Myeloma Patients Europe

Question & Answer

MYELOMA PATIENTS EUROPE

Cytogenetics and Risk Testing in Myeloma

www.mpeurope.org

Edition: Myeloma Patients Europe (MPE)

Updated: February 2025

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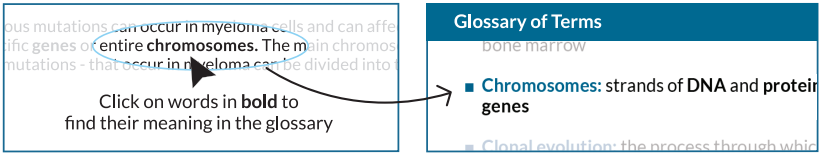
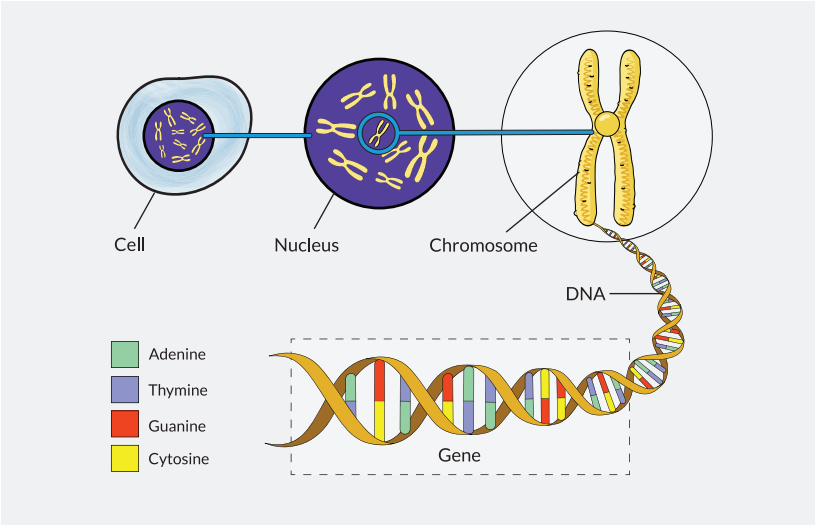


What is cytogenetic testing in myeloma?

Genetics is the study, at a molecular level, of how our **genes** are passed down from one generation to the next. A sub-branch of genetics is **cytogenetics**. Cytogenetics is the study of numerical and structural variations in **chromosomes**. Myeloma is a genetically complex blood cancer and cytogenetics play an important role in the risk stratification of disease, since the prognosis of myeloma is mainly dependent upon chromosomal changes.

Cytogenetic testing is a type of genetic test performed in a laboratory and that looks at strands of **DNA** (deoxyribonucleic acid) called chromosomes that are housed deep inside cells. DNA is the genetic information that cells in our bodies need to develop, function and reproduce. Because of this, DNA is often referred to as "the instruction book for life."

The information in DNA is written as a genetic code made up of four chemical bases: adenine (A), guanine (G), cytosine (C) and thymine (T). These chemical bases are organised into genes, which are small sections of DNA that our cells use to make **proteins**. Each gene is read similarly to how we would read a sentence in a book. Like letters in a word, the order in which the chemical bases of a gene are read determines which protein is made. Proteins have many functions in our bodies. For example, proteins provide structural support, strengthen our immune system (through antibody proteins), send messages (hormones), provide energy for our bodies and transport nutrients into and out of cells.



Cell, chromosome, DNA and genes

Like grammatical mistakes made when writing a sentence, errors can occur in our genes as well. For example, the chemical base "A" may be switched with a "T", resulting in the production of a completely different protein. Many of these errors (also called **mutations**) are harmless. Other errors, however, can change the way a cell functions, lead to disease or disorders in our body and even cause cancer. There are many different types of gene mutations, which are discussed below.

Cytogenetic testing focuses on changes that can occur in **chromosomes** (e.g. broken, missing, re-arranged or extra chromosomes) and aims to identify the specific mutations found to cause disease and cancer. Identification of these mutations in cancerous myeloma cells can guide treatment decisions and provide more details on prognosis or the anticipated disease course[1].

How is cytogenetic testing performed in myeloma?

Cytogenetic tests are performed in a laboratory on a sample of **bone marrow** – the flexible and spongy inner layer of our bones where most of our blood cells are made. Bone marrow samples are usually taken by needle from the hip bone, under a local anaesthetic, in a procedure known as a **bone marrow biopsy**. While you are lying down on your side or your stomach, a sample of bone marrow is drawn up using a syringe. Bone marrow biopsies are often short procedures, and you may feel a sting, pain, or pressure as the test is performed. Most patients can go home right after the procedure. You may be advised to avoid strenuous exercise and heavy lifting for 24 hours after the procedure, and your medical team will tell you about any symptoms that you should seek care for such as pain, fever, swelling, or bleeding. Complications of bone marrow biopsies are rare and most people can resume their usual activities within 24 hours.

After collection, the bone marrow sample is then sent to a lab and later examined under a microscope by a specialist trained to evaluate cells and tissues. With specific lab tests, the specialist will then look for gene mutations that are commonly present in myeloma cells and report this information back to your oncology team. This cytogenetic testing process can take several days, or even weeks, to complete before you get results.

Why is cytogenetic testing helpful for myeloma patients?

