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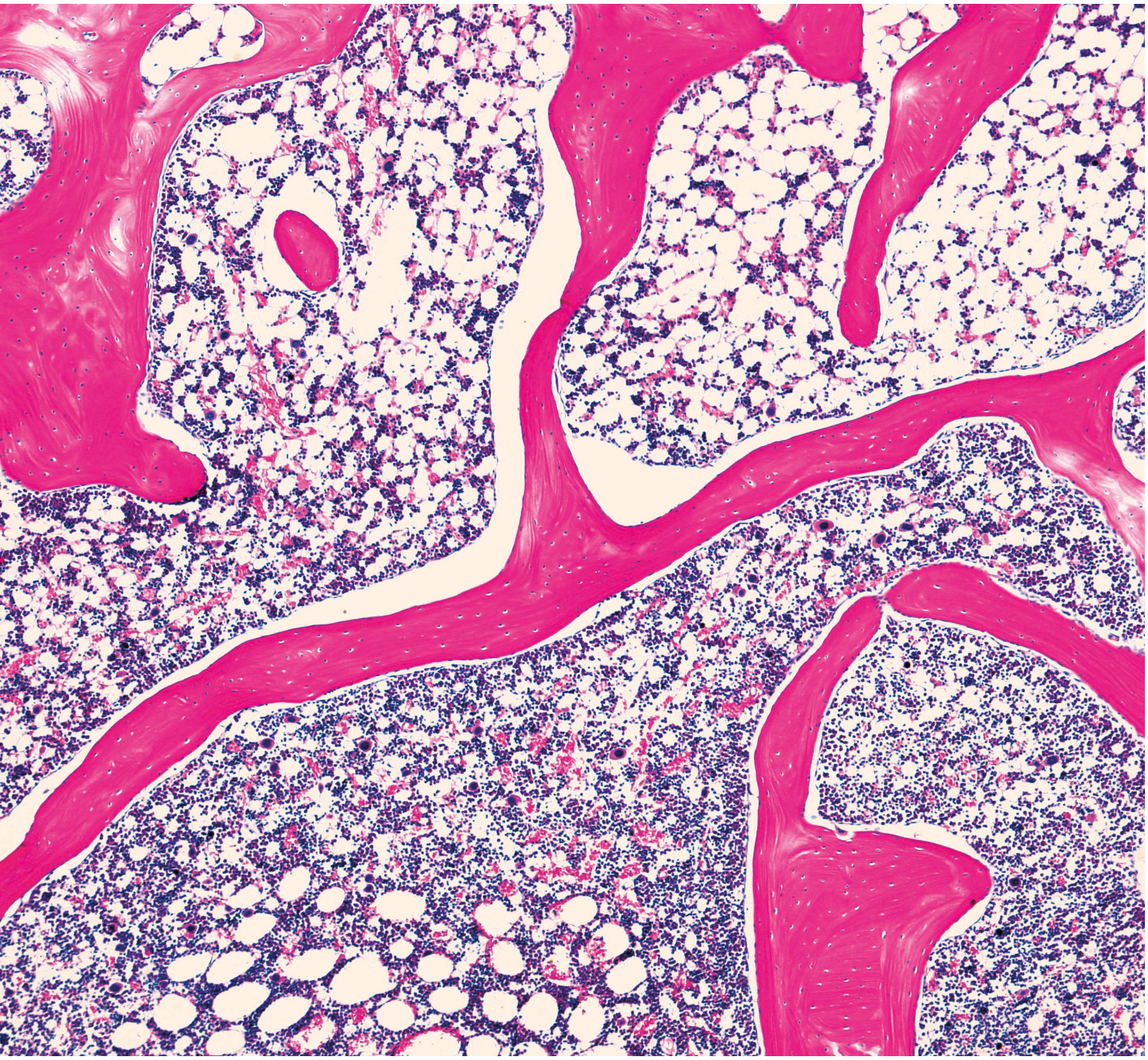
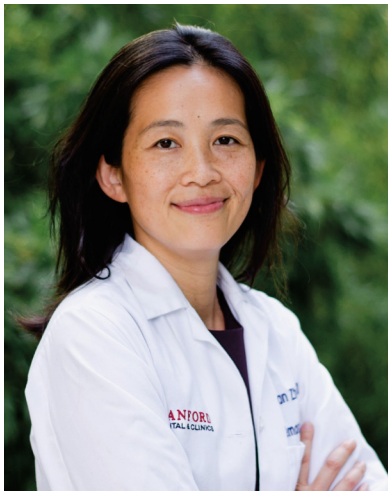


The CHIP Clinic at Stanford Medicine

DISCOVERING EARLY WARNINGS OF CANCER AND OTHER PATHOLOGIES



"We know that certain CHIP mutations have bad potential, but there's a bigger proportion of mutations that still have an indeterminate risk. We're here to determine which ones those are—and their potential."

