Understanding Freelite® and Hevylite® Tests

A publication of the **International Myeloma Foundation**

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FOUNDATION

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Improving Lives **Finding the Cure**®

INTERNATIONAL MYELOMA FOUNDATION

Founded in 1990, the International Myeloma Foundation (IMF) is the first and largest organization focusing specifically on multiple myeloma. The IMF's reach extends to more than 525,000 members in 140 countries worldwide. The IMF is dedicated to improving the quality of life of myeloma patients while working toward prevention and a cure through our four founding principles: Research, Education, Support, and Advocacy.

RESEARCH The signature project of the IMF's Research division is the Black Swan Research Initiative®, a groundbreaking and collaborative effort to develop the first definitive cure for myeloma. Each year, the IMF also awards Brian D. Novis Grants, which promote research for better myeloma treatments, management, and practices in the field. In addition, more than 200 leading myeloma researchers comprise the IMF's International Myeloma Working Group (IMWG), a research body that has developed myeloma guidelines that are followed around the world. Finally, the IMF's Nurse Leadership Board (NLB), comprised of nurses from leading myeloma treatment centers, develops recommendations for the nursing care of myeloma patients.

EDUCATION The IMF Patient & Family Seminars and Regional Community Workshops are held around the world to provide up-to-date information presented by leading myeloma specialists and researchers directly to patients and their families. The IMF's library of more than 100 publications, for patients and caregivers as well as for healthcare professionals, is updated annually and available free of charge. Publications are available in more than 20 languages.

SUPPORT The IMF's InfoLine is staffed by information specialists who answer myeloma-related questions and provide support via phone and email to thousands of families each year. In addition, the IMF sustains a network of more than 150 myeloma support groups and offers training for the hundreds of dedicated patients, caregivers, and nurses who volunteer to lead these groups in their communities.

ADVOCACY The IMF's Advocacy team has educated and empowered thousands of individuals who make a positive impact each year on issues critical to the myeloma community. Working in the US at both federal and state levels, we lead coalitions to advocate for parity in insurance coverage. We also represent the myeloma community's interests before the US Congress and agencies such as the National Institutes of Health, the Food and Drug Administration, the Centers for Medicare and Medicaid Services, and the Veterans Administration. Outside the US, the IMF's Global Myeloma Action Network (GMAN) works to help patients gain access to treatment.

Learn more about the ways the IMF is helping to improve the quality of life of myeloma patients while working toward prevention and a cure.
Contact us at 818.487.7455 or 800.452.CURE,
or visit myeloma.org.

Improving Lives **Finding the Cure®**

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What you will learn from this booklet

The IMF's *Understanding* series of booklets is designed to acquaint you with treatments and supportive care measures for **multiple myeloma** (which we refer to simply as "myeloma"). Words in **bold+blue** type are explained in the "Terms and definitions" section at the end of this booklet, as well as in a more complete compendium of myeloma-related vocabulary, the IMF's *Glossary of Myeloma Terms and Definitions,* located at glossary.myeloma.org.

Myeloma is a **cancer** that is not known to most patients at the time of diagnosis. To be empowered to play an active role in your own medical care and to make good decisions about your care with your doctor, it is vital for you to learn as much as possible about myeloma and its treatments. The information in this booklet will help you in discussions with your healthcare team. The more information you have about resources that are available to you, the better and more fruitful that discussion will be.

Understanding Freelite® and Hevylite® Tests presents information on two tests used to diagnose and monitor myeloma and to detect **relapse**: the serum free light chain assay (Freelite®) and the serum heavy/light chain assay (Hevylite®).

Important: The total light chain assay is not useful for myeloma patients and can sometimes get confused with the Freelite test. The Freelite test (free kappa, free lambda with ratio, serum) must be specified by your doctor in order to benefit from the newest and most effective diagnostic testing available. (Serum is the liquid part of the blood after the blood cells have been removed.)

A cancer of plasma cells

Our blood contains **red blood cells**, which carry oxygen from our lungs to all our organs and tissues, **white blood cells**, which make up our **immune system**, and **platelets**, which help clot the blood after an injury. These blood cells start their development in the **bone marrow** before they make their way into our circulating blood.

Figure 1. **Myeloma cells as seen in a bone marrow aspirate**

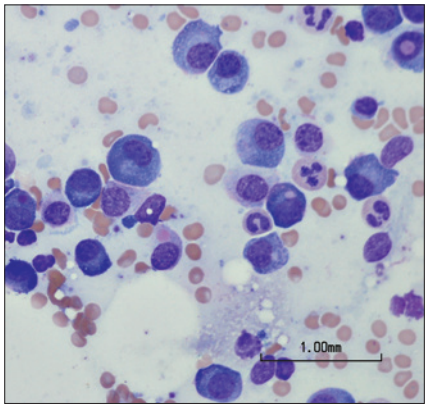
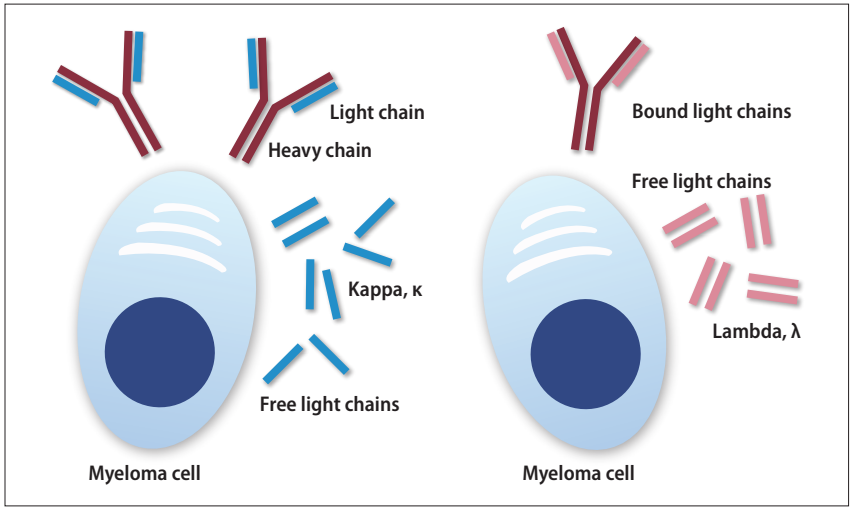