Cytogenetic testing can help you and your medical team better understand the specific characteristics of your myeloma. Results may be used to determine your individual treatment options, as myeloma cells with certain mutations are expected to respond better - or worse - to specific treatments. In addition, cytogenetic testing can help determine the aggressiveness and **risk of progression** for your disease. Based on **cytogenetics** and other features, myeloma can be classified as

either standard-risk or high-risk, the latter being associated with a less favourable prognosis. For more information on risk categories and treatment implications, please see the section on *"What are the impacts of common genetic mutations in myeloma?".*

Like all genetic tests, it is important to discuss with your medical team whether cytogenetic testing is right for you currently. While some patients may appreciate the extra knowledge and insight provided by testing, others may find it difficult, psychologically, to be assigned a "risk category". In addition, it is possible that cytogenetic test results can impact your eligibility - or ineligibility - for clinical trials as certain mutations may be listed in the trial exclusion/inclusion criteria.

What types of cytogenetic testing are available for myeloma patients?

There are multiple ways to test for cytogenetic abnormalities or mutations, including:

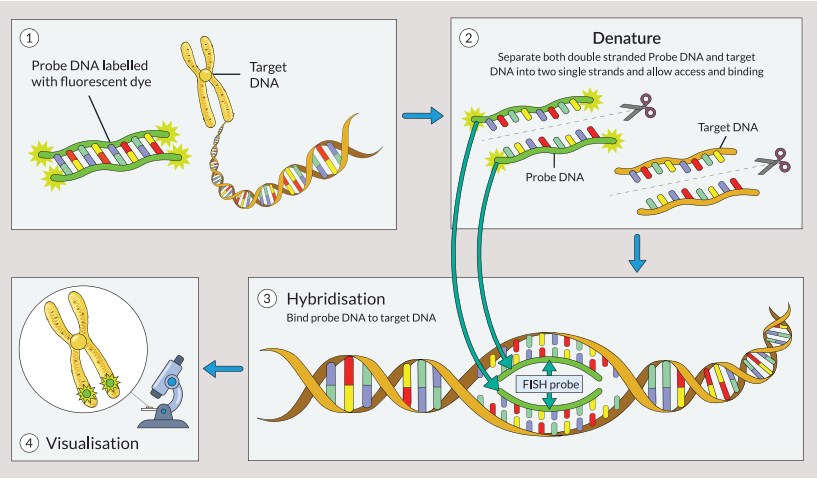
- Fluorescence In Situ Hybridisation **(FISH)** testing
- Karyotyping

These tests differ from one another in technique and reliability, and both are described in greater detail below. Notably, the availability, reimbursement and use of each of these tests in the clinical setting varies, and it is important to consult your medical team when determining which of these are appropriate for your individual medical care. Other techniques to evaluate genetic abnormalities exist and are described in the section titled *"What additional genetic testing options exist for myeloma?"*

Fluorescence In Situ Hybridisation (FISH) testing

FISH testing is a type of cytogenetic test that uses fluorescent tags to visualise specific gene mutations that may be present in your cells. After your **bone marrow** sample is received by a lab, a technician prepares the **DNA** for testing. The technician will then create and mix the sample with DNA probes, which are short sequences of DNA with fluorescent dye that correspond to mutations commonly seen in myeloma cells. If the DNA probe attaches to the myeloma cell, it means the specific mutation is present in the cell[2]. Results from FISH testing take time to process and vary depending on the particular lab and country, however, most results are available within 1-3 weeks.

FISH testing is the most frequently used cytogenetic test for myeloma patients, and it is generally regarded as the **standard of care**[3]. However, availability of FISH may differ by country. Research has shown that FISH can detect more than 90% of known cytogenetic abnormalities in 60-90% of myeloma patients[4]. The **sensitivity and specificity** of the test is reported to be greater than 95%[5].



FISH technique

Karyotyping

Karyotyping is an older method of cytogenetic testing that is still used today, albeit less frequently[3]. Karyotyping allows technicians to see the size, number and shape of the **chromosomes** in a provided sample of myeloma cells[6]. Unfortunately, research has shown that conventional karyotyping can only detect 20-30% cells with abnormal karyotypes[4], meaning many abnormalities can be missed. Although karyotyping is not as precise and efficient as **FISH** testing, karyotyping may still be useful when FISH is not available[7].

When and how often should I undergo cytogenetic testing?

To assess risk categories and determine treatment options, cytogenetic testing (when available) is performed most often at the time of diagnosis. In addition, some patients may undergo testing during first relapse to determine if new mutations have occurred that may be causing treatment resistance. Cytogenetic testing may also be performed multiple times throughout the course of the disease, since myeloma cells can change over time and acquire additional or different mutations to those that were present at diagnosis. These changes occur through a process called **clonal evolution**.

The timing and frequency of testing will depend on several factors including your individual disease, treatment exposure and response, whilst test accessibility and reimbursement will depend on the national policy. You should speak with your doctor if you have questions about undergoing testing.

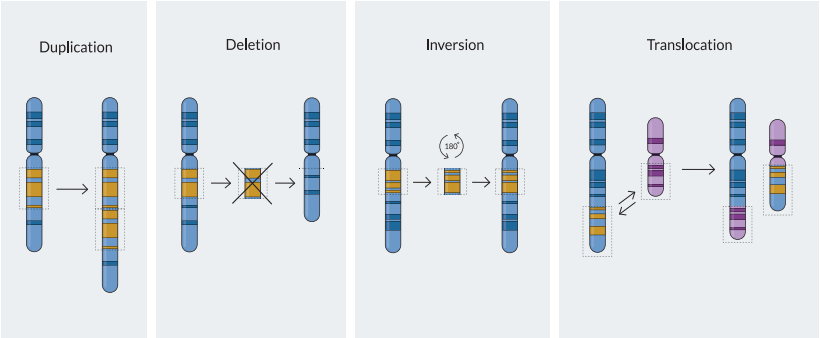
What types of chromosomal changes can occur in myeloma cells?

