and clinical trials can cause further fear anxiety for cancer patients; this can act as a barrier to clinical trial participation. It is also possible that patients on clinical trials may not get the same level of support as on standard treatment.

It is already well known that a cancer diagnosis can cause high levels of anxiety for cancer patients. In addition to this anxiety caused by receiving a cancer diagnosis, treatment and **clinical trials can cause further anxiety**.

There is an overall fear of the unknown related to cancer, cancer treatment, and clinical trials, as well as a general fear of clinical trials.¹ A small qualitative explored the **fears associated with clinical trial**:

Study- investigating fear associated with clinical trials¹

When interviewees were asked about clinical trials they reported a mixture of **positive and negative terms**. Positivity was often in terms of having some **control over their cancer experience**, whereas negative responses were around **fears related to various aspects of clinical trials**, which themselves could be a barrier to participation. This includes fear related to experimental testing.

The **physician's influence in trial participation** was also explored. In some cases patients accepted their physicians' recommendations to enrol in clinical trials because of their relationship and trust in their physician. In other cases, physicians negative portrayal of health outcomes put patients off enrolling. However, all patients reported that they ultimately made their own decision.

Those participants who had previously refused a clinic trial said they **would consider** one for the future if their **physician provided them with sufficient information and strongly recommended it**, particularly if they had no further treatment options.



- **Small** qualitative (in-depth interviews) study (n=48)
- Based on limited cancer types- lung (n=22), breast (n=9), haematological (n=6), genitourinary (n=5), head and neck (n=4) and not disclosed (n=6)

Interviewees also suggested that for patients who are on monitoring arm of a clinical trial and not on a new treatment, the **constant monitoring could add further to anxiety**. In particular, this may be around processes and interpretation of results (e.g. blood tests) for monitoring. It is possible that these **patients may not get access to the level of support that they need**.

For example, research nurses may be in regional centres, and not be aware of local support offers and may not be linked into CNS teams.

Clinical trials – participation

In 2010, one in six cancer patients participated in the clinical trial in the UK, a higher proportion than in any other European country or the US. However, research is still only discussed with a minority of PLWC in England, leaving room for improvement.

In 2010, it was calculated that one in six cancer patients participate in a clinical trial in the UK, a fourfold increase from 10 years before. This exceeds that of any other European country or the US, with fewer than one in twenty cancer patients participating in clinical and research studies in America.¹ Additionally, UK university expertise in conducting clinical trials has led to the UK hosting the 2nd highest number of clinical trials registered in the International Clinical Trials Registry Platform after the USA (2015).²



One in six cancer patients participate in clinical trials in the UK (2010)

However, in England only 29% of cancer patients said they had a discussion about whether they would like to take part in cancer research with anyone (2016).³ 66% said that they didn't, 5% said that they didn't, but would have liked to have a discussion. Having a discussion about research participation vary by age, cancer type and trust (shown in figure 1).⁴

Five years of CPES results have shown that cancer patients are happy to be approached about research participation, but the majority still do not discuss it.4

> Cancer patients should be made aware of opportunities to take part in cancer research. It is not possible for HCPs to be aware of all clinical trials.

RESULTS 29% of patients nationally reported having had a discussion about research participation. This is broadly consistent with CPES results 2012-2015, which ranged from 33% (2012) to 28% (2015).4 HIGHEST PERFORMING TRUST: 59% By Trust the responses extend from 11% to 59%. **OF PATIENTS REPORTED** Previously ranges were 10%-14% to 55%-61%. AVERAGE PERFORMING TRUST LOWEST PERFORMING TRUST: f 1OF PATIENTS REPORTED

Figure 1³ – Results of CPES 2016 in England.

(1) NCRI 2010: Number of cancer patients taking part in clinical studies quadruples in a decade. Available from: https://ecancer.org/news/1340-ncri-2010enumber-of-cancer-patients-taking-part-in-clinical-studies-quadruples-in-adecade.php . (2) The UK's Contribution to Health Globally. Benefiting the country and the world. APPG on Global Health. 2015. (3) R Stephens, et al. Is This As Good As It Gets? The English Cancer Patient Experience Survey 2016 - Research Discussions Reported by Patients Since 2012. NCRI (2017).. Available from: http://www.ncri.org.uk/wp-content/uploads/2017/02/AO-poster-NCRINHIR-PRINT_Is-This-As-Good-As-It-Gets.pdf . (4) England National Cancer Patient Experience Survey 2016. Quality health. Don't know./don't remember responses excluded in calculations.

Clinical trials – expectations and motivations

The main motivations for participation in clinical trials is for personal benefit and for altruistic reasons. Patients on early stage clinical trials may be motivated by tumour shrinkage or a cure, when the response rate for these early trials is typically very low.

Expectations and motivations

Multiple factors influence patients' motivations to participate in cancer clinical trials; the most important reasons for participation tend to be that patients feel that:^{1,2,3}

- the trials offer the best treatment available
- the trial could benefit others and contribute to scientific research.

In phase 1 clinical trials patients motivation can often be the prospect of clinical benefit, with a small study showing 80% of patients expressing this as a motivation. Around half of the patients anticipated tumour shrinkage, and a tenth expected cure. However, in phase 1 clinical trials, response rates are typically low (4-20%), with low median overall survival (6 months). For this reason, these trials are usually restricted to those with advanced malignant disease who have usually received several lines of previous treatments.

This shows **the gap between the expectations and the reality of enrolling in these trials**, which can present challenges for healthcare professionals and patients during their interactions on phase 1 trials.²

Royal Marsden clinical trial survey

Clinical trials participants in the Gastrointestinal and Lymphoma unit were surveyed on their participation. The majority of patients were happy to be approached about participating in cancer research and were keen to participate in clinical trials.

Factors that influenced the decision are summarised below (n=241), based on what the patients *felt*:

Result could benefit others	91%
Contribute to scientific research	68%
Trial offered the best available treatment	51%
Trusted the doctor treating them	50%
Monitored more closely	33%
Patient's family were keen for patient to participate	22%
Have better quality care	20%
Otherwise their cancer will get worse	14%

(1) S.Y.Moorcraft, et al. Patients' willingness to participate in clinical trials and their views on aspects of cancer research: results of a prospective patient survey. Trials (2016); 17: 17. (2) SO Dolly, et al. A Study of Motivations and Expectations of Patients Seen in Phase 1 Oncology Clinics. Cancer (2016); 122(22): 3501-3508. (3) JM Unger, et al. The Role of Clinical Trial Participation in Cancer Research: Barriers, Evidence and Strategies. Am Soc Clin Oncol Educ Book (2016); 35: 185-98.

Clinical trials – barriers to enrolment

There are several barriers in the decision making process to enrol in clinical trials, including structural (e.g. absence of available clinical trial), clinical (i.e. not meeting eligibility criteria), attitudinal (for both patients and physicians), and demographic and socioeconomic status (SES).

A patient's decision to take part in a clinical trial is complex and personal (see slide 39). The flow diagram below can be used as a guide to understand the trial decision-making process, and it summarises the barriers in involvement in clinical trials as structural (e.g. absence of available clinical trial), clinical (i.e. not meeting eligibility criteria), attitudinal (for both patients and physicians), and demographic and socioeconomic status (SES).¹

Cancer diagnosis Clinic access Clinic visit Structural Trial available No trial available Assessment of trial availability Assessment of Patient eligible Patient ineligible patient eligibility Clinical for available trial Demographic and SES Trial discussed Discussion of trial Trial not discussed participation with Macmillan could play a Attitudinal physician role in ensuring these (physician) opportunities are fully Trial offered Trial not offered Trial participation explained to all PLWC, offered/not offered and that there is an opportunity for shared decision making. Attitudinal Patient agrees Patient declines Patient decision (patient) to participate to participate

Summary of process of enrolment in clinical trials (including possible barriers in blue)¹

Clinical trials – barriers to enrolment (cont.)

People from minority groups are less likely to participate in cancer clinical trials. Barriers to participation include cultural factors, lack of knowledge regarding clinical trials, and mistrust of the medical system.

We have already seen that there is regional variation in participation in clinical trials (see slide 36), however further variation can be seen in participation and access to clinical trials. There is patchy evidence in this area, however evidence available has been summarised.

