60 years of life-saving research

Blood cancer UK

Foreword

The report you're about to read tells the story of the research we've funded and the lives that have been saved over the last 60 years.

It's the story of scientific breakthroughs that have collectively changed the world for people with blood cancer. It tells you how blood cancer has gone from a condition that was almost always a death sentence, to one that can often be put into long-term remission or lived with as a long-term condition.

It's a story of ingenuity, determination and sometimes luck. A story of how each generation of researchers has built on the breakthroughs of previous ones.

As I read this report, I feel hugely proud of what we have achieved through research. Blood cancer researchers in the UK have been pioneers in their field, and continue to inspire young researchers who will continue their vital work.

But while the breakthroughs contained in these pages – some we funded on our own, some in collaboration with others – are amazing, the researchers responsible for them are just a part of the story.

Every breakthrough and every life that's ever been saved as a result, has only been possible because of our fundraisers. Over the last 60 years, we've been incredibly lucky to have the support of thousands upon thousands of people to count on. They've run marathons, baked cakes, shaken buckets, and so much more. Every single one of these people have a different "because" story, but they are all united by a single cause: to beat blood cancer.

Their passion and tenacity over decades have been nothing short of a phenomenon and has been the foundation of our work. The science in this report is every bit as much their achievement as it is our researchers. It simply wouldn't have happened without them.

Our story is made up of thousands of people, who each have their own story to tell, and who continue to play a vital role in shaping our charity's story.

The other thing that occurred to me as I read this report, is that it is missing a final chapter. It ends at the point in the story where outcomes for people with blood cancer have been improved dramatically, but there is still much more to be done.

Blood cancer still claims 15,000 lives a year in the UK and many more people have to endure the side effects of harsh treatments.

We're now at the point where the day we beat blood cancer is finally in sight. A generation from now, we could be in a position to add a final chapter, which will explain how we finished the job. This would say how we all played our part in funding the research that means no one dies of blood cancer.

But that will not happen just because we want it to. It will only happen if we're able to keep funding research at the same level over the next 30 years as we've managed to do for the last 60.

Whatever donation you're able to make – whether it's thousands or a few pounds – you'll be helping make sure the incredible story set out in this report gets the ending that people with blood cancer deserve.

Gemma Peters

CEO of Blood Cancer UK

Because our story begins with one family's wish

Blood Cancer UK was started in 1960 by the Eastwoods, whose daughter Susan died just weeks after being diagnosed with blood cancer. Susan's parents wanted to stop others from having to go through what they had, so they started raising money to fund research into finding a cure.

From their first fundraising efforts of selling "two-bob hankies" sewn in their living room, they were joined by more and more families that had been affected by blood cancer. These families soon became a movement of people dedicated to beating blood cancer.

Over the last 60 years, their fundraising efforts have led to an incredible £500 million being invested in blood cancer research. This has led to a long line of breakthroughs that have improved treatments and saved lives.

This report describes the impact of our investment in a range of different types of blood cancer. We've invested in lab research, resources and people. We started out as a leukaemia focused charity but soon decided to apply our knowledge across all types of blood cancers to increase our impact and improve outcomes for everyone with these diseases.

Here are just some of our breakthroughs over the past 60 years:

Clinical genetics test

Our researchers have identified important changes in genes linked to different blood cancers.

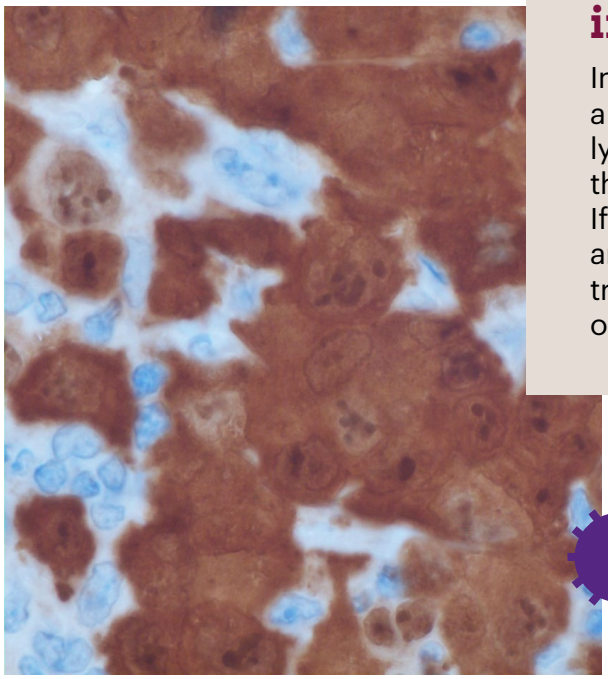
This allows people to be grouped according to how likely their cancer is to respond to treatment and doctors can then select the best treatment. This has transformed survival rates in leukaemia and is starting to have an impact on the treatment of myeloma.

Minimal residual disease (MRD) tests

The first MRD test was developed by Blood Cancer UK scientists for children with leukaemia. These tests allow doctors to see how well people with blood cancer have responded to the first stage of treatment, and can be used to help plan the next stage of their treatment. These tests are used across the globe.

Revealing how childhood leukaemia develops early in life

Our researchers found that a genetic change in the womb increases the risk of a baby developing childhood leukaemia. Our work to improve our understanding of what happens in the body before the disease develops could lead to a preventative vaccine.



Improving diagnosis in lymphoma

In 1997, researchers developed a system to diagnose types of lymphoma based on markers on the surface of cancerous cells. If you look at any of the new antibody-based drugs used to treat cancers today, most target one of these markers.

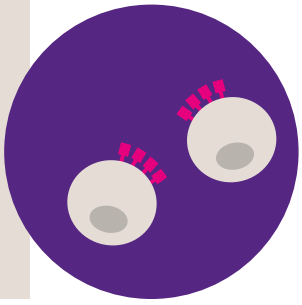
Establishing a thriving blood cancer research community in the UK and beyond

Our funding from the 1960s to the 1980s helped to establish a world-class community of researchers. Virtually all the leading British blood cancer researchers have been supported by us during their careers.

Today, the UK's thriving blood cancer research community of doctors, researchers and scientists have an international reach and positive impact on the lives of patients, carers and their families. We're immensely proud of our community who have saved many thousands of lives through research.

Antibody treatments for cancers involving the immune cells, B-cells

In the 1970s, our researchers in Southampton laid the foundations for today's antibody-based treatments that target specific molecules on cancer cells. Their work in the 2000s led to a new generation of antibody treatments for chronic lymphocytic leukaemia and lymphoma that are used today.



In 1960, when Susan Eastwood was diagnosed with leukaemia, survival for her type of leukaemia was just one in 10. Today, eight in 10 children are expected to survive, and we're still seeing progress.

Thanks to research, six in ten people diagnosed with blood cancer in the UK will now survive for 10 years. In general, the survival rates for blood cancer has increased at a much faster rate than for any other type of cancer.

The over £500 million that we've been able to invest in research, thanks to the generosity of thousands of people, has taken us to a point where scientists now think we can beat blood cancer in the next generation.