Various mutations can occur in myeloma cells and can affect either specific **genes** or entire **chromosomes**. The main chromosomal changes - or mutations - that occur in myeloma can be divided into the following categories:

- **Translocations:** A translocation occurs when a part of one chromosome breaks off and reattaches to another chromosome, or when two **chromosomes** swap segments[8]. Translocations are named in the following way: t(A;B), where t stands for translocation and A and B represent the specific chromosomes that are involved. Thus, t(11;14), for example, refers to a translocation (swap) between a part of chromosome 11 and a part of chromosome 14, which are two of the 23 pairs of chromosomes in humans.

- **Deletions:** A deletion occurs when one or more of the chemical bases in a gene sequence is erased. If you think of a gene sequence as a word, you can see how deletions can have an impact – what was originally TAG might now only read TG. Sometimes, only a single chemical base is deleted, and other times an entire gene can be deleted. An example of a deletion that occurs in myeloma is deletion17(p) – abbreviated del(17p), where p stands for a part of chromosome 17.

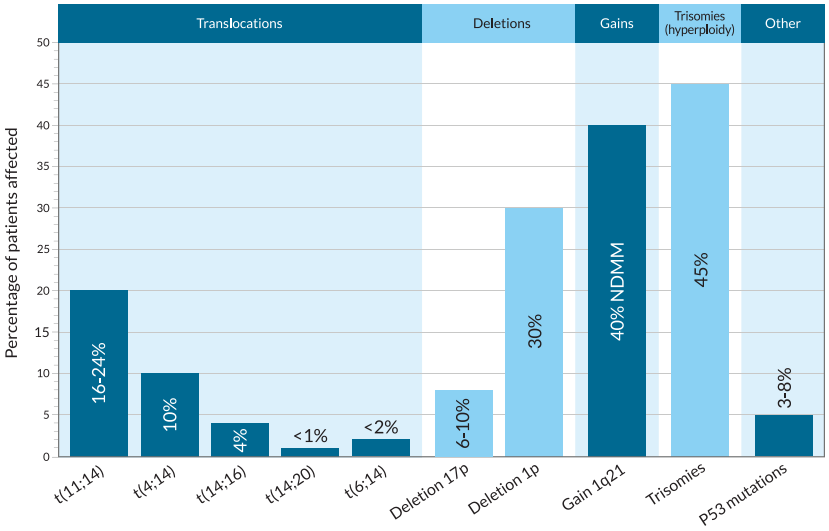
- **Gains or amplifications:** The presence of extra copies of **genes**, or parts of a chromosome, in a cell. An example of a common gain **mutation** found in myeloma is gain 1q21 (also written as 1q21+). In this case, a small amount of genetic material on chromosome 1 is abnormally duplicated on the long (q) arm of the chromosome at a location designated q21. Chromosomal changes with three copies are defined as gain(1q) while at least four copies are defined as amplification (amp)1q.



Main chromosomal changes in myeloma

What are the impacts of common genetic mutations in myeloma?

Although various chromosomal abnormalities occur in myeloma, some **mutations** are more common and well-researched than others. In addition, some mutations are known to respond better to certain medications, whereas other mutations may result in treatment resistance and therefore aggressive disease. Table 1 provides a summary of some of the most common mutations that can occur in myeloma, along with their impacts on the body, disease presentation and treatment response. For more information on these mutations, please see Appendix I.



Frequency of common chromosomal changes in myeloma

For more information on each chromosomal abnormality, see Table 1 and Appendix I.

***NDMM** = newly diagnosed multiple myeloma*

Chromosomal abnormality	Smouldering myeloma		Myeloma				
	Risk of progression to myeloma	Median time to progression	% Patients affected	Risk stratification (mSMART*)	Median overall survival (OS)	Clinical impact	Treatment impact
	Translocations						
t(11;14)	Standard-risk	5 years	16-24%	Standard-risk	7-10 years	Higher rates of bone disease, higher incidences of IgM, IgD, light chain and non-secretory disease Often found in primary plasma cell leukaemia (33-71% of patients)	Benefits from targeted therapy with BCL-2 inhibitors (e.g. venetoclax) Potential limited benefits of treatment with proteosome inhibitors (PIs) and may benefit from intensive therapies or ASCT Potentially associated with reduced CD38 expression
t(4;14)	High-risk	2 years	10%	High-risk	5 years	Associated with shorter duration of remission and more aggressive relapses	Benefits from early ASCT followed by bortezomib-based consolidation / maintenance
t(14;16)	Standard-risk	5 years	4%	High-risk	3 years	High levels of FLC; 25% of patients present with kidney failure	Resistance to proteasome inhibitors
t(14;20)	Standard-risk	5 years	<1%	High-risk	3 years	Limited data available, may have higher disease burden and poorer prognosis	Benefits from early ASCT followed by bortezomib-based consolidation / maintenance Associated with resistance to proteasome inhibitors
t(6;14)	Standard-risk	5 years	<2%	Standard-risk	7-10 years	Light chain myeloma, kidney dysfunction and bone disease are more common, although these findings are based on small samples of patients	Limited data, however, some suggest potential benefits of venetoclax

Table 1: Common chromosomal changes in myeloma and their clinical applications

Chromosomal abnormality	Smouldering myeloma		Myeloma				
	Risk of progression to myeloma	Median time to progression	% Patients affected	Risk	Median overall survival (OS)	Clinical impact	Treatment impact
	Deletions						
Deletion 17p	High-risk	2 years	6-10%	High-risk	3 years	Associated with low rate of complete response, rapid disease progression, plasma cell leukaemia and central nervous system involvement	Loss of p53 increases the likelihood that myeloma cells will be resistant to many treatments
Deletion 1p	Limited data available		30%	Not classified using mSMART	Shorter OS but limited data	Limited data available, although may have a higher disease burden and poorer prognosis	Limited data available, although may have poorer prognosis and increased treatment resistance
	Gains						
Gain 1q21	High-risk	2 years	40% NDMM	High-risk	5 years	More aggressive disease and higher disease burden	Benefits from early ASCT followed by bortezomib-based consolidation / maintenance Can impact drug resistance; myeloma cells with 1q21+ seem to be more sensitive to drugs that inhibit MCL1 protein
	Trisomies (hyperploidy)						
Trisomies	Intermediate	3 years	45%	Standard-risk	7-10 years	Common to have myeloma bone disease at diagnosis	Respond well to lenalidomide-based therapies
	Other						
P53 mutations	High risk of progression, however limited data available		3-8%	High-risk	Variable, estimated to 36 months	Limited data available, although may have higher disease burden and poorer prognosis	Increased risk of treatment resistance

