Genetics in Acute Lymphoblastic Leukaemia (ALL)

A Guide for Patients

Leukaemia Care
YOUR Blood Cancer Charity

Introduction

Genetics is the study of genes. Understanding how your normal cells work may help you understand the changes that normal cells undergo to become ALL cells. This can also explain why these cells are cancerous. If you have any questions about the genetics in types of ALL - this booklet covers the basics for you.

The booklet was written and updated by our Patient Information Writer, Isabelle Leach, and peer reviewed by consultant haematologists.

We are also grateful to our patient reviewers, Ross Happell, Meryl Simons and Karen Collier for their contribution.

Throughout this booklet, you will see QR codes that will take you to the relevant webpage for further support. Open the camera app on your phone and hover it over the QR code to open the link (suitable for Android, iPhone 7 and above).

Alternatively, if you are not able to use QR codes and would like to be sent the relevant webpages as URLs, or you would like the list of references used for this booklet, please email **communications@leukaemiacare.org.uk.**

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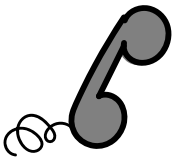
In this booklet

About Leukaemia Care

Leukaemia Care is the UK's leading leukaemia charity. For over 50 years, we have been dedicated to ensuring that everyone affected receives the best possible diagnosis, information, advice, treatment and support.

Our services

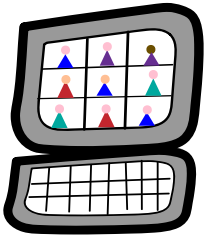


Helpline

Our helpline is available 9am to 5pm Monday to Friday. If you need someone to talk to, call **08088 010 444**.

Alternatively, you can send a message via WhatsApp on **07500 068065** on weekdays 9am to 5pm.

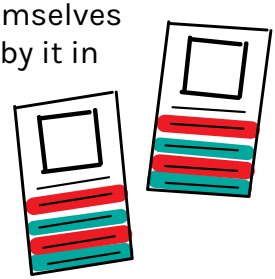
Support groups



Our nationwide support groups are a chance to meet and talk to other people who have been affected by a ALL diagnosis. For more information, scan this QR code:

Buddy support

We offer one-to-one phone support with volunteers who have had ALL themselves or been affected by it in some way. You can speak to someone who knows what you are going through. For more information on how to get a buddy call **08088 010 444** or email support@leukaemiacare.org.uk



Counselling service

Our counselling service helps ALL patients and their loved ones access up to six sessions of counselling. To apply, scan this QR code:

Advocacy and welfare

Our advocacy and welfare officers are here to help you find the support you need for many issues surrounding a ALL diagnosis. These include insurance, benefits and clinical trials. If you would like support from our advocacy or welfare officer, email **advocacy@leukaemiacare.org.uk** or call **08088 010 444**.

Cost of living fund

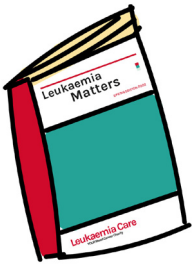
This fund provides grants to patients and families affected by ALL, to help with essential living costs. All applications must be made via the form which can be found by scanning the QR code:

Write a free will

Using our complimentary service, you can write a simple will so you know what happens to your estate when you die. To start writing your free will today, scan this QR code:

Patient magazine

Our magazine includes inspirational patient and carer stories as well as informative articles by medical professionals. To subscribe to our magazine, scan this QR code:



Glossary of medical terms

Acute lymphoblastic leukaemia (ALL)

Leukaemia in which lymphocytes start multiplying uncontrollably in the bone marrow, resulting in high numbers of abnormal, immature lymphocytes. Lymphocytes are a type of white blood cell involved in the immune response.

Chemotherapy

Therapy for cancer using chemicals that stop the growth of cells.

Clinical trial

A medical research study involving patients with the aim of improving treatments and their side effects. You will always be informed if your treatment is part of a trial.

Consolidation (phase)

Treatment following remission intended to kill any cancer cells that may be left in the body (also called intensification phase).

Induction (phase)

First treatment after diagnosis intended to kill the majority of the leukaemia cells and stimulate remission.