Because of you, the finish line is now in sight.

Our impact across all blood cancers

1. Investment and impact across all blood cancers

1.1 Haematological Malignancy Research Network (HMRN)

Professor Eve Roman leads the Epidemiology and Cancer Statistics Group (ECSG) at the University of York, which is core-funded by us and Cancer Research UK. Much of the unit's research takes place through the HMRN – a network of clinical teams that gather information on 24 different types of blood cancer from a population of 4 million people around Yorkshire. They record a wealth of information throughout a patient's journey - from initial diagnosis, through treatment, and to their long-term survival.

The data HMRN collects is the gold standard source of information about blood cancers. This is helping to benchmark the UK's survival rates against other countries, and pinpointing areas within the patient's journey where improvements need to be made.

1.2 Cancer UK Childhood Leukaemia CellBank

The Blood Cancer UK Childhood Leukaemia CellBank collects, stores, and processes samples from children with leukaemia. It was established in 2004, in response to a need for researchers to access clinical samples. These samples are invaluable to scientists globally who are looking for new ways to diagnose, treat, and prevent the disease.

More than 98,000 samples have been donated by almost 8,000 children and young adults with different types of leukaemia. Every child who has tests to diagnose leukaemia will be asked to donate a sample to the Blood Cancer UK Childhood Leukaemia Cell Bank. This means that every child with leukaemia is helping to benefit other children who will develop leukaemia in the future.

Researchers worldwide can use these samples, which have underpinned many important studies. This includes the research we funded into chromosome abnormalities in ALL, (see section 3.2) as well as the research into twins with ALL, led by Professor Mel Greaves (see section 4.1).

1.3 Trials Acceleration Programme

Blood Cancer UK launched the Trials Acceleration Programme (TAP) in 2011 to deliver better treatments for people with blood cancer to the NHS faster. Advances in blood cancer research mean there are many potential treatments waiting to be tested, but there is a bottleneck when it comes to getting them into clinical trials.

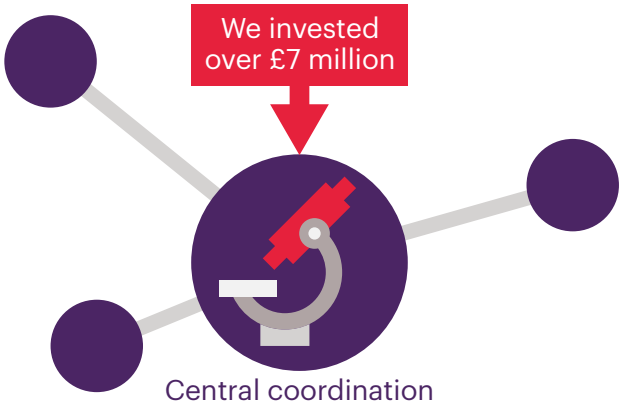
For patients to benefit as quickly as possible from these new treatments, they need to be rapidly assessed in early-phase clinical trials. Through TAP, we have invested over £7 million which funded a central coordination hub for clinical trials and a further £3 million to 13 specialist treatment centres – each with its own specialist research nurse. The TAP hub in Birmingham is home to experts in all aspects of clinical trial design and delivery.

Twenty early-phase clinical trials were set up through the programme, on average 18 months quicker than the national average. More than 1,000 people with blood cancer have been treated with over 150 new drugs or drug combinations, many of which have been life-changing.

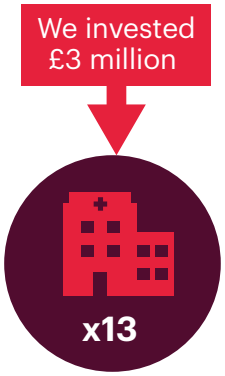
Some of the achievements from these trials include:

- The MAJIC trial tested a new drug called ruxolitinib for myeloproliferative neoplasms (MPN). Results from MAJIC suggest ruxolitinib may be as effective as the treatment which is currently available for essential thrombocythaemia (ET; where too many platelets are made) and gives a longer lasting response for polycythaemia vera (PV; too many red blood cells). Following promising results, the trial has led to a further trial looking at giving ruxolitinib as a treatment for MPNs
- The IciCLLe and CLARITY trials tested ibrutinib and venetoclax as a new combination therapy for CLL, a disease where you make too many white blood cells that don't work properly. The ibrutinib and venetoclax combination was so effective in the CLARITY trial that this is now being tested in a phase 3 trial which will provide evidence to show whether it should be used in routine care.
- The VIOLA trial was the first to test the combination of lenalidomide and azacytidine. They wanted to see if this combination could improve outcomes for people with acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS) following a stem cell transplant.

  The addition of azacytidine prevented the graft-versus-host disease, which can be caused by treatment containing lenalidomide. Between 40% and 50% of people responded well to this treatment and this combination can now be tested in a larger trial.



Central coordination hub for clinial trials



Specialist treatment centres

12 months

20 early-phase clinical trials were set up

1,000+ people with blood cancer

have been treated with more than 150 new drugs or drug combinations

1.4 Training the next generation of blood cancer specialists

Over several decades, we have supported and nurtured the careers of young scientists, clinicians and blood cancer researchers. Many recipients of our training awards have gone on to establish their own research groups. Their work has, and continues to, save and improve the lives of thousands of people with blood cancer.

To name a few of our brilliant researchers:

Professor Tessa Holyoake, discovered the CML stem cell. She also had her PhD funded by Blood Cancer UK when she was a Clinical Training Fellow and went on to become a Blood Cancer UK-funded lecturer (see section 6.3).

Professor David Grimwade, a Bennett Fellow who developed the MRD tests for APL and for NPM1 mutated AML (see section 5.1).

Professor John Radford, consultant haematologist and lymphoma specialist who led the practice-changing RAPID trial. He was also a Blood Cancer UK Clinical Training Fellow (see section 9.4).

Both **Dr Mhairi Copeland** and **Dr David Vetrie**, who, together with Professor Holyoake, pioneered potential epigenetic drug combinations for CML (see section 6.3).

Dr Richard Dillon had his PhD funded by Blood Cancer UK as a Clinical Research Training Fellow in Professor Grimwade's lab. He continues to transform treatment for people with AML and APL (see section 5.1).

Dr Nick Goulden and **Professor Colin Steward** were Blood Cancer UK Clinical Training Fellows who went on to develop the life-saving MRD test for childhood ALL (see section 3.4).

Professor Richard Clark was a Blood Cancer UK Clinical Training Fellow who played a key role in the development and approval of tyrosine kinase inhibitor drugs for CML (see section 6.2).

Professor Ghulam Mufti is an international expert in aplastic anaemia and other bone marrow disorders which can develop into blood cancers. He began his career as a Blood Cancer UK Clinical Training Fellow.

Professor Chris Bunce, former Research Director for Blood Cancer UK, was one of the first Bennett Fellows. Professor Bunce's research focuses on finding ways to repurpose existing drugs in combinations that can help to treat blood cancer, particularly myelodysplastic syndromes that can transform into AML. This has now led to a network of trials on blood cancers across the world.