Table 1 continued: Common chromosomal changes in myeloma and their clinical applications

*mSMART is one of the most used risk-stratification systems for myeloma. For more information on mSMART, please see Appendix II.

**Abbreviations: ASCT = autologous stem cell transplant; FLC = free light chain; NDMM = newly diagnosed multiple myeloma; OS = overall survival

References: [9–28]

How are cytogenetics used to define risk categories and stages of disease?

How far or advanced cancer has become is often reported as the cancer "stage". However, the approach to staging in myeloma is different from the typical staging systems used for solid tumour cancers. Myeloma staging uses **cytogenetics** and other characteristics to determine how advanced the cancer has become. The most commonly used staging systems for myeloma are the Revised International Staging System (R-ISS), which stratifies patients from stage I-III, and the mSMART model, which separate patients into two groups - standard and high-risk. These staging systems are further described in Appendix II. They are based on several criteria, including the presence or the absence of one or more cytogenetic abnormalities. It is important to know that risk stratification is an evolving field and criteria often change.

Although staging and risk stratification systems based on **cytogenetics** can be helpful when making treatment decisions and assessing the aggressiveness of disease, there are limitations to these systems, as well. For example, existing risk stratification systems do not account for the many other factors that contribute to one's risk of progression such as age, the presence of other health conditions, frailty and overall health status. In addition, some patients may not meet the mSMART or R-ISS criteria for high-risk myeloma, however, experience poor disease response to induction or initial therapy. This then results in a patient being categorised as having **functionally high-risk myeloma** (myeloma that relapses within 18 months of treatment initiation and/or within 12 months of frontline autologous stem cell transplantation)[29].

What additional genetic testing options exist for myeloma?

In addition to the **cytogenetics** testing described above, **genomic testing** and **gene expression profiling (GEP)** are two other types of tests that can be useful in assessing treatment options and aggressiveness of myeloma. **Genomic testing** focuses on the entire genome or genetic code of the myeloma cells and includes techniques like **whole genome sequencing** (WGS) or next generation sequencing (NGS) with the Myeloma Genome Project Panel. **Gene expression profiling**, by comparison, looks at the activity (expression) of **genes** within myeloma cells. Details of genomic tests and gene expression profilers are provided in Appendix III.

Summary

In summary, **cytogenetics** and other genetic testing options are useful tools to assess the characteristics of your myeloma, including treatment options, expected outcomes and risks of progression. Although **FISH** and **karyotyping** are currently the most common tests, they have limitations. FISH is the current "gold-standard", but its **sensitivity** is limited. Genetic testing is an evolving field. Flow cytometry and next generation sequencing (NGS) are more sensitive methods, which are increasingly being used to detect **mutations** or measure residual **plasma cells**. They may be used for disease monitoring, or analysis of tumour plasma cells circulating in the blood, outside of the **bone marrow**. Those techniques are well known and used in research, but their use in clinical practice is still limited due to high costs and lack of expertise. It is likely that in the future, access to these tests will improve and new tests will emerge, changing the myeloma diagnostic and monitoring landscapes, and thus its treatment. The more we understand about the myeloma genome, the better we can treat the disease.

Glossary of Terms

- **Albumin:** a protein that is produced by your liver and may be an indicator of your overall health and nutrition
- **Apoptosis:** a normal biological process of cell death that, when interrupted, can lead to cancer and the uncontrollable growth of abnormal cells
- **Beta-2 microglobulin (B2M):** a tumour marker protein; higher levels may indicate more cancerous cells are present and/or your cancer is growing faster
- **Biomarkers:** biological indicators of a disease process (can be **proteins**, cells, **genes**, etc.)
- **Bone marrow:** the spongy material found in the centre of large bones in the body. This is where many cells are produced, including white blood cells (also called **plasma cells**) and red blood cells
- **Bone marrow biopsy:** a procedure using a needle to obtain a small sample of bone marrow
- **Chromosomes:** strands of **DNA** and **proteins**; each chromosome contains many **genes**
- **Clonal evolution:** the process through which one cell replicates to form many daughter cells known as subclones; throughout the replication process the **DNA** changes, so that the subclones differ from the original cell
- **Cytogenetics:** analysis of the structure and function of **chromosomes**
- **Deletion:** a genetic mutation that occurs when one or more chemical bases in a gene sequence is deleted (see Appendix I)
- **Deoxyribonucleic acid (DNA):** a molecule that contains the genetic information that cells need to develop, function and reproduce
- **Fluorescence In Situ Hybridization (FISH) testing:** a type of cytogenetic test that uses **DNA** probes with fluorescent dye to identify genetic **mutations** in myeloma cell DNA
- **Functionally high-risk myeloma:** a type of myeloma that is not initially categorised as high-risk using the mSMART or R-ISS risk stratification systems, however, patients experience poor disease response to initial/induction treatments

