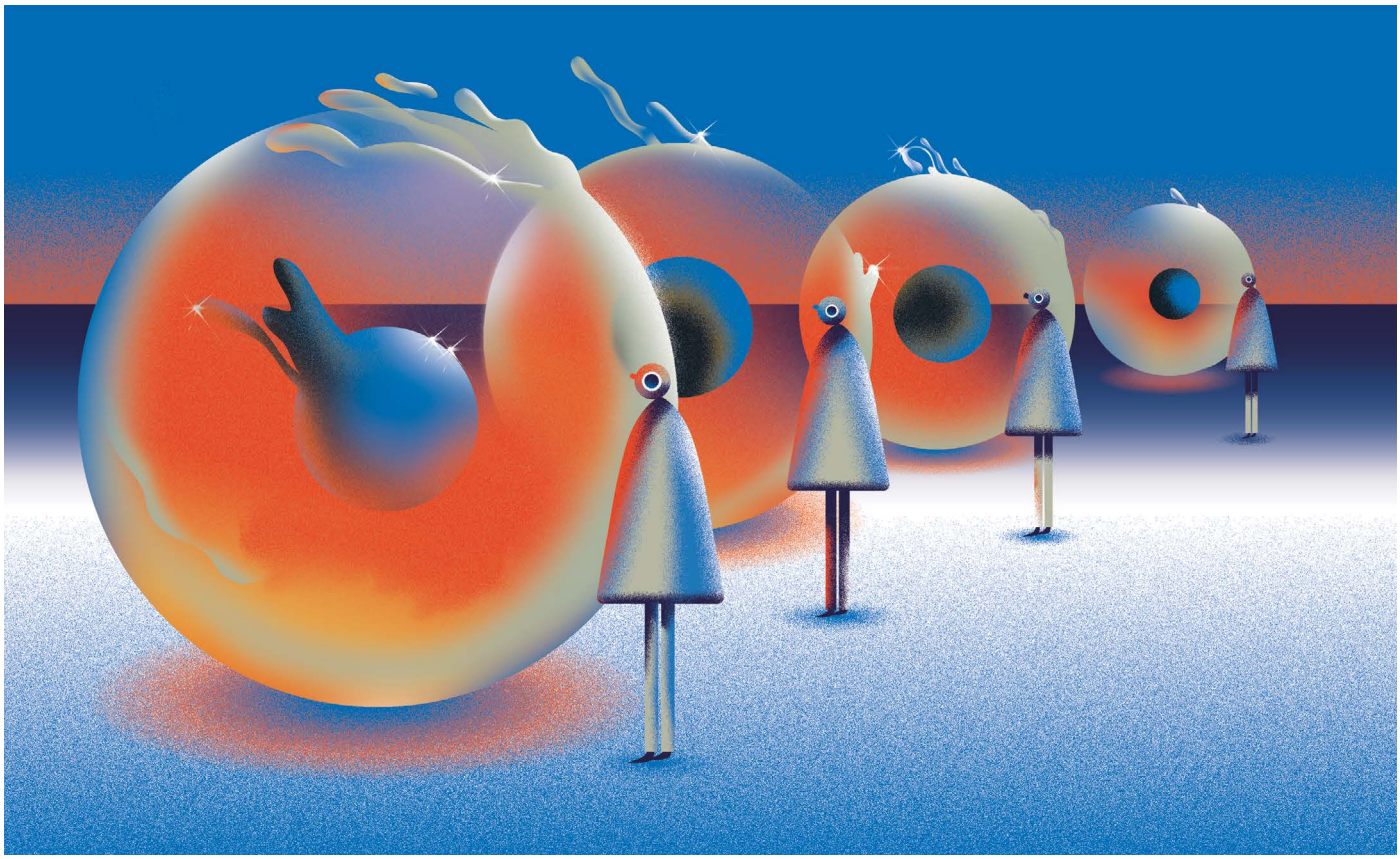


SANDRO RYBAK FOR *NATURE*

A diversifying disease

Multiple myeloma is now recognized as not one, but several genetically distinct cancers. How this will change treatment is unknown. **By Benjamin Plackett**

In the past few years, it has become increasingly clear that multiple myeloma is not one condition, but a family of similar – yet genetically distinct – cancers. The term should be multiple myelomas rather than multiple myeloma. Although this diversity is now widely accepted by specialists, there's still a debate about whether it matters. Some advocate for a broad-strokes strategy in which little attention is given to the cancer's genes. Others argue for a more tailored approach for each genetic subtype.