Our impact in leukaemia

2. Funding pioneers in leukaemia research

Many of the leading doctors looking into finding cures for leukameia in the 1960s and 1970s were either directly funded by us or played a crucial role on our scientific advisory board.

At the time, there was broad scepticism about some of the emerging treatments for blood cancers, especially for children. Many scientists questioned whether it was appropriate to use highly toxic drugs at doses that had as much chance of causing death as the disease itself.

It was down to a handful of brave and tenacious doctors, who were prepared to keep trying and learning from their experiences, that we see a significant improvement in the number of people being cured from leukaemia today.

We helped them to set up research units, funded travel fellowships and international networking opportunities. All of this made sure that the UK stayed at the forefront of the global effort to beat leukaemia.

In the 1970s, we started funding researchers, who were pioneers in leukaemia research:

Professor John Dacie

Professor Dacie was head of the leukaemia research unit at Hammersmith hospital, which we supported and was the first UK centre dedicated to treating leukaemia in adults. It was one of the first to offer bone marrow transplants (see section 6).

Professor Frank Hayhoe

In 1968, we funded the first professorship in leukaemia research in Britain. This cemented the importance of leukaemia research as an academic discipline in its own right – an area for talented doctors and scientists to specialise in. This was first held by Professor Hayhoe at Cambridge University. We gave him funding to establish a lab with a number of fellows working in leukaemia research.

Hayhoe pioneered the use of cytochemistry for studying leukaemia cells (staining of cells with different dyes to reveal their shape and structure) and he made significant contributions in helping to identify the individual diseases that make up acute leukaemia.

Professor Roger Hardisty

One of the doctors at the forefront of pioneering new treatments was Professor Hardisty. He was the first professor of paediatric haematology in Britain and the Director of the first leukaemia unit in the UK at Great Ormond Street Hospital (GOSH), set up using the Eastwoods initial donation.

He studied abnormalities in the number of chromosomes found inside leukaemia cells to try to pinpoint the causes of the disease. They also tested drugs against leukaemia cells to see if they could be used as potential treatments.

Professor Hardisty conducted one of the first clinical trials of the chemotherapy drug vincristine in the UK using 65 children, which we funded (Hardisty et al, British Medical Journal, 1969). This research used a dose of vincristine that was high enough to induce remission but low enough to not cause damage. It demonstrated that this carefully chosen dose, alongside a steroid treatment, achieved similar remission rates as other treatments. This meant that other drugs could also be used to maintain remission.

3. Transforming treatments in childhood leukaemia

Tackling childhood leukaemia was the main area of focus for our founders and is where we have had some of our biggest research breakthroughs. This includes a minimal residual disease (MRD) test, which now benefits children all around the world.

3.1 Supporting life-saving childhood leukaemia trials

The success in improving childhood acute lymphoblastic leukaemia (ALL) survival is often held up as a beacon of hope for other cancers, especially as the survival rate was transformed in just two decades. In 1960, survival for children with ALL was measured in months. Today, 80% of children will survive ALL.

Survival rates for children with ALL

We've played a crucial role in this success. We funded the collection of samples from children with ALL and the research that went hand-in-hand with the UK childhood ALL trials, since the 1970s. This work helped to group patients by risk category, ensuring every child was given a treatment that was most likely to be successful for them.

In 2011, Blood Cancer UK became the funder of the latest UK ALL study (UKALL 2011). This trial looks at treatment for children and young people with ALL or a type of non-Hodgkin lymphoma (NHL) called lymphoblastic lymphoma (LBL).

The trial aims to further reduce harmful side effects by testing a different dose and timing of steroid treatment, and to prevent leukaemia returning in the brain by using a different, hopefully less toxic, combination of chemotherapy. The MRD test is also used to see if treatment doses can be reduced, making treatment kinder and reducing long-term side effects. This support has improved how children are treated worldwide.

3.2 Understanding different types of childhood leukaemia

One of the significant contributions we've made to childhood leukaemia is our work to understand how different subtypes of leukaemia can affect how likely someone's disease is to progress. This work has enabled doctors to group children according to their level of risk. Children who are at a high risk will receive an intensive treatment and those considered a low risk will have a gentler treatment schedule. This gives children the best chance of survival and some are prevented from experiencing the side effects of intensive treatment they do not need.

Professor David Hardisty and Professor Mel Greaves showed that it was possible to group patients according to risk using antibodies. They were able to split childhood ALL into four types and these subtypes had different responses to treatment.

In the most common form of childhood leukaemia (known as common-ALL), remission lasted much longer than the rarer subtype, T-ALL, and this could be predicted by looking at the number of white blood cells in the blood at the time of diagnosis (Chessells et al, Lancet 1977). This discovery has transformed survival rates and much of it was funded by us.

3.3 Studying chromosomes to improve treatments

Professor Lorna Secker-Walker was a pioneer in cytogenetics (the study of chromosomes) and with funding from us, in the 1990s established the UK Cancer Cytogenetics Group (UKCCG) which started to collect data on the chromosomes of all leukaemia patients entering UK clinical treatment trials. Her work led to a

strong network of centres that conduct world-leading clinical genetics testing.

Professor Christine Harrison is now Director of the UKCCG and we now have many powerful sequencing technologies that help us understand more about chromosome abnormalities in leukaemia. The UKCCG has been at the forefront of using these new methods to develop new clinical tests. These tests allow a more extensive analysis of a child's leukaemia cells, ensuring that they get the most effective treatment for their individual cancer.

All the cytogenetics data of more than 30,000 patients, who were treated on UK leukaemia trials, are now available to researchers worldwide. They have already been used to make several crucial discoveries. For example, it was found that people with a chromosome abnormality called iAMP21 had a high risk of their disease returning. Previously, these people were treated as having a standard risk when they required additional treatment (Moorman et al, Blood 2007). Testing for this abnormality is now routine clinical practice.

3.4 The minimal residual disease test: one of the biggest cancer breakthroughs of the last 30 years

In the 1990s, two researchers we funded, Dr Nick Goulden and Professor Colin Steward at the University of Bristol, developed a very sensitive method for detecting cancer cells that are left behind in the blood or bone marrow after treatment. This method is called the minimal residual disease (MRD) test.

This test is now used worldwide as the gold standard for assessing how someone has responded to their initial treatment and helps doctors to plan whether they should increase or decrease the intensity of subsequent treatment. This will also mean those responding well can be spared intensive treatment, decreasing harsh side effects, while people who need more intensive treatment get it. This test and other tests based on this method are now a key part of routine clinical practice around the world.

3.5 Research to refine chemotherapy

In 1994, it was discovered that there can be differences in how the body breaks down chemotherapy drugs, including 6-Mercaptopurine (6-MP), used to treat children with ALL. Some children either get rid of the drug from their body before it could be effective and some don't break it down quickly enough, leading to harmful side effects (Lilleyman and Lennard, Lancet 1994).