Glossary of Terms

- **Gains and amplifications:** the presence of extra copies of **genes**, or parts of a **chromosome**, in a cell (3 copies = gain, 4 or more = amplification (amp)) (see Appendix I)
- **Gene expression:** the turning on of a gene to make **proteins**
- **Genes:** small sections of **DNA** containing information to make **proteins**
- **Gene expression profiling (GEP):** tests that look at how frequently **genes** are being expressed
- **Genetics** focuses on the study of **genes**, inheritance and functions of genes in our bodies
- **Genomics** focuses on the study of the entire genome, **chromosomes**/**DNA**, or genetic code
- **Heavy chains:** the larger protein chain that makes up an antibody; the five types of heavy chain **proteins** are known as IgA, IgM, IgD, and IgE
- **Hyperploid:** occurs when there are more **chromosomes** than usual present in a cell
- **Karyotyping:** a method of cytogenetic testing that allows researchers to see the size, number and shape of the **chromosomes** in a sample of myeloma cells
- **Lactate dehydrogenase (LDH):** a protein naturally found in multiple places throughout our body. Increases in LDH can indicate tissue damage, and LDH levels can be used to help assess how far your cancer has progressed
- **Light chains:** the smaller protein that makes up an antibody; the two types of light chains are kappa (k) and lambda (l)
- **Monoclonal gammopathy of undetermined significance (MGUS):** a precursor condition to myeloma characterised by abnormal **proteins** in the blood and **bone marrow**; approximately 1% of people with MGUS progress to myeloma per year (however, some may never develop myeloma)
- **Mutation:** a change in a sequence of **DNA**
- **Oncogene:** a gene that can cause or contribute to developing cancer
- **Plasma cells:** a type of cell found in **bone marrow** that produces antibodies

Glossary of Terms

- **Primary mutations (clonal genetic events):** mutations that happen early on when a normal **plasma cell** transforms into the state of **MGUS**, a precursor myeloma condition
- **Proteins**: important molecules that perform many functions in our bodies, including providing structural support, strengthening our immune system (antibody proteins), sending messages (hormones), providing energy for our bodies and transporting nutrients in and out of cells
- **Proto-oncogene:** genes involved in normal cell growth and division but have the potential to become genes that cause cancer (**oncogene**)
- **Risk of progression:** risk of transforming from the precursor condition **smouldering myeloma** to active multiple myeloma
- **Secondary mutations (subclonal genetic events):** **mutations** or genetic changes that happen later, in subsequent generations of cells, as myeloma progresses
- **Sensitivity and specificity:** measures that evaluate the performance of a diagnostic test and the tests' ability to correctly identify individuals with or without a condition
- **Smouldering Multiple Myeloma (SMM):** a myeloma precursor condition characterised by the presence of abnormal **plasma cells** in the **bone marrow** but without the classic symptoms of myeloma (high calcium, kidney failure, anaemia and bone lesions [CRAB])
- **Standard of care:** the universally accepted and utilised approach to treatment or disease diagnosis
- **Transcription:** the process through which RNA is made from **DNA**. Proteins are made from RNA
- **Transcription factor:** protein that regulates the **transcription** of **DNA**
- **Translation:** the process through which **proteins** are made from RNA
- **Translocation:** a genetic **mutation** that occurs when a part of one **chromosome** breaks off and reattaches to another chromosome, or when two chromosomes swap segments (see Appendix I)
- **Whole genome sequencing (WGS):** a test that analyses the entire genome

Appendix I

Most common chromosomal abnormalities

Translocations

A **translocation** occurs when a part of one **chromosome** breaks off and reattaches to another chromosome, or when two chromosomes swap segments[8]. The most common translocations that occur in myeloma are **immunoglobulin heavy chain** (IgH) translocations. In IgH translocations, genetic **mutations** cause the production of abnormal **heavy chain proteins**, therefore resulting in the production of abnormal antibodies.

IgH mutations occur in approximately 40% of newly diagnosed myeloma patients[30]. When an IgH translocation occurs, it can lead to the overexpression of one or more **oncogenes** (a gene that can cause or lead to the development of cancer). Translocations can be present at various stages of the condition, including **monoclonal gammopathy of undetermined significance** (MGUS), **smouldering multiple myeloma** (SMM) and multiple myeloma (MM), however, the impact varies based on disease stage.

The most common IgH translocations are t(11;14); t(6;14); t(4;14); t(14;16) and t(14;20).

t(11;14)

t(11;14) is the most common primary **translocation**, occurring in 16-24% of myeloma cases. t(11;14) is considered a standard-risk **mutation** and patients with t(11;14) tend to have better outcomes than those with other genetic mutations[31]. For patients with smouldering myeloma, the median time to progression is five years[10]. And in active myeloma, t(11;14) is associated with a median overall survival of 7-10 years[10]. The impact of t(11;14) on overall survival differs among races, as research suggests African American patients with t(11;14) mutations have longer overall survival compared with non-African American or white patients[9].

Patients with t(11;14) often have high rates of bone disease and kidney dysfunction, and high incidences of disease variations (such as immunoglobulin M and D, **light chain** and non-secretory disease)[9].

Appendix I

Most common chromosomal abnormalities

t(11;14) mutations can have an impact on multiple **genes** and **proteins**. For example, the t(11;14) mutation can lead to:

- overexpression of cyclin D1 (CCDN1)[9], a **proto-oncogene**. Proto-oncogenes are genes involved in normal cell growth and division but have the potential to become **oncogenes** (genes that cause cancer)[32]
- higher levels of B-cell leukaemia/lymphoma protein (BCL-2)[9], which helps control whether cells live or die by influencing a process called **apoptosis** (cell death)[33]
- increased activity of CD20[9], a protein that plays a role in the development of **plasma cells**

Having t(11;14) positive myeloma may have an impact on treatment options and disease course. Because of the higher levels of BCL-2, patients with t(11;14) positive myeloma may benefit from targeted therapy with drugs such as venetoclax, which inhibits BCL-2[9]. t(11;14) myeloma cells are also associated with reduced expression of CD38 (a drug target for several myeloma treatments), which may impact the use of drugs that target CD38 (e.g. daratumumab)[9].

t(4;14)

t(4;14) is the second most common IgH **translocation** in myeloma, occurring in approximately 10% of myeloma patients[10]. Labelled as a high-risk **mutation** in the mSMART classification system, t(4;14) is associated with a shorter time to progression (median time to progression of 2 years) in smouldering myeloma and a worse prognosis in active myeloma (median overall survival - five years)[10]. Patients with t(4;14) myeloma have common features. For example, patients with t(4;14) myeloma demonstrate a shorter duration of remission and more aggressive relapses characterised by kidney failure, low levels of blood cells and extramedullary disease[17].