Minorities¹

People from minority groups are less likely to participate in cancer clinical trials. However, evidence on the difficulties in recruitment particular races is mixed.² Barriers to participation include cultural factors (such as fear and stigma), lack of knowledge regarding clinical trials, and mistrust of the medical system. The most commonly quoted barrier to minority recruitment to cancer-related trials is mistrust of research and the medical system. The table below summarises the impediments to optimal care for minority populations, including the barriers to clinical trial recruitment, as well as potential solutions.

Parameter	Impediment	Potential solutions	
Fiscal	Insurance: medical, drugs	Create indigent safety net(s); regulation of pharmaceutical industry; evidence-based use of cancer therapies; limit provider incentives that may promote disparities of care; education regarding diet, smoking, and so on. among indigent; strategies to deal with diet and carcinogen exposure among indigent	<u>Caveat</u>
	Poverty; lack of family support (especially the working poor)	Health insurance; minimum wage; create indigent safety net(s); improved social support systems; improved patients transport systems for indigent	This research applies to all clinical trials, and not
Cultural	Cancer stigma; fear; poor expectations of outcome of cancer treatment	Education within community; education of politicians and legislators regarding the problem	necessarily newer treatments.
	Suspicion regarding clinical trials and experimentation	Education within community; use of community role models; engagement of community physicians	
Access	Lack of medical 'home'	Accessible cancer care centres; patient navigator systems; education regarding availability and use of medical facilities; outreach facilities within the community	
	Alienation of minority patients from the majority medical community	Involve community leaders; train more minority oncologists; increase minority support staff; cultural competency training of majority physicians	
Knowledge base	Insufficient knowledge of the specifics of cancer in minority populations	Increase diversity and disparity research and funding; education of majority physicians and scientists; expand access to minority-specific clinical trials; expand minority pharmacology research; create local and national databases to monitor progress in disparities of care	

Table I Impediments to optimal cancer care for minority populations

Reproduced with permission from Raghavan (2007).

There is limited evidence on which strategies to increase participation are most effective. It is suggested that strategies should aim to overcome all of the parameters above, as well as aiming to overcome specific issues relating to the design and conduct of trials.

(1) RP Symonds, et al. Recruitment of ethnic minorities into cancer clinical trials: experience from the front lines. Br J Ca (2012); 107: 1017-1021. (2) JM Unger, et al. The Role of Clinical Trial Participation in Cancer Research: Barriers, Evidence and Strategies. Am Soc Clin Oncol Educ Book (2016); 35: 185-98.

Clinical trials – barriers to enrolment (cont.)

Despite the fact that cancer disproportionately affects the elderly, the population in cancer clinical trials is relatively young. Moreover, the least-deprived patients are almost twice as likely to be referred to a clinical trial compared with the most deprived.

Elderly¹

Despite the fact that **cancer disproportionately affects the elderly, the population in cancer clinical trials is relatively young**. These barriers to enrolment of elderly people with cancer (65+) can be categorised as patient-, physician and trial-related. The table below shows selected barriers, as well as solutions to increase recruitment. This **misrepresentation in clinical trials impacts the care of elderly patients**.

	Patient-Related	Physician-Related	Trial-Related	Caveat
Barriers	Logistics Finances Lack of understanding of benefits Autonomy	Perceptions Culture Complex pharmacokinetics/pharmacodynamics Lack of evidence	Strict inclusion criteria Poor methods for evaluating functional status Lack of funding dedicated to elderly population	This research applies to all clinical trials, and not
Solutions	Provide transportation Provide lodging Research nurses, trial coordinators Improved communication	Elder-focused studies Improved communication Increase physician training in geriatrics specialty	Create geriatric-focused trials Increase/fund studies of elderly population	

Table. — Selected Barriers and Solutions

Socioeconomic status²

There is evidence to suggest that **socioeconomic status affects early-phase cancer trial referrals**; the least-deprived patients are almost twice as likely to be referred compared with the most deprived. This may be because of correlated factors, such as increased likelihood of comorbidities with patients of a low SES, or could be because of inequalities that could be addressed by patient or referrer education.

Clinical trials recruitment is potentially discriminatory, meaning that there may be a particular lack of understanding of the impacts of personalised treatments on different groups. This lack of involvement will continue to impact the experience of minority groups, and Macmillan should look to understand this further.

(1) AC Denson, et al. Participation of the elderly population in clinical trials: barriers and solutions. Cancer Control (2014) ;21(3): 209-14. (2) AM Noor, et al. Effect of Patient Socioeconomic Status on Access to Early-Phase Cancer Trials. Journal of Clinical Oncology (2013); 31(2): 224-230.

Policy and new treatment approval

Development of new cancer medicines

The main stages that lead to cancer patients using new drugs are Research, Authorisation, Recommendation and Use. The main bodies involved are the EMA, MHRA and NICE (with some variation in the devolved nations).

The diagram below summarises the complex pathway from initial research to use of a new cancer medicine in the NHS in England, in the wider context of the UK and the EU. It shows the main route to routine NHS use, as well as showing some alternative routes. Some of the bodies and processes differ in the devolved nations. The following slides look at each of these stages in more detail.



Key Summary of terms EAMS - Early Access to Medicines Scheme 0/I/II/III/IV - Phases 0-4 of clinical trials Process Body Scheme CDF - Cancer Drugs Fund or state EMA – European Medicines Agency PPRS – Pharmaceutical Price Regulation Scheme MHRA - Medicines and Healthcare products Direct route to routine NHS use UKIPO - UK Intellectual Property Office Regulatory Agency Other routes to NHS use NICE – National Institute for Health and Clinical Routes back to earlier stage Excellence

Research

The research stage of development of new cancer medicines consists of pre-clinical research in the laboratory, and phases 0 to 3 of clinical trials prior to authorisation. Some trials also include phase 0 as well as phase 4 trials after a medicine has been authorised.

Drug development **starts with pre-clinical research**, which is the scientific basis for drug discovery, including all research prior to a drug being tested on humans. This is likely to involve in vitro (test tube or cell culture) and in vivo (animal) experiments, to prepare for the clinical phase of research.¹

Some clinical research will start with a Phase 0 clinical trial, a preliminary trial with an individual. Phases 1 to 3 are the **three main phases of clinical (human) research**, which have increasingly large patient cohorts. This can then be followed up by a Phase 4 trial after a drug has been licensed (already used in clinics). The stages of research and clinical trials are summarised in figure 1.

All clinical trials in the UK are **authorised by the MHRA**; the MHRA makes sure trials meet international standard of good practice, which are there to protect people taking part. All serious side effects must be reported.



Figure 1 – phases of research and clinical trials. Image directly adapted from Pharmaceutical Biotechnology²

(1) Trial stages of clinical research. Profil. Available from: https://www.profil.com/knowledge-center/trial-stages . (2) Image adapted from: M Vharshini. Clinical Trials. Pharmaceutical Biotechnology. Available from: https://www.slideshare.net/VharshiniManoharan/phases-of-clinical-trials . (3) Understand cancer research trials (clinical trials). Booklet. Macmillan Cancer Support. 45

Authorisation

Once a new drug has shown its safety and efficacy through clinical trials (up to and including phase 3), the drug can apply for a marketing authorisation through the EMA (EU route) or the MHRA (UK route).

Once a new drug has shown its safety and efficacy through clinical trials (up to phase 3), the drug can apply for a marketing authorisation (aka license or registration). In the UK, drugs are licensed through:

- European Medicines Agency (EMA) central route for EU authorisation
- Medicines and Healthcare products Regulatory Agency (MHRA) national route for UK authorisation

The great majority of new, innovative medicines pass through the EU centralised authorisation process coordinated by the EMA, so that they can receive a license to market across the EU, not just in one nation.

The MHRA works independently, and also with the EMA as part of a regulatory network and doing a significant amount of work on behalf of the EMA.² (see slide 55 more information).

Market authorisation will only be issued if clinical trials have proved that the medicine: $^{2} \ensuremath{\mathsf{C}}$

- · Successfully treats the indication (condition) it was developed for
- Has acceptable side effects
- Meets high safety and quality standards

The total process from initial pre-clinical research to drug approval is around $12\frac{1}{2}$ years and costs around £1,150M (2014- see figure 1)^{3.} However, estimates of the cost of this process do vary considerably.