To overcome this, researchers funded by us developed a routine diagnostic test, and gave children a personalised chemotherapy dose, based on the understanding of how they would break down the drug. All children now have this test before treatment, which minimises the risk of harmful side effects such as bone marrow failure.

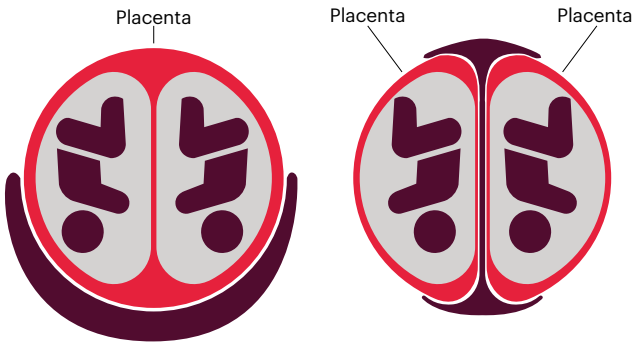
4. Leading the way in understanding what causes childhood leukaemia

4.1 Understanding what goes wrong in the lead-up to childhood leukaemia

In the mid-1980s, we invested in several specialist units dedicated to understanding the causes of leukaemia. One of these was the Centre for Molecular and Cellular Biology of Human Leukaemia at The Institute of Cancer Research in London, established in 1983 and led by Professor Sir Mel Greaves. He has published some of the most important advances in our understanding of the origins and evolution of childhood leukaemia.

After studying 1,500 cases of childhood ALL in the UK, scientists realised that the ages between two and five were when children were most likely to get the disease. Greaves and others speculated that leukaemia could begin from a developmental abnormality that can occur at any point after six weeks of pregnancy. He then came across a pair of twins with leukaemia at Great Ormond Street Hospital, which suggested both twins developed leukaemia because the disease had spread from one to the other through the placenta.

Then they found two sets of triplets with leukaemia: in one set of triplets, where they all shared a placenta, they developed ALL and sadly passed away. In the other set, the two identical triplets that shared a placenta developed ALL, but their non-identical twin who had her own placenta was healthy, backing up the theory that leukaemia cells were spreading through the placenta.



Identical twins **Non-identical twins**

Greaves then showed that in most cases of leukaemia in children, there was a unique genetic alteration in their blood cells that was present at birth. This is called the TEL-AML1 gene rearrangement.

However, in twins who shared a placenta, one developed ALL and the other didn't and, in 2002, they showed for the first time that for every child who develops leukaemia, there are another 100 who carry the same mutation but never develop the disease (Mori et al, PNAS 2002). This is important because it identifies two distinct time windows: one before birth and one after birth when critical events or exposures might cause leukaemia.

There were many competing theories about the causes of leukaemia at the time. One study showed that infants who attended playgroups in the first year of life, therefore potentially picking up more infections, had a lower risk of childhood ALL (Gilham et al, BMJ 2005). This gave weight to the growing evidence that exposure to infections early in life could affect the risk of leukaemia.

In 2009, research we funded at the ICR, led by Dr Anthony Ford, found that the preleukaemic cells – first identified in the same lab by Greaves and colleagues – rapidly multiplied in numbers when exposed to a molecule called TGF. This molecule is made by the body in response to an infection. This provided part of the missing link between the pre-leukaemic cell in early development, and the event that triggers it to progress to leukaemia (Ford et al, JCI 2009).

We now know far more about the events before and after birth that lead to the development of childhood ALL. We now hope it might be possible to design a preventative vaccine that mimics the protective effects of natural infections in infancy. If this can be done, it means that some, if not all, forms of childhood ALL could one day become preventable diseases.

4.2 Finding the root cause of childhood ALL

With our funding, Professor Greaves and his colleague Professor Tariq Enver were the first to analyse all of the RNA (a type of genetic material) in a single cell. This is now the most widely-used method for looking at how cancers evolve over time.

In 2011, we funded research by Enver and Greaves that showed leukaemia cells have a dark Darwinian secret: they evolve over time by adapting and changing their genetic make-up. They studied the genetic make-up (what the cells 'look' like) of ALL cells and showed that in the early stages of disease, the original cancer stem cell makes 'subclones' of itself, with different combinations of mutations. These subclones then go on to develop further subclones, like branches of a tree.

This explains why cancers are so difficult to treat: you need to target multiple 'branches' (or subclones), and some of them can become dominant and resistant to treatment (Anderson et al, Nature 2011). This research has redefined accepted wisdom about cancer biology.

In 2017, Enver proved that cancer arises when a tumour promoting gene, prevents a blood stem cell from becoming a 'specialised' blood cell like a red or white blood cell. Instead, lots of immature pre-leukaemic white blood cells are produced that have the potential to develop into leukaemia.

4.3 Understanding the causes of leukaemia

Epidemiology is the study of where and how often diseases occur and what causes them. We have invested in this area since the 1980s and in 1987 we established a new Centre for Clinical Epidemiology of Human Leukaemia and Related Diseases in Leeds.

In 1990, the results of the unit's first five-year study were published, which was the first study examining the distribution of cases of leukaemia, lymphoma and other blood cancers.

We invested a further £1.2 million in 1991 to help fund the UK Childhood Cancer Study (UKCCS). This study was the first of its kind in the UK – a specialist research project to

collect personal and clinical information from all children diagnosed with blood cancers between 1992 and 1996. It looked at areas of potential risk: exposure to natural or man-made radiation, potentially damaging chemicals, occupational hazards, electromagnetic fields, viruses and infection, medical history, and environmental factors.

In 1999, the team published a paper showing that there was no evidence that exposure to magnetic fields linked to the electricity supply in the UK increased the risk of childhood leukaemia or any other childhood cancer (Day et al, Lancet 1999). A further study provided strong evidence that giving newborn babies vitamin K injections does not increase their risk of leukaemia (Roman et al, BJC 2002; Fear et al, BJC 2003) and led to a change in the Department of Health Policy.

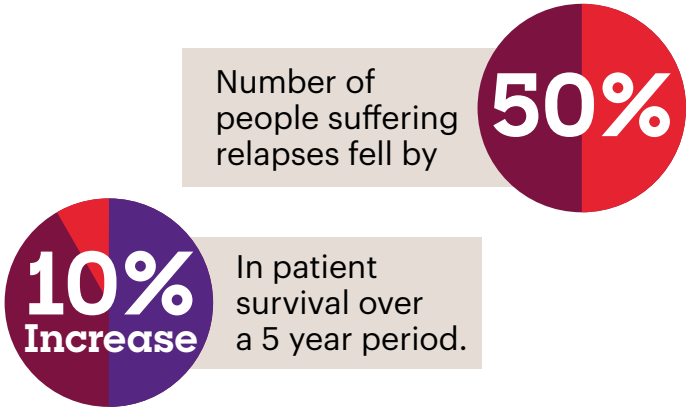
5. How we've helped to reduce the risk of acute myeloid leukaemia (AML) returning

5.1 The MRD test for acute promyelocytic leukaemia (APL)

Acute promyelocytic leukaemia (APL) is a subtype of AML that is usually caused by two genes sticking together in an abnormal way. With funding from us, Professor David Grimwade at Kings College London used this discovery to develop a minimal residual disease (MRD) test specifically for APL. This looked at the levels of cancerous cells with this abnormality over time. The test allows doctors to monitor how people respond to treatment.

