15 YEARS OF RESEARCH

WORKING TOWARDS A CURE

2006-2021

BONE CANCER RESEARCH TRUST
15TH ANNIVERSARY
UNTIL THERE'S A CURE

THE BONE CANCER RESEARCH TRUST

In 2004, a group of families who had lost children and young people to primary bone cancer came together. At that time, there was virtually no accessible information and practically no funding for research into this disease.

Determined not to accept the *status quo*, the families pooled funds they had already raised, and together with guidance from Professor Ian Lewis, a consultant paediatrician and adolescent oncologist at St James's University Hospital, Leeds, the Bone Cancer Research Trust was registered in 2006.

Today, the Bone Cancer Research Trust is the leading charity dedicated to saving lives and fighting primary bone cancer.

OUR VISION IS A WORLD WHERE PRIMARY BONE CANCER IS CURED

OUR MISSION IS TO SAVE LIVES AND IMPROVE OUTCOMES FOR PEOPLE AFFECTED BY PRIMARY BONE CANCER THROUGH RESEARCH, INFORMATION, AWARENESS, AND SUPPORT

RESEARCH: As of July 2021, the Bone Cancer Research Trust has committed over **£4.2 million** to primary bone cancer research with the aim of better understanding the disease and finding a cure.

INFORMATION: Our portfolio of information helps patients, their families, friends, and the public, to understand more about primary bone cancer and how it is diagnosed and treated.

AWARENESS: We are the voice of the primary bone cancer community; raising awareness amongst the public, healthcare professionals, researchers, and policy makers.

SUPPORT: We provide a dedicated Support & Information Service, which is freely available to anyone affected by primary bone cancer.

THE BONE CANCER RESEARCH TRUST RECEIVES NO GOVERNMENT FUNDING FOR OUR LIFE-SAVING RESEARCH

FIND OUT MORE AT BCRT.ORG.UK

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WELCOME

As we look back over the last 15 years of research, it fills me with enormous pride to think of what the Bone Cancer Research Trust has achieved. In 2006, there was little investment into primary bone cancer research; fast forward 15 years and the research landscape is now unrecognisable.

We could not have done this without the support of the primary bone cancer community. Together, you have raised a phenomenal amount of funds, which has allowed us to invest into pioneering research aimed at improving outcomes and saving lives.

With your support, we have improved surgical techniques that have gone on to improve survival in chondrosarcoma patients and developed protocols for primary bone cancer patients to receive specialised radiotherapy and proton beam therapy. We stepped up when osteosarcoma was identified as an urgent clinical priority and funded our first ever clinical trial, ICONIC, and our laboratory research continues to identify potential new ways to treat all primary bone cancers.

Aside from our successes in research, it has been heart-warming to see the important role the Bone Cancer Research Trust is playing in forging collaborations between researchers and uniting the community to tackle this research together. This collaborative approach has accelerated research and made new important discoveries possible.

This report is our way of celebrating the impact and successes of our research funding and to say a huge thank you to all our patients, researchers, clinicians, and supporters for their continued efforts.

I am beyond excited to see what the next 15 years brings.

Dr Zoe Davison
Head of Research, Support and Information, Bone Cancer Research Trust

A SNAPSHOT OF THE IMPACT OF OUR RESEARCH FUNDING

We have provided funding for **94 research projects** Totalling over **£4.2 million**.

Bone Cancer Research Trust-funded researchers have published **2 book chapters** about pre-clinical models in osteosarcoma research.

We have funded our **first clinical trial**. ICONIC is the largest osteosarcoma research collaboration in the UK, aiming to recruit every newly diagnosed osteosarcoma patient.

Our Infrastructure Grants have facilitated the collection of **4686 patient samples** which were delivered for specific research projects, **4623 samples** have been bio-banked for later and **3015 samples** have been sent to researchers from bio-banked stocks.

We have supported:
- **94 Principal investigators**
- **232 Co-applicants and collaborators**
- From **204 academic institutions and hospitals** around the UK, and more recently internationally.

We have facilitated and supported **7 international research events**, bringing together the best researchers in the field, to promote collaboration and exchange of ideas.

We have invested over **£1.2 million** to nurture the next generation of primary bone cancer researchers and as of July 2021, we have supported the training of **9 PhD Students**.

Following initial funding by the Bone Cancer Research Trust, researchers have been able to secure over **£1.7 million** from other charities and organisations to support and advance their research. A growth of £4.15 for every pound initially invested.

Research funded by the Bone Cancer Research Trust has resulted in **88 scientific publications**. These publications, acknowledging our funding, have been **cited 2,370 times**, contributing to the generation of new knowledge.

DEDICATED TO CHANGING THE LANDSCAPE OF BONE CANCER RESEARCH FUNDING

Approximately 560 patients are diagnosed with primary bone cancer in the UK every year. Primary bone cancer represents 4% of all childhood cancers and 0.2% of all new cancer diagnoses annually in the UK.

The overall cancer survival of common cancers has almost doubled in the last 40 years in the UK[1]. Unfortunately, survival rates for primary bone cancer have remained unchanged for over 30 years. This data reflects the complexity of primary bone cancer, but also a continuous lack of national research funding.

Data collected by the National Cancer Research Institute (NCRI) indicates a 4-year continuous reduction in the funding that major UK cancer charities commit to primary bone cancer research. In 2020, only 0.022% of the £669 million invested in cancer research in the UK was spent on primary bone cancer[2].

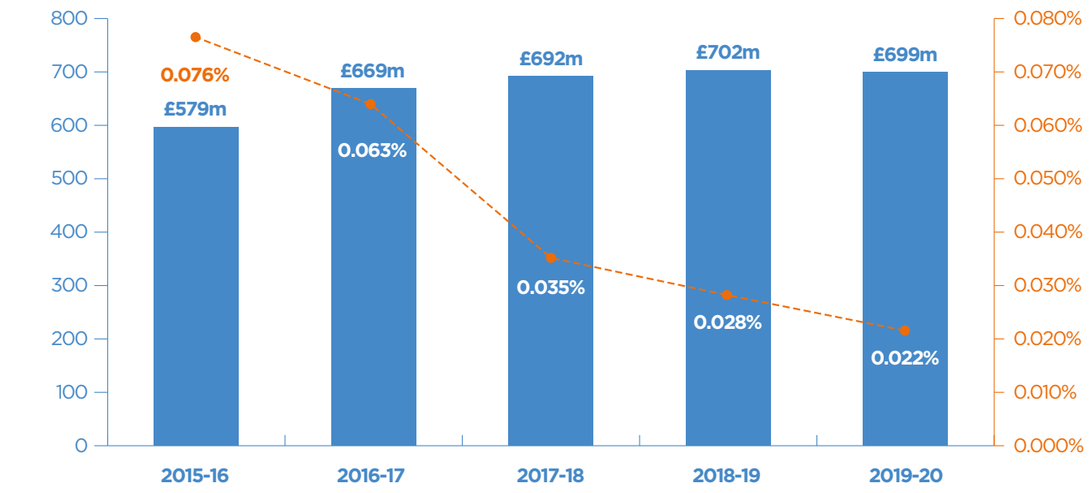
WE WANT TO CHANGE THESE STATISTICS! TO DO SO, THE BONE CANCER RESEARCH TRUST IS COMMITTED TO:

- Facilitate collaborative research into primary bone cancer.
- Invest in and grow the bone cancer research community.
- Work collaboratively with other organisations and charities, to accelerate progress.

TOTAL NCRI CANCER RESEARCH FUNDING (£ MILLIONS)

PROPORTION OF NCRI SPEND ALLOCATED TO BONE CANCER RESEARCH

% NCRI FUNDING FOR BONE CANCER RESEARCH



OF THE

£669 MILLION INVESTED IN CANCER RESEARCH IN THE UK IN 2020

ONLY

0.022% WAS SPENT ON PRIMARY BONE CANCER

"Over the last 15 years we have worked hard to diversify and grow our income, so we can continue our unwavering commitment to support primary bone cancer research.

It cannot be underestimated how grateful we all are at the Bone Cancer Research Trust to every member of the primary bone cancer community. You have baked, ran, swam, climbed, cycled... and so much more to support us.

From the first two research grants we awarded in 2006, we are now able to fund a wide range of pioneering research projects, from early stage to clinical/translational studies, to directly benefit primary bone cancer patients.

Our dedicated research community, the clinicians, surgeons, and scientists we fund, work tirelessly to ensure the treatments of the future are being developed now.

Above all, we are proud of our patients and for them we will remain steadfast in our fight against this cruel disease... Until there's a cure.

Mat Cottle-Shaw, Head of Fundraising and Communications, Bone Cancer Research Trust

OUR COMMITMENT TO RESEARCH

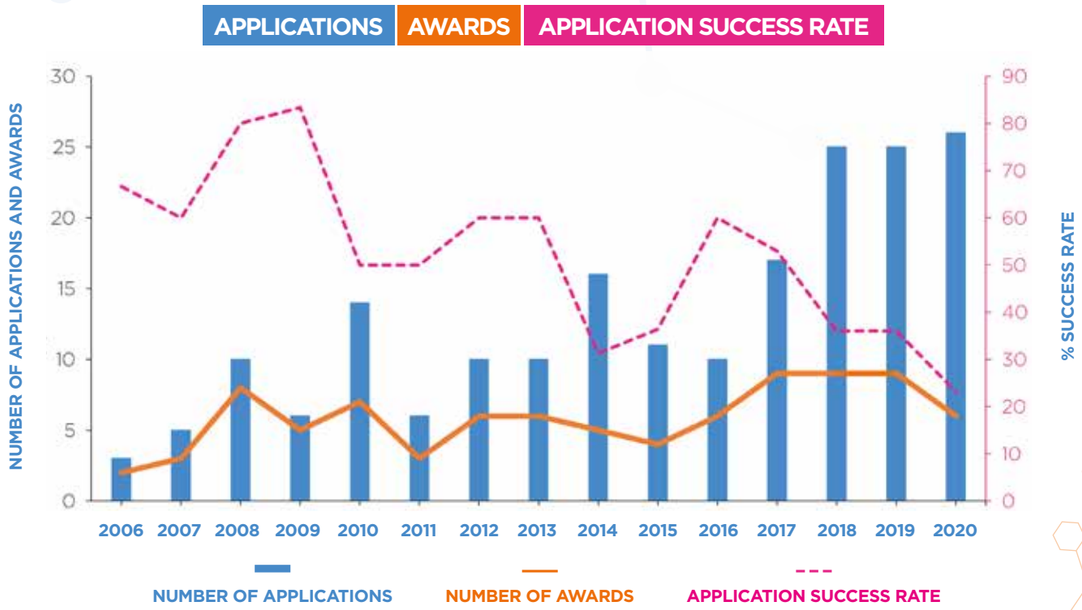
As of July 2021, we have funded 94 grants, totalling a research investment of over £4.2 million. This makes the Bone Cancer Research Trust the largest, dedicated funder of research into primary bone cancer in the UK.

In the same period, we have received and assessed 210 research applications, involving approximately 390 expert peer reviewers in the UK and across the world.

We fund research into all forms of primary bone cancer at institutions across the UK. In 2019, we introduced our first international grant, which was awarded to Professor Aykut Üren at Georgetown University, USA. It has now been followed by another international funding call in March 2021.

Over the years, we have seen a clear increase in the number of applications for funding being received. In response, we have grown our investment in research. The increased number of applications for funding received by the Bone Cancer Research Trust in recent years is a positive sign and evidences a growing community of primary bone cancer researchers.

The transition from 2019 to 2020 marks the effect of the COVID-19 pandemic on research. Several grants were paused and some laboratories and researchers were asked to divert their efforts towards the processing of samples for viral testing. During this difficult period, we supported our researchers with extensions to their funding and deferred some new awards to 2021. Whilst this has been a challenging year for the research community, the record-breaking number of applications we received for our March 2021 grant call demonstrates how eager researchers are to return to their life-saving work.