Figure 2. **Plasma cells release intact antibodies and free light chains**



There are many different types of white blood cells; one type is the **plasma cell**. Myeloma is a cancer of the plasma cells, and the cancerous plasma cells are called myeloma cells. There are some plasma cells that circulate throughout the body, but most plasma cells live in our bone marrow. Myeloma is a cancer of plasma cells that live and reproduce in the bone marrow.

The normal job of plasma cells

The normal job of plasma cells is to produce and release special **proteins** called **antibodies**, which can attach (or bind) to bacteria and viruses to stop them from infecting our cells and making us sick. Each plasma cell makes one type of antibody to match one particular type of bacteria/virus. At any one time, our bodies are making a large number of plasma cells, which, in turn, are making billions of different antibodies to protect us against all the different bacteria/viruses that may try to infect us.

What is an antibody?

An antibody is a special protein that is also called an **immunoglobulin** (abbreviated "Ig"). Each antibody molecule is made up of smaller pieces called heavy chains and light chains. Two identical heavy chains are attached to two identical light chains to make a complete antibody (or "intact immunoglobulin").

There are five different types of heavy chains, giving us five different antibody "isotypes," abbreviated as IgG, IgA, IgM, IgD, and IgE. There

are two different types of light chains called kappa (κ) and lambda (λ). When the light chain is attached to the heavy chain, it is known as a "bound light chain." For unknown reasons, plasma cells typically make more light chains than heavy chains, so not all the light chains will be used to make antibodies. When a light chain is not attached to a heavy chain, it is known as a "free light chain."

Table 1. **Isotypes of Immunoglobulins**

IgG kappa	IgG lambda
IgA kappa	IgA lambda
IgM kappa	IgM lambda
IgD kappa	IgD lambda
IgE kappa	IgE lambda

Each plasma cell can make only one type of heavy chain and one type of light chain. Each patient with myeloma has one of the 10 different antibody subtypes as shown in the accompanying Table.

What happens in myeloma – too many plasma cells in the bone marrow

The hallmark of a cancer cell is its continued replication. When a plasma cell becomes a myeloma cell, it starts to make copies of itself. The result is too many copies, or clones, of one plasma cell. Because the plasma cell can only make one type of antibody, the result is an unusually high amount of that antibody type in the blood. It is called **monoclonal protein (myeloma protein, M-protein, M-spike)**.

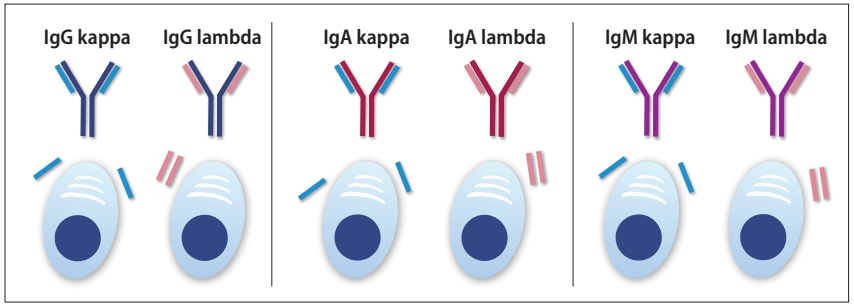
Myeloma cells' activity in the bone marrow can be assessed in the blood

Since each type of plasma cell releases only one type of antibody, and these antibody **molecules** circulate throughout the body by traveling through the blood, a simple blood test can measure M-protein. **Bone marrow biopsy** is still necessary before and often after treatment, but blood tests are a much simpler way to:

- Establish a baseline for how much M-protein is present at diagnosis,
- Monitor how well treatment is working, and
- Detect a possible relapse of the disease after a period of remission.

The laboratory technique that measures how much antibody protein is present in the blood or urine is called serum or urine protein **electrophoresis** (SPEP or UPEP). Serum protein electrophoresis (SPEP) or urine protein electrophoresis (UPEP) plots the result of the test as a line graph. If M-protein is present, the graphed amount of protein looks like a sharp and narrow peak, or "spike," called an M-spike.

Figure 3. **Each plasma cell makes one type of antibody**



Since each plasma cell makes one type of antibody, we can detect, categorize, and track myeloma in patients by measuring the specific M-protein released by myeloma cells.

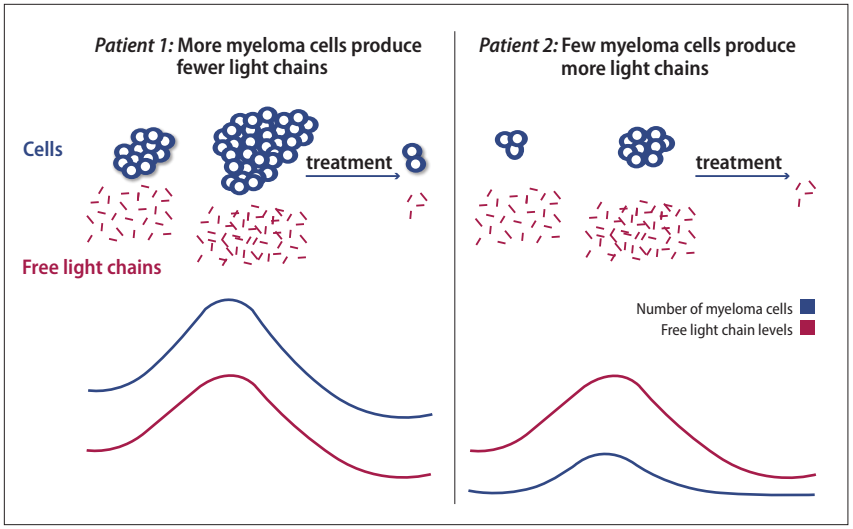
What does the Freelite test tell us?