It also allows doctors to pick up relapses around three months before someone starts showing clinical symptoms, giving a window of opportunity to pre-empt relapse with additional treatment. This has lead to a 50% fall in the number of people with APL who relapse. It also helped increase patient survival over a five-year period by around 10%. (Grimwade et al, JCO 2009).

Professor Grimwade also published a paper describing an effective MRD test for people with types of AML that have a change in the NPM1 gene found in 69 out of 70 cases of people with AML that had returned (Ivey et al NEJM 2016). For people who relapse and require a bone marrow transplant, early detection of relapse now gives doctors more time to find a suitable donor. The results of this study have changed clinical practice worldwide.



5.2 Improving the diagnosis and treatment of myeloproliferative neoplasms (MPNs)

We part-funded research led by Professor Anthony Green that has transformed the diagnosis and treatment of people with MPNs. These conditions cause additional problems such as heart disease and blood clotting disorders and can also develop into acute leukaemia. This means it is crucial to spot them early. However, they are difficult to diagnose because they are rare, the signs are subtle and the symptoms are similar to other diseases.

Professor Green was the first to identify a common mutation in people with MPNs in a gene called JAK2 (Baxter et al Lancet 2005).

Testing for the JAK2 mutations is now firmly embedded in national and international guidelines to help doctors diagnose MPNs faster and more accurately. Green's research has also led to new treatments called JAK2 inhibitors. He has revolutionised the care for people with MPNs.

See also work by Professor Nick Cross in section 6.

5.3 Predicting the risk of AML in babies with Down's syndrome

Blood Cancer UK-funded researchers pinpointed a genetic change that puts babies with Down's syndrome at a higher risk of AML. These babies can develop a leukaemia-like illness at birth and some of them will go on to develop leukaemia that requires treatment, usually within the first two years of life. Remarkably, in the majority of

babies that start with this leukaemia-like illness the disease goes away spontaneously.

Professor Paresh Vyas and paediatrician Professor Irene Roberts conducted a study in 43 hospitals, where they collected blood samples and clinical information from around 450 newborns with Down's syndrome. They found that 18 babies had a mutation in a gene called GATA1. This gene is known to control some aspects of blood cell production. They have since found that a third of all babies with Down's syndrome have this genetic change and are at increased risk of leukaemia.

GATA1

Only babies who still have the genetic change three months later are likely to develop AML. This study has given many parents peace of mind, because the majority of babies with Down's syndrome are unlikely to develop leukaemia. It also means that those babies who do have the GATA1 mutation at three months old, and are likely to develop leukaemia, can be looked after by a specialist team and given treatment as early as possible (Tunstall et al., 2018).

5.4 Identifying inherited risk of AML in families

Some families have more cases of blood disorders and/or leukaemia than average and we have funded a programme of research to find the genetic basis of these inherited cancers, led by Professors Inderjeet Dokal, Jude Fitgibbon and Tom Vulliamy at the Queen Mary University of London.

They identified 112 families with AML, along with their clinical information and blood samples. Using powerful gene sequencing methods on their blood samples, they were able to identify the inherited genetic faults that run in the families.

In 2020, the group published the initial results of their genetic analyses of 86 families with AML or myelodysplastic syndrome (MDS) (Rio-Machin et al Nature Comms 2020).

This information is crucial for understanding how diseases develop and progress in individuals, and what gene faults are linked with different outcomes. In turn, this will help doctors to monitor people with inherited gene faults carefully. It will also help them to provide treatment quickly if another blood disease progresses towards an aggressive type of leukaemia. This genetic information has already been used to plan treatment for individuals involved in the study and for the genetic counselling of family members who are at an increased risk of leukaemia.

6. Improving treatments for chronic myeloid leukaemia (CML)

6.1 The first CML bone marrow transplants

In the 1970s we funded Professor John Goldman, a haematologist who pioneered bone marrow transplantation as a treatment for CML.

To make transplants successful in CML, the idea was to harvest and store bone marrow cells when someone's disease was stable, so they could be used to treat the patients whose cancer was more aggressive. This meant Goldman needed to be able to freeze the cells for a long period of time without damaging them. Goldman and his colleagues spent a long time perfecting a technique called 'cryopreservation' (freezing) of bone marrow from CML patients. This led them to discover that CML stem cells, cells which can form a steam of more cancerous cells, can be found in the blood at diagnosis. This meant that instead of having to collect bone marrow cells, which can be an invasive procedure, they could instead extract the stem cells from blood samples and use these in future transplants. This heralded the start of autologous (using the patient's own cells) stem cell transplants. In total, we've invested over £3 million in helping to pioneer bone marrow transplants in the UK.

In the early 1990s, Goldman was joined by Professor Nick Cross. Almost all people with CML have a change in their DNA which causes two of their genes to stick together, known as the Bcr-Abl gene fusion or Philadelphia chromosome. This prompted Cross to develop a way of measuring the number of Bcr-Abl molecules in the bone marrow for people with

CML. The method was found to better predict relapse than conventional genetic tests (Cross et al Blood 1993). The team showed that when relapse was picked up earlier in people who had received bone marrow transplants, patients then responded better to treatment with infusions of their own white blood cells. This research, which we funded, proved the principle that this way of testing for circulating Bcr-Abl molecules could predict relapse and guide further treatment.

With Blood Cancer UK funding, Junia Mello, who worked in Goldman's lab, tested a new drug called imatinib which had been shown to destroy CML cells. Goldman's team at the Hammersmith hospital conducted the initial phase two and phase three clinical trials of imatinib for CML in the UK, a vital treatment for blood cancers today. At the same time, Professor Nick Cross started to standardise methods for detecting CML, so they could be used in clinics worldwide. This would help them to monitor the response and relapse of people with CML after they received imatinib. The technique Cross developed is still used today to monitor CML patients after treatment.

Professor Cross has also studied other CML-like cancers that cannot be treated using imatinib. These CML-like conditions cause additional problems, such as heart disease and blood clotting disorders, which can then transform into acute leukaemia. Therefore, it's crucial to spot these diseases early. Professor Cross' work has identified a range of rare genetic abnormalities in these CML-like cancers and has shown that they can be treated with a range of different tyrosine kinase inhibitor (TKI) drugs like imatinib. This research has led to a new standard of care.

6.2 Finding more effective CML drugs

Professor Richard Clark at the University of Liverpool conducted research into understanding why some people with CML do not respond to imatinib. Clark discovered the channel that transports the drug into CML cells and found that the levels of this channel on the surface of CML cells could predict response to imatinib (Wang et al Clin Pharm Ther 2008).

He later showed that two other TKI drugs called nilotinib and dasatinib were transported into cells without using this channel so could be used when imatinib did not work (Giannoudis et al Blood 2008; Davies A, Leukemia 2009; both funded by Blood Cancer UK). Both drugs are now approved for CML in the UK.