"When my son, Anthony, was diagnosed with osteosarcoma back in 2001, we could find no information, support or research being carried out and had to accept our consultant's word as to what was available and what was best. Because of this, following Anthony's death, I wanted things to change. I was involved at the very first meeting of the Bone Cancer Research Trust and I am absolutely amazed as to where we have got to in such a relatively short period of time. The money that has been raised and the amount of research that has been and continues to be funded is just unbelievable. As our Bone Cancer Research Trust family has grown, so has our reputation in the bone cancer research community. We are the go-to charity for everything to do with primary bone cancer and this is down to the hard work and commitment of every supporter, employee, trustee and researcher that is, or has ever been, involved with the charity. Every piece of research that we fund will get us closer to our vision of a world where primary bone cancer is cured. I am so proud to be involved with such a fantastic charity.

Gill Johnston, Founding Member and Trustee, Bone Cancer Research Trust

FIFTEEN YEARS OF ACHIEVEMENTS

In this report, we present key outcomes and celebrate 15 years of research funded by the Bone Cancer Research Trust. We have chosen examples from seven areas of impact that complement, influence, and facilitate each other.

Together, these interconnected areas lead to clinical improvements that directly benefit the lives of primary bone cancer patients and their families.

SUPPORTING PRIMARY BONE CANCER SAMPLE COLLECTION TO FACILLITATE COLLABORATIVE RESEARCH

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SUPPORTING THE PRIMARY BONE CANCER RESEARCH COMMUNITY AND INVESTING IN THE FUTURE

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GENERATING NEW KNOWLEDGE AND EXPANDING OUR UNDERSTANDING OF THE CAUSES OF PRIMARY BONE CANCER

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IMPROVING EXISTING THERAPIES

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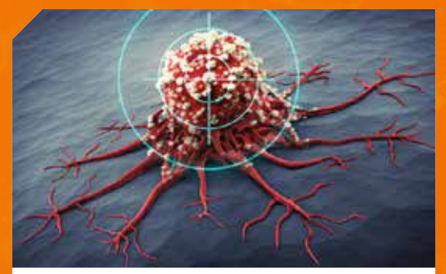

IDENTIFYING DETECTION TECHNIQUES FOR DIAGNOSIS AND DISEASE MONITORING

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CLINICAL IMPROVEMENTS THAT DIRECTLY BENEFIT THE LIVES OF PRIMARY BONE CANCER PATIENTS AND THEIR FAMILIES

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SUPPORTING THE PRIMARY BONE CANCER RESEARCH COMMUNITY AND INVESTING IN THE FUTURE

We firmly believe that difficult problems are better solved by working together. The Bone Cancer Research Trust is committed to supporting collaborative research. The grants we award bring together the ideas, knowledge and skills of talented scientists and clinicians to create innovative, multi-disciplinary research teams.

In our fifteen years of funding research, we have awarded 94 grants, headed by 94 principal investigators, that were supported by 232 co-applicants and collaborators from 204 academic institutions and hospitals.

The primary bone cancer research community comprises a small and dedicated group of experts who, in many cases, have devoted their entire careers to the field. Our research community collaborates across a network of leading academic institutions and specialist orthopaedic surgery centres, to some of which, we have awarded funding on an ongoing basis to support their pioneering work. We are committed to continuing our support for the primary bone cancer research community.

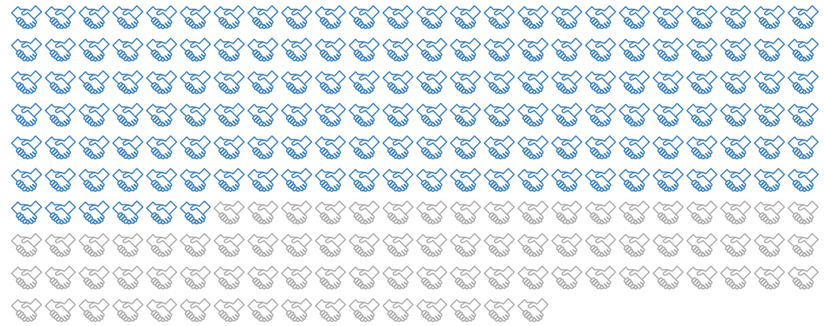
Particularly during periods of constrained public research funding, and in a difficult economic environment, it is even more important for researchers to pool resources and expertise, to enable them to access wide-ranging facilities, equipment and to share knowledge and ideas.

15TH ANNIVERSARY

94
PRINCIPAL INVESTIGATORS

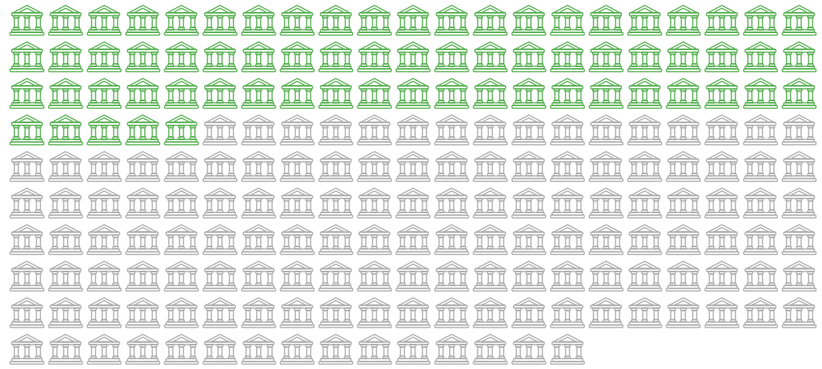
55 DISTINCT PRINCIPAL INVESTIGATORS | 39 REPEAT FUNDED

232
CO-APPLICANTS & COLLABORATORS



150 DISTINCT CO-APPLICANTS & COLLABORATORS | 82 REPEAT FUNDED

204
ACADEMIC INSTITUTIONS



68 DISTINCT ACADEMIC INSTITUTIONS | 136 REPEAT FUNDED

WE HAVE BROUGHT TOGETHER EXPERTS

FACILITATED AND SUPPORTED 7 INTERNATIONAL RESEARCH EVENTS

During the last 15 years, we have facilitated, organised and supported **5 international research conferences** and **2 international consensus meetings**, bringing together the best researchers and clinicians in the field.

2017. 1ST SHEFFIELD WORKSHOP OF TRANSLATIONAL RESEARCH IN BONE SARCOMA

A Europe-wide workshop for young researchers to gain training in primary bone cancer research.

2017. 4TH EUROPEAN BONE SARCOMA NETWORKING MEETING

An international meeting to develop proposals for collaborative research and trials for osteosarcoma.

2019. 1ST INTERNATIONAL OSTEOSARCOMA RESEARCH SYMPOSIUM

In collaboration with Children with Cancer UK, we brought together the most prominent, academic and clinical researchers in the osteosarcoma field, to progress our understanding of osteosarcoma and collaborate in developing new treatments.

2019. 1ST CHONDROSARCOMA PLANNING SYMPOSIUM

The workshop brought together clinical and academic researchers, to discuss the progress being made in current trials and biological studies in chondrosarcoma and to plan future projects.

2020. 1ST INTERNATIONAL EWING SARCOMA RESEARCH SYMPOSIUM

At this virtual meeting, researchers from across the world showcased current translational research and identified avenues for future research and collaboration.

SIGNIFICANT OUTCOMES AND RESEARCH COMMITMENTS FOLLOWED THESE CONFERENCES.

- At the International Osteosarcoma Symposium, Children with Cancer UK announced £500,000 worth of funding ringfenced for osteosarcoma.
- Surgery remains the only approved treatment option for chondrosarcoma and the Bone Cancer Research Trust is determined to change this. After the Chondrosarcoma Planning Symposium, we launched a dedicated research funding call restricted to chondrosarcoma. We have now awarded research that will examine the potential protective effect of oestrogen in chondrosarcoma.
- The International Ewing Sarcoma Research Symposium concluded with the announcement of our second international grant call for Ewing sarcoma research. The successful grants, provided in co-operation with the Ewing's Sarcoma Research Trust, will finance research focused on translational scientific research with a clear line of sight towards patient benefit.
- Recognising the importance of networking, communication and sharing of skills and ideas among researchers, we introduced our Skills Development Grants. Launched on World Cancer Day 2020, these grants support researchers to travel to research conferences and laboratories to expand their knowledge and learn essential new skills.

2007. 1ST EWING SARCOMA INTERNATIONAL CONSENSUS MEETING
2017. 2ND EWING SARCOMA INTERNATIONAL CONSENSUS MEETING

Ewing sarcoma patients require coordinated and individualised treatment with chemotherapy, surgery and radiotherapy. Their needs vary widely and approaches to treatment can differ between centres across the world who use radiotherapy and surgery in different ways. These differences were highlighted following an international study in the 2000s and stimulated the first Ewing Sarcoma International Consensus meeting in Birmingham in 2007. This in turn led to the development of the UK National Ewing's Sarcoma Multi-disciplinary Team (NEMDT). Building on this, the 2nd International Ewing Consensus meeting was held in 2017 and involved teams from 34 centres in 19 countries, including the UK, Netherlands, Germany, the USA, India and Japan. 59 attendees discussed many cases and the sharing of ideas and different approaches to local treatment ultimately led to the publication of a consensus document. The meeting was critically important in identifying differences in treatment, and has been invaluable in informing the development of new clinical trials in this difficult disease.

"The Bone Cancer Research Trust and the Ewing's Sarcoma Research Trust were at the heart of these meetings, providing financial, logistical and moral support - we couldn't have done it without you!

Mr Craig Gerrand, Consultant Orthopaedic Surgeon, Clinical Lead for Cancer, Royal National Orthopaedic Hospital, Stanmore

PBCMetNet
PRIMARY BONE CANCER METASTASIS NETWORK

COLLABORATIONS AND PARTNERSHIPS HAVE DEVELOPED BECAUSE OF THE RESEARCH WE FUND

Following the 1st International Osteosarcoma Research Symposium in 2019, a group of 6 researchers with common areas of expertise came together to form the Osteosarcoma Metastasis Network (OMeNet). 2 years later, in 2021, this group have expanded their membership and research to encompass several types of primary bone cancer, developing into the Primary Bone Cancer Metastasis Network (PBCMetNet).

The PBCMetNet is the first formal, pre-clinical research collaboration dedicated to understanding primary bone cancer metastasis. The group work together, sharing their knowledge, ideas and expertise as well as obtaining further funding to advance pre-clinical research into primary bone cancer metastasis. The current aim of the PBCMetNet is to pave the way for faster and more accurate translation of novel findings to initiatives such as ICONIC and the 100,000 Genomes Project in addition to setting the standard for future pre-clinical research into primary bone cancer.

DR HELEN ROBERTS

PROF ALISON GARTLAND

DR DARRELL GREEN

DR KATIE FINEGAN

PROF AGI GRIGORIADIS

MR KENNY RANKIN

PROF LEE JEYS

15TH ANNIVERSARY

"We are indebted to the Bone Cancer Research Trust. This new co-operative has already yielded great results with mine and Dr Green's team, working together to make the first big breakthrough in osteosarcoma in nearly 40 years, by together identifying new treatment possibilities for osteosarcoma. This work would not have been possible without the research vision and support of the Bone Cancer Research Trust.

Dr Katie Finegan, Senior Lecturer in Cancer Biology and Therapy, The University of Manchester

By working together, Dr Finegan and Dr Green have already made the first potential breakthrough in osteosarcoma treatment for nearly 40 years. The research outcomes, published in 2020[3], were facilitated by the patient samples provided by the Royal Orthopaedic Hospital at Birmingham, which is funded by one of our Infrastructure Grants. This is a clear example of the importance of collaboration in research.

This research identified the protein MMP9 as a driver of metastasis in osteosarcoma, however, drugs to target this protein have shown little effect in the clinic. To overcome this, the team looked at other ways to indirectly target this protein and showed that by silencing the *MAPK7* gene, the levels of the MMP9 protein reduced and osteosarcoma cell growth and spread was also reduced. Dr Finegan is now developing drugs against the MAPK7 protein that will hopefully benefit primary bone cancer patients in the future.