If the myeloma cells are releasing kappa free light chains, the Freelite test will show a high level of kappa light chain protein and a normal, or lower than normal, level of lambda light chains. If the myeloma cells in the bone marrow are secreting lambda free light chains, then the Freelite test will show a higher level of lambda chains and a normal, or lower than normal, level of kappa free light chains. A higher level of free light chains in the blood suggests that there are more cancer cells in the bone marrow releasing them. If the free light chain levels are going down, then this suggests that there are fewer cancer cells in the bone marrow.

Comparing Freelite test results for a single patient over the course of the patient's disease is a meaningful way to monitor the course of the patient' myeloma. However, it is not appropriate to compare the level of light chains in one patient to the level in another patient because each myeloma cell in one patient may be releasing a few free light chains, while another patient may have myeloma cells that each release many free light chains. A lower level of light chains in one patient compared to another does not necessarily mean that the patient with fewer light chains has fewer myeloma cells than the patient with more light chains. ***Do not compare light chain levels between patients.***

Each healthy person has many intact antibody molecules circulating throughout the blood, but there are fewer free light chains floating around in the blood of healthy individuals. Healthy people usually have between 3.3–19.4 mg/L of free kappa light chains and 5.7–26.3 mg/L of free lambda light chains. The normal ratio of kappa/lambda is between 0.26 and 1.65. A ratio below 0.26 or above 1.65 indicates there is monoclonal free light chain protein.

Figure 4. **Example of light chain levels and number of myeloma cells in two different myeloma patients**



The small amount of free light chains in healthy individuals makes it easier for doctors to detect increases in free light chain levels in the blood. This is one of the reasons that the Freelite test is so helpful.

Understanding Freelite test results

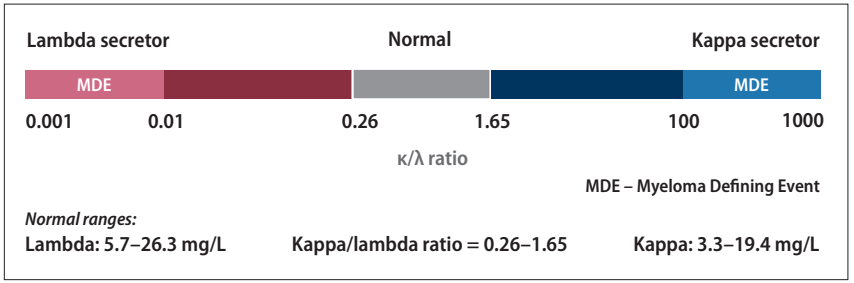
Your Freelite test lab report will specify three values:

1. kappa (κ) free light chains,
2. lambda (λ) free light chains, and
3. the κ/λ ratio (kappa free light chains divided by lambda free light chains).

A normal range is given for each result. If any one of your numbers is above or below the normal range, then this is considered an abnormal result. To learn which type of myeloma plasma cell is growing too much, you can look at the individual numbers for free kappa and free lambda.

- If either kappa or lambda numbers are higher than the normal reference range, then the myeloma clone is likely producing that type of light chain.
- The type of light chain that is coming from the myeloma cells is called the "involved" light chain (for example, kappa light chains in a patient with IgG kappa myeloma).
- The other light chain is called the "uninvolved" light chain (for example, the uninvolved light chain would be lambda in a patient with IgG kappa myeloma).

Figure 5. **Free light chains in the serum of healthy individuals**



- If your kappa/lambda ratio is high (greater than 1.65) and other tests and symptoms have confirmed your diagnosis, you may have a kappa-type myeloma clone.
- If your kappa/lambda ratio is low (less than 0.26) and other tests and symptoms have confirmed your diagnosis, you may have a lambda-type myeloma clone.

Please note that each laboratory may use a different reference range. Also, in patients with renal impairment, it is recommended to interpret the results of the kappa/lambda ratio with a modified reference range of 0.37–3.1.

How abnormal is your Freelite ratio?

There are a few concepts to think about when looking at Freelite results. When looking at a ratio as a new patient, though any result outside of the normal values (below 0.26 or above 1.65) is considered abnormal, results that are abnormal but close to the reference range (i.e., 0.25, 0.2, 1.8, 2.0) have a low chance of being due to myeloma. Ratios up to 3.1 could simply be due to poor filtering of light chains by the kidneys. For example, if a patient is tested for myeloma and the ratio is 3.0, it would be appropriate to ask if this result was due to renal (kidney) impairment. Since renal impairment can be monitored by creatinine measurements, elevated creatinine plus a slightly abnormal kappa/lambda ratio may explain the abnormal ratio as the result of kidney problems rather than myeloma.

