When science is personal

Spurred on by the loss of her mother and four relatives, scientist Nancy Wexler has been tracking a cure for Huntington's disease. She is among nine being honored by the Franklin Institute.

By Tom Avril

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Neuropsychologist Nancy Wexler is in town to be honored for her quarter-century of pioneering medical work.

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It might seem hard to convince a roomful of strangers to let you gouge a few skin cells from their arms for genetic testing, especially when you are a foreigner in a poor Venezuelan community ravaged by disease, and you speak very bad Spanish.

So, Nancy Wexler played her ace card. She held out her arm. A bilingual nurse then guided the American scientist through the crowd.

¡Mira! the nurse said, again and again. *Ella tiene la marca.* "Look! She has the mark."

Wexler had undergone the same skin biopsy that she was asking of the skeptical villagers. The reason, they were astonished to learn, was that she, like them, was at risk for Huntington's disease - a killer that slowly lays waste to the brain, causing its victims to speak as if they are drunk, to jerk uncontrollably, and, finally, to die.

Wexler, a Columbia University neuropsychologist, is in Philadelphia this week as one of nine people being honored by the Franklin Institute for achievement in science and technology. Other winners of the prestigious

awards range from a native of Wenonah, Gloucester County, who is the lead scientist on NASA's Mars Rover mission, to an IBM engineer whose work transformed computers.

Yet, none has so personal a connection with his research as Wexler. Her mother, a grandfather and three uncles all were stricken with the genetic disease that would become her life's work.

More than a quarter-century has passed since Wexler and her colleagues started to collect skin and blood samples in northwestern Venezuela, part of a research trail that also winds through Philadelphia.

Now 61, she is past the age when most Huntington's sufferers start to display symptoms, so she may be in the clear - and is thus able to continue the quest for a cure.

One at a time

In this day of the sequenced genome, when every week brings the announcement of a new gene connected to this trait or that disease, it is worth recalling what the field of genetics was like in 1979.

Nancy Wexler, a psychologist by training, had turned gene hunter after her mother's death the year before.

Backed by the Hereditary Disease Foundation, which her father had established upon her mother's diagnosis in 1968, she made the first of two dozen annual trips to Venezuela. Three villages on the shores of Lake Maracaibo are home to the largest concentrations of Huntington's sufferers in the world, a fate passed down for generations.

But the lab tools available to Wexler and her colleagues were primitive by today's standards. And the available genetic road maps were sketchy at best, says Kenneth Fischbeck, a former University of Pennsylvania researcher who went on three of the trips.

"It's kind of like map-making in the days of exploration and discovery back in the 1500s," says Fischbeck, now at the National Institutes of Health.

Once they gained the trust of the villagers, recording their family trees and convincing them to give skin and blood samples, the researchers began the laborious hunt for what the sick people had in common.

They looked at different genetic markers - small variations in DNA - to find one that might be associated with the disease. They chopped the DNA into bits with bacterial enzymes, looking at the candidates one by one. In comparison, today's robotic machines can do 500,000 such analyses in a single run.

Yet, faster than anyone predicted, the team found a marker in 1983, just two years after testing had begun in earnest. The find was a "major motivator" that helped galvanize support for the Human Genome Project, Fischbeck says.

Still, the marker was only a guidepost for the disease - allowing scientists to narrow their search to a region of Chromosome 4 - not the fatal mutation itself. Scientists proceeded to look on that chromosome for the omission or misspelling of genetic code that they presumed caused the disease.

Not until eight years later did a Philadelphia scientist make a key discovery: A mutation could consist of a mere genetic stutter. Albert La Spada, then a doctoral candidate in Fischbeck's lab at Penn, found a different disease that was caused by an ordinary three-letter sequence of DNA that simply repeated too many times.

Wexler's team then looked to see if Huntington's might follow a similar pattern. It did. (Since then, two dozen more diseases have been found to fit this pattern.)

Fellow scientists say her infectious passion was key to moving the work along.

Says Penn biologist Nancy Bonini, who has attended one of the energetic workshops sponsored by the Wexlers' foundation:

"You feel like you're part of a mission."

Genetic quandary

But now that people could be tested for the disease, Wexler wrestled with a sobering thought: Would they want to find out?

People who learned they had the mutation could see their lives disrupted - perhaps losing the ability to get health insurance or land a job.

"After we found it, I think all of us realized that there was more to knowing than we thought," she says. "As the Human Genome Project goes on, we're all going to be uninsurable. We're all going to have something."

She declines to say whether she has been tested, calling it a "private issue." Her sister, Alice, who wrote about the family's struggle in a 1995 memoir, *Mapping Fate*, says she does not wish to learn the truth.

Because their mother carried the gene, each had a 50 percent chance of developing the disease.

Wexler has garnered numerous awards for her work, but says this one, named for Benjamin Franklin, has special - and bittersweet - meaning. Her father, who joined her for decades in trying to find a remedy for what struck down his wife's family, died last month at 98.

Milton Wexler was "a huge, huge gigantic fan" of the famous inventor, his daughter says. He even wrote a nonfiction book (unpublished) titled *Winning Ways* - based in part on the 13 virtues that Franklin espoused, among them resolution, industry and humility.

As he lay in his hospital bed in March, father and daughter joked about how he, too, had won an award named for Franklin - in high school. She told him how she would have to give a public lecture the week of the award ceremony and asked what she should call it.

Exhausted from his bout with pneumonia, Wexler's father suddenly brightened and said, "The Lucky 13." And, indeed, that is the title of her free talk tomorrow night.

Then, she hopes, it is back to Venezuela.

The team has identified nearly 1,500 people who have symptoms of Huntington's or have already died from it, dating to the early 1800s.

An additional 1,000 or so are carrying the fatal mutation, and will get the disease at some point. As many as 10,000 more are at very high risk.

"It's going to get much worse," Wexler says.

The team has not been to Venezuela since 2002, temporarily dissuaded by U.S. officials because of political unrest. But now Wexler is in talks to return.

The reason, she says simply: "There's a cure down there."

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