AMMF
THE CHOLANGIOCARCINOMA CHARITY

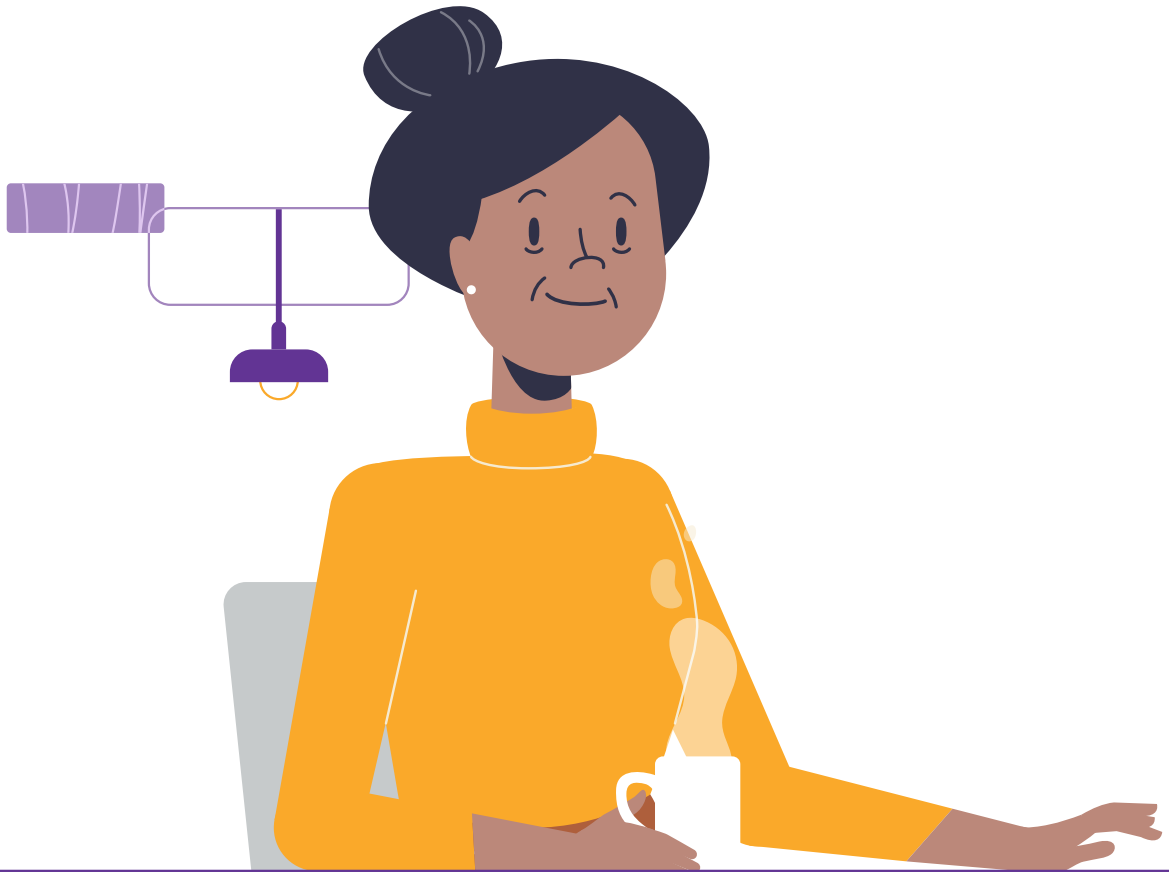
Incyte

Molecular testing in cholangiocarcinoma

Learn about tests for faulty genes and how they can guide your treatment if you have bile duct cancer (cholangiocarcinoma)

This guide was produced by Incyte Biosciences and AMMF for people who have cholangiocarcinoma, their friends and family.

Contents



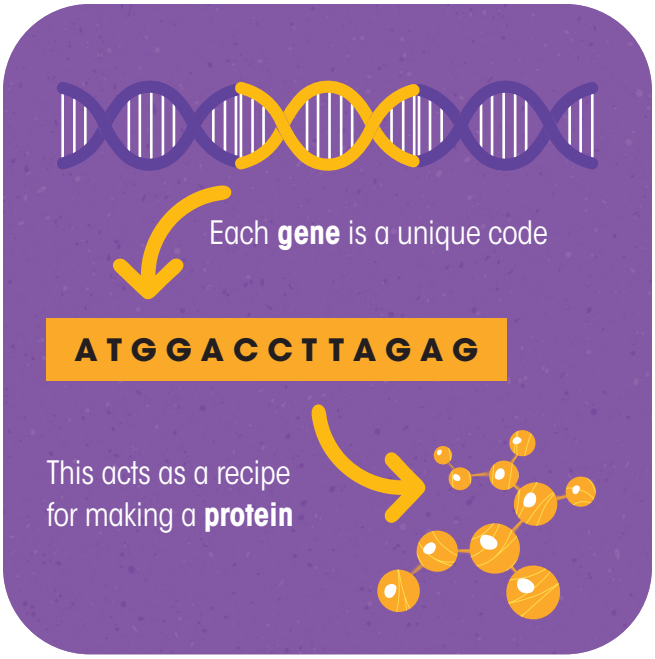
Genes and cancer

What is a gene?