Professor Clark also led a Blood Cancer UK-funded trial (DESTINY) that looked at whether it was possible to reduce treatment after 12 months and stop it completely in people with CML. Of the people in the study, 72% of people with CML had no recurrence of their disease after three years of reducing and stopping treatment. All of the people who had relapsed regained remission again within five months of resuming TKI treatment. The results showed that it may be possible to pause treatment for several years in some patients with CML. During this period, they wouldn't be taking TKIs or experiencing their associated side effects (Clark et al, Lancet Haematology 2019).

6.3 Heading towards a cure for CML

Despite the huge success of the TKI drugs, people with CML still face a lifetime of having to take these treatments to keep their leukaemia under control. Professor Tessa Holyoake began her research career in 1993, with funding from us, as a Clinical Research Fellow. In 1999 she made the landmark discovery of a CML stem cell (Holyoake et al, Blood 1999). Her goal was not only to manage CML, but to get all patients off their treatment. She believed that targeting the stem cell would be key in achieving this.

In a 2002 paper, Holyoake described how a small group of 'cancer stem cells' are not killed by current drugs and can produce a steady stream of new CML cells (Holyoake et al, Blood 2002). This demonstrated that the typical treatment for CML would be unlikely to cure it (Holyoake et al, Leukaemia 2002 review).

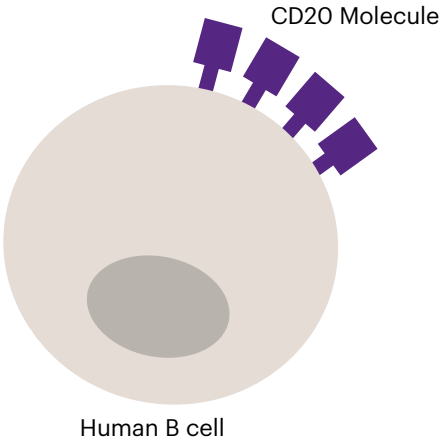
Holyoake had also shown that a cancer-causing gene called Myc, and a gene responsible for keeping tumours at bay called p53, were both important for CML stem cell function. In 2016, Professor Holyoake and Professor David Vetrie, who was also studying CML, showed that targeting these two genes could eliminate CML stem cells while leaving normal blood stem cells unharmed (Abraham et al, Nature 2016).

They also showed that CML cells have an abnormality in their 'epigenetic control systems', the system that involves tags being added to DNA which can alter how a gene works. They found that this makes them more sensitive to a

certain class of drugs. When these drugs were used together with TKI drugs, the combination made the CML cells self-destruct (Scott et al, Cancer Disc. 2016). This is now being taken further in clinical trials funded by Cancer Research UK.

7. Paving the way to find a new generation of treatments for chronic lymphocytic leukaemia (CLL)

Professors Mark Cragg, Stephen Beers and Martin Glennie at Southampton University have been instrumental in the development of the next generation of antibody drugs for CLL. These drugs are more effective at destroying cancerous cells than rituximab, the first drug that targeted a molecule on the surface of CLL cells called CD20.



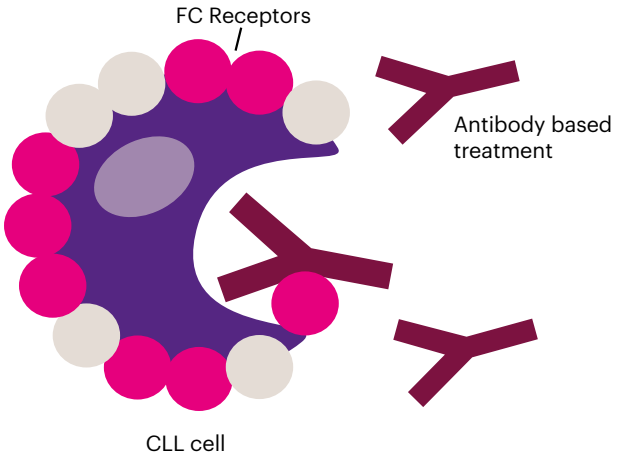
In 2002, Cragg and Glennie discovered that drugs bind to CD20 and trigger an immune response in different ways and this can affect how effective these drugs are (Cragg Blood 2003; Teeling et al Blood 2004; Beers et al 2008). They grouped antibody treatments into two types, based on the way they kill cancer cells.

The team's findings caught the attention of Roche, the pharmaceutical company that developed rituximab. The Southampton team's results were important in Roche selecting their new antibody treatment called obinutuzumab for further development and it has now been shown to be more effective than rituximab for CLL.

7.1 Tackling drug resistance in CLL

More recently, we have funded the Southampton team to look at how CLL cells develop resistance to rituximab. They found that some CLL cells have too much of a molecule called an Fc receptor on the surface of the cells. When an antibody-based treatment sticks to the surface of a tumour cell, this molecule pulls the drug inside the cancer cell.

This means the antibody can no longer be detected by immune cells. Therefore, the immune system will not receive a signal to come and destroy the cancer. (Lim et al Blood 2011; Roghanian et al Cancer Cell 2015). Having discovered this, the Southampton team collaborated with the Swedish biotech company, Bioinvent, to develop drugs that can block this molecule on the surface of CLL cells. This research culminated in a potential antibody drug called BI-1206 that is now being tested in clinical trials.



Our impact in myeloma

8. Research that's improved treatment for myeloma

8.1 Studying chromosomes to predict outcomes

Until recently, we knew little about how myeloma was likely to progress. To address this, we funded the UK Myeloma Forum Cytogenetics Group (UKMFCG) led by Dr Fiona Ross at the Wessex Regional Genetics Laboratory.

The programme was established to understand the genetic abnormalities of blood samples from people with myeloma. The team analysed 1,140 samples from the study and linked different chromosomal abnormalities to individual patient survival. The results showed that having certain chromosomal abnormalities was directly linked to poorer survival (Leone et al, Clin Cancer Res 2008).

In another study we funded, the team were able to show that people with myeloma who didn't have chromosome 13 were likely to have a poor prognosis. This confirmed that it was important for predicting the course of a person's disease (Chiecchio et al, Leukaemia, 2006).

Based on the chromosomal abnormalities identified by the team, they went on to develop a model for predicting the prognosis for people with myeloma (Boyd et al, Leukaemia 2012). When Ross and her colleagues added the chromosome abnormalities to the current staging system for myeloma, they found it was possible to group people with myeloma into low, intermediate or high-risk categories. As a result of Dr Ross' research, UK clinical guidelines recommend that people with myeloma have a test for chromosome abnormalities.

Since the initial discoveries made by the UKMFCG, further mutations and changes have been found to have helped this group of patients. With our funding, Professor Gareth Morgan identified some further key genetic features that affect clinical outcomes in newly diagnosed myeloma, some of which could be potential drug targets. His team also identified common changes in the levels of genes in myeloma cells that are typical of more aggressive disease. This was used to develop a way of identifying individual patients who were unlikely to respond to conventional treatments (Dickens et al Clin Cancer Research 2010). The data generated in this work was patented and further developed into a clinical test, which is currently used in the clinic.