Members of the PBCMetNet are also actively collaborating on several projects. For example, Dr Finegan and Professor Gartland are investigating novel therapeutic targets for adamantinoma, and Dr Green has joined Professor Gartland and Professor Jeys to study the potential of oestrogen as a protective agent in chondrosarcoma.

WE HAVE FORGED LINKS WITH OTHER CHARITIES AND WORKED TOGETHER FOR OUR PATIENTS

We have collaborated with the **Ewing's Sarcoma Research Trust (ESRT)**, **Sarcoma UK** and **Children with Cancer UK** to fund research projects, organise research meetings and deliver awareness campaigns.

By reaching out to these charities, we have been able to co-fund research that otherwise would not have been possible and deliver ambitious awareness and educational campaigns reaching healthcare professionals, the general public, bone cancer patients and their families.

We would also like to thank the following organisations who have helped us with our commitment to primary bone cancer research over the last 15 years.

PATIENT INVOLVEMENT

Patients are at the heart of of everything we do, they were involved in the design of research projects, such as ICONIC, and participate every year in our Bone Cancer Conference.

The Bone Cancer Conference is an annual event that has grown year on year since the charity began in 2006. Attended by patients and their families, researchers and medical professionals, it provides a unique and inspirational space of communication and support for anyone affected by primary bone cancer. The Conference offers the opportunity for patients to engage with researchers and clinicians and influence the future direction of primary bone cancer research and treatment. The Bone Cancer Conference was recognised with an Advocacy in Action award at the 10th SPAEN (Sarcoma Patients EuroNet) Annual Conference in February 2020.

EURO EWING CONSORTIUM (EEC)

The Bone Cancer Research Trust has represented patients at the EURO EWING Consortium (EEC) – International Clinical Trials to Improve Survival from Ewing Sarcoma; this collaborative project involves the coordinated efforts of 20 European partners. Through collaborative working, the EEC has provided Ewing sarcoma patients with greater access to clinical trials, allowed efficient acquisition of knowledge and delivered clinically meaningful results that will contribute to improved survival for Ewing sarcoma patients.

"Patients and carers have generously given their time and energy to the EURO EWING Consortium over many years. EEC members have welcomed the perspective that they bring to the group and see them as an essential part of the team that is trying to improve outcomes for patients and acting as a reminder of why research into Ewing sarcoma is so important.

Dr Abigail Evans, Scientific Project Manager,
EURO EWING Consortium

MEPACT

In 2011, the National Institute for Health and Clinical Excellence (NICE) approved the use of Mepact (mifamurtide) in combination with postoperative, multi-agent chemotherapy as an option for treating high-grade, resectable, non-metastatic osteosarcoma. This decision by NICE to reverse their initial rejection of Mepact was brought about by the tireless campaigning of the Bone Cancer Research Trust Research Trust and primary bone cancer community.

The Institute now recommends Mepact as an option for children, adolescents and young adults below 30 years old that meet the criteria under a patient access scheme, a way by which pharmaceutical companies lower the acquisition cost of a medicine to the NHS.

Mifamurtide is added to standard treatment and works by boosting the immune system against the cancer cells. However, the use of Mepact is not generalised and therefore further studies on its clinical effectiveness are needed.

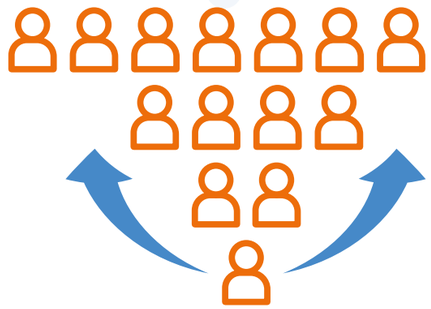
ICONIC, the Bone Cancer Research Trust-funded observational clinical trial is currently doing exactly that; by monitoring osteosarcoma patients that receive Mepact and comparing with those that do not, we will be able to collect sufficient clinical evidence to determine the size of its effect. This analysis will also help clinicians identify which patients are likely to benefit from the treatment, so informed recommendations can be made.

The priorities of patients influence our research strategy and the future direction of primary bone cancer research and treatment.

The Bone Cancer Research Trust is committed to supporting primary bone cancer researchers at all stages of their career and across all areas of research, from lab-based research and early drug development work, all the way through to clinical trials.

Only by supporting established and emerging researchers, can we maintain the strong community of primary bone cancer investigators and nurture the next generation, ensuring they remain in the field.

We have facilitated the coming together of patients and researchers, to ensure communication and to ensure that the needs, priorities and interests of people affected by primary bone cancer are reflected in our research.



WE ARE GROWING THE PRIMARY BONE CANCER RESEARCH COMMUNITY

NURTURING THE NEXT GENERATION OF PRIMARY BONE CANCER RESEARCHERS

During the last 15 years, we have supported the training of 9 PhD students.

We have fostered a holistic approach towards the training of our PhD students, involving them in our research seminars and communications, and facilitating their interaction with other researchers and patients.

Following initial funding from the Bone Cancer Research Trust, the researchers we have supported have secured additional awards to continue their projects and training.

For every £1 invested by the Bone Cancer Research Trust, researchers have been able to secure an additional £4.15 in further grants and awards of which £3.77 is specifically destined to support the training of new researchers. We are committed to growing the primary bone cancer research community and will continue to invest in the next generation of talented young researchers.

"It is so important to continue research into primary bone cancer. The funding for my PhD allowed me to train in the lab of Professor Alison Gartland, who is an expert in bone cancer. I learned many skills and techniques that have prepared me and will help me continue in this field of research.

Now funded by the Hannah's Willberry Wonder Pony charity, I continue to work in this field as a postdoctoral researcher.

I have had many personal interactions with the Bone Cancer Research Trust community, including patients. Hearing their stories inspires and motivates me to continue pursuing a career in this field and to establish my own independent research path in the future. I am passionate about improving the lives of primary bone cancer patients.

Dr Luke Tattersall, Post-Doctoral Researcher,
The University of Sheffield

WE ARE WORKING HARD TO ENGAGE WITH OUR RESEARCHERS...

In 2020, our very own Head of Research, Information and Support, Dr Zoe Davison, together with Professor Alison Gartland and Dr Luke Tattersall from the University of Sheffield, published a book chapter summarising the current and recent advances in osteosarcoma pre-clinical research. The chapter is a reference and study resource, published in the Encyclopedia of Bone Biology, which aims to raise awareness of osteosarcoma among biomedical sciences students and healthcare professionals.

Unable to meet the primary bone cancer community during the 2020 lockdown, our funded researchers, including two of our current PhD students, participated in a series of webinars called #BiteSizeResearch, which were delivered in the summer of 2020.

To access the chapter, you can find the book widely available online

THE WEBINAR SERIES INCLUDED:

The changing landscape of bone cancer research
Dr Zoe Davison & Dr Viqui Vinader

Understanding DNA & RNA in bone cancer research
Dr Darrell Green

Bone development and what can go wrong
Professor Alison Gartland

Immune-based treatments in Ewing sarcoma
Tyler Barr & Dr Fiona Errington-Mais

Modifying Methotrexate for Osteosarcoma – a magic bullet?
Professor Robert Falconer & Hannah Spencer.

Progress in chondrosarcoma research
Professor Adrienne Flanagan

Progress in chordoma research
Dr Adam Cribbs & Dr Lucia Cottone

Progress in research – bone cancer stem-like cells
Dr Elizabeth Roundhill

To access the webinars, visit bcrt.org.uk/research

....AND WITH THE NEXT GENERATION OF MEDICAL PROFESSIONALS

In recent years, we have established a partnership with the University of Sheffield Medical School, to host students undertaking their social accountability placements. During that time, students have had an opportunity to access our patient stories and speak to patients. This allows them to appreciate, first-hand, the physical, emotional, and socio-economic impact of primary bone cancer on patients and their families, and to understand, as future medical professionals, what it truly means to live with, and beyond, primary bone cancer.

15TH ANNIVERSARY

"Primary bone cancer is a very small part of the curriculum at our medical school. We were aware of it, but we knew little about it. The placement provided us with a great opportunity to learn more and gain an insight into the social issues that can affect patients and their families.

Amy, Emma, Pallavi and Dhruv,
third year medical students,
The University of Sheffield.

Lauren O'Connor, medical student,
The University of Sheffield, presenting at the Bone Cancer Conference

SUPPORTING SAMPLE COLLECTION TO FACILITATE PRIMARY BONE CANCER COLLABORATIVE RESEARCH

Patient samples are an invaluable resource for researchers trying to understand the biology of primary bone cancer. Although there are other laboratory models to study primary bone cancer, patient samples give us the greatest insight into the disease and are essential for the development of new treatments.

THE 100,000 GENOMES PROJECT

The 100,000 Genomes Project, announced by the UK Government in 2012, was the largest whole genome sequencing (WGS) initiative in the world and ran for 5 years, with recruitment closing on 31st December 2018.

The project aimed to sequence 100,000 whole human genomes (all the information in our DNA) from patients with cancer and rare diseases.

By combining the genome sequences with patients' clinical information, scientists aimed to:

- Better understand the causes of diseases.
- Discover new diagnostic tools to identify and monitor conditions.
- Drive the development of new drugs and find new uses for existing ones.

Primary bone cancers were not initially included in the 100,000 Genomes Project, but in 2016 Genomics England confirmed sarcoma patients' eligibility for the project. In response to concerns raised by our community that primary bone cancer patients would miss out on this opportunity, in 2017, the Bone Cancer Research Trust introduced a new Infrastructure Grant funding scheme. Our Infrastructure Grants enable the 5 surgical centres in England to approach patients, obtain consent and collect primary bone cancer specimens. The grants ensured that primary bone cancer patient samples were included in the 100,000 Genomes Project - without this support, it would not have been possible!

Sarcoma represents 1% of all cancers, with approximately 3,700 new sarcomas diagnosed annually in the UK. Despite this, the number of sarcoma patients whose samples were sent for sequencing as part of the 100,000 Genomes Project ranked third highest overall. Only patients with breast and colorectal cancers (representing respectively 55,000 and 42,000 new cancers diagnosed annually in the UK) had a higher number of sample submissions.

The success of this project has ensured that from February 2021 onwards, all sarcoma tumour samples can be submitted to NHS England for whole genome sequencing as part of routine treatment. The genomes will also be added to those tumours still being analysed as part of the 100,000 Genomes Project.

The information obtained from the 100,000 Genomes Project and the further genomic analysis of patients' samples will provide unprecedented genetic and biological insights into primary bone cancers. It will hopefully help medical professionals tailor treatments for their patients. Results will also help scientists identify new targets for more effective treatments.

INFRASTRUCTURE GRANTS

Funding has been provided to all 5 primary bone cancer surgical centres in England to facilitate patient consent and recruitment, as well as the collection and processing of these samples for research.

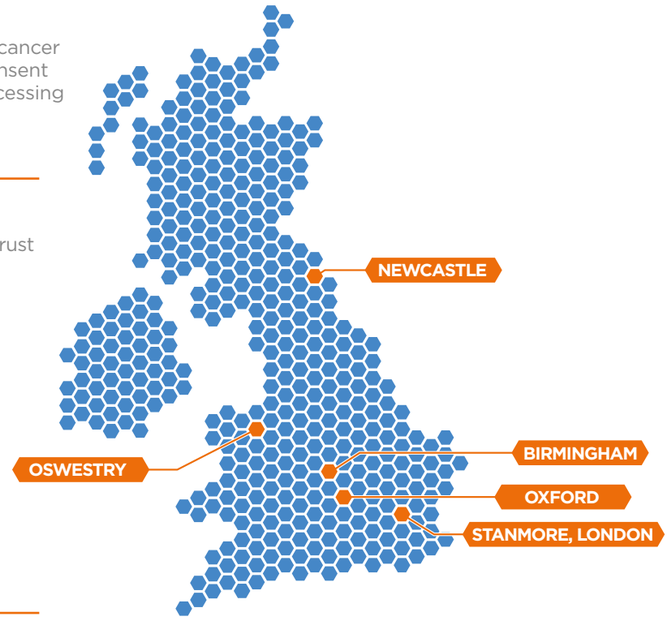
BIRMINGHAM
The Royal Orthopaedic Hospital NHS Foundation Trust

NEWCASTLE
North of England Bone and Soft Tissue Tumour Service, Newcastle upon Tyne Hospitals NHS Foundation Trust

OSWESTRY
The Robert Jones and Agnes Hunt Orthopaedic and District Hospital NHS Trust

STANMORE
Royal National Orthopaedic Hospital NHS Trust

OXFORD
Nuffield Orthopaedic Centre NHS Trust



All samples are fully documented with patients' clinical history and have been used to support primary bone cancer research projects.