Your body is made up of trillions of cells.[1] Each cell contains a library of about 20,000 genes, known as the genome.[2] Each gene is a code – like a chemical recipe – for making one or more proteins.[3] The code is made from a chemical called DNA.[3]

Your cells use genes to make the specific proteins they need.[3] Proteins are large molecules used for all kinds of things. For example, some make up structures while others carry chemicals or act as messengers.

When a new cell is made in your body, all the DNA in an existing cell is copied. The cell then divides in two, each with its own identical set of genes.



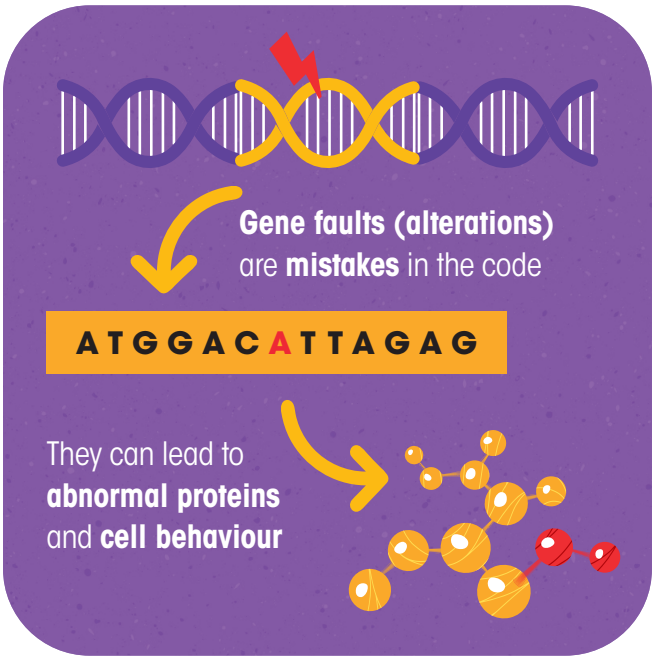
What faults can occur in genes?

Sometimes, a gene's DNA can be damaged.[4] Mistakes can also happen when a cell's DNA is being copied during the process of making new cells.[4] Our cells have safety checks to spot and correct DNA faults. Uncommonly, these checks fail and a fault remains in the DNA of a cell.[5]

Most gene faults don't matter. However, some can cause the cell to make abnormal proteins or behave strangely.[4]

The fault – also known as a genetic alteration – can be as simple as one letter being changed or missed in the DNA code (called a mutation).[6]

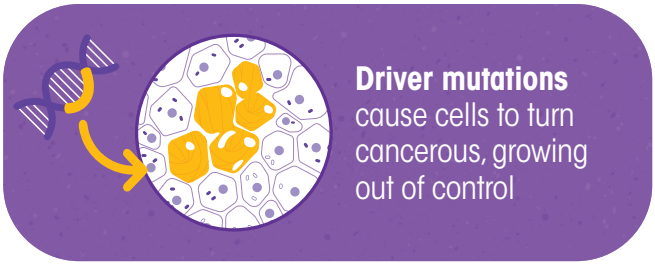
Other changes are more complicated and can involve part of a gene's code being deleted, repeated or moved. If the code gets jumbled out of order, this is called a rearrangement. When a rearrangement causes the codes of two different genes to get stuck together, this is called a 'fusion gene'.[7]



How can gene faults cause cancer?

If a gene fault encourages a cell to divide into new cells more often than usual, it can lead to cancer.[4,5] Any new cells made from this one will contain the gene fault and divide too often as well. In this way, the cancer cells grow in number, forming a lump. This is a tumour.

Sometimes, cancer cells can get additional gene faults which can lead to further abnormalities.[5] These faults sometimes help the cancer cells to survive attack from certain cancer treatments.[4]



Driver mutations cause cells to turn cancerous, growing out of control

Resistance mutations change cancer cells, helping them to avoid attack by cancer treatments

How do you get a gene fault?

Sometimes, a person is born with a gene fault. Some of these inherited faults make a person more likely to develop cancer in their lifetime.[6]

During our lives, there is a chance that a new gene mutation or rearrangement will appear in a cell due to DNA damage or a copying error.[4,6] Our DNA can be damaged by many things. For example, the sun's rays are well known to cause DNA damage that can lead to skin cancer.[8]

We don't know the cause of most cholangiocarcinomas.[9,10] Some may start from DNA damage caused by hepatitis virus infection or perhaps toxins found in alcohol or cigarette smoke.[9,10] However, many cholangiocarcinomas are probably caused by multiple random errors in DNA copying and damage that mount over years.[9-12]

Inherited mutations are passed down from a parent to child at conception

Acquired mutations and rearrangements happen during a person's lifetime

Treatments targeted at gene faults

Although gene mutations and rearrangements are a problem, they can sometimes be used to our advantage against a cancer.