Appendix I

Most common chromosomal abnormalities

t(4;14) primarily impacts two specific **genes** and **proteins**:

- fibroblast growth factor receptor (FGFR-3), a growth factor that plays a role in many important processes such as controlling cell growth and division, the formation of blood vessels, wound healing and others[34]
- the NSD2 gene, which provides instructions for making the multiple myeloma SET domain protein (MMSET), a protein myeloma cells rely on to survive, grow and form tumors[35]

All patients with t(4;14) myeloma express MMSET, making MMSET a potentially promising target for treatments[35]. Ongoing research is investigating inhibitors of FGFR-3, which may show promise for those with myeloma t(4;14) mutations as well. Currently, benefits have been seen when patients with t(4:14) mutations are treated with early autologous stem cell transplantation followed by bortezomib-based consolidation and maintenance[18].

t(14;16) (q32;q23)

Like t(4;14), t(14;16) is labelled as a high-risk **mutation** in the mSMART classification system and is associated with a standard-risk of progression (median time to progression – five years) in smouldering myeloma and worse prognosis in active myeloma (median overall survival of 3 years)[10]. Many patients with t(14;16) present with high levels of free **light chains** (FLC) (abnormal protein produced by myeloma cells) and 25% of patients present with acute kidney failure, reflecting the severity of the disease[10].

t(14;16) impacts c-MAF, which is a **transcription factor** (or protein that regulates the **transcription** of **DNA**). c-MAF promotes myeloma cells' growth, survival and resistance to treatments[36]. When c-MAF is overexpressed, other **genes** and **proteins** are affected, including CCND2, ARK5, ITGB7 and APOBECs[13], which can lead to a more aggressive and adaptable disease[37].

The overexpression of c-MAF that occurs in t(14;16) can contribute to resistance to proteasome inhibitors, a class of drugs used to treat myeloma[19]. Therefore, knowing that your myeloma has the t(14;16) mutation can help you and your medical team plan your myeloma treatment.

Appendix I

Most common chromosomal abnormalities

t(14:20) (q32;q11)

t(14;20) is the least common IgH **translocation**, occurring in less than 1% of patients[10]. t(14;20) is associated with a poor prognosis in active myeloma (median overall survival of three years). However, it is associated with long-term stable disease when it is discovered in **MGUS** or **SMM** (standard-risk of progression, median time to progression of five years)[10,12,38].

t(14;20) impacts MAFB, a protein that supports the production of blood cells in the **bone marrow**[39]. High levels of MAFB may contribute to myeloma cells' resistance to proteasome inhibitors[22]. Like patients with other high-risk **mutations**, patients with t(14;20) myeloma typically benefit from early autologous stem cell transplant, followed by bortezomib-based consolidation and maintenance[18].

t(6:14) (p21 ;q32)

t(6;14) is another, less common **translocation** that occurs in less than 2% of myeloma cases[12]. A standard-risk **mutation** according to mSMART classifications, t(6;14) is associated with a standard-risk of progression and median time to progression of five years in smouldering myeloma, and a median overall survival of 7-10 years in active myeloma[10]. Studies suggest that **light chain** myeloma, kidney dysfunction and bone disease are more common among those with t(6;14) positive myeloma, however these findings are based on small samples of patients[20]. t(6;14) impacts cyclin D3 (CCDN3)[10] – a protein that plays an important role in regulating the growth of tumour cells[40].

Deletions

A **deletion** occurs when one or more of the chemical bases in a gene sequence is deleted. If you think of a gene sequence as a word, you can see how deletions can have an impact – what was originally TAG might now only read TG, which has a different (or no) meaning. Sometimes only a single chemical base is changed and other times an entire gene can be deleted. While there are many gene deletions identified in myeloma cells, the two used for risk stratification are deletion 17p and 1p.

Deletion 17p

Deletion 17p is a high-risk abnormality that is seen in 6-10% of newly diagnosed

Appendix I

Most common chromosomal abnormalities

myeloma patients[12]. Like other high-risk abnormalities, del(17p) is associated with a high-risk of progression from smouldering myeloma (median time to progression of two years) and a median overall survival of three years in active myeloma[10].

Del(17p) commonly causes the loss of another gene, p53 which is an important gene involved in the development of multiple types of cancer[12,14]. One of p53's main functions is to prevent damaged cells from multiplying by stopping the cell cycle and causing abnormal cell death (**apoptosis**)[14]. Dysregulation in p53 can allow tumours to form. When loss of p53 occurs in patients with del(17p), it also increases the likelihood that myeloma cells will be resistant to treatment[25]. Therefore, deletion 17p is associated with low rates of complete response to treatment, rapid disease progression, plasma cell leukaemia and brain or central nervous system involvement[24].