More extreme ratios such as 10 or 0.026 are more likely to be attributable to myeloma. In the case of patients who have a confirmed myeloma diagnosis, the marginally abnormal ratios could still be due to renal impairment, but they could also be due to low levels of the myeloma. In patients who already have myeloma and are undergoing treatment, the ratio should be moving towards the normal range. Since many myeloma therapies kill both the myeloma cells and the normal plasma cells, the ratio of kappa to lambda may not change. For this reason, it is

Table 2. **Possible test results**

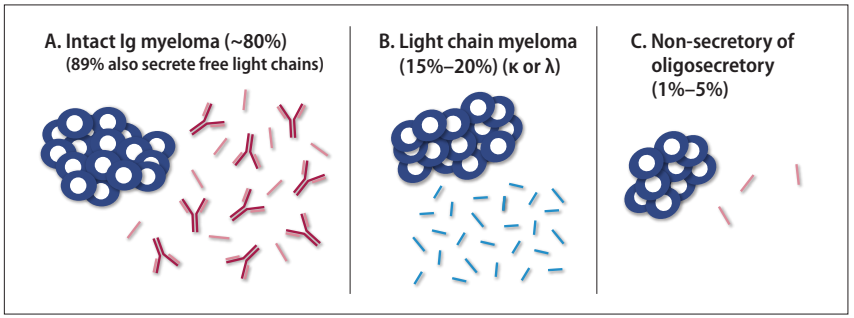
Kappa/lambda ratio (0.26–1.65)	*Kappa (3.3–19.4 mg/L)*	*Lambda (5.7–26.3 mg/L)*	*Interpretation*
Normal	Normal	Normal	No evidence of monoclonal light chains. Confirm with other lab tests.
High	High	Normal	Monoclonal kappa free light chains
Low	Normal	High	Monoclonal lambda free light chains
Normal	High	High	Plasma cells of both light chain types are secreting antibodies (possible infection, autoimmunity, or kidney damage).
Normal	Low	Low	General immune suppression (possibly due to chemotherapy or other reasons).
High	Normal	Low	Possible low-level monoclonal kappa free light chains or immune suppression of lambda.
Low	Low	Normal	Possible low-level monoclonal lambda free light chains or immune suppression of kappa.
"Slightly" high	"Slightly" high	Normal or slightly high	Possible kidney damage ("slightly" = up to approximately 3.1).

always important to interpret all Freelite results: free kappa light chains, free lambda light chains, and the kappa/lambda ratio.

The Freelite test is useful for patients with any type of myeloma

Myeloma patients are classified based on what type of protein their myeloma cells are releasing. For example, 80% of patients with myeloma have myeloma cells that release intact immunoglobulin (two heavy chains with two light chains all bound together). This is called intact immunoglobulin multiple myeloma (IIMM). Approximately 15% of patients with myeloma have myeloma cells that do not release intact immunoglobulin but release only free light chains. For detection of myeloma, the International Myeloma Working Group (IMWG) and the National Comprehensive Cancer Network (NCCN) recommend using a combination of three blood tests: serum Freelite, SPEP, and serum **immunofixation** (sIFE). For more information, please read the IMF's *Understanding Your Test Results* booklet.

Figure 6. **Myeloma patients are classified based on the M-protein that their cells release**



Free light chains are found in the serum (blood) before they are detected in the urine

Since free light chains are produced by plasma cells and myeloma cells that are in the bone marrow and are circulating throughout the blood, they are first seen in the **serum**. Our blood is always being filtered by our kidneys. Any waste material in our blood is filtered out by our kidneys and ends up in our urine. Normally, the kidneys filter light chains and then break them down and recycle them so that they do not go into the urine. But if there are too many light chains, as in the case of myeloma, they may overwhelm the kidneys' recycling ability, leading to the appearance of light chains in the urine. Light chains can also be found in urine if the kidneys' filters are damaged and larger proteins like intact or whole immunoglobulins pass into the urine. Because light chains only appear in the urine when there is a large amount of cancer or a lot of damage to the kidney filters, it is more effective to test the serum for free light chains rather than the urine. A few cases of myeloma (and **AL amyloidosis**) have been observed where light chains are detectable in the urine but not the serum. Keep in mind that urine tests are still recommended for the initial work-up of myeloma patients.

How can the Freelite assay help detect and monitor myeloma?

Changes in free light chain levels are useful for tracking the disease status in almost all people with myeloma, not just those with light chain (**Bence-Jones**) myeloma or nonsecretory disease. The Freelite test can help in the detection and monitoring of myeloma by quantifying monoclonal protein in multiple disease settings.

Intact immunoglobulin multiple myeloma (IIMM)

To recap, an intact immunoglobulin is made up of four chains (two heavy chains and two light chains). The intact immunoglobulin amounts can be measured by an SPEP test. The result of the SPEP is an M-spike, which reflects the amount of M-protein in the blood.

IIMM accounts for more than 80% of myeloma cases. In IIMM, the cancerous plasma cells produce one type of intact immunoglobulin, and in the majority of these cases, either kappa or lambda free light chains are also produced. Because free light chains are filtered by the kidneys rather quickly (within just a few hours), changes in free light chain blood levels in response to treatment occur rapidly. Decreases in free light chain levels can therefore be a very sensitive indicator of early response in IIMM.

In cases where the M-spike is difficult to measure with standard protein electrophoresis, doctors can take advantage of the fact that the Freelite test can track myeloma in 90% of IIMM patients. In addition, a more sensitive and specific test than SPEP that can measure the amount of the intact immunoglobulins is called Hevylite, which is explained in more detail later in this booklet.

Light chain multiple myeloma (LCMM)

In the approximately 15% of cases where myeloma cells do not release intact immunoglobulin, but instead release only free light chains, a patient's cells will release either kappa light chains or lambda light chains, but not both. For light chain-only myeloma, one of the best ways to track the disease is the serum Freelite test. Some physicians may also use urine electrophoresis testing to assess the amount of light chain protein in the urine. Urine testing, however, is less sensitive than Freelite, which is able to assess light chains in the circulating blood before they accumulate in the kidneys.