—**TIAN YI ZHANG, MD, PHD**
Assistant Professor of Medicine–Hematology

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As humans, we have all come to recognize the outward signs of the aging process: lines and wrinkles and graying hair, less-robust muscles and creaky bones, hearing and eyesight that just aren't what they used to be. Yet there's also an internal one that can't be seen, heard, or felt—or perhaps even pronounced with ease: clonal hematopoiesis. And it has the potential to affect people's health in a dramatic way.

Strikingly common yet discovered only within the past several years, clonal hematopoiesis occurs when hematopoietic stem cells—those that are involved in forming blood—develop mutations, often as a natural consequence of aging. As these cells divide, they produce daughter cells carrying the same mutations. Those daughter cells in turn divide and proliferate, or clone themselves, eventually causing a significant percentage of the person's DNA to contain the same mutations as those from the parent stem cells.

Widely considered a normal part of the aging process, clonal hematopoiesis becomes more common after the age of 40, affecting an estimated 10% of people by the time they reach 70. While it is a nonmalignant condition, clonal hematopoiesis can, in certain cases, increase the risk for developing blood cancers, such as acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS).

It is these types of clonal hematopoiesis that Tian Yi Zhang, MD, PhD, an assistant professor of medicine and a board-certified hematologist at Stanford Medicine and the Stanford Cancer Institute, is dedicated to investigating at a special clinic she has established at Stanford.

The CHIP Clinic at Stanford Medicine—One of only a handful of such clinics in the country, Stanford's CHIP Clinic is dedicated to studying all forms of clonal hematopoiesis, but particularly those that could have the potential to lead to blood cancers and other pathologies. These types are called CHIP, or clonal hematopoiesis of indeterminate potential. Interestingly, although this name was assigned to the condition when it was first discovered because it was, at the time, of indeterminate potential, Dr. Zhang, who is the clinic's director, says the name is a misnomer. "While we still refer to it as CHIP, we now know that in many cases, the condition is not really of indeterminate potential," she says.

Dr. Zhang explains that mistakes happen as stem cells divide and replicate, with these mistakes, or mutations, accumulating over time—which is why CHIP typically isn't detected until a person is older. "These mutations usually are at such low levels that you can't pick them up before age 40," she says. "That tells us they're probably bubbling under the detection limit for quite some time."

Certain genes that contain these mutations are strongly linked to hematologic malignancies; people with these mutations are estimated to be about 10 times more likely to develop a blood cancer than the general population, research has found. And when it comes to AML, with certain mutations, that risk is 40 to 50 times higher than if a CHIP mutation isn't present.

Still, there's much research to be done in determining the full range of CHIP mutations and whether they're linked to cancer or other disorders—in other

HOW CHIP IS DIAGNOSED

Many of the patients Dr. Zhang sees at the CHIP Clinic, which operates within the Division of Hematology, discover that they have CHIP incidentally, often through an over-the-counter DNA test such as 23andMe. "They get their test results back, and it tells them that they have something called clonal hematopoiesis, and they have no idea what that means," Dr. Zhang says. After consulting with their primary care physician, these patients are often referred to a hematologist at Stanford—and, ultimately, the CHIP Clinic. "This is such a specialized field of study, and so new, that many practitioners need to refer CHIP patients out," she says. "That's where I come in."

Once Dr. Zhang receives a new CHIP patient, she largely serves in a consultative/advisory role, as there currently is no treatment for CHIP. "Because some CHIP mutations are now known to predict MDS and AML development, I do further testing to determine which exact mutation is involved," she says, adding that this includes blood tests, next-generation sequencing, and blood marrow sampling, if indicated. "If I do determine that a patient has a high-risk mutation based on current data, then we can discuss the possibility of them being monitored for the development of a blood cancer."

words, to shift their potential from being indeterminate to determinate. And that's where Dr. Zhang hopes to make a profound impact. "We know that certain CHIP mutations have bad potential," she says, "but there's a bigger proportion of mutations that still have an indeterminate risk. We're here to determine which ones those are—and their potential."

Building Out the CHIP Clinic—While great strides have been made in establishing and operating the CHIP Clinic, Dr. Zhang says there's more work to be done. With time and funding, she hopes to be able to build the clinic further, hiring more clinicians who can see and counsel more CHIP patients. To allow for further study of this landscape-altering discovery, she also aims to create a biobank of deidentified patient samples and a CHIP registry filled with protected patient demographics—and, of course, to conduct the type of research that is so vitally needed to advance the field of CHIP discovery and treatment.

Dr. Zhang emphasizes that CHIP research is still sorely needed. For instance, she points to one particularly devastating mutation that doesn't arise naturally, as a consequence of aging, but as a consequence of receiving treatment for an earlier cancer. "Therapy-related clonal hematopoiesis occurs as a result of the DNA damage that is caused by chemotherapy and radiation," she says. "People can develop very high-risk mutations that predict AML development. It's just brutal: Here they are, trying to be cured of one cancer, and the very treatment they receive can cause another, perhaps even more deadly, cancer later."