8.2 Identifying inherited risk of myeloma

Research we helped to fund identified the first risk genes for myeloma. Family members of myeloma patients are known to be between two and four times more likely to develop the disease. This is in comparison to the general population.

Professor Richard Houlston at the ICR discovered the first genes responsible for some of this increased risk and estimated that they could account for more than a third of myeloma cases in European countries (from press release; Broderick et al 2012 Nature Genetics).

Since that first discovery, research we funded alongside Myeloma UK and Cancer Research UK has led to the identification of a further 23 genetic changes that can increase a person's risk of myeloma (Chubb et al Nature Genetics 2013).

8.3 Understanding the role of bone cells in myeloma

Some cancers, including myeloma, cause cancer-induced bone disease: lesions in the bone that lead to potentially serious fractures. These can occur in the pelvis or thigh bone, seriously limiting the person's mobility. We funded Professor Peter Croucher during his time at Sheffield University, where he made important advances in understanding how myeloma cells become established in the bone, and how they destroy bone tissue.

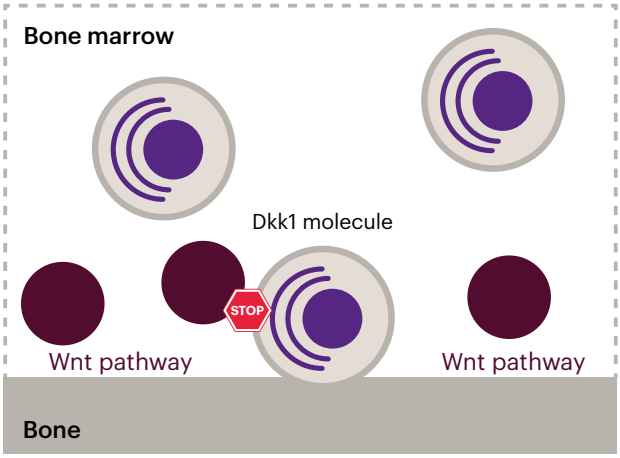
In 2001, he discovered the pathway that cells use to communicate that drives bone disease that occurs in myeloma (Croucher et al Blood 2001). This finding opened up the possibility of targeting this pathway with drugs to prevent bone destruction in myeloma.

In another Blood Cancer UK-funded study, Croucher showed that a drug called zoledronic acid could prevent myeloma bone disease and the progression of the cancer itself. (Croucher et al, J Bone Min Res 2003).

Professor Croucher was joined in the lab in 2005 by Professor Andy Chantry. In 2009, they discovered that a signalling pathway called Wnt, which is important in growth and development, may also play a critical role in causing myeloma bone disease. A molecule that blocks the Wnt pathway, called Dkk1, is found in higher amounts in people with myeloma. This is linked to myeloma-induced bone disease. They showed that removing Dkk1 in mice with myeloma restored bone renewal and prevented the development of bone disease. This highlighted a potential new approach to treatment (Heath et al, J Bone Miner Res 2009).

In 2010, the duo showed that stimulating the bone to grow new cells by blocking a molecule called activin prevents bone damage in mice with myeloma and prevents cancer spreading in mice with breast cancer. This paved the way for new approaches to treating cancer-induced bone disease (Chantry et al, J Bone Miner Res 2010).

In 2015, Professor Croucher reported results from research that tracked dormant or 'sleeping' cancer cells in the skeleton. Myeloma relapse is thought to start from dormant cancer cells that are resistant to treatment and later start growing. In this study, they tracked myeloma cells from when they first start growing within the bone, to when they become dormant, and when they subsequently become activated again, causing relapse. They showed that the sleeping status of the cancer cells can be switched on when they interact with cells lining the bone. The results mean it could be possible to target the bone cells that surround myeloma to overcome drug resistance and prevent relapse (Lawson et al, Nature Comms 2015).



Our impact in lymphoma

9. Improving treatments for lymphoma

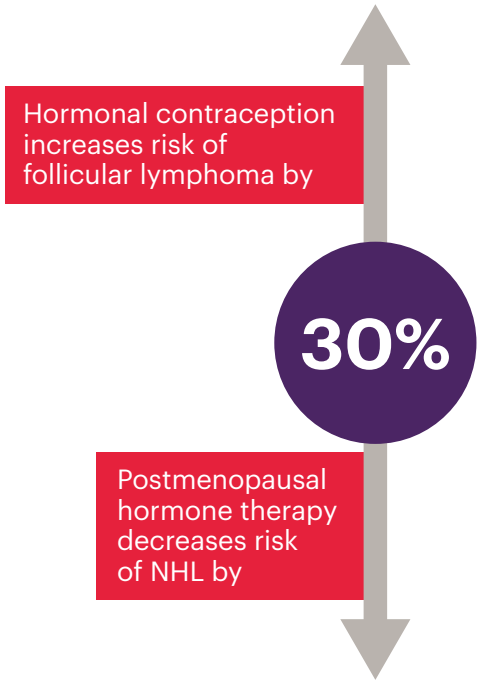
9.1 Understanding the causes of lymphoma

In 1998, the Blood Cancer UK-funded Epidemiology and Cancer Statistics Group (ECSG) began a study to investigate the possible causes of Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). The study looked at: family history and other genetic factors; lifestyle factors such as smoking, alcohol and obesity; and illnesses and health events that precede a diagnosis of lymphoma.

The study has provided evidence that infections do not increase the risk of getting NHL (Becker et al, Int J Cancer 2012), and that postmenopausal hormone therapy decreases the risk of NHL by around 30% (Kane et al, Ann Oncol 2013). It has also found that women who take hormonal contraception are 30% more likely to develop follicular lymphoma, but that there is no increase in the risk of diffuse large B-cell lymphoma (DLBCL) (Kane et al, Ann Oncol 2012). They also found that obesity may cause lymphoma by causing chronic inflammation (Kane et al, Cancer Epid Biomarkers Prev 2015).

9.2 Diagnosing lymphoma earlier

Research that we funded has transformed the diagnosis of lymphoma. We funded Professor David Mason between 1976 and 1986 and he developed several methods for using antibodies (molecules which stick to cancer cells) to diagnose lymphoma.



Professor Mason developed an antibody against an anaplastic large cell lymphoma (ALCL) protein, called ALK1, (Pulford et al, Blood 1997). This antibody was subsequently used to split ALCL into two subtypes (Benharroch et al, Blood 1998). These two distinct forms of ALCL are now globally recognised. His discovery has improved the diagnosis and management of ALCL.

Mason also helped to pioneer a new way of naming molecules on the surface of white blood cells. He was one of the most enthusiastic promoters and organisers of meetings on human leukocyte differentiation antigens (HLDAs) that led to the introduction of a new classification system called 'cluster of differentiation' (CD). If you look at any of the new antibody-based

drugs available today, many target different 'CD' molecules, named using the system that Professor Mason developed.