Figure 1: Diagram produced by CRUK³

(1) EMA: What we do. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000091.jsp&mid=WC0b01ac0580028a42 (2) Briefing Paper- Brexit and medicines regulation. House of Commons Library. November 2017. (3) Dances with Pharma: part 1 – why are drugs so expensive? CRUK (2014). Available from: https://scienceblog.cancerresearchuk.org/2014/12/16/dances-with-pharma-part-1-why-are-drugs-so-expensive/

Recommendation and Use

NICE approval decisions are based on cost and clinical effectiveness, giving a 'Yes', 'No' or 'Maybe' decision. A 'Maybe' decision means that the drug shows promising results, but not sufficient to be approved for routine use, and can be considered for use in the CDF.

NICE can evaluate the applications for any new drugs and devices – these are known as technology appraisals. Technology appraisals take one of three forms:¹

- A single technology appraisal (STA) which covers a single technology for a single indication (condition).
- A fast track appraisal (FTA) which also covers a single technology for a single indication but with a shorter process time to speed up access to the most cost-effective new treatments.
- A multiple technology appraisal (MTA) which normally covers more than one technology, or one technology for more than one indication.

This process can begin after authorisation but often takes place in parallel. The decision making **process is designed to ensure that all NHS patients have access to the most clinically- and cost-effective treatments available**.¹ The basic process for technology appraisals is shown below (England).

A '**Maybe**' decision means that the drug shows promising results, but not sufficient to be approved for routine use, and can **be considered for use in the Cancer Drugs Fund** (CDF- see slide 48 for further explanation). A drug will only be recommended for observation in the CDF if:²

- it has potential to meet the value for money criteria
- the pharmaceutical company agrees to the terms of the CDF
- there is a way to collect information about how well it works or to fill in a gap which is stopping NICE from making a final decision.

After 2 years of use in the CDF, NICE reconsiders its decision and gives a final 'Yes' or 'No' decision. A summary of NICE's decisions since 2000 can be found <u>here</u>.



(1) Technology appraisal guidance. NICE. Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance (2) Cancer Drugs Fund. 47 CRUK. Available from: https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/access-to-treatment/cancer-drugs-fund-cdf

Cancer Drugs Fund (CDF)

The Cancer Drugs Fund was introduced in England in 2010, but due to increasing criticism on the unsustainable costs and lack of evidence of clinical benefit it was reformed in 2016. The reforms brought the CDF under NICE control, and changed it to a managed access fund with a fixed budget.

Previous Cancer Drugs Fund (2010-2016)

The Cancer Drugs Fund was **introduced in 2010** in England under the control of NHS England as an interim fund to **reduce delays and improve access to promising drugs** that had not been approved by NICE. However, the **fund came under increasing criticism** due to:

Unsustainable costs

The fund had an original budget of £200 million, which increased to £340 million by 2016.² In total, it had cost £1.27 billion, the equivalent of 1 year's total spend on all cancer drugs in the NHS.¹ This ever increasing spending was widely agreed to be unsustainable. It was also shown that the ring-fenced fund provided a negative incentive for drug price negotiation, ultimately driving costs of the cancer drugs up, where under normal NICE processes discounts would be applied in order to meet NICE's costeffectiveness thresholds.¹ There was also no clear criteria on the length of time a drug could stay in the CDF.

Lack of evidence on clinical benefit

A lack of follow up evidence was collected from patients on drugs in the CDF, so it was unclear if they were delivering clinical benefit. Despite making collection of basic outcome data collection mandatory in 2014 (e.g. side effects, 30day mortality), 93% of outcome data was incomplete for 2014-2015.¹ A study published after reforms were made, found that of the drugs in the CDF prior to January 2015 (47 drug indications), only 38% (18) reported a statistically significant overall survival benefit.

New Cancer Drugs Fund (post July 2016)

Due to recognition of flaws in the old systems, following a consultation period, **reforms were made to the CDF** in 2016. All patients on drugs in the previous fund had their treatment continued. The **major changes** to the process were:

Under NICE control

NICE now controls the CDF, giving them the option to send a drug to the CDF when they require further clinical data.

Managed access fund

It now funds cancer drugs for up to two years whilst NICE assesses them, allowing industry to collect further data on clinical effectiveness. This enables NICE to make a final 'Yes' or 'No' decision after the two years, and makes the new fund more sustainable.

• Fixed budget

The new CDF has a finite budget and so needs to make sure new treatments are cost-effective, which has placed pressure on pharma to lower their prices. The new reforms require industry to lower their prices even further, and potentially also rebate, if patients are to get early access to treatments whilst further data is collected on clinical benefit.³ Indeed, the new CDF has kept within its budget of £340m a year, and the new system has been seen to drive down prices charged by manufacturers.

(1) A Aggarwal, et al. Do patient access schemes for high-cost cancer drugs deliver value to society?-lessons from the NHS Cancer Drugs Fund. Ann Oncol (2017); 28(8): 1738-1750. (2) Cancer Drugs Fund (CDF). CRUK. Available from: https://www.cancerresearchuk.org/about-cancer/cancer-drugs Fund (CDF). CRUK. Available from: https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/access-to-treatment/cancer-drugs-fund-cdf. (3) https://prostatecanceruk.org/about-us/news-and-views/2016/7/cancer-drugs-fund-cdf. (3) <a href="https://prostatecanceruk.org/about-us/news-and-views/about-us/news-and-views-and-views-and-views-and-views-and-views-and-views-and-views-and-views-and-views-and-views-and-views-and-views-and-views-and-views-and-views-and-views-and-views

Variation in access between nations in the UK

Drug approval process vary in the devolved nations, with all following NICE decisions to a degree, but also with Scotland and Wales having their own regulatory bodies and CDF equivalents. These differences can lead to variation in access to cancer treatments across the UK.

Regulatory bodies (NICE equivalents) and new treatment funds (CDF equivalents), vary in the devolved nations. Recommendation and use bodies and procedures can vary in the devolved nations:¹

Scotland

- <u>Regulation</u>: The Scottish Medicines Consortium (SMC) manages the recommendations for NHSScotland.
- <u>Treatments fund</u>: Scotland has its own '**new medicines fund**', which pays for some medicines for patients with rare or end of life conditions, thus has more narrow specification than the CDF.

Wales

- <u>Regulation</u>: The All Wales Medicines Strategy Group (AWMSG) makes some decisions for the NHS in Wales, but it generally follows NICE decisions.
- <u>Treatments fund</u>: There is a **New Treatment Fund** for Wales, somewhat similar to the CDF, set up in 2017, which aims to speed up access to new treatments. The fund is worth £16m a year.

Northern Ireland

- <u>Regulation</u>: Health and Social Care Services in Northern Ireland usually follow NICE decisions.
- <u>Treatments fund</u>: There is currently no equivalent to the CDF in Northern Ireland. However, it was recently announced that drugs funded in the recommended for use in the CDF (England) will now be considered in line with existing procedures in Northern Ireland.⁴

Due to the differences in regulatory bodies and access to new medicines funds, **speed of adoption and access to new cancer drugs can vary across the UK**. Evidence of the extent of the variation and the impact is patchy, but several examples can be found which demonstrate this variation. For example:

- In May 2018, it was revealed that **seven drugs used to treat cancer and other conditions are unavailable to Scottish patients but are available in England**. This includes Perjeta (breast cancer), Tecentrip (lung cancer) and Gazyvaro (leukaemia). It was also revealed that the cancer drugs Avastin (many cancer types), Faslodex (breast cancer) and Strivarga (gastrointestinal) were **available on the NHS in Scotland, but not in England.**²
- Wales, along with introducing the New Treatment Fund, also set a target to introduce new drugs 60 days after they are brought to market; the target set by NICE for introduction of new medicines in England is 90 days. Within six months drugs were being made available within 17 days and this has since been reduced even further. This means that in some cases new cancer medicines are available in Wales before elsewhere in the UK.³

(1) Cancer Drugs Fund. CRUK. Available from: https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/access-to-treatment/cancer-drugs-fund-cdf (2) Seven drugs available in England but not Scotland, Holyrood hears. The Scotsman. Available from: https://www.scotsman.com/news/politics/seven-drugs-available-in-england-but-not-scotland-holyrood-hears-1-4738565 (3) New drugs access 'faster than ever' – Welsh Government. BBC. Available from: https://www.bbc.co.uk/news/uk-wales-42775136 (4) Department Announces Improved Access to New Drugs. Available from: https://www.bbc.co.uk/news/uk-wales-42775136 (4) Department Announces Improved Access to New Drugs. Available from: https://www.health-ni.gov.uk/news/department-announces-improved-access-new-drugs

Variation in access within England

CCGs may choose not to fund certain NICE recommended drugs, which can lead to a 'postcode lottery' in access to specific treatments. Similarly, the provision treatments recommended by NICE may be restricted nation-wide.