Intrathecal therapy

Injection of chemotherapy into the cerebrospinal fluid that surrounds and protects the brain and spinal cord.

Maintenance

Treatment given to prevent cancer from coming back after it has disappeared following the first-line treatment.

Monoclonal antibody

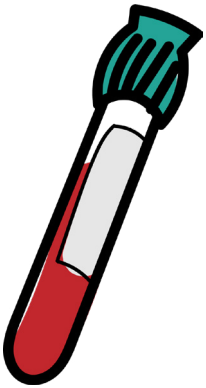
Man-made antibodies created from identical cloned immune cells so that they all bind to the same protein commonly found on the leukaemia cells such as CD20.

Palliative care

Also known as supportive care, this is a type of care that focusses on improving the quality of life for a patient with a life threatening illness and their loved ones.

Summary: Genetics in ALL

- There are two types of **acute lymphoblastic leukaemia** (ALL):
  - **B-cell ALL**
  - **T-cell ALL**
- The exact cause of ALL is unclear. The names of the ALL types are those of the lymphocytes in which the cancerous change occurs.
- Increasing evidence points to a genetic component being linked to the cause of ALL.
- Distinctive and recurrent changes in the chromosomes and gene mutations are seen in leukaemia cells.



What are genetics in the context of ALL?

Genetics is the study of genes. Understanding how your normal cells work may help you understand the changes that normal cells undergo to become ALL cells. This can also explain why these cells are cancerous.

Genes, chromosomes and DNA

Genes provide instructions for making active molecules called proteins. Genes are contained within your cell's DNA. Your DNA is like an instruction manual for making your cells. Genes are the basic physical and functional unit of heredity. Your genes are a mixture of those from your mother and those from your father.

The proteins in your genes provide instructions for the growth, development and functioning of your cells.

Leukaemia cells develops when the cells are without the right proteins. Examples include:

- Making too little of a protein
- Making too much of a protein
- Making an abnormal protein

A chromosome is a long string of DNA. There are 46 chromosomes in cells in your body. Genes in your DNA exist as 23 pairs of chromosomes in each cell (23 chromosomes from your mother and 23 chromosomes from your father).

Changes to chromosomes can make normal cells become ALL cells. This is because changing chromosomes also then changes the genes contained within them. Therefore, if your genes become damaged throughout your life as described above, you could develop ALL.

Researchers have compared the genes of patients with normal cells and those with leukaemia cells over period of time. They have identified distinctive and recurrent changes in the chromosomes and gene mutations of the leukaemia cells.

Specific problems that are commonly seen in the cells of ALL patients are discussed below.

Why is the specific genetics of my ALL cells important?

Different factors come into play when making decisions about your care. The exact changes to your genes that have happened to create your ALL cells may be different to those of another person with ALL. This makes the ALL cells behave differently.

The genetic changes within your ALL affects:

- Which subtype of ALL you have
- Your treatment plan
- Your likelihood of relapse

Not all genetic changes make ALL harder to treat. Some can make your ALL easier to treat. Either way, your ALL will still need immediate treatment.

We explain the impact on your prognosis later in this booklet. The genetic changes we are talking about in this booklet only occur in the leukaemia cells in your body. They develop after you have been created from the sperm and egg of your parents. You do not receive the mutations or changes from your parents.

Genes provide directions for the growth, development and functioning of the cells.

Leukaemia cells have distinctive and recurrent changes in their chromosomes and gene mutations.

How are genetic changes identified?

Karyotyping is a widespread method of detecting physical and numerical abnormalities in chromosomes. By pairing and ordering all your chromosomes, it helps in checking your karyotype.

A karyotype is the general appearance of a person's complete set of chromosomes. It looks at the size, shape and number of chromosomes in a sample of cells from your body.

Staining the chromosome shows the structure for each chromosome that might be seen on a karyotype. Genetic changes include:

- **Deletions:** Loss of one of a pair of chromosomes.
- **Duplications:** Extra copy of one of a pair of chromosome.
- **Translocations:** Part of a chromosome swaps over with part of the same or different chromosome. This results in a reordering of the genes.
- **Inversions:** Reversal of a chromosome segment end-to-end. This can occur when a single chromosome undergoes breakage and has a rearrangement within itself.
- **Insertions:** An extra piece of DNA attaches itself to another DNA strand.