Some cancer treatments are designed specifically to target a tumour's abnormal proteins (caused by gene faults).[13] These new treatments are called targeted therapies. Some are already approved in the UK, and others are being tested in clinical trials.

By testing a sample of your cancer cells using molecular testing, your doctor can find out whether any targeted treatments might work for you. They will do this by matching the profile of your cancer cells with treatments that target those abnormalities.

Read on to find out more about molecular testing.

Having molecular testing

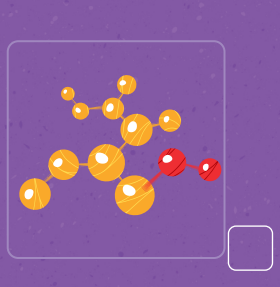
What do molecular tests look for?

In molecular testing, a small sample of your tumour or blood is tested for faulty genes.[14] Molecular testing can also look for changes to protein structures or the amount of different proteins in your cancer cells.[14]

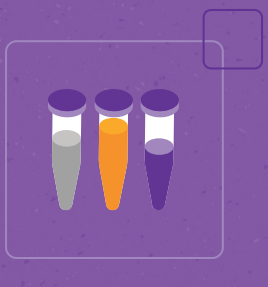
Molecular testing is sometimes called 'molecular profiling', 'biomarker testing', 'genomic testing' or 'mutation testing'.

Molecular tests can look for…

Gene mutations and rearrangements



Abnormal proteins



Altered amounts of certain proteins

Why have molecular testing?

Cholangiocarcinoma tumours are not all the same. Even when they start in the same place, one person's cancer cells can be very different from another person's. In part, this depends on which gene faults are present. These changes can alter the way the cancer cells look, behave and react to different cancer treatments.

Molecular testing gives your treatment team a profile of your cancer.[14] They can use this to select the best treatment options for you.[14]

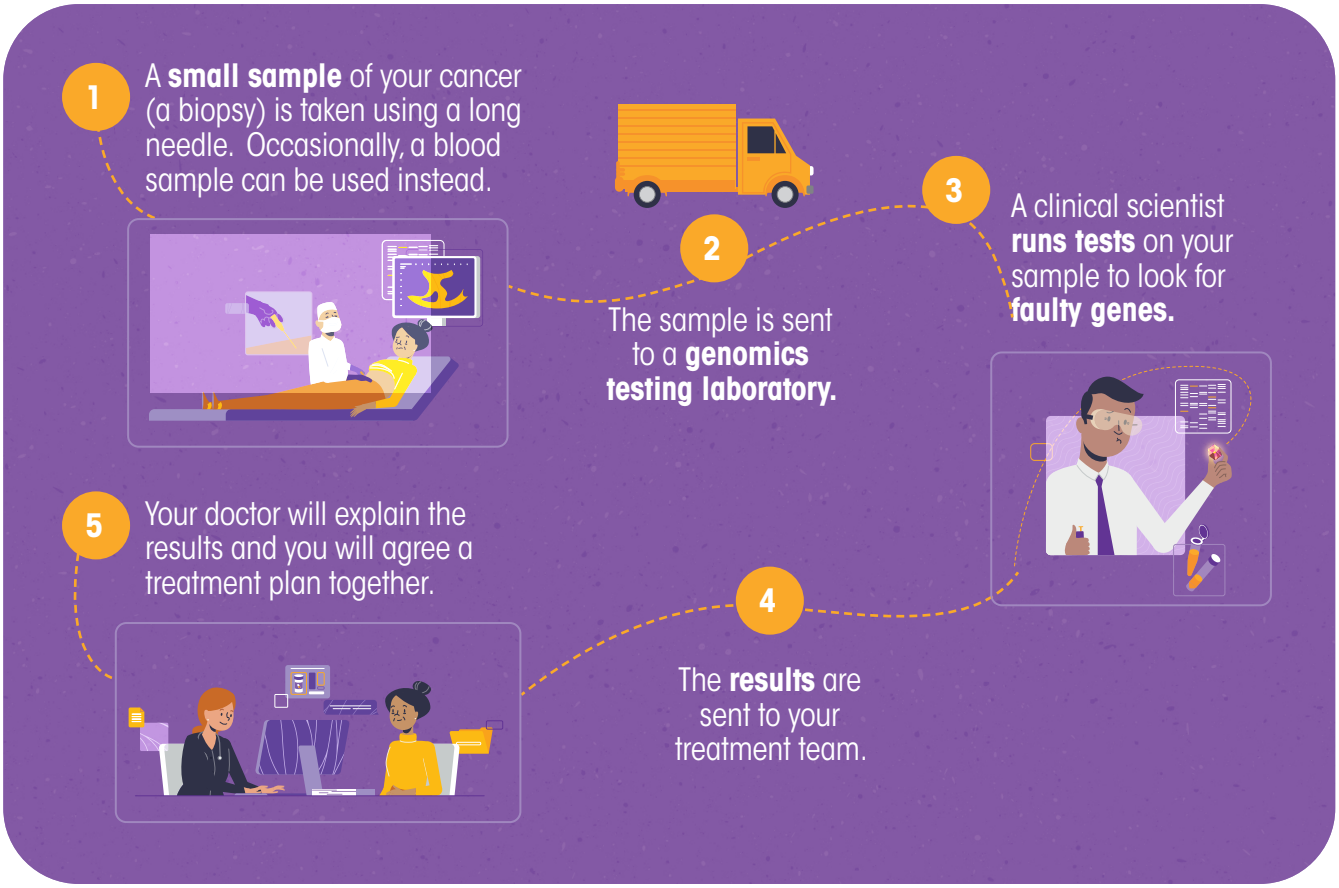
How is molecular testing done?