Deletion 1p

Deletion 1p refers to the deletion of a portion (or all) of the **genes** on **chromosome** 1. Deletion 1p occurs in approximately 30% of newly diagnosed patients and is considered a high-risk **mutation**[13]. In a study of 453 newly diagnosed patients treated with autologous stem cell transplant (ASCT), patients with del(1p) had shorter progression-free survival (median of 2.43 years versus 3.98 years), shorter time to next treatment (median of 2.72 years versus 6.17 years) and shorter overall survival (median of 4.11 years)[16].

Depending on which portion of the chromosome is deleted, several different genes can be affected by 1p deletions, including CDKN2C, FAF1, RPL5, EVI5 and FAM46C[13]. These genes are involved in a variety of different functions, including regulating the cell cycle and replication, cell growth and cell death in response to **DNA** damage[13].

Gains

Gains or amplifications are a mutation that results in the presence of extra copies, **genes**, or parts of a **chromosome**.

Gain 1q21

Gain 1q21 is associated with a high-risk of progression in smouldering myeloma

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Most common chromosomal abnormalities

(median time to progression - two years) and a worse prognosis in active myeloma (median overall survival of 5 years)[10]. This **mutation** is more common than any other cytogenetic abnormality[27]. The incidence increases with disease progression (0–20% in **MGUS** to >50% in relapsed refractory myeloma), implying the mutation may be associated with disease progression and drug resistance[13].

Gain 1q21 may result in three copies of **chromosome** 1q21 (gain 1q21), or four or more copies (known as amplification 1q21)21. Research suggests that amplification 1q21 carries a worse prognosis[13].

Patients with gain 1q21 myeloma "tend to be older and at diagnosis are found with more organ damage and higher tumour burden, low red blood cell levels, high calcium levels [and] higher stage disease"[27]. The gain 1q21 mutation often occurs along with other abnormalities such as t(4;14), t(14;16), del(1p), and del(17p)[27].

The specific **gene** that causes high-risk progression in gain 1q21 myeloma has not been fully identified, however region 21 of chromosome 1 has several genes that are known to cause cancer and others whose expression is changed by gain 1q21 mutations[26]. These genes include MCL-1, CSK1B, IL6R, ILF2, and BCL9[26]. They are involved in a number of different activities that promote disease progression, interfere with normal cell cycles, cause genomic instability and promote myeloma cell survival[26].

Having a 1q21 mutation can contribute to myeloma cells' resistance to treatments[13]. Myeloma cells with 1q21 seem to be more sensitive to drugs that inhibit MCL1[13]. Patients with this mutation may benefit from early autologous stem cell transplantation (if eligible), followed by bortezomib-based consolidation and maintenance[10]. In addition, clinical trials have shown improvement in progression-free survival (PFS) for patients with gain 1q receiving lenalidomide maintenance (Myeloma XI), selinexor (BOSTON) and isatuximab (IKEMA and ICARIA)[41].

Trisomies

Trisomies occur when cellular **DNA** gains an extra **chromosome**. This **mutation** is commonly caused by a duplicate of an odd-numbered chromosome, e.g. chromosomes 3, 5, 7, 9, 11, 15, 19 and 21[28].

Trisomies are fairly common, occurring in around 45% of myeloma cases[10].

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Most common chromosomal abnormalities

Considered to be standard-risk mutations, they are associated with an intermediate risk of progression from smouldering myeloma (time to progression of three years) and a good prognosis in active myeloma (median overall survival of 7-10 years)[10]. Some trisomies (e.g. trisomy 3 and 5) are associated with improved overall survival, whereas other trisomies (e.g. 21) are associated with shorter overall survival rates[28].

It is common for patients with trisomies to present with bone disease at diagnosis[10]. Treatment options may vary, but patients with trisomies also tend to have excellent responses to lenalidomide-based therapies[10].

Other chromosomal abnormalities

P53 mutations

The p53 gene, as described above, is an important gene involved in the development of multiple types of cancer[12,14]. p53 helps cells respond to damage by stopping cellular replication and causing cell death (**apoptosis**) of cells with genetic mutations[14]. Dysregulation in p53 can therefore allow tumours to form.

p53 dysregulation can occur because of a deletion of 17p (8% of newly diagnosed patients), a mutation (6% of newly diagnosed patients) or an inactivation (4% of newly diagnosed patients)[14]. Having any loss of p53 is associated with a poor prognosis[42]. However, the median overall survival is lower (36 months) for patients with p53 inactivation compared to patients with deletion 17 (53 months)[15]. There is an unmet need for treatments that effectively target dysregulated p53[14].

Appendix II

Myeloma staging systems

Revised International Staging System (R-ISS) model

The R-ISS model was developed based on a sample of 3,060 patients with newly diagnosed myeloma, who were enrolled in one out of 11 international clinical trials. Patients were followed-up for a median time of 46 months[24,43]. Although R-ISS staging may be helpful to better estimate prognosis, it is important to remember that prognosis is dependent on many factors outside of those covered by the R-ISS, including age, the presence of other complex medical conditions or diagnoses and overall health status.

R-ISS categories consider several factors, including the following:

- Levels of **B2M (beta-2 microglobulin):** B2M is a tumour marker protein (biomarker). Higher levels may indicate more cancerous cells are present and/or myeloma is growing at a faster rate.
- **Albumin** levels: Albumin is a naturally present protein in the body made by the liver and may be an indicator of overall health. Low levels of albumin may indicate that myeloma is more aggressive.
- Levels of **LDH (lactate dehydrogenase):** LDH is an enzyme found in multiple places throughout the body. Increases in LDH can indicate tissue damage and LDH levels can be used to help assess how far myeloma has progressed. Higher levels of LDH at the time of diagnosis can be a marker of a poorer prognosis[44].

An overview of the R-ISS criteria is presented on the following page in Table 2.