Any of the changes above can lead to the genes on that chromosome being changed.

What are the most common chromosome abnormalities or gene mutations in B-cell ALL?

Around 60-80% of patients with B-cell ALL have chromosome abnormalities and gene mutations. The remaining patients do not have any detectable chromosomes or mutation abnormalities. It is possible that these patients may have genetic changes that have not yet been discovered by researchers.

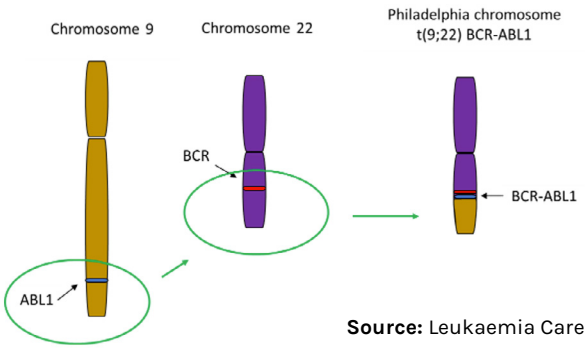
The following genetic abnormalities are common in patients diagnosed with B-cell ALL:

Philadelphia chromosome

This chromosome occurs as a result of a translocation abnormality. It does not exist in normal cells. It occurs when a section of the DNA from chromosome 22 swaps over with a section from chromosome 9 and fuses. Chromosome 22 contains the BCR gene and chromosome 9 contains the ABL1 gene. This translocation results in the Philadelphia chromosome which includes the fusion gene BCR-ABL1 (Figure 1).

t(9;22) BCR-ABL1 is another way of writing the Philadelphia chromosome. You may see this written in your medical notes instead. Around 20% to 30% of patients with ALL have the Philadelphia chromosome. It does not run in families.

Figure 1: Formation of the Philadelphia chromosome BCR-ABL1



Source: Leukaemia Care

Its occurrence increases with age. It is found in up to 50% of patients aged 60 years of age or older.

The Philadelphia chromosome is present in other types of leukaemia. It is also seen in cases of acute myeloid leukaemia (AML) and chronic myeloid leukaemia (CML).

TKIs are drugs that inhibit the tyrosine kinase enzyme which controls the function of a cell. They stop the cell growing and dividing. This is because chemotherapy drugs do not work as well against your ALL if you have the Philadelphia chromosome.

Philadelphia-like chromosome t(12;21)

Philadelphia-like ALL is a new B-cell ALL subtype that has genetic changes similar to those of Philadelphia-positive ALL. However this subtype does not have the chromosomal rearrangement BCR-ABL1. Philadelphia-like ALL is characterised by numerous other different genetic rearrangements and mutations.

It is associated with an unfavourable clinical outcome when treated with conventional chemotherapy.

Around to 5-10% of patients with ALL have the Philadelphia-like chromosome. The incidence of Philadelphia-like chromosome varies with age.

Conventional chemotherapy does not produce good results in patients with a Philadelphia-like chromosome. Patients with a Philadelphia-like chromosome are a high risk subset of ALL meaning they are at higher risk of relapse.

Other chromosomes abnormalities and gene mutations in ALL

Aside from the Philadelphia chromosome and the Philadelphia-like chromosome, the most common chromosome abnormalities seen in patients with B-cell ALL include:

- t(4;11) (q21;q23)
- t(1;19) (q23;p13)

- ETV6-RUNX1

The most common gene mutations seen in patients with B-cell ALL include:

- *CRLF2*
- *NOTCH1*
- *FBW7*

Table 1 shows the genetic abnormalities seen in ALL and how they affect the prognoses for patients with ALL.