To have molecular testing, you'll probably need to have a sample of your cancer taken (called a biopsy).[14] However, if the hospital already has a sample of your tumour (from when you were diagnosed or from surgery to remove the tumour),[9,14] your doctor may be able to send that for testing.

Some people have a sample of blood tested instead of a solid biopsy. This is called a 'liquid biopsy'. This type of biopsy is not routinely available for all patients at the moment.

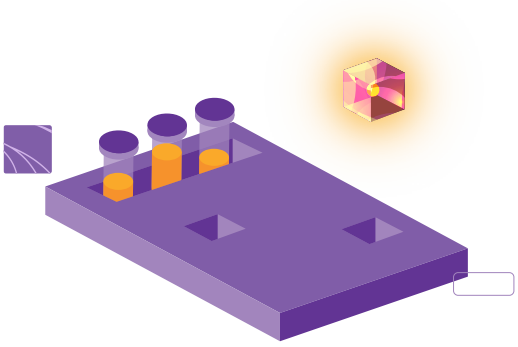
Your sample is sent to a specialist lab to test it for gene mutations and rearrangements.[15-18] This can take a few weeks.

Here is a summary of the process:



You can find more detail on the process on pages 9 and 10.

When is molecular testing used?



Patients with cholangiocarcinoma usually receive surgery or chemotherapy or a combination of both in the first instance.[9,19] The treatment you receive will depend on things like the size and location of your tumour.[9,19]

If these treatments don't work completely or your cancer returns, you and your treatment team will agree on the next steps. This is where molecular testing is very helpful. It can show whether any targeted treatments are likely to work against your cancer.

Molecular testing is also used in research to help scientists discover more gene faults that they can design treatments against.

How to get molecular testing

Molecular testing can be done on the NHS for people with certain health conditions where the results will help to plan their care.[17] Cholangiocarcinoma is one of the conditions covered.[15,16,18,20]

Ask your cancer specialist for molecular testing and to explain how it might help you if you have cholangiocarcinoma.

For example questions you might want to ask your doctor about molecular testing, see page 14.

Getting the results

It can take several weeks for your doctor to get your results back from the testing lab. This is why it's good for you and your doctor to discuss and plan molecular testing early.

Once your doctor has the results, they'll discuss the findings with you and explain which treatments might work well for you and why. They will also let you know if there are some treatments that are unlikely to help you.

The results can make a big difference for your treatment plans. You may wish to take a friend or relative with you for support.

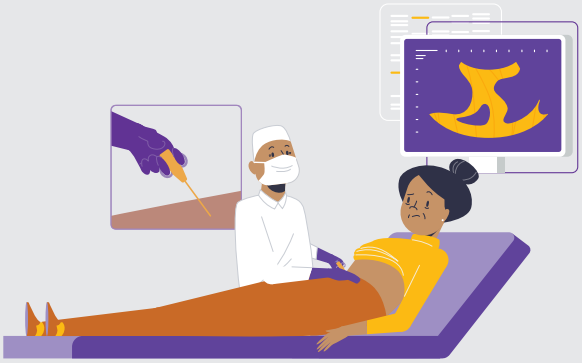
It's a good idea to ask your doctor to give you a written summary, as you might not remember all the details later.

For example questions you might want to ask your doctor about molecular testing, see page 14.

More detail on the process of molecular testing

Taking a sample of your tumour

For you to have molecular testing and some other diagnostic tests, a sample of your tumour cells (called a biopsy) is needed.[9,14] If you've previously had a biopsy of your cholangiocarcinoma taken or have had surgery to remove the cancer, there might be enough tissue left for molecular testing. If not, you'll need to have a new biopsy taken.