Appendix II

Myeloma staging systems

Stage	Criteria	5-year overall survival[43]	5-year progression free survival[43]
Stage I	All the following: ■ **B2M*** <3.5 mg/L ■ Serum (blood) **albumin** ≥3.5 g/dL ■ Normal **LDH**** ■ Absence of specific cytogenetic abnormalities: del(17p), t(4;14), or t(14;16) by **FISH** testing	82%	55%
Stage II	Criteria that do not fit stage I or stage III	62%	36%
Stage III	Both of the following: ■ B2M ≥5.5 mg/L ■ Elevated LDH and/or the presence of specific cytogenetic abnormalities: del(17p), t(4;14), or t(14;16) by FISH	40%	24%

Table 2: An overview of the myeloma Revised International Staging System (R-ISS)[24]

*This table was adapted from Laubach J. Multiple myeloma: Staging and prognostic studies - UpToDate. Published September 25, 2023. Accessed April 2, 2024. *B2M: beta-2 microglobulin, **LDH: lactate dehydrogenase.*

mSmart risk stratification model

mSMART is another commonly used risk-stratification system developed by the Mayo Clinic in the United States. mSMART 3.0 identifies two risk categories: standard and high-risk. The high-risk category also includes sub-categories: "double hit myeloma" and "triple hit myeloma." Approximately 75% of myeloma patients have standard-risk **mutations** according to mSMART criteria, while 25% are considered high-risk[18]. Table 3 provides a summary of the mSMART risk categories.

Appendix II

Myeloma staging systems

Risk category	Features
High-risk	■ At least one of the following high-risk genetic abnormalities: t(4;14), t(14;16), t(14;20), del(17p), p53 mutation, chromosome 1 abnormalities (gain or amp(1q); or del(1p)) ■ R-ISS stage III ■ High proportion of plasma cell in S-phase* ■ High-risk gene expression profiling (GEP) signature
	Double-hit myeloma: Any two high-risk genetic abnormalities
	Triple-hit myeloma: Three or more high-risk genetic abnormalities
Standard-risk	All others including: trisomies, t(11;14) and t(6;14)

Table 3: An overview of the mSMART risk stratification system for myeloma

**S-phase: the synthesis or S phase is a phase of the cell cycle when DNA is replicated*

Appendix III

Additional genetic tests

Genomic Testing

Whole genome sequencing (WGS)

Whole genome sequencing (WGS) is a comprehensive test that analyses the entire genome of myeloma cells[45]. The WGS method can potentially be used to identify abnormalities that are not detected by other tests and unknown **mutations** that cannot be detected by **FISH**[46]. However, there are some limitations. For example, WGS is expensive, takes a longer time to process and requires specialised equipment that may not be available at smaller or non-academic medical centres[47]. In addition, it can be difficult to use WGS to identify mutations in patients with myeloma precursor conditions such as **monoclonal gammopathy of undetermined significance** and **smouldering myeloma**[47].

The Myeloma Genome Project Panel

Developed by a global initiative, the myeloma genome project is a comprehensive targeted **genomics** panel (i.e. a comprehensive genetic test) that can be used to identify common genomic abnormalities in patients with myeloma. The test uses a technology called next generation sequencing (NGS) that can sequence hundreds and thousands of **genes**, or a whole genome, in a short period of time[47]. The myeloma genome project panel looks at 228 genes for **mutations** and various other genetic abnormalities[47]. The benefits of this test are that it is cost-effective, thorough and clinically useful for understanding a patient's risk status[47]. Research has suggested that the myeloma genome project panel may be as good as - or better than - **FISH** testing and **whole genome sequencing**[47]. For more information on the myeloma genome project, please see this link.

Gene expression profilers (GEP)

While **FISH** testing and **karyotyping** look directly at the sequences of **DNA** in myeloma cells, **gene expression profiling** (GEP) looks at how frequently the **genes** are expressed. **Gene expression** refers to "the process by which a gene gets turned on in a cell to make **proteins**"[48]. **Mutations** change the frequency of gene expression and these changes can be assessed to better understand the aggressiveness of myeloma. Like other cytogenetic tests, GEP tests have been shown to improve risk stratification and patient outcomes[49]. MMprofiler and

Appendix III

Additional genetic tests

MyPRS are two of the more well-known GEP tests and details on each of them are provided below.

MMprofiler

The MMprofiler is a gene expression profiler used for risk-stratification in myeloma. The test measures the gene expression of 92 different **genes** directly and indirectly related to myeloma[50]. These 92 different genes are referred to as the "SKY92 gene signature". Results are based on the person's "SKY92 risk score", which determines whether SKY92 high-risk is present or absent. Researchers hope the MMprofiler will be used alongside other standard of care markers such as **FISH** testing to help providers and patients understand the aggressiveness of their disease. Because it is a newer technology with a different approach, this test has the potential to identify patients with high-risk myeloma that might not have been detected by other tests alone[51].

Studies have supported the use of MMProfiler in assessing prognosis, risk status and treatment in myeloma[51–53]. However, the availability of this test is very limited and, because it is a relatively new technology, more research is needed before it is widely adopted[51].

MyPRS/ MyPRS Plus GEP70

The MyPRS/ MyPRS Plus GEP70 is a gene expression profiler that looks at 70 of the most common **genes** found in cancerous myeloma cells. Like the MMprofiler, the MyPRS classifies patients into either a 'high-risk' or 'low-risk' group based on the gene signature present[54]. MyPRS is a newer test that is currently only available commercially through specific labs[40]. And, unlike MMprofiler, studies have not been conducted to evaluate the clinical utility of MyPRS, and therefore more research is required[55].

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MPE is a network of European myeloma patient organisations. It supports national patient organisations to improve treatment and access for patients in their countries, and helps inform and raise awareness on a European level through its educational programmes. Please note, this information does not replace the information provided by your doctor. If there is anything that is not clear to you, please always ask your clinical team.

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