Table 1: Genetic abnormalities predictive of standard and high-risk ALL

Genetic abnormalities	**Standard-risk ALL Good prognosis**	**High-risk ALL Poor prognosis**
Translocation	t(12;21) or t(1,19)*	t(4;11), t(1;19) or t(8;14)*
Deletion		del(13q), del(11q) or del(17p)*
Gene mutations	NOTCH-1 or FBXW7	CRLF2 mutation
Abnormal chromosome	ETV6-RUNX1	Philadelphia chromosome BCR-ABL1**
		BCR-ABL1-like chromosome
		ETP-ALL (early thymic precursor T-cell ALL) chromosome
		Complex chromosome abnormalities

* Only one of these genetic abnormalities is required

** ALL associated with Philadelphia chromosome is a high-risk but the risk is reduced if treated with tyrosine kinase inhibitors

What are the most common chromosome abnormalities or gene mutations in T-cell ALL?

The following genetic abnormalities are common in patients with T-cell ALL. These are acquired mutations that cannot be passed on to your children. Only chromosome abnormalities and gene mutations that affect the sperm or egg cells can be inherited.

- Deletion of the *CDKN2A (p16)* and *CDKN2B(p15)* genes
- Mutation of the *NOTCH1* gene
- Mutations in the *FBXW7* gene
- Translocation t(10,14) (q24;q11.2)

Mutations of the *NOTCH1* gene occur in the majority of T-ALL cases and predict a good prognosis.

Deletions of the *CDKN2A* gene is present in about 70% of T cell ALL cases. Patients with this deletion have a poor prognosis.

A group of patients with T-cell ALL, known as the early thymic precursor (ETP) T-ALL also have a poor prognosis.

Inherited genetic syndromes

The genetic changes we have described so far are ones that are only present in leukaemia cells. They are the changes that led a normal cell to become an ALL cell.

There are also some genetic factors you can be born with that can increase the risk of you developing ALL.

Acquired mutations are mutations that cannot be passed on to your children. Only chromosome abnormalities and gene mutations that affect the sperm or egg cells can be inherited.

Genetic syndromes are a combination of signs and symptoms that result from one or more chromosome or gene abnormalities. These are abnormalities that affect all cells in the body. They are conditions people are born with. A familiar example of this

is Down's syndrome in which individuals have an extra copy of chromosome 21.

The following genetic syndromes are common in patients with B-cell ALL.

Down's syndrome

With Down's syndrome, patients have an extra copy of chromosome 21. The risk of developing ALL in people with Down's syndrome is 10 to 20 greater compared with the general population.

Other genetic syndromes

Patients with the following genetic syndromes have a 5% greater risk of getting ALL compared with the general population:

- Klinefelter syndrome
- Fanconi anaemia
- Ataxia-telangiectasia

ALL in children and adolescents

The following abnormal chromosomes or genes are present in children and adolescents with ALL:

- Philadelphia chromosome (*BCR-ABL1* gene) is present in 3-5% of children with B-cell ALL. Adding a tyrosine kinase inhibitor to the treatment of these children will improve the efficacy of treatment.

In children with T-cell ALL, the following gene mutations are present:

- *NOTCH1* (70.3% of children)
- *FAT1* (32.8% of children)
- *FBXW7* (28.1% of children)
- *KMT2D* (28.1% of children)

Children with a *NOTCH1* mutation have a favourable outcome.

You may find it helpful to speak to people who understand what it is like to be living with leukaemia through a local in-person support group or by attending our virtual national ALL meeting. Scan the QR to find out more:

Genetic analysis techniques

Genetic testing is the examination of chromosomes to establish chromosome abnormalities. Genetic technologies to detect structural and numerical chromosomal abnormalities include:

- Karyotyping (detection of chromosomal abnormalities)
- Fluorescence in situ hybridization (FISH)
- Chromosomal microarray analysis (CMA)
- Next-generation sequencing (NGS)

There have been great improvements in cytogenetic testing over recent years. These techniques have led to an increased understanding of the current techniques.

Karyotyping

Staining the chromosome shows the structure for each chromosome. This can reveal major genetic changes including the following:

- Deletions
- Duplications
- Translocations
- Inversions
- Insertions

But there is no evidence that ALL itself has a strong inherited component. It does not seem to run in families, so a person's risk is not increased if a family member has the disease.