The biopsy is usually a small, solid piece of tissue collected using a needle, although some patients might be offered a blood test ('liquid biopsy') instead.[21]

For a solid biopsy, a long needle is put through your skin into your tumour, so that a small piece can be taken out.[21]

Before your doctor inserts the needle, they will put a numbing ointment (local anaesthetic) on your skin.[21]

They will use imaging (for example, ultrasound) to see inside your body.[21] This is so they can see exactly where to take the sample from. It usually takes a few seconds to take the sample.[22]

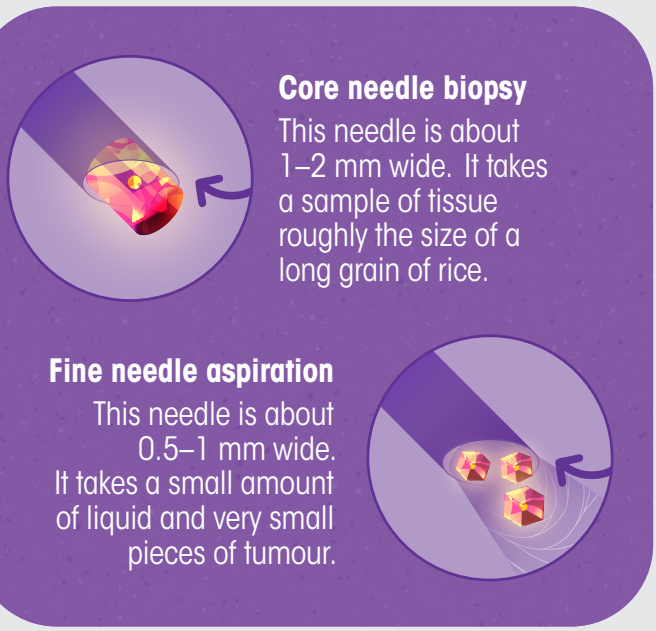
Afterwards, your doctor will put a bandage or dressing on the site.[23]

Techniques used to take a needle biopsy include:[24,25]

- **Core needle biopsy**
- **Fine needle aspiration.**

The risks with either technique are small.[24] A core biopsy gives a bigger sample which means that more tests can be run if needed.[26] However, your doctor might suggest the finer needle if this would be easier to get to your tumour.[24]

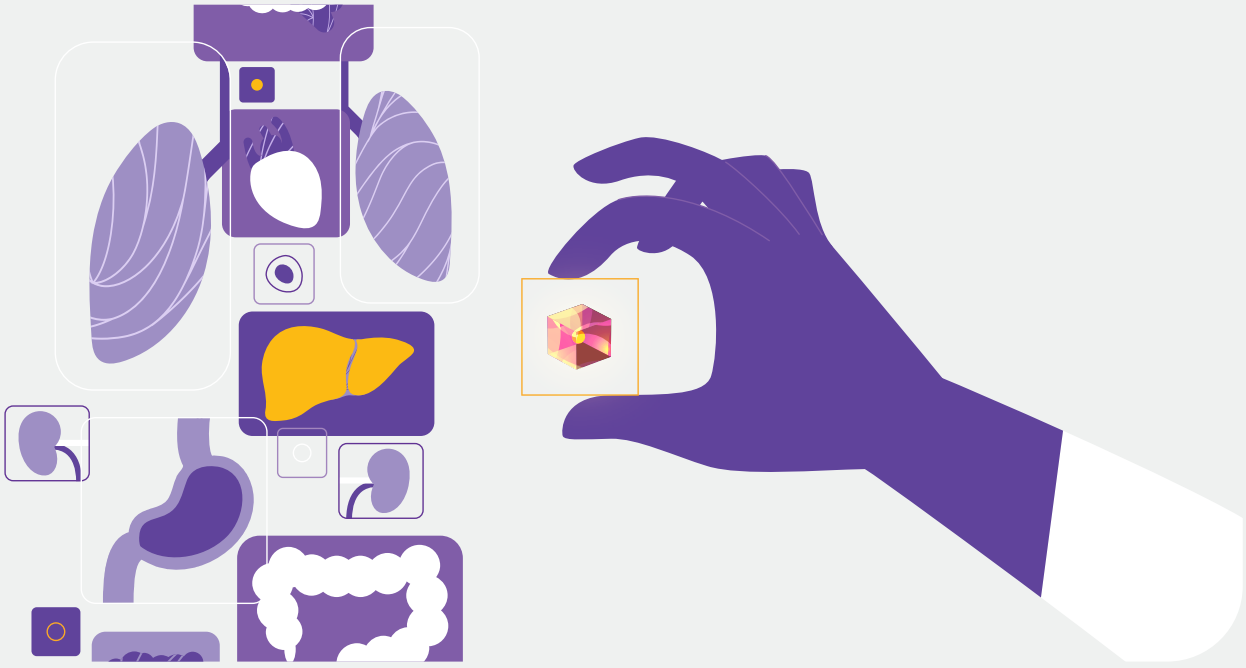
If you can't have either type of needle biopsy, you might be offered a 'liquid biopsy'. This uses a sample of your blood or other body fluid to look for cancer cells and DNA shed by your tumour.[14] This method isn't standard practice but can be useful for some patients. Your doctor can explain the advantages and disadvantages of having a liquid biopsy versus a needle biopsy.