Professor Mason's work at Oxford University was continued by Professor Alison Banham, with funding from us. She also made a major contribution to improving the diagnosis of lymphoma. In 1999, Professor Banham identified a new molecule called FOXP1 which could be used to understand how someone's cancer was likely to progress (Banham et al, Cancer Res 2001; PCT/GB00/04590). It indicated that people with DLBCL who had excessive levels of FOXP1 had poorer outcomes. Professor Banham's work was the first indication of FOXP1 as a clinically relevant gene in DLBCL (Banham et al, Clin Cancer Res 2005). A test for FOXP1 is now used to diagnose DLBCL worldwide.

9.3 Creating kinder treatments for Hodgkin lymphoma

We have funded pivotal clinical trials in lymphoma that have led to new standards in treating the disease.

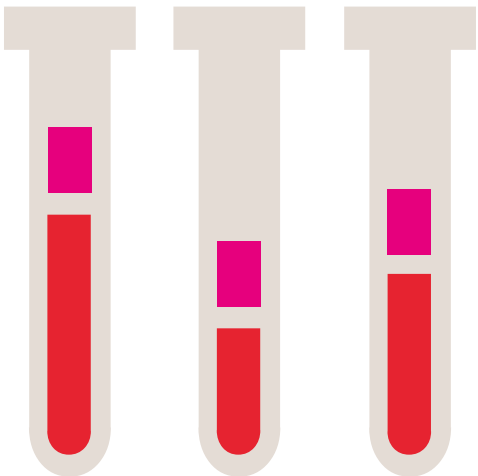
We funded the RAPID trial, which looked into the treatment of Hodgkin lymphoma. This trial was led by world-renowned lymphoma specialist, Professor John Radford, at The Christie in Manchester. Before the RAPID trial, people with Hodgkin lymphoma did not get PET scans before treatment. Instead, they would undergo one PET scan at the end of treatment. Everyone with early stage Hodgkin lymphoma was treated with chemotherapy and radiotherapy.

The RAPID trial looked at whether PET scanning could be used to determine if a patient needs radiotherapy. The trial tested whether chemotherapy alone would be sufficient for those patients who have a negative PET scan after three cycles of chemotherapy. RAPID showed that people who had a clear PET scan after chemotherapy had a very good outcome without having radiotherapy (Radford et al NEJM 2015). This is important because less intensive treatment means patients experience fewer side effects, which can include secondary cancers and heart disease. This research has changed clinical practice worldwide.

9.4 Improving treatment in hard-to-treat lymphomas

We've invested nearly £3 million in the Precision Medicine in Aggressive Lymphoma (PMAL) consortium. PMAL is a team of researchers based in the UK, compromising clinicians, bioinformaticians, and lab-based researchers. Together, they are working on gaining a deeper understanding of the genetics behind different kinds of lymphoma and how those genetics can differ from person to person. This means doctors can match the right treatment to each individual.

The first clinical trial from PMAL was REMoDL-B and was led by Professor Peter Johnson and Professor Andy Davies at Southampton University. This proved it was possible to use tests to look at the different levels of genes in lymphoma samples. The test results would then be used to group people for treatments, giving people the most appropriate treatment for their disease. As a result of this investment, the PMAL team has already established a new classification system for aggressive lymphoma (Davies et al 2019 Lancet Oncol). As a result, we expect to see changes in how people with aggressive lymphomas are treated in future trials.



Our impact across other cancers

10. How our research has helped other types of cancer

Our investment in blood cancer research has provided crucial understanding of how cancers develop, as well as tests and treatments. Some of this learning has helped people with other types of cancer and other diseases. Here are a few examples.

Establishing the pathology tests of today

Professor David Mason showed that it was possible to use antibodies in the routine diagnosis of blood cancer. His work led to a whole new approach to testing tissue samples: hundreds of tests for other cancers and many other diseases have been developed as a result of his work.

A prototype for childhood cancer

Our research has shown that childhood leukaemia is caused by a change that occurs in the womb, combined with further genetic alterations that happen in infancy. Researchers now believe that this research can be applied to other childhood cancers, especially in those occurring before age 10. This could pave the way to similar discoveries in other types of cancers that affect young children.

The origins and evolution of cancer

Genetic analysis of childhood ALL first revealed that even a simple cancer can undergo complicated genetic changes in response to pressures in the cancer's environment or in response to treatment. This leads to parts of cancer having different combinations of mutations, like many different branches of a tree. This discovery explains why cancers are so difficult to treat. You can't just target a single 'branch', multiple branches need targeting. This research redefined what was originally thought about the development of cancer and could also be applied to solid tumours of the kidney, breast, brain, bowel and prostate.

Cancer stem cells as key drivers of cancer

The concept of a cancer stem cell had been proposed since the 1970s. However, it was only seen as important when our researchers showed it was responsible for generating a steam of cancer cells and causing drug resistance. (Greaves et al, Nature Reviews Cancer 2016). Blood Cancer UK made a significant contribution to improve the understanding around the importance of cancer stem cells.

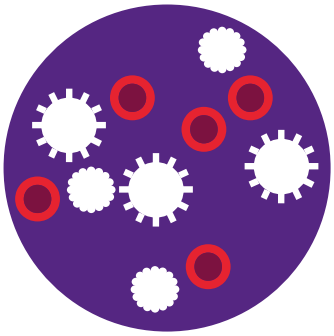
Using antibodies as drugs

Many of today's targeted treatments are antibody-based, and blood cancers played a pivotal role in the initial research which lead to the development of these drugs (Bachireddy et al, Nature Reviews Cancer 2015). These drugs are used to treat cancers as well as autoimmune disorders such as multiple sclerosis and arthritis.

Monitoring treatment responses

The blood-borne character of leukaemia facilitated Blood Cancer UK-funded researchers to create the first minimal residual disease (MRD) test that detects left over cancer cells in the blood after treatment and can predict relapse.

With more sophisticated genetic analysis tools, researchers working on solid tumours are now adapting this technique. They can look for tumour DNA in the blood using something called a liquid biopsy. This can reveal whether the tumour is responding to treatment, or whether someone is likely to see their disease return.



Because of you, the finish line's in sight

Together we've achieved an incredible amount in the last 60 years, but there's still much more to be done before we see a day where blood cancer is finally be beaten.

We believe that if we continue funding research at the same pace as we have been for the last 60 years, in the next 30 years we will get to a point where no one dies of blood cancer. We can beat it. But we can't do it without you.

None of what we've achieved would have been possible without you. With your continued passion and commitment we want to create more personalised treatments for every type of blood cancer and ensure these are effective for every person's individual disease.

We want to reduce the side effects of treatment so people can continue to live life to the fullest, despite their diagnosis. We want to make sure that more people achieve long-term remission from blood cancer, so that it no longer governs their day-to-day life. And there's more we want to achieve, with you.

Be part of our journey to the next big breakthrough at: **bloodcancer.org.uk/get-involved/ways-give**

Because the finish line's in site, but we need your help to get there.

Contact us on **0808 2080 888**
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