Common genetic abnormalities detected by karyotyping

These abnormalities include trisomies (three copies of one of a chromosome instead of two). Three common types of human trisomies are those of:

- Chromosome 13 - Patau's syndrome
- Chromosome 18 - Edwards' syndrome

- Chromosome 21 - Down's Syndrome: Children with Down's Syndrome are at a 20-fold higher risk of ALL than children without Down's Syndrome

Fluorescence in situ hybridization (FISH)

Fluorescence in situ hybridization (FISH) is a technique for determining complex DNA sequences. It can determine the number and structure of chromosomes as well.

Genes control all the actions that a cell does. This includes its reproduction and growth. FISH tests look for detailed genes or parts of genes. FISH does not analyse full sets of chromosomes. It looks for gene changes within cells.

Changes in genes can cause the production or suppression of a protein. This can make the leukaemia cells grow and reproduce more than normal.

With FISH, small portions of DNA are labelled in the laboratory with fluorescent dye to detect DNA sequences.

FISH can:

- Detect sequences of DNA
- Locate a gene on a chromosome
- Determine the number of copies of a gene
- Detect chromosomal abnormalities

Chromosomal microarray analysis (CMA)

CMA is the principal genetic test used to diagnose patients with observable traits that do not match a syndrome. It can test individuals with the following:

- Unexplained developmental delay and intellectual disability
- Autism spectrum disorders
- Many congenital anomalies (not explained by a syndrome)

In suspected patients, CMA increases by 20% the diagnosis of:

- Cognitive impairment
- Developmental delay
- Autism

Cognitive impairment is when a person has trouble:

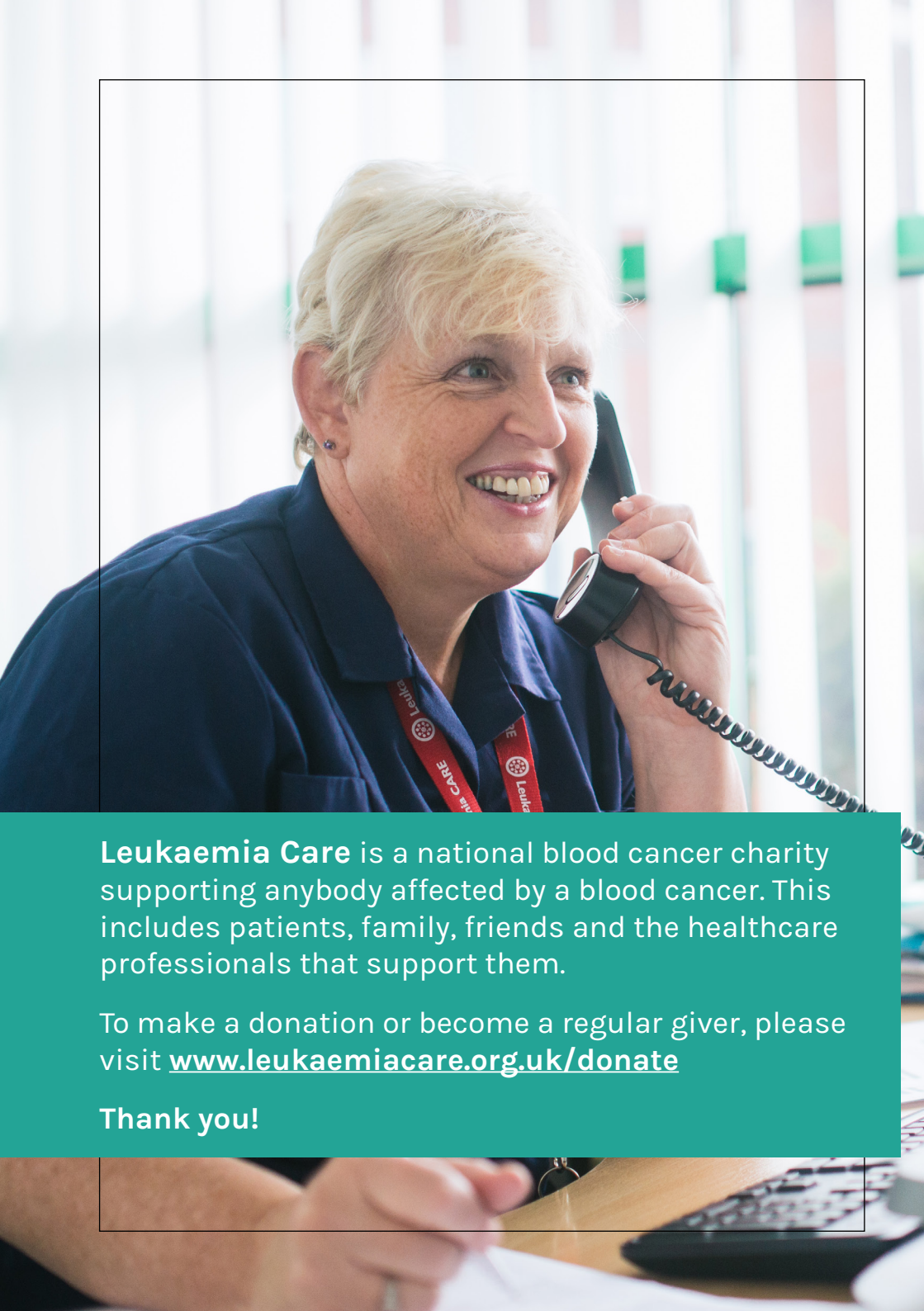
- Remembering facts
- Learning new things
- Concentrating
- Making decisions that affect their everyday life