Most patients approached were happy to donate samples as part of this initiative. As of July 2021, the average consent across all sites was 89% since the project began 3 years ago. This willingness of primary bone cancer patients to engage in this initiative is extraordinary and will benefit research for years to come.

89%
OF PATIENTS CONSENT TO TAKE PART

During the first 3 years, **4686** samples were collected and sent to support **21 unique research projects**. Primary bone cancer specimens that were not directed to specific studies were bio-banked locally and are available for request by individual researchers nationally. For this purpose, a collection of **4623** blood, paraffin embedded, snap frozen and other samples have been obtained.

TYPE OF PRIMARY BONE TUMOUR	BLOOD, PARAFFIN EMBEDDED AND FROZEN TISSUE SAMPLES BIO-BANKED
Osteosarcoma	1254
Ewing sarcoma	405
Chondrosarcoma	1745
Chordoma	395
Spindle Cell Sarcoma of the Bone	49
Giant Cell Tumour of the Bone	501
Adamantinoma	38
Angiosarcoma of the Bone	21
Other	215
Total	**4623**

RESEARCH PROJECTS SUPPORTED WITH SAMPLES

OSTEOSARCOMA

- Osteosarcoma circulating tumour cells
- Osteosarcoma CTC and single cell RNA sequencing
- ICONIC
- Osteosarcoma heterogeneity
- The 100, 000 Genomes project-osteosarcoma extension

EWING SARCOMA

- Euro Ewing 2012 biological studies[4]
- GenoEwings
- PREDICT study
- Neurexin-1
- Ewing sarcoma ctDNA

CHONDROSARCOMA

- Condrosarcoma circulating tumour DNA (ctDNA)
- Condrosarcoma microRNA (miRNA sequencing)
- Chondrosarcoma multi-omics
- Chondrosarcoma primary cultures

CHORDOMA

- Chordoma multi-omics
- Chordoma genotyping

GIANT CELL TUMOUR OF THE BONE

- Characterisation of Giant Cell Tumour (malignant and benign)

ALL PRIMARY BONE CANCER TUMOURS

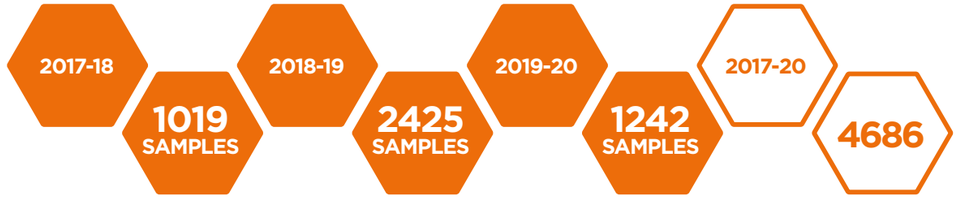
- The 100,000 Genomes project[5]
- Chemosensitivity study
- NHSE long read sequencing
- DNA methylation classifier

In the first three years, **3015** samples were requested by researchers for their projects and sent from the bio-banked stocks. These samples have enabled and facilitated research and have already contributed to 8 scientific publications.

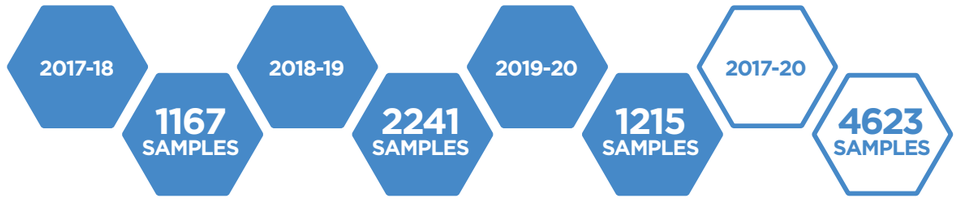
"I decided to take part in the study because if I can help other people, and if something can come out of my experience, it would be worth it.

Evie Henderson, osteosarcoma patient and sample donor at the Royal Orthopaedic Hospital Birmingham

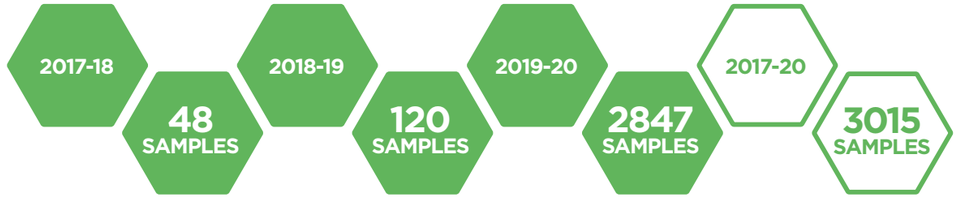
SAMPLES COLLECTED AND SENT FOR SPECIFIC PROJECTS



BIO BANKED SAMPLES



SAMPLES SENT FOR SPECIFIC PROJECTS FROM BIO-BANKED STOCKS



"Donating tissue and blood samples makes a difference. The Infrastructure Grants have boosted our ability as researchers to collect more samples and to collaborate. Long may it continue.

Mr Kenneth Rankin, Consultant Orthopaedic Surgeon, The Newcastle upon Tyne Hospitals NHS Fundation Trust and Newcastle University

Infrastructure Grants have facilitated the collection of 9309 primary bone cancer specimens for research.

This initiative represents a long-term commitment by the Bone Cancer Research Trust to support researchers and provide the essential patient samples needed for their studies. We initially committed to supporting these grants for 5 years and, to date, have awarded 4 years of funding for Birmingham, Newcastle, and Stanmore, 3 years to Oswestry and 1 year to Oxford.

LOOK INSIDE FOR OUR

RESEARCH TIMELINE

15TH ANNIVERSARY

2006-2021

RESEARCH TIMELINE

Through the dedicated support of our community, over the past 15 years the Bone Cancer Research Trust has been able to fund a plethora of innovative and pioneering research projects aiming to improve the lives of patients with primary bone cancer.

We have helped forge new collaborations, facilitated the collection of essential patient samples, supported the next generation of primary bone cancer researchers and our focus remains on developing new and kinder treatments of the future.

Whilst we are proud of every research project that we have funded, we cannot detail them all for you in one report. This timeline exemplifies key research findings and highlights the research journey we have gone on over the last 15 years and demonstrates what we, as a community, have achieved in relatively a short period of time.

BONE CANCER RESEARCH TRUST

2006

- The Bone Cancer Research Trust is registered as a charity.
- We award our first two pioneering research grants to study the potential genetic and environmental risk factors for primary bone cancer and to investigate ways to utilise the body's immune responses against Ewing sarcoma.

2007

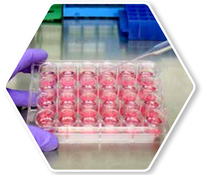
- We fund a study looking at why osteosarcoma patients respond differently to chemotherapy and experience varying levels of toxicity. This research provided the first evidence that genetics play a role in these differences. This is an area of research that continues to be explored.

First in-depth study to determine if environmental factors contribute to the incidence of primary bone cancer. The study concluded that addition of fluoride to water does not lead to greater risk of developing osteosarcoma or Ewing sarcoma.

- We award a research grant that led to the development of the first pre-clinical model of Ewing sarcoma that shows the same metastatic process as the human disease. The team used advanced imaging techniques to study how Ewing sarcoma spreads to the lungs.
- We fund the first dedicated study examining how characteristic tumour hypoxia and hypoglycaemia affect the behaviour of Ewing sarcoma and osteosarcoma cells.
- We support the first International Ewing sarcoma Consensus meeting, leading to the establishment of the National Ewing Sarcoma Multi-disciplinary Team (NEMDT) to improve outcomes for patients through a cohesive approach.

2008

- Bisphosphonates such as zoledronic acid are used to prevent bone destruction in primary bone cancer patients. We fund the first study dedicated to understanding the mechanisms of their anti-tumour effect in osteosarcoma. The research concludes that osteosarcoma tumour associated macrophages, are particularly sensitive to bisphosphonates. This was the first real evidence of how bisphosphonates exert their anti-tumour effects in osteosarcoma. Research interest in the tumour microenvironment has since become a key area of focus.
- We award a research grant to study the combination of fenretinide and TRAIL, as a potential strategy for the treatment of Ewing sarcoma. Results concluded that their combination was more effective at killing cancer cells than either of these agents used alone.



2009

- In 2009 and 2010 we fund research to investigate if PARP inhibitors increase the effectiveness of chemotherapy in Ewing sarcoma. The results contributed to the evidence base needed to include Ewing sarcoma patients in a clinical trial.
- We provide a grant to study STAT3 as a potential new target for slowing down the growth of Ewing sarcoma. STAT3 has a role in cell survival and can modify the immune environment of the tumour. Although challenging to target, STAT3 remains a potential therapeutic target.
- Funded research identifies proliferation index (PI) as a potential predictive biomarker for relapse free survival and overall survival and could be developed for risk staging of patients with Ewing sarcoma at diagnosis.

2010

- Research to assess the efficacy of computer-assisted pelvic sarcoma surgery commences. The research published in 2020 has resulted in significant improvement for chondrosarcoma patients in survival and quality of life.
- Recognising a barrier to teenage and young adult participation in sarcoma clinical trials, we fund research to identify these obstacles and make recommendations to healthcare professionals involved in clinical trials to encourage participation.

- Our funding contributes to the first genome-wide study to identify genetic risk factors for osteosarcoma, and to establish the first bank of documented tumour and plasma samples of primary bone cancer for further study.

The HIF1α protein allows tumour cells to survive in the hypoxic conditions often found in tumours. Funded research investigates what effect inactivating HIF1α, with drug CL67, has on osteosarcoma and Ewing sarcoma cells.

2011

- Following our campaign to reverse the refusal by NICE to include Mepact as treatment for osteosarcoma, approval is granted.

- Initial results from Bone Cancer Research Trust-funded research demonstrate the potential for epigenetically inactivated tumour suppressor genes in Ewing sarcoma as prognostic markers.

2012

- Bone Cancer Research Trust-funded research starts to develop the protocols for intensity-modulated radiotherapy and proton beam radiotherapy for primary bone cancer patients. The protocols developed were incorporated into the IMRIS clinical trial. As of 2018, proton beam therapy is now available at the The Christie NHS Foundation Trust, Manchester, for primary bone cancer patients.
- Initial results demonstrate the potential for epigenetic targeting of genes in chordoma, a theme that continues to develop as part of our research programme.
- We fund a studentship to identify osteosarcoma specific cancer genes. The study provided evidence for the inclusion of osteosarcoma patients in FGFR1 inhibitor trials and that PARP inhibitors may be effective in a subset of osteosarcoma patients.

2013

- Research commences to detect biomarkers such as, circulating tumour cells and tumour DNA, in the blood. This work is now being directly applied into ICONIC.

- We fund work to establish patient derived osteosarcoma cell lines that can be used in models of the disease. These cell lines were used to interrogate the biological relevance of the genetic alterations discovered by an International Cancer Genome Consortium (ICGC) bone tumour project.

Bone Cancer Research Trust-funded research continues the investigation into CL67, a drug that blocks the production of the HIF1α protein. Unfortunately, initial promise did not translate into significant results, however, HIF1α remains an attractive drug target.

We award funding to researchers to investigate the use of nuclear export inhibitors to prevent the resistance to TRAIL treatment in osteosarcoma cells.

