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### Is that thyroid lump benign?

Medical technology is increasingly good at detecting abnormalities, but not so good at telling whether they are harmless.

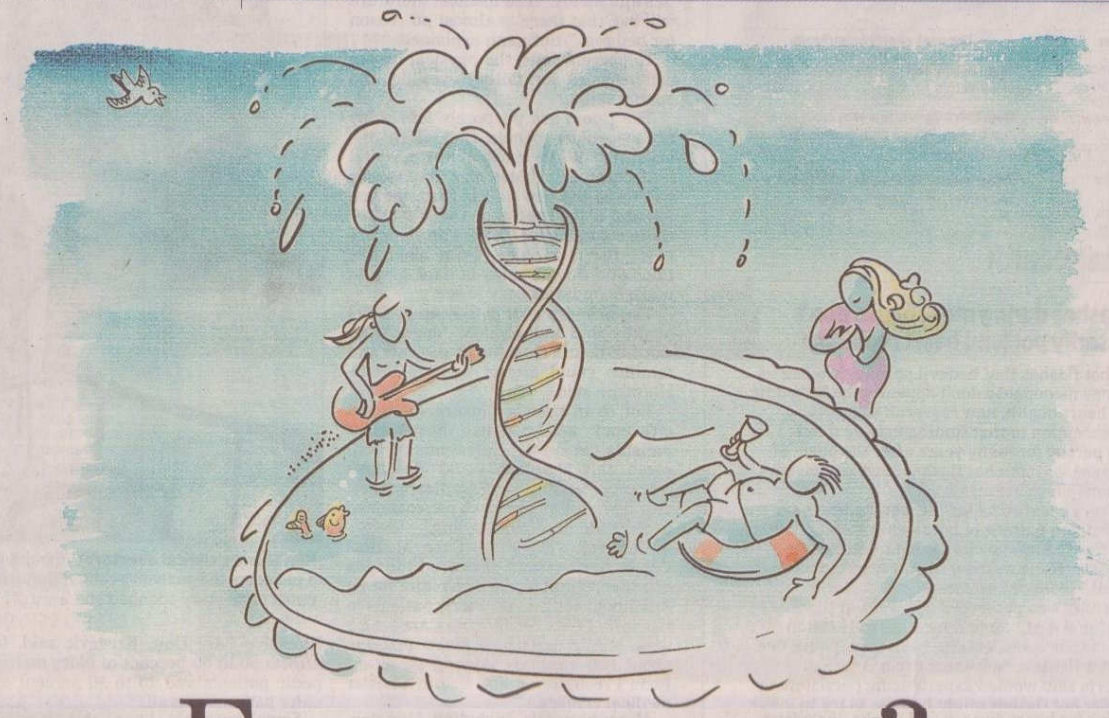
Afirma, a new gene expression test that University of Pennsylvania specialists helped to validate, promises to relieve this quandary for people with lumps on their thyroid gland.

Thyroid "nodules" typically were detected only after they grew big enough to be felt in the neck, or interfered with the function of the thyroid, which makes hormones vital to metabolism. Now, most nodules are found incidentally during imaging tests — and studies suggest half of all adults have them.

After a nodule is discovered, a tiny tissue biopsy is taken with a needle, then evaluated under a microscope. If it's malignant, the thyroid is surgically removed.

But while the chance of cancer is about 1 in 10, the chance of an inconclusive biopsy result is about 1 in 3. As a result, about 75,000 people a year have their thyroids partly or completely removed, only to learn from more detailed testing that there was no cancer.

Afirma, made by Houston-based Veracyte, could prevent an estimated 25,000 of these unneeded surgeries. It analyzes the activity pattern of 142 genes in the biopsy sample, then classifies the tissue as benign or "suspicious."



# Forever young?

*New research is showing that with some molecular tinkering, people could live longer, healthier, making 60 the new 30.*

By Margie Patlak
FOR THE INQUIRER

Researchers seeking to unravel the mysteries of aging have yet to find the legendary fountain of youth, but they have found intriguing clues to living longer, healthier lives.

The findings suggest that with a little molecular tinkering, the age of 60 may someday be the new 30, giving baby boomers a way to defy the aging process and prolong the age of Aquarius.

"The idea that lifespan is plastic and can be changed is a huge paradigm shift," said Cynthia Kenyon, an expert in aging at the University of California San Francisco. "Someday people may be able to take a drug that makes them naturally more resilient to disease and able to live longer."

See YOUTH on C5

**These two rhesus monkeys** are part of a study of the links between diet and aging at the University of Wisconsin Madison. Canto (left ) is on a restricted diet and Owen is on an unrestricted one. JEFF MILLER photo

# Molecular tinkering for youth

YOUTH from C1

The new research is converging on one genetic pathway, the somatotropic axis, which generally enables animals to grow and reproduce.

About 15 years ago, Kenyon and others discovered simple gene mutations in that pathway that doubled the life spans of worms, and even made them look and act young. "They were not in nursing homes, but instead were going skiing," she joked.

"It was a big shock to see these results," recalled Joseph Baur, a University of Pennsylvania aging researcher. "Before researchers showed a change in just one gene could change lifespan, most people thought there were thousands of different factors driving aging and you would never be able to change enough of them to make a difference. This gave us hope that we might understand aging eventually."