Next-generation sequencing (NGS)

Next-generation sequencing (NGS) is a new process to determine the sequence of the genes on the DNA. NGS means determining the order of the nucleic amino acids in the DNA. The nucleic amino acids in DNA are adenine, guanine, cytosine, and thymine.

NGS allows a rapid sequencing of a strand of DNA. Knowing the sequence of the nucleic amino acids helps haematologists identify genetic alterations in the DNA. This enables the monitoring of drug response and treatment toxicity.

Genetics in Acute Lymphoblastic Leukaemia (ALL) is part of our ALL information suite. If you would like to read any of our additional booklets on ALL, you can order or download them by scanning this QR code:



Leukaemia Care is a national blood cancer charity supporting anybody affected by a blood cancer. This includes patients, family, friends and the healthcare professionals that support them.

To make a donation or become a regular giver, please visit **www.leukaemiacare.org.uk/donate**

Thank you!

Useful contacts and further support

There are a number of helpful sources to support you during your diagnosis, treatment and beyond, including:

- Your haematologist and healthcare team
- Your family and friends
- Your psychologist (ask your haematologist or CNS for a referral)
- Reliable online sources, such as Leukaemia Care
- Charitable organisations

Leukaemia Care

Leukaemia Care is the UK's leading leukaemia charity. For over 50 years, we have been dedicated to ensuring that everyone affected receives the best possible diagnosis, information, advice, treatment and support. We are here for everyone affected by leukaemia and related blood cancer types – such as myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN). We believe in improving lives and being a force for change. To do this, we have to challenge the status quo and do things differently.

Helpline: **08088 010 444**
www.leukaemiacare.org.uk
support@leukaemiacare.org.uk

Blood Cancer UK

Leading charity into the research of blood cancers.

0808 2080 888
www.bloodcancer.org.uk

Cancer Research UK

Leading charity dedicated to cancer research.

0808 800 4040
www.cancerresearchuk.org

Macmillan

Provides free practical, medical and financial support for people facing cancer.

0808 808 0000
www.macmillan.org.uk

Maggie's Centres

Offers free practical, emotional and social support to people with cancer and their loved ones.

0300 123 1801
www.maggiescentres.org

Citizens Advice Bureau (CAB)

Offers advice on benefits and financial assistance.

08444 111 444
www.adviceguide.org.uk

How you can help us

If you've been affected by ALL, sharing your story can help others going through a similar situation and help the public to better understand.

Scan the QR to share your story:

Alternatively, you can email our Communications Team at communications@leukaemiacare.org.uk.

We are continually working to make sure our information is up to date and includes everything you need to help feel supported and empowered to advocate for yourself. With this, it is important for us to listen to any feedback you might have about our genetics in ALL booklet.