2014

- We fund the first study to translate known genetic alterations in chondrosarcoma into biomarkers of disease progression and diagnosis.
- We award a research grant to produce the first 3D cancer cell laboratory model incorporating the proteins and mineral components of the bone microenvironment. The project aimed to understand how osteosarcoma cells adapt in response to changes in their surroundings and respond to drug treatment.

2015

- Launch of the 'LIVING WITH, AND BEYOND, PRIMARY BONE CANCER' report, which became the foundation of our 2017-2022 strategy, providing the basis of our research Grant Programme.
- Research into the detection and characterisation of circulating tumour cells in osteosarcoma is expanded, leading to its eventual incorporation into ICONIC.
- Focusing on the development of new treatments for osteosarcoma and investing in the next generation of primary bone cancer researchers, we fund two PhD Studentships.

2016

- We fund a study which confirms that the current practice of determining tumour resection margins by MRI before chemotherapy for Ewing sarcoma is safe and provides better tumour removal than scanning after chemotherapy.

- We provide funding for the development a sarcoma-specific patient-reported outcome measure (S-PROM) to understand the experience of being diagnosed with and surviving primary bone cancer and to develop a strategy for its incorporation into clinical practice.
- We award funding to support the analysis of the recommendations from the National Ewing Sarcoma Multi-disciplinary Team (NEMDT), incorporating patients' views and defining best practices for therapy.
- A Bone Cancer Research Trust-funded project investigates ANGPTL4, a protein highly expressed in osteosarcoma prior to metastasis, as a potential novel target to reduce metastasis and prevent bone destruction.

2017

- We facilitate 3 international primary bone cancer meetings including the 2nd Ewing Sarcoma Consensus Meeting to harmonise the treatment of Ewing sarcoma.
- In response to primary bone cancer being eligible for the 100,000 Genome Project, we launch our Infrastructure Grants.
- After promising results in previous Bone Cancer Research Trust-funded research, we award funding to continue the study of circulating tumour DNA as potential biomarker for chondrosarcoma.
- We award research funding for pilot studies studies exploring new therapeutic opportunities for osteosarcoma treatment that take advantage of the mechanical forces on tumours and emerging signalling pathways.

Bone Cancer Research Trust-funded research identifies how autophagy can help cancer cells thrive under chemotherapeutic stress and how it could be targeted to combat resistance to chemotherapy in osteosarcoma.

2018

ICONIC
IMPROVING OUTCOMES THROUGH COLLABORATION IN OSTEOSARCOMA
A BONE CANCER RESEARCH TRUST FUNDED PROJECT

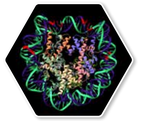
- We fund our first clinical trial, ICONIC, Improving Outcomes through Collaboration In Osteosarcoma. As of July 2021, the trial has recruited 102 patients across 22 study centres.
- Oncolytic viruses as a potential immunotherapy-based treatment for Ewing sarcoma, a new Bone Cancer Research Trust-funded PhD project commences.
- Funding continues for the second year of our Infrastructure Grants after 2,186 samples were collected in year 1.
- Proton beam radiotherapy becomes available for primary bone cancer patients at the The Christie NHS Foundation Trust.

Modifying methotrexate to reduce toxicity and enhance efficacy, an additional Bone Cancer Research Trust-funded PhD project commences. This additional project was made possible by the fundraising efforts of our community.

2019

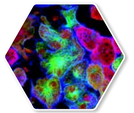
- 4,666 samples were collected and Infrastructure Grant funding was expanded to cover all five English surgical centres.
- We host the 1st International Osteosarcoma Research Symposium bringing together researchers from across the world to accelerate progress and coordinate efforts.
- Our funded research identifies Neurexin-1 as a potential biomarker to identify Ewing sarcoma patients with localised disease who will experience disease progression and poor outcomes, so their treatment can be tailored appropriately.
- OMeNet (Osteosarcoma Metastasis Network) is formed, bringing together expertise from across the osteosarcoma field to speed up and improve pre-clinical research.
- The Bone Cancer Research Trust receives the Award of Healthcare and Medical Research Charity of the Year in recognition of our Infrastructure Grants.

We fund research that demonstrates the potential to use epigenetic modifications in the treatment of chordoma. The team discovered a drug that can switch off the brachyury gene, killing chordoma cells.

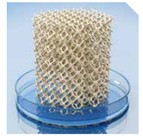


2020

- We carry out our 2020 Patient Survey, the most comprehensive piece of research focused on presenting symptoms and routes to diagnosis for primary bone cancers and tumours in the UK to date.



- The Bone Cancer Research Trust launches the UK's first adamantinoma research programme.
- We award our 9th PhD Studentship to develop the first tissue bio-engineering/ cancer biology collaborative project in osteosarcoma.



- We host the first International Ewing Sarcoma Research Symposium to stimulate international collaboration, resulting in our largest research grant call for Ewing sarcoma.
- We award our first cancer evolution research project trying to understand how chondrosarcoma develops and changes over time.
- We award an Ideas Grant to investigate the potential protective effect of oestrogen in chondrosarcoma.

2021

- We expand our research internationally with the award of our first International Explorer Grant to a team at Georgetown University, USA. This research aims to develop CD99 inhibitors as a new treatment for Ewing sarcoma.
- OMeNet evolves to PBCMetNet, as researchers extend their efforts to include other forms of primary bone cancer.

PBCMetNet
PRIMARY BONE CANCER METASTASIS NETWORK

- Funding continues for the fourth year of our Infrastructure Grants. As of July 2021, 9,309 samples have been collected overall and 7,701 have been sent to support 21 primary bone cancer research projects.
- We award three pilot research awards in osteosarcoma. The pioneering projects investigate the potential for RNA technology to target the *TP53* gene, extracellular vesicles that facilitate lung metastasis and novel gallium containing drugs that seek and destroy chemotherapy resistant osteosarcoma cells.

BONE CANCER RESEARCH TRUST
15th ANNIVERSARY
UNTIL THERE'S A CURE

In June 2019, the Bone Cancer Research Trust received the Award of **Healthcare and Medical Research Charity of the Year** in recognition of our sample collection work.

"The Bone Cancer Research Trust demonstrated great success in getting an awful lot of patients to donate samples, in a very cost-effective way. The charity has listened closely to its beneficiaries and was driven to act by their needs.

Awards Judge, Lynne Berry OBE

2019 THE CHARITY AWARDS WINNER

GENERATING NEW KNOWLEDGE AND EXPANDING OUR UNDERSTANDING OF THE CAUSES OF PRIMARY BONE CANCER

Understanding the causes of cancer is crucial for developing novel therapies. In the same way you cannot drive a car until you know the accelerator will make the car go faster and a brake will slow it down, researchers cannot design new drugs until they understand what makes a cancer cell divide so quickly. We need to understand the accelerator and brake pedals of the cells.

Once the mechanisms that drive changes in cancer are understood, new therapies emerge but there is a secondary bonus. Based on the new knowledge, researchers can use the observed changes as markers for disease which can be used to inform diagnosis, prognosis and response to treatment.

USING TUMOUR BIOPSIES TO INFORM TREATMENT FOR EWING SARCOMA PATIENTS

By understanding the biology and characteristics of the cancer cells that are resistant to current treatment, we can discover new tools to identify the patients who might benefit from different management and discover new targets for treatment.

Professor Susan Burchill has a long-standing interest in Ewing sarcoma. She initiated the GenoEwing study and has identified specific genes and proteins that can be used as biomarkers for disease monitoring, diagnosis and to influence treatment options.

Her research funded by the Bone Cancer Research trust has discovered that a protein named Neurexin-1 is present at high levels in self-renewing Ewing sarcoma cancer cells that are resistant to current treatment. Its expression is particularly relevant in patients with localised disease who unfortunately experience disease progression and poor outcomes.

This discovery can have a direct impact; by identifying these patients at an early stage, their treatment can be tailored at diagnosis and potentially improve the outcome.

Professor Susan Burchill, Professor of Cancer Research, University of Leeds

Dr Adam Cribbs, Group Leader in Systems Biology and Next Generation Sequencing Analysis, University of Oxford

ONCOGENIC DRIVERS OF CHORDOMA

The genes that control cell division can be broadly categorised into 2 groups: tumour suppressors, genes that slow down or stop cell division and tumour promoting, genes that speed up cell division. In cancer, these genes become unbalanced; tumour suppressor genes can be switched-off. Alternatively, tumour promoter genes can be switched-on. This loss of control leads to increased cell division resulting in a tumour.

In 2012, the Bone Cancer Research Trust funded Professor Farida Latif at the University of Birmingham to identify some of these genes, to understand what causes chordoma and to develop biological markers that can be used to diagnose and/or predict the likely course of the disease.

Genes can be switched on or off without alteration of their DNA sequence by a process known as epigenetic alteration.

A unique feature of epigenetic inactivation or activation is that it can be reversed. Drugs can switch-on genes that have been switched-off, or swich-off genes that are switched-on. The use of these drugs to reverse the effects of epigenetic inactivation/activation is called epigenetic therapy. Fast forward to 2019, Dr Adam Cribbs from the University of Oxford and Dr Lucia Cottone from University College London have joined forces in a collaborative, Bone Cancer Research Trust-funded, project aiming to find epigenetic targets for the treatment of chordoma.

The *TBXT* gene (also known as brachyury) is largely responsible for the uncontrolled growth of chordoma cells, therefore switching-off the *TBXT* gene is a very attractive approach to find new therapies for chordoma.

Dr Cottone and Dr Cribbs found that when 2 proteins, KDM6A and KDM6B, were restricted, the *TBXT* gene was silenced, causing chordoma cells to die[6].

"By screening more than 90 drugs, we have been able to identify a compound that switches off the TBXT gene and kills chordoma cells.

Dr Lucia Cottone, Post-Doctoral Researcher, University College London

This is an exciting discovery and, although still at an early stage, it suggests that targeting KDM6A and KDM6B could provide a route for new treatment options for chordoma.

"I was diagnosed with a skull based (clival) chordoma in 2017.

After spending that year in a "medical fog" with multiple hospital visits, surgeries and proton beam therapy, I became obsessed with finding out what chordoma was all about.

Every information recourse I found online was rather basic, minimal, and disappointing until I found the Bone Cancer Research Trust and Chordoma UK websites.

It was so comforting to see that both charities were deploying all their knowledge and funds towards research.

The latest research project, funded by BCRT, has brought so much more clarity in understanding how chordoma arises and develops as well as providing that little glimmer of hope that had been missing from the chordoma world.

One of my favourite life quotes is that, "Knowledge is power" and this couldn't be more true when it comes to understanding chordoma in order to be able to stop it one day.

I feel very hopeful for the future thanks to continuous research, however I understand that research is expensive, which is why the amazing fundraising work by BCRT is so important.

This summarises it all for me:

Without funds, there will be no research.

With research, there will be hope.

Sylvie Leslie, Chordoma patient

FINDING NEW THERAPIES –

DEVELOPING TAILORED AND TARGETED TREATMENTS

Several ongoing and completed projects have aimed to find new targets that can be exploited as new treatments for primary bone cancer. As of July 2021, the Bone Cancer Research Trust has funded over 50 projects focusing on the development of new therapies. We have chosen 2 exciting examples to illustrate this area.

COMBINATION OF TARGETED THERAPIES TO COMBAT OSTEOSARCOMA METASTASIS.

Professor Agi Grigoriadis at King's College London aims to understand the fundamental mechanisms of osteosarcoma cell growth and lung metastasis. Cancer cells are regulated by many signaling proteins that control their behaviour, growth and migration. Supported by the Bone Cancer Research Trust, he has demonstrated that the FGFR1 signaling protein is abnormally high in osteosarcoma cells and drives the formation of lung metastases in pre-clinical models of bone cancer. Blocking FGFR1 with an inhibitor (AZD4547) that is already being tested in the clinic for other cancers, inhibits lung metastasis in laboratory models.