Multiple myeloma affects white blood cells known as plasma cells, and it is a relatively rare collection of disorders. In the United States, the lifetime risk of having any form of the cancer is just 0.76%. But just 54% of people who do get it are alive 5 years after their diagnosis. According to the charity Cancer Research UK, it's also more common in men than in women and in Black people compared with white people or people of south Asian descent.

Scientists used to consider multiple myeloma a single condition because one malignant plasma cell looks much the same as the next. "It's been hard because, unlike other diseases where you can look down the microscope and say it's different, that's not the case with multiple myeloma," says Kumar Shaji, a haematologist at Mayo Clinic in Rochester, Minnesota. "Some of the difficulties in getting this cancer nailed down have come from the lack of specificity of the phenotype."

The apparent uniformity was an illusion, however. In the 1990s, evidence began to suggest that myeloma cells are more varied than they first appear under the microscopic lens. Researchers started to log the primary mutations that cause an otherwise normal plasma cell to become cancerous. It is now well established that these various genetic origins translate into different outcomes for people.

Multiple myeloma is now classified as a collection of five disease subgroups, each defined by the main mutation responsible for the onset of the cancer. "The list is a moving target because we're still sequencing and finding new mutations that we didn't know about two years ago," says Hervé Avet-Loiseau, head of the myeloma genomics laboratory at the Cancer Research Centre of Toulouse in France.

Crucially, these various classes of myeloma respond differently to treatment options. One review[1] indicated that the drug bortezomib can lengthen life expectancy for people with a fairly common genetic subtype known as t(4;14), but doesn't seem to give any survival advantage to other subtypes, such as the rarer t(14;16).

A 2020 study showed that a drug called venetoclax – when combined with boretzomib and the steroid dexamethasone – can, in some people, significantly improve outcomes and help to stem the cancer's progression[2]. Those

with the t(11;14) subtype, which occurs in around 17% of people with myeloma, or high expression of the gene *BCL2*, had the most promising responses to the drug. But the news wasn't so encouraging for other groups, which had an increase in mortality.

"It's clear that you don't want to give everyone venetoclax," says Leif Bergsagel, a haematologist at Mayo Clinic in Phoenix, Arizona.

These studies show that genetic differences are important. "In short, it has become clinically relevant," says Gareth Morgan, director of multiple myeloma research at New York University Langone Health's Perlmutter Cancer Center. "It's really the last decade where we started to realize that the different types showed different natural histories and responded differently."

This information can help physicians to tailor existing treatments to better target the specific biology of a person's multiple myeloma. The main genetic test for people with myeloma is fluorescence *in situ* hybridization (FISH). Cells from bone-marrow biopsies are treated with special dyes, which cling on to specific parts of a chromosome and reveal mutations.

Although these data are undoubtedly helpful, they are not necessarily the be all and end all. One study[3] found that roughly two-thirds of people who relapsed within 18 months of therapy had not been classed as having high-risk disease from their original genetic screening.

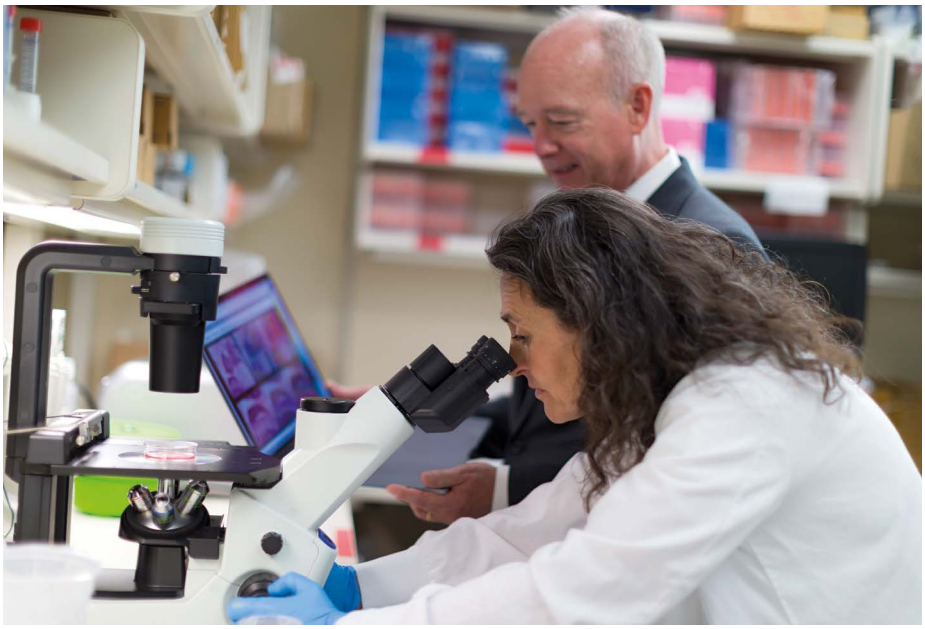
"There are other influential risk factors to consider, such as age and co-morbidity," says Avet-Loiseau, who co-authored the study.