Scan the QR to take you to our shop to leave a review of our booklet:

Alternatively, you can email our Information Team at information@leukaemiacare.org.uk, call our office line on **01905 755 977** or write a letter to our Head Office at **Leukaemia Care, One Birch Court, Blackpole East, Worcester, WR3 8SG**.

Take on a challenge for Leukaemia Care

We have a range of fundraising challenges that you can get involved in to help us continue to provide care and support to those affected by a leukaemia, MDS or an MPN.

Running, swimming, cycling and adrenaline challenges are available to take part in, both in the UK and abroad. There really is something for everyone.

If you're interested in taking part in a challenge, speak to a member of our Fundraising Team by emailing fundraising@leukaemiacare.org.uk or calling **01905 755977**.

Alternatively, scan this QR code to find out all the ways you can get involved with Leukaemia Care:

"It was a pleasure to meet you and to take part in my first half marathon together with the Leukaemia Care team! I'm a scientist and work in immunology research. A dear family member passed away from leukaemia seven years ago this month, so I did this in his memory. I smashed my goal of under two hours with a final time of 1:53! I'm extremely happy, thank you so much for all your hard work and it was great to see you cheering us on along the track. I loved the look of the vests too! See you again, next year maybe!" **- Alexandru Bacita ran London Landmarks for Leukaemia Care in 2022**

Your gift today will ensure that Leukaemia Care can continue to offer support to leukaemia patients and those who love them

Yes, I want to make a regular gift to Leukaemia Care of £5 or £ ☐ a month starting on the 1st ☐ or the 15th ☐ of each month (please tick one).

Please note: the minimum for a direct debit is £2 a month.

Title: .....

First name or initial(s): ..... Surname: .....

Full home address: .....

.....

Postcode: ..... Phone: .....

Email: .....

☐ **Gift Aid Declaration: Please tick here if you want Leukaemia Care to reclaim the tax that you have paid on all your donations you make in the future or have made in the past four years.**

Instruction to your Bank or Building Society to pay by Direct Debit

Name of Account Holder(s): ..... / .....

Bank/Building Society account number: ☐

Branch sort code: ☐

Name and full postal address of you Bank or Building Society: .....

.....

Instruction to your Bank or Building Society: Please pay Leukaemia Care from the account detailed in this instruction subject to the safeguards assured by the Direct Debit Guarantee. I understand that this instruction may remain with Leukaemia Care and, if so, details will be passed electronically to my Bank/Building Society.

Signature(s): ..... / .....

Date: ☐

This guarantee should be detached and retained by the payee.

The Direct Debit Guarantee

DIRECT Debit

This Guarantee is offered by all banks and building societies that accept instructions to pay Direct Debits.

The efficiency and security of the scheme is mentioned and protected by your own Bank or Building Society.

If the amounts to be paid or the payment dates change, Leukaemia Care will notify you 10 working days in advance of your account being debited or as otherwise agreed.

If an error is made by Leukaemia Care or your Bank or Building Society, you are guaranteed a full and immediate refund from your branch of the amount paid.

You can cancel a Direct Debit at any time by writing to your Bank or Building Society. Please also send a copy of your letter to us.

Leukaemia Care is the UK's leading leukaemia charity. For over 50 years, we have been dedicated to ensuring that everyone affected receives the best possible diagnosis, information, advice, treatment and support.

Every year, 10,000 people are diagnosed with leukaemia in the UK. We are here to support you, whether you're a patient, carer or family member.

Want to talk?

Helpline: **08088 010 444**
(free from landlines and all major mobile networks)

Office Line: **01905 755977**

www.leukaemiacare.org.uk

support@leukaemiacare.org.uk

Leukaemia Care,
One Birch Court,
Blackpole East,
Worcester,
WR3 8SG

Leukaemia Care is registered as a charity in England and Wales (no. 1183890) and Scotland (no. SC049802).

Company number: 11911752 (England and Wales).

Registered office address: One Birch Court, Blackpole East, Worcester, WR3 8SG

Leukaemia Care
YOUR Blood Cancer Charity

Trusted Information Creator
Patient Information Forum