Further studies have revealed that FGFR1 cooperates with another signaling protein, mTOR, and that blocking FGFR1 together with an inhibitor to mTOR (AZD8055), showed a greater reduction of metastasis in the lungs than when each inhibitor was used alone. These exciting experiments in pre-clinical models must now be validated in clinical samples, but they suggest that combinatorial therapy might be beneficial for osteosarcoma patients that present high levels of both FGFR1 and mTOR.

With additional funding from the Bone Cancer Research Trust, Prof Grigoriadis has expanded his research to study the tumour environment in which cancer cells reside. It is known that some cells in the tumour environment, for example M2 macrophages, can suppress the body's own ability to target the cancer by producing proteins that suppress the immune response, and thereby indirectly control cancer cell behavior. One of these proteins is the enzyme Heme oxygenase-1. So far, results have shown in pre-clinical models that both M2 macrophages and HO-1 are found at high levels within primary osteosarcoma tumours and lung metastasis.

Fortunately, there is already a clinically approved drug against HO-1, tin mesoporphyrin, also known as SnMP and further *in vivo* studies are examining the effects of the SnMP inhibitor on tumour formation and metastasis.

> ***"The Bone Cancer Research Trust recognised the importance of these pathways in osteosarcoma and enabled the progress of these research projects. The initial awards have allowed us to secure further longer-term funding to pursue these discoveries.***
>
> ***The Bone Cancer Research Trust has established a successful network of basic, translational and clinical research that disseminates their findings to the public, in particular to patients and their families. With their unique dialogue and interaction style, the management and research support offered by the Bone Cancer Research Trust for students, postdocs, young investigators and senior researchers is second to none.***

Professor Agi Grigoriadis, Professor of Bone and Cartilage Cell Biology, King's College London

PRE-CLINICAL STUDIES TO HIGHLIGHT THE POTENTIAL FOR USING CHEMOTHERAPY AND RADIOTHERAPY SENSITISERS IN EWING SARCOMA – PARP INHIBITORS.

Radiotherapy and chemotherapy kill cancer cells by damaging their DNA. Cancer cells contain proteins that repair the DNA and therefore "undo" this damage. One such protein named poly ADP-ribose polymerase (PARP), is present in Ewing sarcoma cells.

PARP inhibitors inactivate this repair protein, enhancing the anti-cancer effects of chemotherapy and radiotherapy.

Professor Nicola Curtin from the Northern Institute for Cancer Research at Newcastle University has been pivotal in developing PARP inhibitors for cancer research. They are nowadays used, whether alone or in combination with other chemotherapeutic agents, to treat breast, ovarian, prostate, pancreatic and other types of cancer.

In 2009 and 2010, the Bone Cancer Research Trust granted research projects to Professor Curtin and Dr Britta Vormoor to determine if agents that prevent DNA repair could be utilised to increase the effects of radiotherapy and chemotherapy drugs in treating Ewing sarcoma. The findings contributed to the pre-clinical evidence needed to initiate a clinical trial (SARC025) to evaluate the safety and toxicity of niraparib, a potent and selective PARP inhibitor, in combination with temozolomide or irinotecan in patients with advanced Ewing sarcoma[7].

Initial results for the trial were published in October 2020[8]; unfortunately, the combination in both arms resulted in high toxicity and therefore limited efficacy. A triple-combination of all 3 drugs, albeit at lower doses was tried, but unfortunately, the trial closed in January 2021 due to lack of efficacy.

Although this trial was not successful, we must acknowledge that in every area of disease, but particularly in oncology, the success rate of clinical trials is limited. Trials involving combinations of drugs are particularly challenging as each individual drug is limited by its associated toxicity and side effects. When administered in combination, the doses that patients can tolerate are drastically reduced and regrettably, this reduces the efficacy of the treatment.

The overall success rate of oncology trials, from Phase I to approval has been estimated at below 5%[9]. This statistic highlights the importance of biomarker research in helping clinicians to direct patients to the trials from which they will likely receive most benefit. Clinical trials also help us to better understand how drugs are handled by our bodies and to determine the optimal dosing regimens for each patient.

The Bone Cancer Research Trust is committed to supporting research in these areas, to hopefully improve these clinical trials statistics and benefit bone cancer patients.

The use of PARP inhibitors in primary bone cancer remains an important topic with a very sound scientific rationale; in fact, it has attracted recent interest from osteosarcoma researchers that are investigating the possibility of using PARP inhibitors in combination with DNA damaging agents like doxorubicin for the treatment of osteosarcoma. We follow their progress with great interest!

> ***"Although PARP inhibitors were originally designed to increase the response to certain anticancer agents, they have been most successful as single agents exploiting DNA repair defects found only in the tumour cells, most commonly ovarian, breast, prostate and pancreatic cancers. Data we generated in our lab, with support from BCRT, suggested that this would work well with temozolomide and topotecan, both drugs used to treat Ewing sarcoma. However, there is always a fine line between increasing the anticancer activity and increasing toxic side effects. It is disappointing that it wasn't possible to achieve this balance in the clinical trials. It is to be hoped that in the future we will be able to identify more exploitable defects in different cancer types and target them with the appropriate drugs and so have more selective, less toxic chemotherapies.***

Professor Nicola Curtin, Professor of Experimental Cancer Therapeutics, Newcastle University

IMPROVING EXISTING THERAPIES

Bone Cancer Research Trust-funded research is improving all current forms of treatment.

SURGERY

Computer navigation-assisted surgery has resulted in dramatic survival improvements for chondrosarcoma patients.

Surgery remains the primary treatment for chondrosarcoma patients. In 2010, the Bone Cancer Research Trust funded the initial investigations by Professors Lee Jeys and Robert Grimer at the Royal Orthopaedic Hospital in Birmingham, to assess the efficacy of computer-guided pelvic sarcoma surgery - Computer Assisted Sarcoma Surgery Is Safer (CASSIS) Trial. This project laid the foundations for computer navigation-assisted surgery and enabled the researchers to obtain further funding to continue the work that has led to a life-saving development.

Results published in 2020[10] demonstrated that navigation-guided surgery resulted in improved surgical control, the 5-year risk of local recurrence was reduced and the 5-year chondrosarcoma specific survival was markedly improved, when comparing the non-navigated with the navigated groups. In addition, the 5-year progression-free survival (when patients live with the disease, but do not become worse) was also improved notably when navigated-surgery was used.

5-YEAR CHONDROSARCOMA-SPECIFIC SURVIVAL IMPROVED FROM 53% TO 76%

"As we currently don't have an effective chemotherapy or routine radiotherapy option for classical chondrosarcoma of the pelvis, the margins achieved at surgery are really important. We have been using computer navigated surgery in the pelvis for about 10 years and have been able to show that we can get better margins and reduce local recurrence. This is the first long term study that shows that doing surgery better with navigation saves lives. The difference is quite massive and if this were a new chemotherapy it would be revolutionary. It is important that we keep on improving on what we do as surgeons, to improve patients' function and if possible, improve their chances of being cured.

I discharged my first navigated pelvic chondrosarcoma patient cancer free at 10 years post-surgery in July 2020 and it was a great feeling for both of us! Hopefully many more patients will have a better chance of being cured with this technology!

Professor Lee Jeys, University of Aston and Consultant Orthopaedic Surgeon at the Royal Orthopaedic Hospital, Birmingham

RADIOTHERAPY

Putting radiotherapy advances into action for primary bone cancer.

In 2012 the Bone Cancer Research Trust funded Dr Franél le Grange of University College London with a clinical fellowship to assess the benefits of using advanced techniques - intensity modulated radiotherapy (IMRT) and proton beam particle radiotherapy in bone sarcoma.

IMRT matches the radiotherapy beams to the shape of the tumour, reducing the amount of radiation delivered to the healthy tissues surrounding the cancer. This should lead to fewer side effects as well as allowing dose escalation, which is of particular relevance in osteosarcoma.

Application of these techniques is especially important for patients with inoperable primary pelvic or spinal bone cancer. Her results demonstrated that when these techniques were applied to a group of young female Ewing sarcoma patients with pelvic tumours they resulted in excellent sparing of bowel, rectum, and bladder. Proton beam therapy also offered superior sparing of the head of the femur, uterus, vagina, and ovaries.

The protocols developed by Dr le Grange were incorporated into a Phase II clinical trial. The IMRT in Primary Bone and Soft Tissue Sarcoma (IMRiS) trial, is a nationwide multi-site study headed by Dr Beatrice Seddon from University College London. It started in 2016, with recruitment ending in December 2019.

The overall aims of the trial were to determine if IMRT reduces side effects, particularly long-term effects and to see if bone cancer patients with tumours in the spine/pelvis can receive the best dose of radiotherapy for their treatment, without causing damage to the surrounding tissues and reducing the risk of relapse.

Results from this trial are being analysed and will set new national standards for routine treatment.

Proton beam radiotherapy is now available to treat primary bone cancer patients at The Christie NHS Foundation Trust in Manchester, which is the first UK-based NHS high-energy proton beam therapy centre. A second centre is due to open at University College London Hospital in 2021.

To help patients and their families with the additional costs of having to travel to access proton beam radiotherapy, in 2020, and as part of our Support & Information Service, we Introduced our Travel Assistance Grants; in under a year, we have already received 22 grant applications and the feedback from the National Sarcoma Forum as part of the British Sarcoma Group conference has been excellent.

"The BCRT grant has been a massive help in patients travelling to the proton centre in Manchester.

Mark Reed, Specialist Radiographer at the Christie's Proton Beam Therapy Centre

One of the aims of our landmark clinical study, ICONIC is to evaluate the benefits of post-operative radio therapy for osteosarcoma patients and to define the parameters for treatment. Together, we are hopeful that the IMRiS and ICONIC clinical trials will usher in a new era of more efficacious treatment for osteosarcoma patients with fewer side effects.

CHEMOTHERAPY

MMP-activated methotrexate conjugates.

Doxorubicin, cisplatin, and high-dose methotrexate (HDMTX) have formed the backbone of osteosarcoma treatment in the UK for many years.

High doses of methotrexate are required to ensure enough drug reaches the target osteosarcoma tumour cells but inevitably, a large proportion is also distributed to other organs. As the drug cannot distinguish between cancerous and healthy cells, high-dose methotrexate leads to very significant toxicity.

Funded with a Bone Cancer Research Trust PhD Studentship in 2018, Professor Robert Falconer and student Hannah Spencer at the University of Bradford, are aiming to create a chemically modified methotrexate ('prodrug'), that remains inactive until it is released within the tumour environment by proteins called matrix metalloproteinases (MMPs) that are absent in healthy tissues. This strategy aims to reduce the devastating side effects caused by damage to healthy cells in normal tissues and will hopefully increase methotrexate's effectiveness in killing osteosarcoma cancer cells, as more of the active drug will be localised at the desired site.

The investigation is progressing and the results from the second year of research are promising. If successful, outcomes from this research have the potential to revolutionise patient care for osteosarcoma patients.

"If this research is successful, the project could proceed to clinic. Ultimately, we could potentially see a new methotrexate drug introduced into mainstream healthcare which is a more effective and efficient attack against osteosarcoma tumours with dramatically reduced side effects.

Dr Zoe Davison, Head of Research Support and Information, Bone Cancer Research Trust

"Methotrexate is a very effective chemotherapy in bone cancer treatment regime, but the horrific side effects from this drug, the preparation required for bloods to be a certain pH and the long stay in hospital awaiting safe levels of methotrexate in the system, mean it's brutal. To be part of the campaign funded by BCRT for Bradford University and Prof Rob Falconer and Hannah Spencer to turn methotrexate into a targeted, kinder drug has been incredible. To turn such toxic chemotherapy into something that targets bone cancer cells and causes little-to-no side effects, will revolutionise treatment for primary bone cancer.