Each **CCG publishes its annual intentions** on how it will spend its allocated budget. Their intention is to 'drive improved outcomes for patients, and transform the design and delivery of care, within the resources available'.¹ Due to limited resources available, **CCG's may not fund a treatment that has been recommended by NICE**.

Annual intentions vary by CCG, and therefore **access** to certain support and **treatments can vary geographically**. This therefore has the potential to lead to variation equity of access to new cancer treatments, and has been seen in some cases. Variation in access to IVF in different CCGs demonstrates this clearly (see example).

In other cases, the use of treatments approved by NICE may be restricted nation-wide (see ibrutinib example).

Variation in access to IVF in England

According to NICE, women aged under 40 should be offered three cycles of IVF treatment on the NHS if they meet eligibility criteria. The **provision of IVF however vary across the country**, dependent on local CCG commissioning intentions.

CCGs may have their own additional inclusion criteria, including not having any children already, being a healthy weight, not smoking, and a narrower age range.³

For some CCGs, only one IVF cycle may be routinely offered and indeed some CCGs have removed IVF from their services altogether. This therefore leads to a **postcode lottery in England**.⁴ In **Scotland, all eligible patients can access up to three full cycles**.⁴

Nation-wide restriction of ibrutinib

One example is the provision of, the cancer drug **ibrutinib**, which was approved by NICE in January 2017 for patients with chronic lymphocytic leukaemia (CLL) whose cancer had returned after earlier chemotherapy. NHS England restricted the use to only those who had relapsed in the last three years, contradicting NICE's clinical guidance. This **cost-cutting** decision reportedly led to 200 patients not receiving the treatment who were otherwise eligible.

Following a **review** by NHS England's Chemotherapy Clinical Reference Group, it was concluded that the drug was "more effective than previously thought" and inclusion **criteria was revised to be in line with NICE recommendations**.²

(1) Commissioning intentions. NHS England. Available from: https://www.england.nhs.uk/commissioning/spec-services/key-docs/ (2) NHS scraps restriction on availability of J&J's Imbruvica in leukaemia patients. Pharmafile. Available from: https://www.pharmafile.com/news/518292/nhs-scraps-restriction-availability-jjs-imbruvica-leukaemia-patients (3) IVF Availability. NHS. Available from: https://www.nhs.uk/conditions/ivf/availability. (4) IVF Provision in England. Fertility Fairness. Available from: https://www.fertilityfairness.co.uk/nhs-fertility-services/ivf-provision-in-england/ 50

Pharmaceutical Price Regulation Scheme (PPRS)

The PPRS regulates the price of branded drugs provided on the NHS, and is renewed every five years. It is up for renewal in 2019 and Macmillan's involvement in the Access to Medicines Coalition presents potential to influence the outcome.

The PPRS is a **voluntary** agreement between the UK Department of Health and The Association of the British Pharmaceutical Industry (ABPI) on behalf of the pharmaceutical industry, that **regulates the price of branded drugs treatments provided on the NHS**. The PPRS does not apply to non-branded ("generic") versions of drugs.¹

The purpose is to ensure that safe and effective medicines are available at **reasonable prices** (reimbursements), **whilst maintaining a reasonable return** for the pharmaceutical industry.¹

The scheme was first introduced in 1957 and is generally renewed every five years or so. The current scheme runs for five years from January 2014. The scheme is **therefore under negotiation for renewal in 2019**.¹

Macmillan's involvement in Access to Medicines Coalition enables us to influence the agenda for the current PPRS negotiations.

The Access to Cancer Medicines Coalition (ACMC) brings together 24 cancer charities and patient representative organisations. Its aim is to ensure that cancer patients have timely access to the most clinically effective medicines for their condition on the NHS, and using our combined knowledge, experience and contact with people affected by cancer we will ensure that the patient voice is strongly heard in both public conversations and official decision-making relating to access.²

Policy links across the UK

England, Scotland, Wales and Northern Ireland's key health and cancer policy documents vary in their mention of new, personalised cancer treatments and priority policy areas.

Below is a summary of the links to new, personalised cancer treatments across the 4 nations in the UK. The next long term plan for health policy in England is currently under consultation, and Macmillan is inputting its recommendations including on the topic of personalised medicine.



(1) National Cancer Strategy 2017-2026. Northern Ireland Department of Health. (2) Beating Cancer: Ambition and Action. The Scottish Government (2016). (3) A Healthier Wales: our Plan for Health and Social Care. Welsh Government (2018). (4) Cancer Delivery Plan for Wales 2016-2020. Wales Cancer Network (2016). (5) Genomics for Precision Medicine Strategy. Welsh Government (2017). (6) NHS Five Year Forward View. NHS England (2014) (7) Next steps on the NHS five year forward view. NHS England (2017). (8) Achieving World-Class Cancer Outcomes: Taking the strategy forward (2016).

Impact of Brexit

Brexit has the potential to impact the delivery of new cancer treatments, from initial research to delivery in the NHS.



The <u>possible</u> impacts of Brexit are presented here. This is a rapidly changing environment and the extent of the impact is dependent on developing negotiations.

Below is a summary of where Brexit could impact Research, Authorisation, Recommendation and Use of cancer medicines. Each of these potential impacts of Brexit on the development and use of new treatments is explored in the following slides.





Cancer research in the UK benefits from both funding and scientists from the EU, and Brexit could negatively impact this. It is unclear how the UK will align with EU Clinical Trial Regulation laws after Brexit. Both of these could have an impact on the UK's position as a hub for cancer research.



Research funding¹

The **UK currently benefits from access to EU research funding programmes**. Without this funding, innovation and progress may be negatively impacted in the future.¹ The UK currently received **around £40 million** for cancer research from the EU. Not only this, but access to the EU programmes enables vital research and collaboration. Also, an estimated **16% of scientists in the UK are from other parts of the EU**.³



Clinical trial recruitment and regulation²

The UK is a leader in conducting clinical trials. It is important to collaborate internationally to aid swift recruitment of patients on clinical trials. The UK Government has confirmed that it will align as closely as possible with EU Clinical Trial Regulation (CTR) after Brexit. The CTR was passed in 2014, with implementation expected in 2019. After Brexit the UK will automatically adopt implemented EU laws, however, there is currently no provision for legislation that is developed as part of EU CTR after the UK leaves the EU. This could leave UK researchers and patients ability to participate in pan-EU trials severely reduced, which may hinder the development of new treatments, including cancer drugs.²

There is also currently no mechanism in the CTR for a country to participate if it is not in the EU, and there are also concerns that Brexit **could impede the flow of data between the UK and EU** around the online portal and central database.

(1) Brexit What does it mean for medical research? Available from: <u>https://www.rcplondon.ac.uk/projects/outputs/brexit-what-does-it-mean-medical-research</u>. (2) TK Burki. UK to align with EU clinical trial rules post-Brexit. The Lancet Oncology (June 2018); 19(6): 289. (3) Brexit will have large impact on health and NHS, say researchers. CRUK (September 2017). Available from: https://www.cancerresearchuk.org/about-us/cancer-news/news-report/2017-09-29-brexit-will-have-large-impact-on-health-and-nhs-say-researchers



The MHRA is likely to take on more responsibility for drug authorisation in the UK, but the government has suggested it would still like associate membership of the EMA.



EMA/MHRA balance

The UK's relationship with the EMA will change; the transition agreement has stated that the MHRA will not be able to lead on EMA wide centralised drug licensing and an MHRA authorisation cannot be used as a starting point for full EMA regulation. The government has suggested it **would like associate membership of the EMA**, but it is difficult to define exactly what this means. This therefore involves a large amount of work moving. However, the MHRA currently does around 20% of the scientific work for the EMA, and often the most complex cases, so may have the expertise to build upon once it takes on more responsibility.