More recent studies in mice and humans reveal that many life-extending mutations also affect the same pathway that Kenyon had linked to longevity in worms. While this pathway gets turned on to promote growth and reproduction when food is abundant, it is suppressed to foster survival when there's a lack of food or other stressors.

The mutations also seem to trigger several health-promoting mechanisms. Some studies linked the mutations to humans who live 100 years or more, remarkably free of heart disease, cancer, diabetes, and Alzheimer's disease.

"Whatever is extending their lives is also protecting them from disease," said aging researcher Andrzej Bartke of Southern Illinois University. "Until the age of 95 or so, they are in very good shape. This teaches us that you can postpone age-related health problems."

## Low-calorie diets

For similar molecular reasons, aging is delayed when animals, including rhesus monkeys and people, have a severely restricted diet. Compared to those who fill their plates, studies find that people who eat only about three-quarters of a normal diet's calories have extremely low blood sugar and cholesterol levels, and blood pressure akin to that of someone half their age.

"They certainly look like they are not likely to get most of the things that kill people, but it remains to be seen whether they will live longer," Bartke said.

Few of us have the will power or desire to turn down delicious food for a longer, healthier life. Indeed, an abundance of food is fostering a growing obesity epidemic that experts say will cause shorter and sicker lives.

"The current generation may be the first generation in recent history that won't live longer than their parents," Bartke pointed out.

## The family of sirtuins

That's why many researchers and drug companies are avidly pursuing molecular shortcuts in the growth-regulating pathway, often involving the sirtuin family of proteins.

Baur and collaborators at the National Institute on Aging have recently gotten encouraging results in mice with the chemical activator sirtuin-1, a key anti-aging compound made by animals living under extreme calorie reduction.

Baur and his colleagues fed mice a high-fat diet along with this sirtuin activator, called SRT1720. In obese middle-aged mice, the compound increased their remaining lifespans by nearly 50 percent. It also improved various health indicators, such as mobility and insulin sensitivity, which resembled those of lean mice fed a normal diet. And it lowered indicators of inflammation, which plays a role in many chronic diseases, such as heart disease, diabetes, and cancer.

**George Vlasuk, Sirtris CEO, said, "We're very excited by the results so far, but there's a still a long way to go."**

But findings are mixed on SRT1720 and other alleged sirtuin activators, including a related compound, resveratrol, which is found in red wine.

The jury is still out on whether some positive findings on sirtuin activators might be due to how the studies were run, and not representative of the real world.

George Vlasuk, who is CEO of Sirtris, a GlaxoSmithKline subsidiary focused on developing sirtuin-targeting drugs, said: "We overcame a lot of those technical concerns and will be publishing data shortly that will really put a nail in that coffin" and refute the skepticism.

Cambridge, Mass.-based Sirtris is testing sirtuin-targeting compounds in people to see if they help counter diseases of aging, including type 2 diabetes and heart disease.

"We're encouraged by the data we're getting so far. We think this area has broad potential for new medicines that can make the aging process less burdened by disease," Vlasuk added.

## Unproven products

In the meantime, several companies already include resveratrol in their health and cosmetic products, despite the lack of definitive evidence on their effects. U.S. sales of resveratrol supplements reached $33 million in 2011, the Nutrition Business Journal estimated, although not all are used for anti-aging purposes.

Baur recognizes that there might be benefits to these products, but "until they are tested in humans, we have no idea if they are fantasy or reality, no idea what dose would be required, and no guarantee that there won't be unanticipated side effects."

## A different approach

Baur is pursuing a different strategy, by blocking a key compound, mTOR, which affects the same genetic pathway that sirtuins influence. One drug thought to do that is called rapamycin. It has been shown to extend the lives of mice by more than 10 percent, even when given to older animals. Rapamycin also prevented plaque buildup in the brain and improved memory in mouse models of Alzheimer's disease.

Doctors now use rapamycin to prevent rejection of organ transplants. Some patients taking it have developed fatal infections, making most experts wary of using it as an anti-aging drug, at least in its current form.

Rapamycin also makes people more likely to develop diabetes. In mice, which tend to be resistant to heart disease, rapamycin creates a cholesterol profile that is likely to be a killer in humans.

"Rapamycin does a lot of other things that we don't want to do to an aging population," Baur said.

## No magic bullet yet

Other studies find the body often has backup pathways that can override the blocking of compounds that influence aging. So using a single drug to block the compounds may be futile if backup pathways exist, and potentially fatal if they don't.

With enough molecular tinkering, researchers might eventually find the sweet spot that keeps aging at bay, without serious side effects. But that will take time. Testing new treatments on mice requires a four-year wait to see if they extend the animals' lifespans. Clinical trials in people can take even longer.

"It's going to be awhile before we understand the underlying aging process enough to intervene. We're probably a few decades away from that," said Penn's Baur.

Vlasuk, the Sirtris CEO, added, "We're very excited by the results so far, but there's a long way to go."

Until that fountain of youth is bubbling in the backyard, baby boomers might want to eat less and exercise more. It's no guarantee but it may be the most effective way to live a longer, healthier life.

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