Peter Lloyd, Patient Ambassador for the Bone Cancer Research Trust

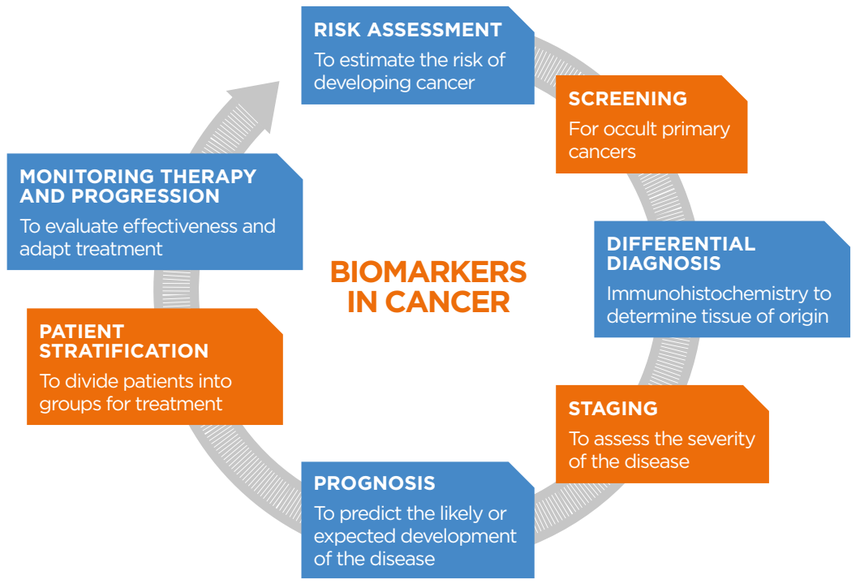
Research funded by the Bone Cancer Research Trust aims to improve survival rates, but also the quality of survival. Improved surgical margins and radiotherapy and chemotherapy treatments will make a significant difference to the quality of life after and during treatment for our patients.

IDENTIFYING DETECTION TECHNIQUES FOR DIAGNOSIS AND DISEASE MONITORING

Biomarkers are a hot topic in research and medicine as they have the potential to revolutionise cancer treatment. But what is a biomarker?

Biological markers, or 'biomarkers', are molecules and cells that can be measured from patient samples to gain an insight into a disease and in some cases make predictions about disease progression. The overall aim of biomarkers is to help clinicians find and diagnose diseases earlier and allow patients to be treated and monitored more effectively.

Some biomarkers are only used in a specific setting, others can serve more than one purpose, as illustrated in the diagram below.



CIRCULATING TUMOUR CELLS

As a tumour develops, it releases factors which promote the formation of new blood vessels in and around the tumour in a process called angiogenesis. Once the vessels have been established, cancer cells can use them to escape the primary tumour and travel to a different part of the body where they form a secondary tumour (metastasis). Cancer cells that make this journey in blood vessels are known as circulating tumour cells (CTCs). Scientists have found a way to detect CTCs in cancer patients and are using them as an indicator of disease progression and to predict response to treatment. CTCs are identified by unique proteins on their cell surface that distinguish them from normal cells.

CIRCULATING TUMOUR DNA

Although scientists are unclear as to exactly how tumour DNA ends up in the bloodstream, circulating tumour DNA (ctDNA) is a widely accepted biomarker for cancer. ctDNA can be isolated from blood samples and sequenced to find any mutations it contains; this information can help direct clinicians towards a diagnosis and could help inform treatment.

EMERGING BIOMARKERS

Extracellular vesicles (EVs) are currently being explored as potential biomarkers for several cancers. EVs are small particles which contain a collection of proteins and microRNA that are secreted by tumour cells. It is thought that EVs are crucial for metastasis formation, either by directly promoting cells to become cancerous or creating a niche ready for metastasis formation. Like CTCs and ctDNA, EVs travel via the bloodstream. It is therefore possible to isolate and analyse them to inform diagnosis and treatment.

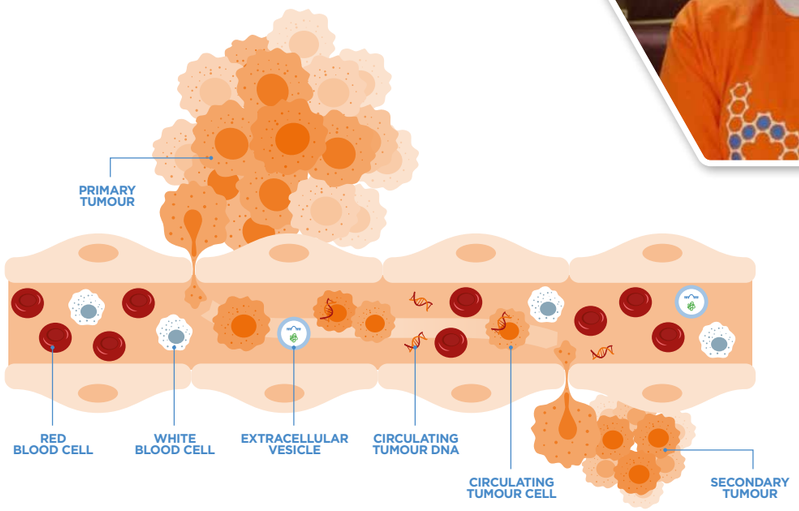
Indeed we have awarded one of our latest Ideas Grants to Dr Karan Shah at the University of Sheffield, to investigate the role that EVs play in osteosarcoma and how they can be targeted to prevent its metastatic spread to the lungs.

Another field of biomarker research showing promise is Epigenetics. Epigenetic modifications sit on top of normal DNA, essentially telling a cell what DNA can be read and what cannot. If these modifications go awry, cells can lose access to essential control genes or vice versa and cells begin to produce too much of a certain protein. Because epigenetic modification is used to determine how cells become specialised, they are a useful biomarker for the disease history. An example of epigenetic biomarkers is DNA-methylation.

As biomarker research advances and the technology becomes more refined, we hope that 'liquid biopsies' will become more common in routine clinical practice, speeding up diagnosis and improving outcomes for patients.

"Biomarkers that facilitate diagnosis, monitor disease progression and response to treatments, have the potential to make a tremendous impact on patients' lives. The Bone Cancer Research Trust is committed to facilitate research in this area and facilitate the incorporation of findings into clinical studies.

Dr Victoria Vinader, Research Manager, Bone Cancer Research Trust



"Bone sarcomas are rare, mineralized and highly heterogeneous malignant entities making them difficult to analyse and less attractive for pharmaceutical companies. The Bone Cancer Research Trust plays a crucial role by supporting researchers working in the field of bone sarcomas. Thanks to their support, my team located at the University of Sheffield could properly develop our project focused on the metastatic disease in osteosarcoma.

The Bone Cancer Research Trust markedly contributes to the structuration of bone sarcoma research in the UK as illustrated by the ICONIC project, a unique programme which has boosted the scientific collaborations in the UK in the field of bone sarcomas.

I am very grateful to patients, their families and the charity.

Professor Dominique Heymann, Head of Histology and Embryology, University of Nantes and Honorary Professor of Bone Oncology, The University of Sheffield

CIRCULATING TUMOUR CELLS (CTCS) - BIOMARKERS FOR CANCER DIAGNOSIS AND MONITORING OF OSTEOSARCOMA

An example of CTCS research funded by the Bone Cancer Research Trust is that of Mr Kenneth Rankin at the University of Newcastle and Professor Dominique Heymann at the University of Sheffield. Together, their main goals were to identify new biomarkers for clinical monitoring of therapeutic efficacy and resistance; to identify osteosarcoma patients with a higher risk of metastasis and to decipher the mechanisms of resistance to treatments, so therapeutic approaches can be adapted accordingly.

They detected, isolated, and characterised circulating osteosarcoma cells in laboratory models (pre-clinical models), these cells can be used as biomarkers to predict early signs of metastatic spread and/or response to treatment[11].

By using the experience acquired with the laboratory research models, the researchers developed the methods for isolating CTCs in patient samples that carry specific proteins on their cell surface (for example MT1-MMP) or by combining the detection of cell surface proteins and the cell content in genetic materials (DNA content).

Progress has now moved well beyond the laboratory and the researchers are now collaborating on the isolation and characterisation of osteosarcoma circulating tumour cells from the blood samples of patients in our landmark clinical trial ICONIC.

"I would like to congratulate the Bone Cancer Research Trust for having such a successful, productive time since the Trust was initiated. I would like to thank the charity for their support over the years as they have made a great deal of my research possible. Their emphasis on biobanking tissue for research is admirable.

The Infrastructure Grants are extremely valuable and because of the data we are producing now it will have a major impact on the understanding of sarcoma. It will also be terrific to see other researchers delving into the published data for patient benefit.

I believe the funds that the Bone Cancer Research Trust have provided have been extremely well used and will bear fruits for the next decade.

Professor Adrienne Flanagan, Professor of Musculoskeletal Pathology, University College London and Royal National Orthopaedic Hospital, Stanmore

CIRCULATING TUMOUR DNA AS CLINICAL BIOMARKER FOR CHONDROSARCOMA AND OSTEOSARCOMA

We have funded Professor Adrienne Flanagan (2017) and Dr Iben Lyskjaer (2019) from University College London to study these signatures and their potential use in chondrosarcoma and osteosarcoma. Professor Flanagan is a recognised expert in the pathology of sarcoma. Initial results from these projects are very encouraging.

These blood tests, are described as liquid biopsies, and the findings so far indicate that they can be used to predict the grade of a patient's tumour and provide a more accurate prognosis; preliminary data suggest that they can also be used to monitor response to treatment and detect the very early stages of recurrence. This research has benefitted from collaboration from the other primary bone cancer units across the UK.

EPIGENETIC BIOMARKERS FOR DIAGNOSIS

Diagnosing bone and soft tissue tumours remains challenging because of the large number of subtypes, many of which lack diagnostic biomarkers.

DNA-methylation provides additional information which is different from whole genome and RNA sequencing and has the potential to become a valuable diagnostic tool.

A European-wide collaboration has recently produced a mathematical model that can predict the type of sarcoma based on their DNA-methylation profile. This classifier of sarcoma type, which was developed by the German Cancer Research Center (DKFZ) in Heidelberg, was based on a dataset of 1077 DNA-methylation profiles from fully pre-characterised sarcoma tumours[12].

Dr Lyskjaer and Prof Flanagan examined the DNA methylation data from 986 soft and bone sarcoma patients collected through the UCL Biobank facility at the Royal National Orthopaedic Hospital (RNOH, Stanmore), which is funded by one of our Infrastructure Grants.

When the DNA-methylation profiles of the RNOH samples were evaluated using the DKFZ classifier, 61% of cases received a sarcoma type prediction and the histological diagnosis agreed with the predicted sarcoma class in 88% of cases. The classifier performed best when diagnosing chordomas (85%).

Although these results require further validation, the research clearly shows the potential for DNA-methylation to be used to support the diagnosis of sarcoma tumours.

CLINICAL IMPROVEMENTS THAT DIRECTLY BENEFIT THE LIVES OF PRIMARY BONE CANCER PATIENTS AND THEIR FAMILIES

Funded by the Bone Cancer Research Trust in 2018, ICONIC is the largest collaboration in osteosarcoma research in the UK. The nationwide project includes sarcoma centres acting as hubs for patient recruitment, sample collection and scientific analysis. Our Infrastructure Grants take a central role in the collection of samples for this clinical study.

Osteosarcoma is the most common form of primary bone cancer in children and young adults (10 to 24 years of age) and is unique in the fact that it has a second peak in incidence, in adults over 40. Yet, patients over the age of 40 have not previously been eligible to participate in osteosarcoma clinical trials.

ICONIC is recruiting every newly diagnosed patient with osteosarcoma in the UK, irrespective of age, to obtain the UK's first osteosarcoma patient registry, including full clinical data and tissue collection.

Tumour samples are being studied at the genetic and molecular levels and the information will be correlated with the patient's diagnosis, treatment journey and clinical outcome.

The knowledge gained from this research will be used to identify and develop promising biomarkers and potential new targets for treatment of osteosarcoma.

ICONIC
IMPROVING OUTCOMES THROUGH COLLABORATION IN OSTEOSARCOMA
A BONE CANCER RESEARCH TRUST FUNDED PROJECT

The study opened in October 2019. With 22 sites on board, by July 2021, the study has recruited **102 patients** of all ages and primary site of disease that have received all modalities of treatment available.