It is also suggested that the work the MHRA does on behalf of the EMA contributes to making the UK an attractive location to carry out clinical trials.¹

The UK has traditionally been a market for early launch of medicines from the EMA, as it is classed as a 'first tier' state. It is possible that that the **UK could become a 'second tier' state for pharmaceutical imports**, which could **reduce access to new and innovative medicines**.4 In Switzerland, despite having a number of bilateral trade agreements with the EU (as the UK may after Brexit), it is estimated that it gains access to new medicines on average 157 days later than the EU.²

The EMA has already begun a **physical move from London to Amsterdam**. This will result in an **estimated cost of €582.5 million**. A June 2017 European Commission position statement on the financial settlement, stated that the UK should cover the costs relating to the withdrawal process, including the relocation of agencies or other Union bodies.¹

If the MHRA takes on more responsibility for authorisation of drugs in the UK, this could present **potential for a fast track stream lined MHRA and NICE parallel approval process**, with closer links to NHS England (although this may not be affordable without an increase in NHS funding.³

(1) Briefing Paper- Brexit and medicines regulation. House of Commons Library. November 2017. (2) Brexit and the impact on patient access to medicines and medical technologies. Brexit Health Alliance (January 2018). (3) PK Lorgelly, The Impact of Brexit on Pharmaceuticals and HTA. PharmacoEconomics (2018); 2(2): 87-81/ (4) The impact of Brexit on the pharmaceutical sector. House of **5** Commons (May 2018).



Forecasts suggest that there will be less money available for public services, so financial pressures on the NHS could worsen. It could also affect supply of medicines, devices and other products between the UK and EU, and may particularly impact movement of radioisotopes which are used to treat cancers.



Increased NHS budget pressures

Brexit is forecast to result in there being less money available for public services, including the NHS. The hit to public finances is expected to be about £15 billion a year by the early 2020s.¹ Drug prices could also increase as a result of Brexit.



Customs and trade

Medicines, devices and other products used by the health service often rely on supply chains which stretch across the EU. Changes to our involvement in the single market and customs union will mean dramatic change for customs and trade.

There may be a **particular impact on those products with a limited lifespan**, which will degrade if they are left at the border. This includes **radioisotopes used to treat cancers**. The UK's certain departure from **Euratom*** will mean there will be a need to develop a new regulatory system for cross border trade.³ However, the government has expressed a clear interest in fully associating the UK with the body's research arm (which would involve UK financial contribution).²

*European body that regulates the nuclear industry across Europe, including safeguarding the transportation of nuclear materials.



Brexit could increase NHS workforce shortages further, and the current vacancy gap may extend beyond repair if EU nurses and doctors feel unwelcome in the UK.



NHS workforce shortages

Many European workers are already concerned about their immigration status, and how it may change after Brexit is enforced. There has already been an **89% drop in the number of nurses and midwives coming to work in the UK from Europe**- a drop from 10,000 to just over 1,000 in just over one year (Sept 2016-17). Around **60,000 people from EU countries work in the NHS and 90,000 in adult social care**. The NHS workforce is already under pressure and many are concerned that the **vacancy gap** will be stretched beyond repair if EU nurses and doctors feel unwelcome or if their immigration status changes.

In Northern Ireland, many nurses and healthcare professionals work in Northern Ireland but live in the Republic of Ireland, and vice versa. Therefore any **Brexit deal affecting cross-border movements has the potential to impact patient care in Northern Ireland** and the Republic of Ireland; there must be a continuation of free movement to mitigate this risk.³

> Brexit has the potential to negatively impact the experience of PWLC, and the end result is dependent on the outcome of current talk. Emerging research and policies on Brexit should be monitored more closely to enable Macmillan to be equipped to act.

(1) Lifting the visa cap for nurses and doctors is not all the NHS needs to relieve its staff shortages. LSE. Available from: <u>http://blogs.lse.ac.uk/politicsandpolicy/nhs-staff-shortages/</u> (2) Brexit will have large impact on health and NHS, say researchers. CRUK (September 2017). Available from: <u>https://www.cancerresearchuk.org/about-us/cancer-news/news-report/2017-09-29-brexit-will-have-large-impact-on-health-and-nhs-say-researchers</u> (3) BRIEFING: The effect of Brexit on the NHS. Royal College of Nursing (March 2018). /brexit-what-does-it-mean-medical-research.

Experience of PLWC

PLWC's understanding of personalised medicine

There is very limited research that addresses the question of what PWLC understand of the concept of personalised medicine. However, this is a topic area that Macmillan's Research Grant Scheme is funding in 2018 in order to start to build a research base on this subject.

There is very limited research that addresses the question of what people understand about the concept of personalised medicine. For this reason, in Macmillan's Research Grants Call for 2018, one of three topic areas was in this area. The box below shows the areas that the Research Grants will cover:

The impact of new developments in cancer treatment (such as immunotherapy, personalised medicine, modern radiotherapy techniques) on the lives of people with cancer

Priority topics

- Access to, and expectations of, newer treatments; the experiences and perspectives of people living with cancer.
- Understanding the real-world experiences of people who are undergoing newer cancer treatments and identifying their support needs.
- The long-term effects of newer cancer treatments on people's lives.
- Managing uncertainty for people on long-term, non-curative treatment who are living with cancer as a chronic condition.

Macmillan must ensure that developments arising from Research Grants Scheme projects are monitored and acted upon. It is important to reflect at the end of these projects, and look at the end at where there are still remaining gaps, and consider how to address these.

PLWC's understanding of personalised medicine (cont.)

The majority of patients understand the concept of testing a tumour to inform treatment decisions, however physicians over-estimate their willingness to delay treatment to allow for additional tumour testing.

A multi-national survey¹ of cancer patients and physicians was carried out, comparing their awareness, understanding and adoption of personalised treatments. Although this research is somewhat out-dated (and there are associated caveats- please see below), it gives an indication of the understanding of the two audiences, and how they differ.



78% of **patients** understood that a tumour can be tested to help inform a doctor's decision making

... and **physicians** accurately predicted this at a close **73%**

 \bigcirc

66% of patients reported willingness to delay treatment to allow for additional tumour testing

...and **physicians** overestimated this, believing that **82%** of their patients would be willing to do so Physicians underestimated the time they would be willing to wait:

- 22% of patients said they'd be willing to wait a month

 physicians estimated this at 14%
- 32% willing to wait as long as it takes – physicians estimated this at 3%

Caveats:

- Limited to specific cancer types (CRC, NSCLC and breast cancer)

 this may affect knowledge, and experience of treatment etc.
- Encompassed 12 specific countries (including the UK), so may not be an accurate representation.
- The surveys were conducted in 2011 (patients, n=811) and 2013 (physicians, n=895), in which time there were advances in biomarker testing, so **may limit the comparability** between groups, and also means that the results may be **out of date**.

(1) F Ciardiello, et al. Awareness, Understanding, and Adoption of Precision Medicine to Deliver Personalized Treatment for Patients With Cancer: A Multinational Survey Comparison of Physicians and Patients. Oncologist (2016); 21(3): 292-300.

Challenges in communication

There are challenges for HCPs in communicating complex subjects to PLWC, which can create a barrier in effective communication. One way to avoid this is to use simple language the public are already familiar with. However, some experts are resistant to doing so.

Interviewees acknowledged that there are **challenges in communicating both complex medical concepts and uncertainty** for HCPs in contact with PLWC. This is only made more challenging by the varying language used by different HCPs that PLWC encounter.

For example, a substantial **gap exists between how different professionals think genomics should be discussed and what the public actually understands**. Some professionals may believe that patients should be educated to use and understand precise technical genomics language when using a genomics medicine service. However, this can be seen as a **barrier to communication** between patients and professionals, as well as creating variation in the language different professionals use.

One way to avoid this unequal power dynamic and increase understanding is to **use language that people are already familiar with**. For example 'glitch' could be used instead of 'variant' or 'mutation'. Similar, technical terms such as 'germline and 'somatic' could be discussed in terms of 'inherited' and 'acquired'.

However, the level of the understanding and desire for the use of technical terms by the public is unclear. **Resistance can be encountered** to the idea of altering genomic vocabulary for the public. It is suggested that more simplified language should be used in the first instance, with the option of more technical detail for those who wish to have it.

Socialising the Genome¹

Socialising the Genome is a research project led by Dr Anna Middleton investigating how issues to do with genomics are currently discussed in natural conversation. Off the back of this, animations were made as one new way to describe genomics to people who know nothing about it. They aim to use metaphors, imagery and conversation to ensure that they are relevant and understandable.



Challenges in communication (cont.)

Personalised cancer medicine brings challenges in communicating treatment eligibly, as HCPs have to explain why a patient is 'eligible' for a certain treatment, but not another. It also causes delays in establishing treatment plans, which may cause further anxiety.

We are in a transition from the more traditional 'population oncology' to 'personalised oncology' (see slide 13). This presents new challenges for the communication with the cancer workforce and PLWC.