The number of people surviving for around five years after their diagnosis has climbed steeply in the past few decades, thanks to the emergence of several drugs that can treat all subtypes of the cancer. One study[4] of more than 45,000 people with myeloma diagnosed between 1973 and 2009 found that in the 1970s, roughly 36% of people aged 50 or under were alive 5 years after their diagnosis. This number jumped to 56% in the 1990s.

Some researchers think that recognizing that multiple myeloma is not a single disease will aid the creation of bespoke therapies for each of the different subtypes and lead to further gains in long-term survival. Whether this clinical aim will be reached, however, is not yet clear.

"I don't think we're there yet in applying this knowledge to new targeted treatments," says Marta Chesi, a molecular biologist at Mayo Clinic in Phoenix. In the end, most people still receive similar combinations of therapies, regardless of the genetics of their myeloma, says Chesi. "To my mind, the only real example of a targeted therapy is venetoclax."

If targeted drugs such as venetoclax are to be the future of treatment, routine testing might need to move beyond FISH, which is labour intensive and requires a large sample of plasma cells. More sophisticated molecular techniques, which sequence the whole genome of a myeloma cell and reveal more information, could help to speed up the process. For example, one study comparing whole-genome sequencing with FISH in 48 people who were newly diagnosed found extra mutations not initially picked up by FISH[5].



PETE PALLAGI/ MAYO CLINIC

Leif Bergsagel and Marta Chesi, shown in 2019, are working to characterize myeloma mutations.

Morgan says a push towards this more sophisticated, molecular-based approach could bear fruit. "The advent of venetoclax will drive molecular testing in the coming years because it's shown a personalized strategy is possible," he says. "Finally, we might go away from a one-size-fits-all model."

But when it comes to developing therapies, opinions are divided. Some researchers argue that the future of treatment will be defined by a broad-spectrum line of attack. A therapy that could neutralize all kinds of myeloma cell, no matter what the genetic subtype, would save more lives.

One example of this is a type of immunotherapy called CAR T-cell therapy. The principle is simple. A sample of specialist white blood cells, known as T cells, is taken from the person. These cells are then modified to make them express chimeric antigen receptors (CARs), which can recognize and bind to the person's malignant plasma cells, irrespective of the myeloma's genetic make-up. The CAR T cells are then amplified in number before being reinfused back to the person. "They specifically target tumour cells and kill them," says Avet-Loiseau.

A review published this year concluded that data from 300 people with multiple myeloma treated with CAR-T was encouraging[6]. "I've spent my life studying genetics and targeted therapies, but it seems like we might not need to understand the genetics," jokes Bergsagel. But, as the authors of the review state, most of the people treated eventually relapsed.

It doesn't have to be one or the other, however. "It could be that general treatment is the answer or that specific and targeted treatments for each of the myeloma subcategories are the solution, but it could also just as easily be a combination of the two," says Michael Kuehl, who studied the genetics of multiple myeloma at the US National Cancer Institute in Bethesda, Maryland, but is now retired. "We just have to stick with getting to know more and more about the disease and using that knowledge as best we can."

Regardless of opinion, these two research goals — specific and general — are being simultaneously pursued by scientists in both camps. Optimistically, that means people with multiple myeloma could soon benefit from both types of drug. That provides hope, says Bergsagel, that multiple myeloma will eventually be seen as a survivable diagnosis.

Benjamin Plackett is a freelance writer based in London and the Middle East.

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