To investigate this issue, Dr. Zhang would like to study whether using a combination of gentle chemotherapy and immunotherapy on such patients—who don't have AML yet but are likely to develop it due to therapy-related clonal hematopoiesis—can help prevent the disease. "I just feel so strongly that we have an ethical responsibility to see if we can reduce the risk of them developing AML," she says.

Another area Dr. Zhang would like to study further relates to mutations in the TP53 gene, which exponentially increase the risk of developing AML. "I'm hoping to launch a clinical trial investigating whether a treatment discovered here at Stanford, called magrolimab, can help prevent AML from developing in patients who have a therapy-related TP53 CHIP mutation," she says. "It would be such a shame if an existing drug could help clear the mutation but we didn't have the funding to investigate it."

Searching for Answers … and Treatments—As the CHIP Clinic expands, Dr. Zhang's fervent hope is that she will be able to conduct the research, hire the staff, and develop the infrastructure to not only discover the mutations that put people at risk for cancer, but to develop treatments that could help prevent these diseases from developing in the first place. And while she says it is incredibly exciting to be involved in the genesis of a new field of study, it is the patients she serves who keep her focused and driven to do the work she does.

"This all comes down to trying to take care of patients but lacking the data, the tools, and the therapy to actually treat them and help avoid negative outcomes," Dr. Zhang says. "I just feel a very strong need to be able to help them."

PHILANTHROPIC OPPORTUNITIES

Thank you for your interest in joining others to advance the CHIP research taking place at Stanford and to help build out our clinic. With your support, we can work toward developing prevention strategies and finding treatment solutions—and, potentially, help save lives.

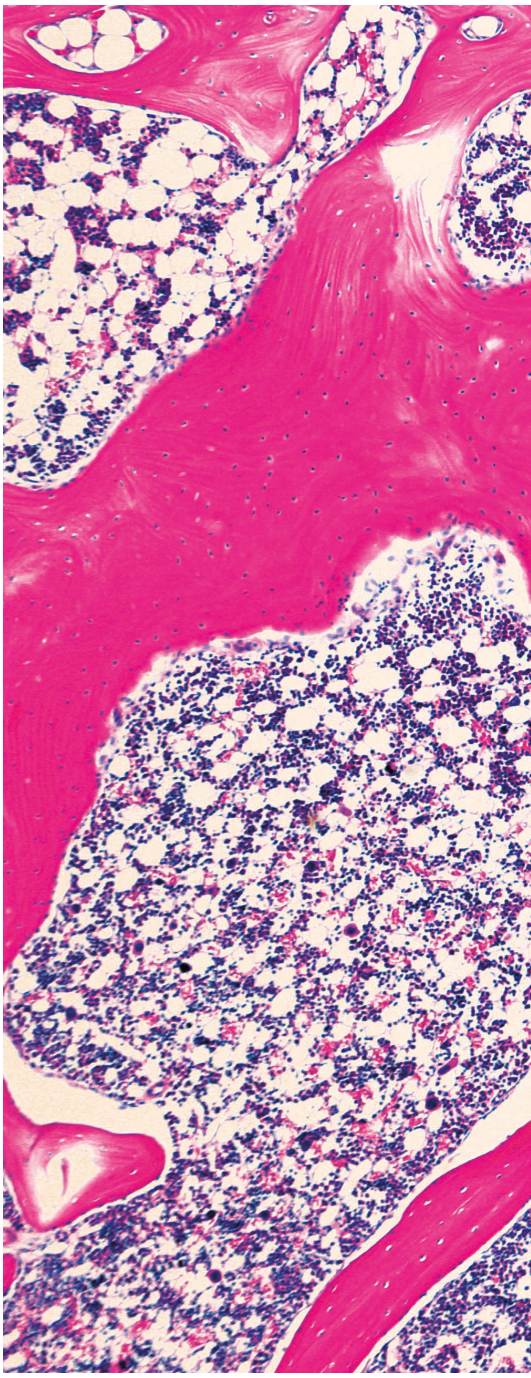
Support of a CHIP Database | $25,000
Funds will support the establishment and curation of a CHIP database.

Analysis of Banked Samples for Studies | $100,000
Funds will support the additional analysis of banked samples so we may learn more about the biology of CHIP cells.

Expansion of the CHIP Clinic | $250,000
Funds will support the addition of postdoctoral fellows to help drive research efforts and patient-care initiatives.

CHIP Clinic Program Development | $500,000
Funds will support the creation and expansion of CHIP Clinic programs aimed at patient education and support.

Investigator-Initiated Clinical Trial | $1 million
Funds will support the launch of a clinical trial to study possible prevention strategies for CHIP patients.



▲ *colorized image of hematopoietic stem cells developing in bone marrow*

CONTACT US

To find out how you can help support the vital work being conducted in the CHIP Clinic, please contact:

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