Nonsecretory and oligosecretory myeloma

Although rare, some patients have myeloma that produces very few intact immunoglobulins and free light chains. In the case where there is no detectable M-protein, the patient is referred to as having **nonsecretory myeloma**. Patients whose myeloma secretes a very low level of antibodies or light chains have **oligosecretory myeloma**. Approximately 70%–80% of patients who have M-protein levels too low to be detected by other methods can instead use the Freelite test.

The Freelite test is useful for patients at different stages of myeloma

During treatment

The Freelite test is useful in the diagnosis of myeloma and for monitoring or tracking disease in patients with myeloma who are releasing intact immunoglobulins, only light chains, or very few light chains.

Monitoring the individual light chain levels and the kappa/lambda ratio during treatment is useful to see if the therapy is working. A decrease in the "involved" (coming from the myeloma cells) light chain levels of 50% or more is considered a partial response. A decrease in light chain levels of > 90% is a very good partial response. The goal is to have the individual light chain numbers and the ratio come back within the normal reference range. It is important to compare your last free light chain number to your current number and the next number. Please note that it is important to evaluate all of your laboratory results, not just your Freelite results, in order to best understand how your treatment is working.

After treatment

Monitoring free light chain levels after treatment is important. Even very small amounts of myeloma that start to grow as part of relapse produce measurable amounts of free light chains in most instances. Depending on the type of myeloma, the levels of free kappa or free lambda light chains may increase before the increases in heavy chains and intact immunoglobulins can be detected by SPEP or immunofixation tests.

The pattern of M-protein production can change. For example, plasma cells that produced both intact immunoglobulins and free light chains may change so that only free light chains are produced. In cases where myeloma cells that produced intact immunoglobulins are killed off by therapy, it is possible that a few myeloma cells that produced only free light chains may survive and expand in number. These situations result in what is called **light chain escape** (LCE): a relapse characterized by the absence of heavy chain protein and the appearance of free monoclonal light chains that were not being released before. The most sensitive way LCE can be detected early in relapse is with the Freelite test.

The Freelite test in conditions that could become myeloma

Monoclonal gammopathy of undetermined significance (MGUS)

Patients diagnosed with MGUS have a plasma cell disorder characterized by comparatively low levels of M-protein in the blood and/or urine. Bone

marrow plasma cell levels are < 10%. Myeloma-related symptoms (i.e., anemia, renal failure, hypercalcemia, and lytic lesions) are absent.

MGUS patients do not have cancer but do have a risk of developing myeloma. The average risk that MGUS patients will develop myeloma is 1% per year. Some MGUS patients have a higher chance of developing active myeloma. For example, patients with MGUS who also have an abnormal free light chain ratio are more likely to progress and develop active myeloma than MGUS patients who have a free light chain ratio within the reference range. In addition, recent studies show that MGUS patients may have other medical conditions or "comorbidities" that can affect their quality of life and life span. For these reasons, it is important for each MGUS patient to be watched carefully by his or her doctor.

Smoldering multiple myeloma (SMM) or asymptomatic myeloma

Patients with SMM have higher levels of immunoglobulins and/or free light chains and/or plasma cells in the blood than patients with MGUS. The chance that they will develop active disease is much greater than patients with MGUS. High-risk SMM (HRSMM) can be evaluated using tests that are routinely used to assess active disease status, including the Freelite test. Asymptomatic patients with a free light chain ratio of ≥ 100 or ≤ 0.01 are now considered to have active myeloma. So are patients who have ≥ 60% bone marrow plasma cells. Lastly, patients with more than one focal lesion detected by MRI are now defined by the IMWG as having active myeloma. Patients who meet any one of these three criteria have an 80% or greater risk of developing CRAB criteria (organ damage) within two years (Rajkumar et al., *The Lancet,* November 2014).

AL amyloidosis

Amyloid light-chain amyloidosis (AL amyloidosis) is a condition in which myeloma light chains cross-link with each other in a beta-pleated fashion and then are deposited in tissues and organs throughout the body, such as the heart, nerves, and kidneys, rather than being excreted by the kidneys. This condition is also known as primary amyloidosis. The serum free light chain test has been recommended for the diagnosis and monitoring of AL amyloidosis.

Patients who benefit most from the Freelite test

- People with myeloma who have abnormal serum free light chain results at the start of treatment; monitoring with the serum free light chain assay often allows a rapid assessment of the effectiveness of treatment.
- People with very low levels of light chains that are undetectable by other tests such as SPEP, UPEP, and IFE; these are people who generally have nonsecretory (also called hyposecretory, oligosecretory, or paucisecretory) myeloma. Approximately 70% of people with nonsecretory myeloma can have their disease monitored using the Freelite test.
- People with deposits of light chains in the form of AL amyloidosis who may or may not have active myeloma. Tracking the light chain levels is very helpful to assess their disease status.
- People with Bence-Jones myeloma due to:
  - Ease of blood testing versus 24-hour urine collection. (It is important to note that periodic 24-hour urine testing is still recommended and necessary, both to double-check the light chain excretion level and to monitor for any evidence of kidney damage.)
  - Greater sensitivity of blood testing. (Mildly increased levels of light chains may be detected in the blood but not detected in the urine.)