Laboratory testing of your sample

Your biopsy will be sent to a genomics testing laboratory. In the UK, NHS testing is carried out regionally in around 12 labs.[15-17,27] This ensures all eligible NHS patients are able to have similar types of genomic tests.[17]

A clinical scientist will run tests on your cancer sample to look for gene mutations.



Testing labs can do molecular testing with a few different methods. Two common methods are:[15,18,20]

- **Next generation sequencing (NGS).** A machine reads the precise code of many genes at once, searching for possible mutations.[28] This technique can spot even a single letter change in the code (a mutation).[28] Using this technology, many genes can be assessed from a single biopsy.[29]
- **Fluorescence *in situ* hybridization (FISH).** Fluorescent markers that stick to parts of a gene's code are used to detect changes.[14] This technique can spot when areas of code have been copied or deleted.[14] It can also detect when the codes of two genes have fused or when genes have been rearranged.[14] FISH can be a good option when the sample of tissue is small.[29,30]

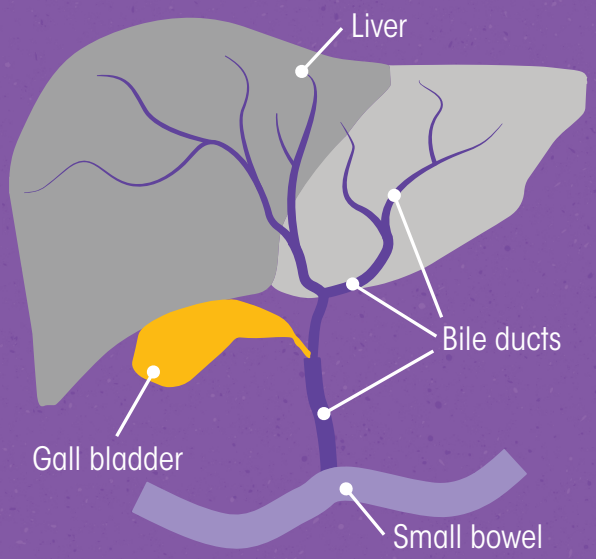
Gene faults in cholangiocarcinoma

Which gene faults are common in cholangiocarcinoma?

Across all types of cancer, scientists have found hundreds of different gene faults that can cause or worsen cancer.[31] Some of these are found in cholangiocarcinoma.[32,33]

The gene faults found in cholangiocarcinoma differ depending on the location of the tumour.[32,33]

Cholangiocarcinoma can occur in three main areas:



Intrahepatic cholangiocarcinoma, occurs in smaller bile ducts within the liver

Perihilar (also called hilar) cholangiocarcinoma occurs in larger bile ducts where they join to leave the liver

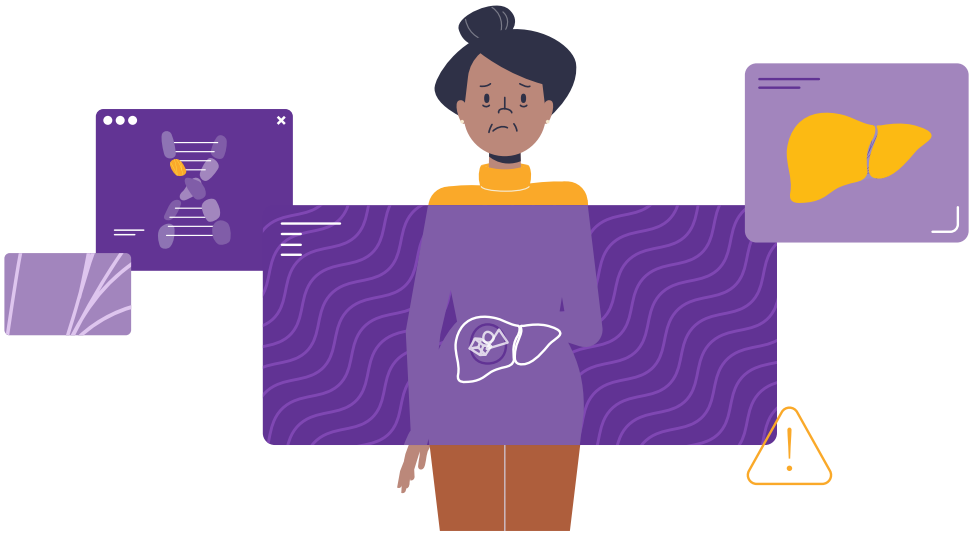
Distal (extrahepatic) cholangiocarcinoma occurs in the main bile duct that travels from the liver to the small bowel