Even with the impact of COVID-19, 153 patient samples have already been collected for analysis.

22 SITES ALREADY OPEN

5+ PATIENTS PER MONTH

102 PATIENTS RECRUITED

18% PATIENTS OVER 40 YEARS OLD

"ICONIC is the first study that brings together scientists, pathologists, oncologists and surgeons from across the UK to work with patients to better understand this challenging disease. It will ultimately build a sustainable platform for ongoing research in the UK, provide opportunities to find new treatments and collaborate more widely across Europe to deliver continued improvements in outcome for osteosarcoma.

The Bone Cancer Research Trust is the only UK charity that focuses on primary bone cancers, understands the challenges of the diseases and is dedicated to improving the lives of bone sarcoma patients. They provide excellent information and support for patients, raise awareness of these rare cancers, provide funds for research where there are few opportunities for funding and their initiative to provide funding for such an ambitious study and for infrastructure to support tissue sample collection is of great importance to osteosarcoma patients.

Dr Sandra Strauss, Senior Clinical Lecturer and Consultant Medical Oncologist, University College London Hospital. Principal investigator of ICONIC

"As a parent, when your child is diagnosed with osteosarcoma, you want to do anything you can to help not only your child, but also future patients. We know we are doing something useful being part of ICONIC, to hopefully help future osteosarcoma patients.

When it came to involving Phoebe, we explained that in the past, there has been research/trials that patients have signed up for, that will have got us to this point where we are today and will have influenced her treatment. In turn, if she consented to ICONIC going forward, she might help someone in the future, and she enthusiastically replied, 'yeah alright'.

When you realise osteosarcoma and bone cancer treatments haven't really progressed in 40 years, it's very disappointing. Until you are faced with it personally and see how little funding goes into research compared to other types of cancers, it is quite shocking, so anything that can help like ICONIC, we're happy to be involved in.

Laura, mother of Phoebe Carter-Darwen, 12-year-old osteosarcoma patient and ICONIC participant

ICONIC represents a unique opportunity to work with experts across all disciplines across the country to make a difference in a challenging disease and ultimately to build a sustainable platform for ongoing research in the UK. The project also provides an opportunity to find new treatments and collaborate more widely across Europe to deliver continued improvements in outcomes for osteosarcoma patients.

The goal of ICONIC is to better understand the treatment that osteosarcoma patients receive. By analysing patient samples collected at and beyond diagnosis and correlating these samples with patient data, researchers aim to improve time to diagnosis, survival and quality of life for patients.

Our research community shared with us what ICONIC means to them, this is represented in the word cloud below.

This highly collaborative, unprecedented approach involving patients, health practitioners, clinicians, surgeons and scientists may pave the way for similar studies to take place for other primary bone cancers.

RESEARCH IMPACT – FROM LAB TO PATIENT BENEFIT

Research leads to landmark discoveries. The Bone Cancer Research Trust endeavours to make such discoveries possible to improve the lives of primary bone cancer patients and their families.

Finding new ways of treating cancers, particularly rare ones like primary bone cancer, is a slow and expensive process. Research often takes a difficult path with a few steps forward and many backwards. In this context, 15 years is a very short time, yet some amazing progress has been made and we are so proud of what it has been achieved so far!

Some of the projects funded by the Bone Cancer Research Trust are at an earlier stage in their discovery journey, others are more advanced or completed, and are already making a difference in the clinic and directly influencing the treatment of our patients.

The diagram below illustrates how some of the research summarised in this report, and other Bone Cancer Research Trust-funded projects, are progressing towards their ultimate goal of directly benefiting primary bone cancer patients.

LOOKING TO THE FUTURE

The world of research is rapidly evolving, harnessing powerful new technologies to gain unprecedented insights into cancer and propel us ever closer to finding a cure. In this era of connectivity, technology is helping break down barriers to collaboration, bringing the global research community together like never before.

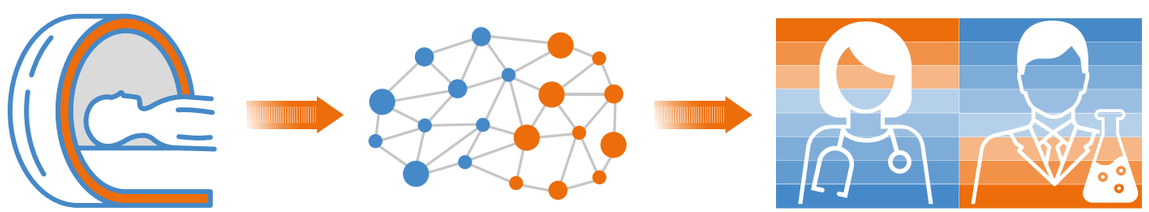
One of the most exciting and talked about advances in medicine and research is Artificial Intelligence (AI). AI, or more specifically 'Deep Learning', is a field of research where the goal is to make a computer that can 'think' like a human, be given a problem, adapt and solve it. This technology is being applied to try and solve the issues surrounding early diagnosis in cancer. Currently, AI can match the accuracy of clinicians in diagnosing some cancers from imaging and patient biopsies. As this technology advances, it is hoped that AI will be able to diagnose patients more accurately and quickly than doctors, dramatically reducing the time waited before commencing treatment.

AI is also being implemented in genomics research to help scientists integrate enormous datasets and bring our understanding of the human genome together in a new way. With the advent of next generation sequencing technologies such as single cell RNA sequencing and high-throughput sequencing, scientists can now dissect the molecular differences in tumours on a previously impossible scale and use this information to design better treatments. When the first human genome was sequenced, it took over 12 years and cost nearly £3.75 billion. Today, an entire human genome can be sequenced in 5 hours, costing as little as £375.

Outside the clinic, incredible new technologies are being created and used to study cancer in greater details and explore new therapeutic opportunities. The 'Organs of Chips' project is the revolutionary result of a collaboration between bio-engineers, biomedical scientists, chemists and physicists. These tiny devices allow researchers to perform experiments in entirely new way, more closely mimicking human tissues. The team behind the technology hope that their invention will accelerate the development of drug discovery, allowing new therapies to reach the clinic and patients significantly faster. The advantages of this technology are vast, from reducing the cost of drug development to further decreasing the use of animals in research.

> ***"It has never been a more exciting time to be a scientist! Armed with these new technologies, researchers are using their expertise and creativity to gain new insights into primary bone cancer that will pave the way for new treatment options.***
>
> **Tobi Firth, Senior Research and Advocacy Officer, Bone Cancer Research Trust**

The true power of science is in collaboration. Together, technology like AI, next generation sequencing, 'Organs on Chips' and the remarkable scientists and clinicians behind them are revolutionising our understanding of primary bone cancer biology. Pioneering research is paving the way to a future of personalised medicine and will continue to push the frontier... *Until There's A Cure*.



1. Images, such as X-rays, are taken of patients

2. Patient images are fed into a computer to be analysed by deep learning algorithms

3. The deep learning models provide clinicians and researchers with incredibly useful diagnostic and prognostic information

CLOSING REMARKS

OUR ANNIVERSARY RESEARCH IMPACT REPORT IS DEDICATED TO ALL PRIMARY BONE CANCER PATIENTS AND THEIR FAMILIES.

THANK YOU TO ALL THE RESEARCHERS, CLINICIANS AND SUPPORTERS, YOUR HARD WORK AND DEDICATION MAKES OUR RESEARCH POSSIBLE.

"As a patient or carer, you often feel gratitude – grateful of the support of a good friend, of the dedication of your medical team, for the days when the symptoms are better, or when a clear scan comes through. You appreciate how we all rely on someone, and how much we need those people who can do the things we can't.

The strength of the Bone Cancer Research Trust is in the name – Research. Research into primary bone cancers is so vital to us, and BCRT sets the highest standards in its work. From mind-boggling genetic science to the cutting edge of drug development, through quality of life studies to improving local therapy, and finding novel medicines to counter relapses, BCRT helps demolish the boundaries. They bring together unique people, experts in their fields to drive advances. In cancer, collaboration is the key and BCRT is at the very centre.

Thanks for all the work you do – we are grateful!

Andrew Westwood, Bone Cancer Research Trust Patient Advocate

"I was diagnosed with Ewing sarcoma back in 1983, undergoing surgery, radiotherapy and chemotherapy. The medical team were amazing. However, there was no facility for information on bone cancer away from a medical environment. In fact, it was more than 30 years until I met another bone cancer patient. It is so helpful to talk with others with experience of bone cancer and I can appreciate the value of the support and information they offer. I am really impressed how the Bone Cancer Research Trust have adapted during the past year with their "Virtual Cuppa" support get togethers and webinars.

In 2018 my wife and I were invited to visit the research laboratories at St James' Hospital in Leeds, to meet some of the team involved in finding a cure for bone cancer. Their dedication and perseverance are so inspiring.

To all the supporters, for their donations and challenges that raise the vital funds to enable this vital research to continue, and for new treatments to become a reality – a heartfelt thank you.

Dave Harley, Ewing sarcoma patient

With your continued support we can fund more research and support more scientists, so that ground-breaking discoveries and new treatments become a reality for patients.

To find out more about our research, please visit bcrt.org.uk/research or contact us research@bcrt.org.uk

GLOSSARY

Autophagy
Literally meaning "self-devouring", autophagy is the process by which cells remove damaged components and recycle them.

ANGPTL4
Angiopoietin-related protein 4. This protein is part of the vascular growth factor family. It has many functions including the formation of new blood vessels.

Basic research
This research aims to better understand a subject, the primary focus is advancing knowledge.

Biobank
A storage facility for biological samples e.g. tissue samples, that are used in research.

Biomarker
Short for 'biological marker'. Biomarkers are measurable indicators of biological processes in both normal and disease states.

Bisphosphonates
Drugs that slow or stop bone thinning.

Brachyury
A protein involved in DNA transcription in early development.

Clinical research
This term encompasses all research involving humans, from clinical trials of new drugs and developing new imaging techniques to healthcare support services.

Epigenetics
The study of alterations to DNA structure that do not involve changes to the DNA sequence.

FGFR
Fibroblast Growth Factor Receptor. This receptor is an example of a tyrosine kinase protein which is involved in cell division and survival.

Genome
The entire DNA content of a cell; the complete set of genetic instructions.

HIF1α
Hypoxia Induced Factor 1 alpha. This master protein regulator controls cellular responses to hypoxia.

Hypoglycaemia
A reduced level of glucose below normal physiological concentrations.

Hypoxia
Reduced oxygen. The core of a tumour is usually described as 'hypoxic' meaning, starved of oxygen.

Immunotherapy
A type of cancer treatment that stimulates the immune system to recognise and destroy cancer cells.

Mesenchymal stem cells
Stem cells found in bone marrow that are used to repair bone and cartilage when damaged.

Necrosis
A term for cell/tissue death. Different from normal or programmed cell death (apoptosis) which is initiated by the body.

PARP
Poly (ADP-ribose) Polymerase. This enzyme is involved in DNA repair.

Proliferation index
A measure of the number of cells in a tumour that are dividing.

P2RX7
P2X Purinoreceptor is a cellular receptor recognising ATP.

RNA
Ribonucleic acid (RNA) is a biological molecule that carries the instructions contained in DNA to the molecular machines that make proteins.

SEMA3A
Semaphorin 3A is a protein involved in bone remodeling.

Sequencing
The process of reading a human genome. Laboratory machines 'read' along DNA, writing down sequential bases- A, T, C or G to find the overall order.

STAT3
Signal transducer and activator of transcription 3. This protein is a transcription factor that promotes oncogenesis.

Translational research
The intermediary step between basic and clinical research. Translational research is the application of knowledge and discovery to a real-world problem.

Tumour-associated macrophages
Tumour-associated macrophages (TAMs) are cells that help create the immune-suppressive environment associated with tumours.

Tumour microenvironment
The tumour microenvironment collectively describes the connective tissues and non-cancerous (stromal) cells that surround a tumour.

To consult a full glossary of terms relevant to primary bone cancer visit the information section of our website www.bcrt.org.uk/information/glossary/

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