Understanding treatment eligibility

Personalised medicine will mean that treatment regimes can be tailored to the genetic makeup of the patient's cancer. Not only does this mean that oncologists will be able to say 'you are more likely to respond to this treatment', but it also means that it will be easier to predict when a patient is less likely to respond. This may bring **challenges in communicating why a patient is 'eligible' for a certain treatment, but not another**. It was broadly agreed by interviewees that **HCPs are well-equipped** to discuss this with patients.

Some new immunotherapies are widely covered in the news as 'wonder treatments', when often results are in early clinical stages (see headlines). This can create challenges for HCPs as patients may ask about **eligibility for these treatments, when they are not yet available** and only show clinical benefit at an early stage or with limited patients.

Uncertainty in treatment plans

Testing patients tumours to determine appropriate treatments can cause significant **delays in establishing a treatment plan**, due to the time taken to get and interpret the results of tests (see slide 60). This can be difficult for patients, and it was suggested that this delay can cause further **anxiety**. This means that there is greater uncertainty for the patients, and HCPs must be well equipped to communicate with patients and support them.

Immunotherapy in the news

A recent case of immunotherapy 'curing' terminal breast cancer for the first time made the headlines. This was a single case and the treatment is not yet available for most cancer patients. Although the results are promising, until a clinical trial has been conducted we don't know how effective this treatment will be.

Woman cured of advanced breast cancer using own immune cells in 'exciting' global first

'Remarkable' therapy beats terminal breast cancer

Doctors hail world first as woman's advanced breast cancer is eradicated

'It feels miraculous and I am beyond amazed': Breast-cancer victim who was on the verge of dying reveals she has been CURED by a new immunotherapy treatment in a world first

It is vital that HCPs are equipped to support PLWC through these challenges in communication (see workforce section).

Patient information & support – immunotherapy

Patients must be well-informed and monitored in order to detect side effects early, so that they can be dealt with appropriately as early as possible. Patient Information Leaflets and Patient education are examples of how patients can learn more about their treatment.

Side effects

Side effects need to be monitored closely because they can range from mild (e.g. rash) to severe (e.g. pneumonitis- inflammation in the lungs), and are unpredictable compared to chemotherapy. In order to detect side effects early, patients ned to be monitored at home between the therapy administrations, and **need to be made aware of the side effects themselves** so that they can notify physicians as early as possible.

Patient Information

Patients can get information on side effects from the Patient Information Leaflets, which tend to include accepted information about the possible adverse effects of a drug, including levels of probability including derived from trials. However, the **information is usually not provided in a structured format**, sometimes mentioning terms that **may not be clear for people with low health literacy**.¹

Further information has been developed to guide patients through their immunotherapy, but at this point is **quite patchy**. Examples include the European Society for Medical Oncology's (ESMO) guide on immunotherapy side effects, and the European Cancer Patient Coalition's (ECPC) brief guide on immuno-oncology for patients.

Further online sources of information are explored in slides 66-69.

Patient education

Some make a case for implementing patient education schemes, similar to schemes such as Surgery School, where patients are prepared mentally and physically for the treatment they are about to receive.



There is some patchy information and education in place for patients, but it not clear how well informed they are and how they monitor their symptoms and self-manage. More should be done in order to understand this area.

(1) EM Zini, et al. Standardization of immunotherapy adverse events in patient information leaflets and development of an interface terminology for outpatients' monitoring. J Biomed Inform (2018); 77: 133-144. (2) Immunotherapy Treatment FAQs. Lancashire Teaching Hospitals. 2018. Available from: <u>https://www.youtube.com/watch?v=_DJLcQaDtf0</u>.

Information provision

Macmillan's role in genomics

The advancement in genomics and services available has implications for the care of PLWC, and therefore for Macmillan. These could be in understanding and communicating, new support offers and influencing.

The advancement of genomics and the development of a National Genomics Medicines services have implications for the care of PLWC. These are seen in five main areas as shown in figure 1, so not only in treatment (therapy selection and clinical trials) but also in diagnosis, prognosis and cancer susceptibility. This has **implications for Macmillan supporting PLWC when they need us most**.

Implications for Macmillan

- 1. Complex and fast-developing field
- Understand it
- Communicate it

2. Shift in types of Macmillan support needed

- Large number of well people needing support
- New decision support tools
- Screening and prevention
- Access to medicines

3. Influencing

- Address personal financial implications of genetic risk
- Reality check on what new technologies can do
- Lead the ethical debate

What we can do now: actionable NHS England information for cancer patients Early analysis found 65% of Project cancer cases have variants in actionable genes ciinica Prognosis **Clinical Trials** openina up eliaibility **Cancer Molecular Lesions** WGS provides extra diagnostic reach (structural variants. copy no. variants etc.) Global patterns of mutation ('signatures') proving informative Defining causal drivers from benign 'passengers' is critical Therapy selection Cancer susceptibility

Figure 1²- NHS England slide demonstrating the five different areas that could be impacted by implementing a National Genomics Service

Macmillan's information provision

Macmillan currently has some information on targeted treatments and immunotherapy, with limited in-depth information on immunotherapy, and on the genetics and cancer. However, there are future plans to create landing pages on personalised treatment, immunotherapy and genomics.

Targeted therapies and immunotherapy			Need to talk? 0808 808 00 00 Monday to Fiscay, Sam-Spin Call us free" >	
Targeted therapy explained				
Find your targeted (biological) therapy	How targeted therapies work		What are targeted (biological) therapies?	
		This attention shows how targeted therepide scots and when effect they have on the body. About our cancer information videos >	Tergeted therepies are sometimes innovin as bological therepies. They interfere with the way cancer calls grow.	
	Anglogenesis Inhibitors >	Cancer growth inhibitors >	Monoclonal antibodies >	
	Anglogenesis inhibitors prevent canceler from making new bload vessels. Whost new food vessels, the cancel cannot grow.	Cancer growth imitators block owtain chemical legines within calls, which show down or steps the growth of the cancer.	Monoclonal antibodies can ettach tremelves to cancer cells, Trey can togare e person's immune system to von against ma cancer or some monoclonal antibodies work in other ways.	
	Vaccines >			
	Cancer vaccines herp the immune system recognise cancer calls and destroy them			

Currently, there is a landing page on 'Targeted therapies and immunotherapy' which covers some examples of personalised treatments.

Immun	otherapy
Immunofrenacy drugs e treatments are occasion	noourage the body's trimune system to light cancer cells. These ally used to treat advanced indresy cancer.
There are many clinical t future in treating kidney	rials looking at new immunol/herapy drugs that may be useful in cancer
Interferon alpha-2a (Rofemn-A®)
Interfertm can be used to bevacizumab (Avaattin)®	o treat advariced kidney cancer and is cometimes given along with).
Interferon is naturally pro drug. It has effects on th	duced by the body in small amounts and can also be made as a e body's immune system that can help fight some cancers.
Interferon is usually give You, a retaine or parer o interferon often causes it and aching in the back, paraceternol, to reduce very fired (tatigue)	In three times a week by nijection under the sim (subcuberiously) an be length hole to do this at home. In the final output of weeks, usine symptomic subch a child an attribute the final subcuber. Joints and muscles. Your doctor can preceitible medicine, such as here symptoms. Another common side effect of interferen is desing
Aldesleukin (interleu	kin-2, Proleukin®)
Aldesleukin is an artificia as a dhip into a vein (intr	of version of a protein that occurs naturally in the body. You have it as enously)
This treatment is very sp in hospital to have it. Co or losing your spetite	ecialised and only given in a few units in the UK. You'll need to stay minor side effects of aldesieukin are flurive symptoms, feeling alok . It may also cause some sensus side effects on the heart and lungs

'Immunotherapy' is explicitly mentioned on the page below, however these are specific drugs for the treatment of kidney cancer, and does not explore wider use and developments in immunotherapy.