Gene faults found more commonly in **intrahepatic** cholangiocarcinomas include:[34]

- *IDH1* faults
- *FGFR2* fusions and rearrangements
- *ERBB2* (also known as *HER2*) faults and extra copies
- *PIK3CA* faults

Gene faults found more commonly in **perihilar** and **distal** cholangiocarcinomas include:[35]

- *ERBB2* (also known as *HER2*) faults and extra copies
- *PIK3CA* faults
- *IDH1* or *IDH2* faults



Gene faults in intrahepatic cholangiocarcinoma

About 50 to 60 out of every 100 people with intrahepatic cholangiocarcinoma don't have a gene fault that can be targeted.[34] This means they won't be eligible for an approved targeted therapy or to take part in a clinical trial of an experimental targeted therapy.

The other 40 to 50 in every 100 will have a gene fault that might match either:[34,36]

- An approved targeted treatment.
- A potential new targeted treatment that is being tested in clinical trials (an experimental treatment).

Some people will have more than one faulty gene.[34]

Examples of gene faults found in intrahepatic cholangiocarcinoma

The number of people out of 100 who are likely to have each gene fault is shown.[34,36]

IDH1	10–22 people
FGFR2	7–11 people
ERBB2 (HER2)	4–8 people
PIK3CA	3–7 people
BRAF	Up to 5
Signs that DNA repair machinery is faulty (MSI)	About 1
NTRK	Fewer than 1

Gene faults in perihilar and distal cholangiocarcinoma

Most people with perihilar or distal cholangiocarcinoma don't have a gene fault that can be targeted.[34]

However, about a quarter have a gene fault that matches a potential new or approved targeted therapy.[34] In most cases, the treatment is still experimental, which means it might be available through a clinical trial only.[35,36]

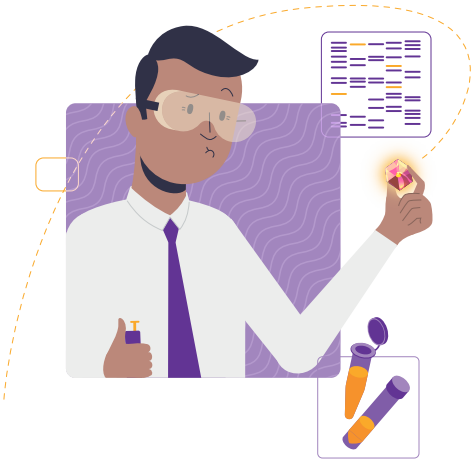
Examples of gene faults found in perihilar or distal cholangiocarcinoma

The number of people out of 100 who are likely to have each gene fault is shown.[35,36]

ERBB2 (HER2)	About 5 people
PIK3CA	About 5 people
IDH1 or *2*	About 5 people
BRCA1 or *2*	About 3 people
FGFR1 or *2*	About 3 people
BRAF	About 2 people
EGFR	About 2 people
NTRK	Fewer than 1

Targeted treatments in cholangiocarcinoma

There are some targeted treatments approved for use in cholangiocarcinoma, and others are being researched in clinical trials. Those being tested in trials are not approved for prescription in the UK. The trials are needed to check whether these potential new treatments work well, are safe, and that any side effects can be tolerated.



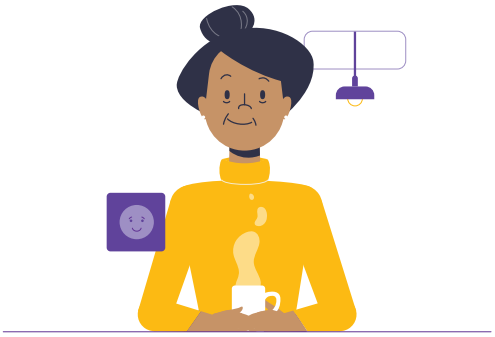
If you have a gene fault that matches an experimental targeted treatment, you might be offered the chance to take part in a clinical trial. This will depend on whether there is a trial looking for new patients like you at the moment.

Ask your doctor about the possibility of taking part in a clinical trial and the possible risks and benefits.

You can find details of clinical trials for people with cholangiocarcinoma on the AMMF website **(https://ammf.org.uk/clinical-trials/)** or you can search for them at **www.clinicaltrials.gov** and **www.clinicaltrialsregister.eu**.

If targeted treatments are not an option for you

If molecular testing shows you don't have a gene fault matching a targeted treatment, this can be upsetting if you had your hopes on a specific treatment.



However, it is good to know which treatments would not be right for you. This means you can avoid taking medicines that could do you more harm than good and reduce your quality of life unnecessarily.