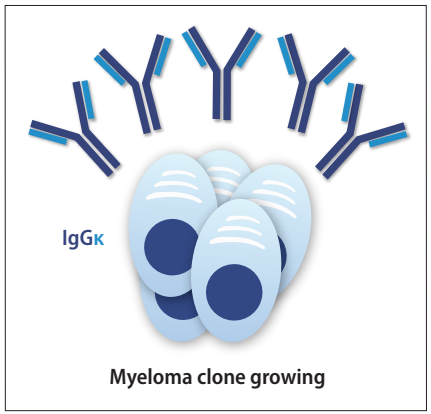
What is the Hevylite test?

While the Freelite test quantifies free light chains and has been most helpful for patients with light chain disease, low-secreting disease, and amyloidosis, the Hevylite test quantifies the intact, or whole, immunoglobulin heavy and light chain pairs involved in a patient's myeloma (IgG kappa or IgA lambda, for example). Hevylite is the only automated **immunoassay** approved by the US Food and Drug Administration (FDA) for monitoring IgG and IgA myeloma. While other test results require the subjective evaluation of a lab technician or pathologist to quantify myeloma protein, Hevylite results are analyzed and calculated by a computer, eliminating the variations of individual subjectivity.

According to the FDA approval, the Hevylite test is to be used for previously diagnosed myeloma in conjunction with other clinical and laboratory findings. The Hevylite test is very sensitive, so it can accurately detect monoclonal immunoglobulins at very low levels in the blood.

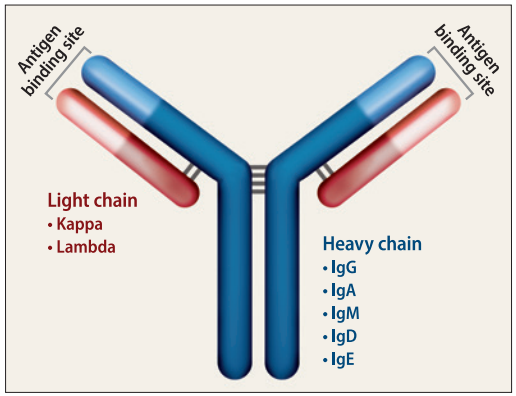
The Hevylite test measures specific heavy and light chain combinations. For example, it can measure the amount of IgG

Figure 7. **Overproduction of one specific immunoglobulin in myeloma**



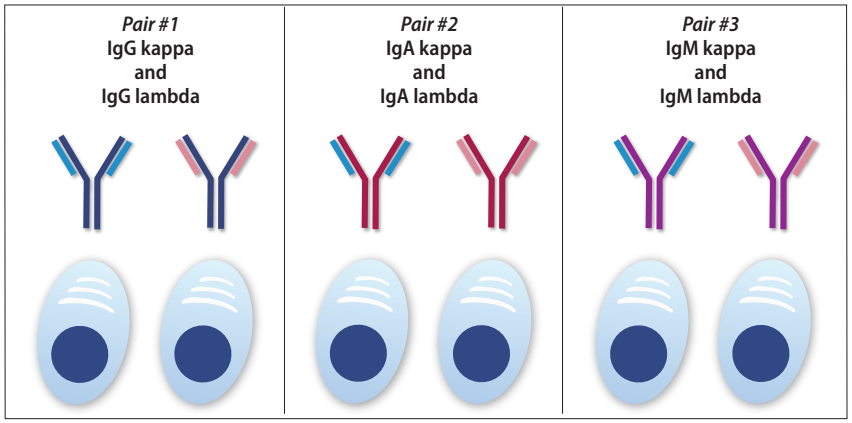
kappa (IgG heavy chains paired with kappa light chains) and the amount of IgG lambda (IgG heavy chains paired with lambda light chains). A patient whose myeloma cells are releasing IgG kappa M-protein can be monitored very specifically for the amount of that heavy and light chain combination that is coming from the tumor cell. Other tests that measure the amount of intact antibodies include SPEP and quantitative immunoglobulin (QIg) tests. Hevylite more specifically measures the amount of immunoglobulin protein involved with the myeloma versus these other tests.

Figure 8. **Hevylite measures specific heavy and light chain combinations by detecting at the junction of heavy and light chain**



Hevylite tests that are currently available are IgG kappa, IgG lambda, IgA kappa, IgA lambda, IgM kappa, and IgM lambda. In the case of an IgG lambda myeloma patient, it would be appropriate to order Hevylite IgG lambda (the involved heavy light chain pair, or iHLC) and IgG kappa (the uninvolved heavy light chain pair, or uHLC). Similarly, for an IgA lambda myeloma patient, Hevylite IgA lambda (the iHLC) and IgA kappa (the uHLC) would be ordered. The "involved" heavy and light chains are those that are released by the myeloma cells; this is the M-protein. The

Figure 9. **Hevylite tests are ordered in pairs**



"uninvolved" HLC combination are those antibodies of the same heavy chain type but the other light chain (if the involved Hevylite is kappa, then the uninvolved light chain would be lambda). The uninvolved HLC combination is a measure of the normal **polyclonal** antibodies of the immune system. Hevylite measures both iHLC and uHLC.

Understanding Hevylite test results

The Hevylite test gives you three numbers: the individual amount of the heavy chain + kappa combination, the amount of heavy chain + lambda combination, and the ratio of these two numbers. In the case of IgG myeloma, the Hevylite ratio would be the IgG kappa/IgG lambda ratio.

The ratio is determined by dividing heavy chain + kappa by heavy chain + lambda. If the ratio is higher than the normal range, then the iHLC is IgG kappa and the uHLC is IgG lambda.

If the ratio is lower than the normal range, then the iHLC is IgG lambda and the uHLC is IgG kappa.

It is true that the iHLC number is important; any result that is higher than the normal range is considered abnormal, and may be a sign that there are too many of that type of plasma cell releasing M-protein. However, the uHLC result (the amount of normal immunoglobulin protein) is also very important. Studies have shown that lower than normal levels of uHLC, or normal immunoglobulins, indicate poorer overall survival.