Causes	and risk f	actors	Need to talk? 0808 808 00 00 Vocar to Total Jan-Jan Call us twe? -
Potential causes of	Genetic condition	ns and inherited ca	incers
Family bistory Genetic conditions	You might be offered the chance to test for some genetic conditions. It's proportiant to understand what might happen and the effect any possible reso might have.		
and investigations Pre-caracteristic conditions	Inherited cancers > I a tartier source more often in a family free often general population, some people in the family may have intentied a cancer succeptibility gime	Inherited cancers: based cancers A small number of based center cases are inset to genetic conditions, which surrise termines	Inherited cancers: bread cancers Seat cancer on ametimas be lined to attend garas, which can up in familias
	Inforcement concerns: ovarian concerns Some cases of overan concerns invest to allowed genes, which can not in families	Industrial concern: prostate concerns Some cases of program provide infect to output infect the concern privation of the sector which can be realized in which can be realized	Particial admortational polyposis (FAP) > Tartila Admortations before Hard an one in bendies it has been an one in bendies. It has been and can increase there is all getting bound cancer
	Lynch syndrome > Cyrch syndrome (LS) is a constant that can run in families in invasions the ran of investiging tome cancers	If you are referred to a genetics specialists The protos specialists of and you sumform allowed your timely to high their rook and if you are impresent which a cancer in your timely.	Genetic counselling > A pende consultation is a dissussion with a pension trained in genetics. They will advice you chrytour risk at developing cance
	Things to consider before having a genetic test> These are several frigs to consider before heres a	Genetic testing> You will any be offered penetic technol your ferrity hates they accepted a cancer	Having a high risk of cancer > Norway you have an increased risk of cancer can be athleted. There are accord

Currently, Macmillan's information on genetics and cancer focuses on causes of cancer and risk, as opposed to genomic testing to enable personalisation of treatments.

A landing page on personalised cancer treatment is currently under development, and will cover the general concept of how cancer treatment can be personalised to the individual. A landing page on immunotherapy is being developed, to ensure that Macmillan is a source of information on newer cancer treatments, and it is easier to navigate to find information on immunotherapy. Scoping a future page on genomics and cancer, to cover personalisation of treatment that may result from the introduction of a National Genomics Medicine Service in England.

Other providers' information provision

Cancer Research UK (CRUK) provides comprehensive information on immunotherapy and personalised medicine. Most information on genomics and cancer focuses on risk and causes of cancer, other than information from more academic providers.

CRUK provides **indepth** information on treatment types, including a **landing page on immunotherapy** with details on what it is and the types of immunotherapy.¹



CRUK has a page with detailed information on Personalised Medicine including describing drugs for specific cancer types.²



Similar to Macmillan's information, most providers **focus on genetic risk and causes of cancer** as opposed to the impact of genomic testing on treatment.

Information on genomics and cancer treatment can be found on more academic/research level sources of information. However, at this point genomics has **not made it to the mainstream** of cancer treatment, but this is likely to change with the mainstreaming of the 100,000 genomes project, launching a National Genomics Medicine Service in England.³



Macmillan is currently collaborating with NHSE to co-create new information on genomics in cancer care and new education and training for HCPs, and should continue work with NHSE to engage the devolved nations in anticipation of the roll out of access to genomics medicines centres across the UK in 2019.

(1) Immunotherapy. CRUK. Available from: <u>https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/immunotherapy</u> (2) Cancer Research UK: Personalised Medicine. Available from: <u>https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/personalised-medicine</u> (3) 100,000 genomes project. Genomics England. Available from: <u>https://www.genomicsengland.co.uk/the-100000-genomes-project/</u>.

Macmillan's information and support – Online Community

Macmillan's Online Community facilitates discussion and support about all aspects of cancer experience. Understanding of newer treatments by Online Community users varies, and it is difficult to generalise their understanding as it has a very large and diverse usership.

<u>Caveats</u>

It is difficult to generalise the experiences and understanding of users of the Online Community. The evidence below is based on searches within the online community for examples from different users.

The Online Community facilitates the discussion on cancer treatments, **offering peer support** (in Groups) and **expert support** (in the Ask an Expert section). This includes questions and discussion on newer treatments such as immunotherapies.

For example, there are lots of people on the Online Community who have a great understanding of the side effects of immunotherapies as their doctors/ nurses would go through them prior to starting treatments and should give information for them to read. However, some have more limited knowledge. The Community also gets questions from family and friends who want to have a greater understanding of what to expect.

It can also be seen that the Online Community often get **asked about new treatments and whether they would be eligible for them**.

Cancer treatments Start a discussion Share experiences and get support about any types of cancer treatment, including chemotherapy, radiotherapy, surgery, biological or hormonal therapies, transplants, and clinical trials. Chemotherapy A support group Your questions for everything about head and about chemotherapy, neck cancer being treated and side effects... Whether your question is Radiotherapy about treatment, dental A group for discussions and care, diet or radiotherapy, questions about ask our team online. radiotherapy. Get together, share your... Surgery A place to discuss anything about surgery. Share your experiences, and ask questions... Ask a question >

Figure 1- <u>Macmillan's Online Community</u>. Clockwise starting from top: Cancer treatments group, Ask and Expert example for H&N cancer and Chemotherapy, Radiotherapy and Surgery groups.

Cancer workforce

Workforce planning – immunotherapy

New treatments, such as immunotherapy, create workforce implications for the ongoing and future use of cancer treatment services, which require estimates to be made on how many workforce and service configurations are needed to deliver best practice treatments to patients.

Workforce shortages have limited the capacity of services to plan in the long-term, focusing more on dealing with immediate issues.

Treatments are becoming more complex, with new treatments including immunotherapies reaching patients, and the volume of patients is increasing. The **workforce needs to be equipped to deal with these newer treatments**, as well as novel combinations, such as radiotherapy and immunotherapy.¹

A 'best practice model' was developed by CRUK to estimate how many staff would be needed to deliver best practice treatments to patients, including ensuring that all staff have time for training and development, service improvement and clinical research and contracted work hours. It is recommended that this model is used to project required workforce numbers based on patient demand, not on affordability.

Immunotherapies create clear workforce implications for the ongoing and future use of cancer treatment services: regular monitoring of treatment response and side effects is essential, and additional workforce capacity is needed for treatment delivery.

Representation of workforce modelling methodology



Figure 1 – directly from CRUK report¹

Macmillan could play a role in supporting workforce model development, including evaluating the cost implications.

Workforce upskilling – immunotherapy

A general education approach is required, as all professionals who are part of cancer patients' pathway must understand immunotherapy. However, the level of upskilling required can be stratified by the level of their involvement in cancer care.

The issue of upskilling the workforce in new developments in cancer treatment was discussed with interviewees. It was broadly agreed that a **general education approach is required**, as all professionals who are part of cancer patients pathway must understand immunotherapy. However, the **level of education required to upskill can be stratified** by the level of their involvement in cancer care.

It was suggested that GPs (competent) should be educated to understand how immunotherapies work, the side effects and how to recognise them, and who to contact if side effects are presented. Whereas highly specialist/specialist workforce should understand immunotherapies in greater detail.

In particular, **upskilling and education related to the side effects** was identified as key for the whole workforce to understand, **not just for those working primarily with PLWC** (e.g. ambulance professionals). However, **time, money and accessibility** of training courses were identified as **strong barriers** for enrolment in Continuing Professional Development (CPD).

Newly qualified professionals may already have this education as part of their qualification, but, for example, consultants who are already qualified may need to learn this as part of their CPD. This means the education is more down to the individual, as they find the **time, money and accessible course** themselves.

There was a suggestion that Macmillan could support the roll-out of immunotherapy Learning and Development (L&D) courses in the geographies, with a national approach adopted to the educate about the core principles.

Competent

newly qualified / generalist (non-cancer) specialist

basic / initial competencies / literacy about cancer and new technologies

provide routine care in uncomplicated / low risk situation

recognise impact of cancer on person & family

Specialist senior / advanced practice role

additional pathway / technical skills & knowledge specific to cancer care

spends a significant amount of time providing care that is complex and / or associated with risk and / or uncertainty to people affected by cancer Highly specialised Leadership and management of

cancer services / service change at local / regional and national level

Provides highest level of complex clinical care that includes significant risk and / or uncertain for most of their time

Figure 1¹- role of competent, specialised and highly specialised cancer workforce.

Although it is promising that newly qualified cancer specialist will have new and personalised treatments included as part of their training, there is still a large ageing workforce who will not have had this training which cannot be ignored.

Workforce roles – immunotherapy

Further work is required to understand whether core roles, like chemotherapy nurses, are required to support the increasing number of patients receiving immunotherapy, or whether upskilling current workforce and looking at different ways of working would be a more appropriate approach.