There might be other treatment options that could work for you.[9,19] You might also be eligible for clinical trials of potential new cancer treatments.[9,19]

Ask your doctor to explain your options.

Questions to ask about molecular testing

Here are some example questions that you might want to ask your treatment team about molecular testing.

When first diagnosed with cholangiocarcinoma

- Will you be using molecular testing to plan my treatment?
- How soon could we run these tests?
- Can you try to ensure my biopsy sample is large enough to run molecular tests?

When offered molecular testing

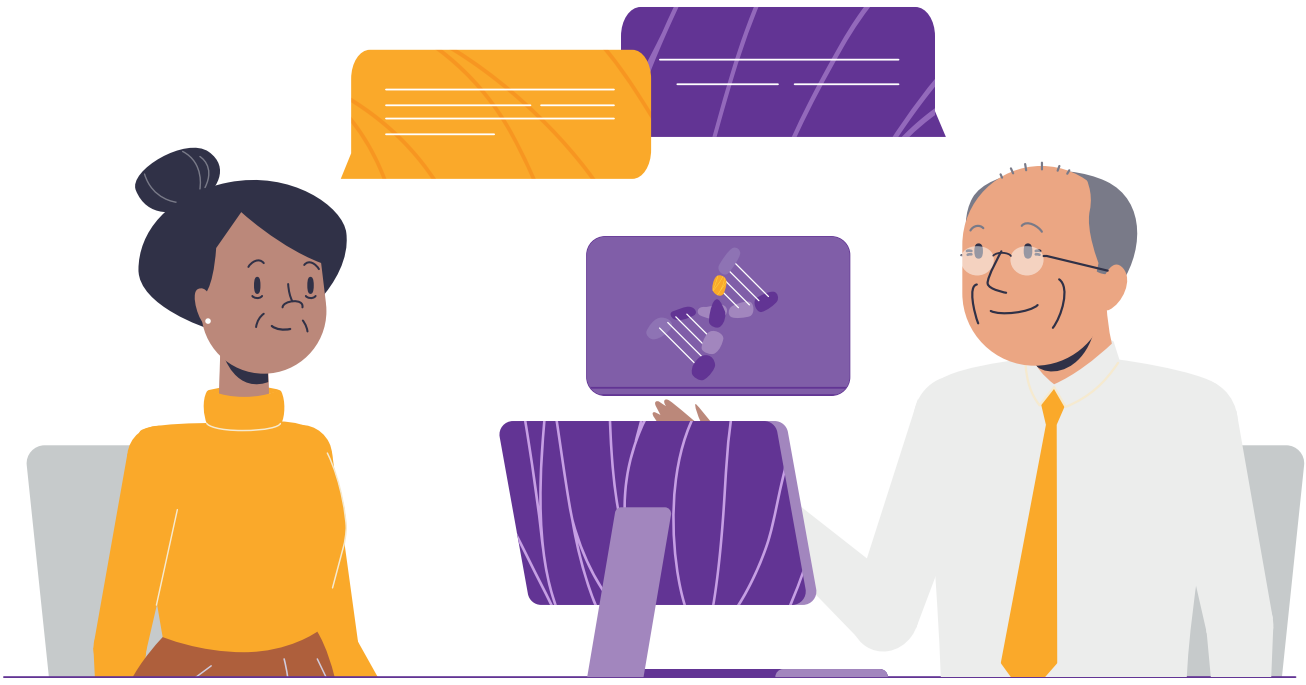
- What will the test look for?
- What will the results tell you about my cancer?
- How might my treatment options differ depending in the results?
- How long will it take to get the results?
- How will I get my results?
- What happens if I don't have a gene fault that we can target?

When getting your molecular test results

- Which abnormalities do my cancer cells contain?
- What does this mean for my treatment options?
- Do the results tell you anything else about my cancer?
- What are the risks and benefits of the options available to me?

If you're offered a clinical trial place

- What is the purpose of the trial?
- Which treatments will I get?
- What does the trial involve?
- How will I be monitored for side effects?
- How might the trial help me and others in the future?
- If I choose not to take part, what other options are available to me?



My notes

My notes

My notes

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About AMMF

AMMF (registered charity no 1091915) is the UK's only cholangiocarcinoma charity, working nationally and collaborating internationally for those with cholangiocarcinoma. AMMF works to raise awareness, to provide information to those who need it (either individually or via our website), and to support research, especially into finding ways to achieve better and clearer early diagnosis.

For more information on cholangiocarcinoma, the work of AMMF, and ways to donate, go to the website www.ammf.org.uk, call +44 (0)1279 661479, or email info@ammf.org.uk.

About Incyte Biosciences

Incyte is a global biopharmaceutical company founded on the premise that investment in strong science and the relentless pursuit of R&D excellence can translate into new solutions that can positively affect patients' lives.

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AMMF
THE CHOLANGIOCARCINOMA CHARITY

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