How does the Hevylite test differ from SPEP?

For patients with IgA kappa or IgA lambda myeloma, the Hevylite test may be more reliable than SPEP for identifying and quantifying M-protein.

The Hevylite test and monitoring for relapse

If a patient's Hevylite test result shows an abnormal Hevylite ratio, this is an indication that the myeloma cells are again producing M-protein. The Hevylite test is very sensitive and can detect a relapse before it is picked up by SPEP or immunofixation.

What are normal Hevylite levels?

Each laboratory may establish its own "normal" ranges. For general guidance, we are listing normal ranges for Hevylite values in the accompanying Table.

Can Freelite and Hevylite be used together?

Since the Freelite and the Hevylite tests measure different proteins and their estimation of myeloma activity, it is important to monitor patients with both tests. These two tests, when used together, are complementary.

Table 3. **Normal Ranges for Hevylite (HLC) Values**

HLC	Range	HLC	Range
IgG kappa (g/L)	4.03–9.78	IgA kappa (g/L)	0.48–2.82
IgG lambda (g/L)	1.97–5.71	IgA lambda (g/L)	0.36–1.98
IgG kappa/IgG lambda ratio	0.98–2.75	IgA kappa/IgA lambda ratio	0.80–2.04

Will insurance cover the cost of Freelite and Hevylite tests?

In the United States, the Freelite tests are covered by Medicare and most private insurers. Hevylite tests are covered under the same medical billing CPT code as Freelite; the cost to the patient may vary, however, depending upon which laboratory performs the testing and which type of insurance the patient has.

In closing

While a diagnosis of cancer is something you cannot control, gaining knowledge that will improve your interaction with your doctors and nurses is something you can control, and it will have a significant impact on how well you do throughout the disease course.

This booklet is not meant to replace the advice of your doctors and nurses who are best able to answer questions about your specific healthcare management plan. The IMF intends only to provide you with information that will guide you in discussions with your healthcare team. To help ensure effective treatment with good quality of life, you must play an active role in your own medical care.

We encourage you to visit myeloma.org for more information about myeloma and to contact the IMF InfoLine with your myeloma-related questions and concerns. The IMF InfoLine consistently provides callers with the most up-to-date and accurate information about myeloma in a caring and compassionate manner. IMF InfoLine specialists can be reached at InfoLine@myeloma.org or 818.487.7455 or 800.452.CURE.

Terms and definitions

Amyloid light-chain amyloidosis (AL amyloidosis): AL amyloidosis is a condition in which myeloma light chains crosslink with each other in a beta-pleated fashion and then are deposited in tissues and organs throughout the body, such as the heart, nerves, and kidneys, rather than being excreted by the kidneys. This condition is also known as primary amyloidosis.

Amyloidosis: A group of systemic diseases characterized by the deposition of amyloid protein in various organs and/or tissues. One type (AL amyloidosis) is related to multiple myeloma; other types include hereditary amyloidosis, AA amyloidosis, wild-type ATTR amyloidosis, ALECT2 amyloidosis, and AB2M amyloidosis. See "**Amyloid light-chain amyloidosis (AL amyloidosis)**."

Antibody: A protein produced by white blood cells called plasma cells in response to an antigen that enters the body. The medical term for antibody is "immunoglobulin."

Bence-Jones myeloma: Myeloma characterized by the presence of Bence-Jones protein, an abnormal protein in urine made up of free kappa or lambda light chains.

Bone marrow: The soft, spongy tissue in the center of bones that produces white blood cells, red blood cells, and platelets. This is the tissue within which abnormal plasma cells build up when myeloma is growing.

Bone marrow biopsy: The removal, by a hollow-bore needle, of a sample of tissue from the bone. The cells are checked to see whether they are cancerous. If cancerous plasma cells are found, the pathologist estimates how much of the bone marrow is affected. Bone marrow biopsy is usually done at the same time as bone marrow aspiration.

Cancer: A term for diseases in which malignant cells divide without control. Cancer cells can invade nearby tissues and spread through the bloodstream and lymphatic system to other parts of the body.

Electrophoresis: A laboratory test in which a patient's serum (blood) or urine proteins are subjected to separation according to their size and electrical charge. For myeloma patients, electrophoresis of the blood or urine allows both the calculation of the amount of myeloma protein via serum or urine electrophoresis (SPEP or UPEP), as well as the identification of the type of M-spike for each patient (immunoeletrophoresis, IFE). Electrophoresis is used as a tool both for diagnosis and for monitoring.

Hyposecretory: Low- or non-secreting disease. Also known as oligosecretory.

Immune system: The body's defense system from pathogens and foreign substances destroys infected and malignant cells, and removes cellular debris. The immune system includes white blood cells and organs and tissues of the lymphatic system.

Immunoassay: Test used in the study of biological systems by tracking different proteins, hormones, and antibodies. Immunoassays rely on the inherent ability of an antibody to bind to the specific structure of

a molecule. Because antibodies are developed to the specific three-dimensional structure of an antigen, they are highly specific and will bind only to that structure. ELISA (enzyme-linked immunosorbent assay) is a commonly used test to detect antibodies in the blood.

Immunofixation electrophoresis (IFE): An immunologic test of the serum or urine used to identify proteins. For myeloma patients, it enables the doctor to identify the M-protein type (IgG, IgA, kappa, or lambda). The most sensitive routine immunostaining technique, it identifies the exact heavy- and light-chain type of M-protein.