Workforce and immunotherapy

Outside of major cancer centres, HCPs are likely to understand the side effects of chemotherapy as they are predictable, tend to present in 7-10 days, and they know what emergencies to look out for (e.g. neutropenic sepsis). However, the side effect profile with immunotherapies is fundamentally different, so a lot of work needs to be done to prepare the workforce in this new area. It is pivotal to understand the impact and changes required to support existing roles and services such as acute oncology (AO), chemotherapy nurses and units and wider workforce in developments in immunotherapy, including toxicities; where we have already seen an increase in input from AO nurses. It is also important to consider the role of specialists.

Suggested role of Immunotherapy nurse

It is suggested that the role of an immunotherapy nurse is in being a key worker for patients and the cancer workforce alike. Their role could be pivotal in understanding new developments in immunotherapy, including their side effects and how to manage them, education and the implications for the wider workforce.

Macmillan needs to better understand the upskilling needs of the workforce and impact of immunotherapy delivery on the cancer workforce (e.g on primary care, acute oncology, chemotherapy nurses, clinical nurse specialists).

Chemotherapy nurse

It was suggested that chemotherapy nurses may play an important role in supporting the increasing number of cancer patients who receiving immunotherapy.

However, there is still more we need to understand about the chemotherapy nursing workforce in order to better understand future implications of new treatments on their workload. The key questions include:

• To what extent are they already at the forefront of delivery of new treatments?

There is a variation in the number of vacant posts across England.³

Chemotherapy nurses

Highest vacancy rate

15 vacancies

per 100 filled roles

Lowest vacancy rate

0 vacancies

per 100 filled roles.

- Will they be a key deliverer of new treatments going forward?
- What are their needs (upskilling, capacity etc.)?

We already know from census work (England and Wales) that chemotherapy nurses have high vacancy rates, exceeding those of specialist cancer nurses and cancer support workers. 1,2

Is this a Macmillan area?

Traditionally chemotherapy nurses were not an area that Macmillan invested in. However, these are posted that Macmillan is now funding- for example the census that 5% of chemotherapy nurses in England are Macmillan badged.¹

(1) Cancer workforce in England. A census of cancer, palliative and chemotherapy speciality nurses and support workers in England in 2017. Macmillan Cancer Support (2017) (2) Cancer workforce in Wales. A census of cancer, palliative and chemotherapy speciality nurses and support workers in Wales in 2017. Macmillan Cancer Support (2017).
Workforce guidance – immunotherapy

Development of guidance on the management of patients on immunotherapy has been patchy, but there is some central guidance developed by UK Oncology Nurses Society (UKONS) for triage services. This could be a good point of reference for HCPs across the cancer workforce.

Guidance on management of patients on immunotherapy, including how to deal with the side effects, has **been developed in centres scattered across the UK**, with many cancer centres developing their own guidance. **Quick access to toxicity management** information ensures **timely access to steroids/immunosuppressive treatment** for cancer patients experiencing immune-related adverse events, **thus reducing length of hospital stays or avoiding hospital admission** entirely.²

Central guidance for AO/triage services

The **UK Oncology Nurses Society (UKONS) 24- Hour Triage Tool** is a risk assessment tool that uses a Red, Amber and Green (RAG) scoring system to identify and prioritise the presenting problems of patients contacting 24-hour advice lines for assessment and advice.¹

V2 was released for use in 2016 and was updated to include use for patients on immunotherapy. Although this tool was developed for triage services, it **could be a good point of reference for professionals across the cancer workforce** to understand what to look out for, particularly in newer development such as immunotherapy.

There are also **AO Apps** for HCPs to use on the go, including at Velindre where 'A Quick Guide to Cancer Emergencies' App has been developed, and there is a UKONs App in development.

There is also potential to **add QR (quick response) code to patient-held alert cards**. Patient-held alert card are already widely used for patients receiving anti-cancer treatment, and with the addition of the QR code allows any HCPs to access clinical management guidelines quickly. Nurses at The Clatterbridge Cancer Centre are leading on development of this system.²







Figure 2³- Velindre AO app

Workforce – genomics There are challenges associated with implementing genomics services, around education and training, as well as in other areas such as lack of awareness and difficulties in engaging different groups.

There are associated challenges for the cancer workforce, in education and training, as well as other areas:¹

Challenges in Education and Training

Motivation and meaningfulness:

Many healthcare workers have not yet used genomics in their practice and so do not understand the relevance of the training and education.

• Manpower:

Limited numbers of specialists capable of delivering highquality genomics education and training.

The clinical pressures limiting the clinicians' capacity to engage in informal training or networking; training approach and delivery must be aligned with their limited time and focus on specific needs.

• Funding:

Finding innovative approaches by partnering with other education stakeholders

Other Challenges

Awareness:

Many healthcare workers are not aware of the importance of genomics. It is important to get the messages right so that they understand the impact of genomics for their role and for their patients.

- Fully understanding the gaps in education in existing workforce
- · Best practise in consent
- Ensuring primary care links
- Maintain the momentum: Ensuring awareness and education in Genomics continues after the 100,000 Genome Project is completed.
- Engagement with CCG's
- Reaching nurses:

Only 46% of nurses feel they have insufficient knowledge of genomics.

Case study: National Genetic Diabetes Nurse (GDN)

Developing skills of specialist nurses is a cost effective and successful means of rapidly increasing genetic knowledge in clinical care, and could potentially be readily transferred to other fields including genetic testing in oncology.¹

 <u>The problem</u>- under-diagnosis of monogenetic diabetes Monogenic diabetes accounts for 3% of UK diabetes diagnosed < 30yrs (40,000 cases) Diabetes teams didn't recognise 'genetic' diabetes Referrals for genetic testing were sporadic, with an average of 9 years from diabetes diagnosis to molecular testing. Different types of monogenetic diabetes require different treatment and management. 	 The solution- Diabetes Nurse Specialists (DNSs) Why DNSs? Already located within diabetes team Have their own patient caseload Enables rapid integration into clinical practise Responsibilities: Presentations to health care professionals across region Identify/refer possible patients Guide treatment choices Organise family follow up Attend initial and extended training
 Implications for other areas – readily transferrable It is an established cost effective and successful project, and readily transferrable to other specialities, particularly suited when: Genetic testing can guide patient diagnosis and management within speciality There is not a tradition of genetic training in the speciality There are experienced specialist nurses / other healthcare professionals with high level of core subject knowledge without specific training in genetics There is an appropriate centre of expertise in the subject area to provide training and support 	 How it went- Successful project with potential challenges Successes Presentations – vast majority (99%) rated excellent/very good, delivery to large number of professionals (935 presentations to >12,950 professionals) >1,250 changed treatment as a result of genetic testing Increase in referrals for patients, family and friends Potential challenges: Costs are modest but obtaining continued funding is challenging Aim for 1 GDN per 1 million population Identifying high calibre GDNs in all geographical areas Time consuming

(1) GEP Nursing and Midwifery Round Table Final Report. 24th January 2018. Not widely available – please ask to view.

Appendix

Appendix A – Interviewees and contributors

Interviewees:

1.	Jon Antoniazzi	Policy and Public Affairs Manager Wales
2.	Nikki Cannon	Specialist Advisor - Workforce Engagement
3.	Elspeth Cumber	[Former] Clinical Fellow
4.	June Davis	National Cancer Rehabilitation Lead
5.	Sam Dick	Policy Officer
6.	Jacqueline Goodchild	advisor - Workforce Engagement
7.	Rebecca Leech	[Former] Senior Policy Officer
8.	Matt Lumsden	People & Communities Engagement Advisor
9.	Niamh Kelleher	Policy Manager – Health Inequalities
10.	Philippa Jones	[external] Associate Acute Oncology Nurse Advisor
11.	Jane Maher	Joint Chief Medical Officer
12.	Archie McNair	[Former] Clinical Fellow
13.	Ellen McPake	Digital Nurse
14.	Sharon Middleton	Partnership Manager
15.	Karen Roberts	Chief of Nursing and AHP
16.	Chris Scally	Partnership Manager
17.	Richard Simcock	Consultant Advisor
18.	Tracy Williams	Cancer Content Manager

Junior Strategic Analyst
Treatment and Recovery Specialist Advisor
Senior Strategic Analyst
Strategic Analyst
Chief Economist
Strategic Analyst
Head of Specialist Advisory - Cancer Support Settings
Policy Officer
Treatment and Recovery Advisor

MACMILLAN CANCER SUPPORT

We're here to help everyone with cancer live life as fully as they can.

For information, support or just someone to talk to, call 0808 808 00 00 or visit macmillan.org.uk