Immunoglobulin (Ig): A protein produced by plasma cells; an essential part of the body's immune system. Immunoglobulins attach to foreign substances (antigens) and assist in destroying them. The classes (also called isotypes) of immunoglobulins are IgG, IgA, IgD, IgE, and IgM. The non-medical word for immunoglobulin is "antibody."

Light chain escape: An increase of free light chains at the time of relapse without corresponding increase of the intact monoclonal immunoglobulin.

Molecule: The smallest particle of a substance that retains all the properties of the substance. A molecule is an electrically neutral group composed of two or more atoms held together by chemical bonds.

Monoclonal: A clone or duplicate of a single cell. Myeloma cells are derived from a "monoclone," a single malignant plasma cell in the bone marrow. The type of myeloma protein produced is also monoclonal, a single form rather than many forms (polyclonal). The important practical aspect of a monoclonal protein is that it shows up as a sharp spike (M-spike) on the protein electrophoresis test.

Monoclonal protein (myeloma protein, M-protein, M-spike): An abnormal protein produced by myeloma cells that accumulates in and damages bone and bone marrow. Antibodies or parts of antibodies found in unusually large amounts in the blood or urine of myeloma patients. A monoclonal spike (M-Spike), the sharp pattern that occurs on protein electrophoresis, is the telltale indicator of M-protein in the blood, a marker for the activity of myeloma cells. See "**Monoclonal**."

Multiple myeloma: A cancer of the bone marrow plasma cells, white blood cells that make antibodies. The cancerous plasma cells are called myeloma cells.

Non-secretory myeloma: Approximately 1% of myeloma patients do not have detectable M-protein in the blood (serum) and urine. Some of these patients can be successfully monitored using the serum free light chain assay; others may be monitored with bone marrow biopsy and/or PET/CT scan. Patients with non-secretory myeloma are treated in the same fashion as those with M-protein-secreting disease.

Oligosecretory myeloma: Low-secreting disease. See also "**Hyposecretory**."

Plasma cells: Special white blood cells that produce antibodies (immunoglobulins). Myeloma is a cancer of the plasma cells. Malignant plasma cells are called myeloma cells. In myeloma, malignant plasma cells produce abnormal antibodies that lack the ability to fight infection. These abnormal antibodies are the monoclonal protein, or M-protein, that functions as a tumor marker for myeloma. The presence of malignant plasma cells in the bone marrow can lead to organ and tissue damage (anemia, kidney damage, bone disease, and nerve damage).

Platelets: One of the three major types of blood cells, the others being red blood cells and white blood cells. Platelets plug up breaks in the blood vessel walls and release substances that stimulate blood clot formation. Platelets are the major defense against bleeding. Also called thrombocytes.

Polyclonal: Consisting of or derived from many clones.

Proteins: Substances composed of amino acids. Proteins are an essential part of all living organisms, especially as structural components of body tissues such as muscle, hair, collagen, etc., as well as enzymes and antibodies.

Red blood cells (RBC, erythrocytes): Cells in the blood that contain hemoglobin, deliver oxygen to all parts of the body, and take away carbon dioxide. Red cell production is stimulated by a hormone (erythropoietin) produced by the kidneys. Myeloma patients with damaged kidneys don't produce enough erythropoietin and can become anemic. Myeloma patients can also become anemic because of myeloma cells' effect on the ability of bone marrow to make new red blood cells.

Relapse: The reappearance of signs and symptoms of a disease after a period of improvement. Patients with relapsed disease have been treated, then developed signs and symptoms of myeloma at least 60 days after treatment ended. Most clinical trials for advanced disease are for patients with relapsed and/or refractory myeloma.

Serum: The colorless, liquid part of blood in which the blood cells are suspended.

White blood cells (WBC): General term for a variety of cells responsible for fighting invading germs, infection, and allergy-causing agents. These cells begin their development in bone marrow and then travel to other parts of the body. Specific white blood cells include neutrophils, basophils, eosinophils, lymphocytes, and monocytes.

Notes

INTERNATIONAL MYELOMA FOUNDATION

You are not alone. The IMF is here to help.

Myeloma is a cancer that is not known to most patients at the time of diagnosis. To be empowered to play an active role in your own medical care and to make good decisions about your care with your doctor, it is vital for you to learn as much as possible about myeloma and its treatments.

The IMF produces and maintains a library of publications to help arm you with one of the most important weapons in the fight against myeloma: INFORMATION. The following is a partial list of publications available in English, and selected titles are also available in other languages.

- *Patient Handbook*
- *Concise Review of the Disease and Treatment Options*
- *Understanding Clinical Trials*
- *Understanding Dexamethasone and Other Steroids*
- *Understanding DARZALEX® (daratumumab)*
- *Understanding EMPLICITI® (elotuzumab)*
- *Understanding Fatigue*
- *Understanding High-Dose Therapy with Stem Cell Rescue*
- *Understanding the Immune System in Myeloma*
- *Understanding KYPROLIS® (carfilzomib)*
- *Understanding MGUS and Smoldering Multiple Myeloma*
- *Understanding NINLARO® (ixazomib) capsules*
- *Understanding POMALYST® (pomalidomide)*
- *Understanding REVLIMID® (lenalidomide)*
- *Understanding Treatment of Myeloma Bone Disease*
- *Understanding Treatment of Myeloma-Induced Vertebral Compression Fractures*
- *Understanding VELCADE® (bortezomib)*
- *Understanding Your Test Results*

All IMF publications and periodicals are always free of charge. Visit **publications.myeloma.org** to read, download, or order printed copies. Subscribe to IMF periodicals at **subscribe.myeloma.org** or by contacting the IMF.

As always, the IMF urges you to discuss all medical issues with your doctor, and to contact the IMF's InfoLine specialists with your myeloma questions and concerns.

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