PRO BONO HUMANI GENERIS
The Rockefeller University 1901

news&notes

APRIL 23, 1999 VOLUME 9, NUMBER 24 THE ROCKEFELLER UNIVERSITY

Hospital hosts Medieval Day event

The Duchess de Rocque held court with several "ladies in waiting" and even a princess last Thursday on the Hospital's fourth floor during a Medieval Day extravaganza. The Duchess's modern-day persona is coordinator of Recreation Therapy, Karen Zaremba. The ladies and the princess were patient-volunteers. Other patients and Rockefeller Hospital staff attended the half-day event.

Medieval Day was the first in a series of topical workshops Zaremba planned, which establish an updated framework for conducting recreational therapy. The other events will include a surrealist exercise to unleash unconscious creative energy. Later in the spring she will also offer a folk arts quilting workshop, only the "quilt" will be one drawn and painted rather than clipped and sewn.

Zaremba originally planned to hold a medieval headdress workshop in February. While she was making some prototypes, patients who came regularly to exercise at the recreational therapy suite started asking questions. "The project took on a life of its own," Zaremba recalls. She organized a field trip to the Metropolitan Museum of Art's "Mirror on the Medieval World" exhibit. She and the patients visited the exhibit three times during their preparation.

"The project gave patients who were here for approximately two months, and on a strict diet, something else to think about," Zaremba explains. Instead of thinking about what they could and could not eat, they became preoccupied with all things medieval. The result was a medieval tableau, with authentic costumes, dining customs, music, dancing and, of course, headdresses. The event offered keen descriptions of life in the 15th century, including the function of the castle moat and an explanation of courtly love.

The workshops unite Zaremba's interests in women's role in the history of art and the "museum education" curriculum model. She directs these interests toward changing the conventions of recreational therapy. The three workshops will also be documented as part of Zaremba's Master's thesis in liberal arts from Empire State College. "The conventional recreation therapy model should be overhauled. It has reached a point of standardization that makes it seem like a checklist: arts and crafts, music and drama, verbalization activities, dance

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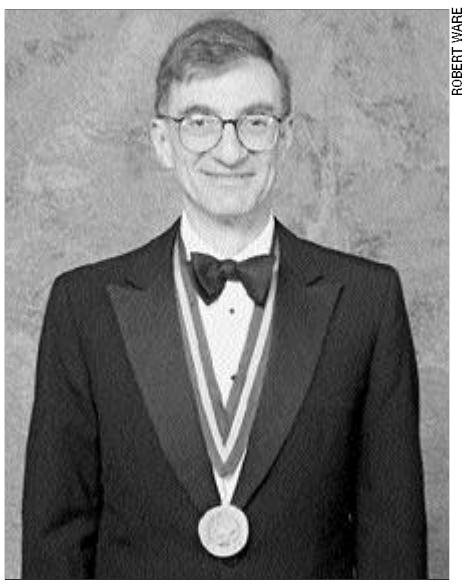
MICHAEL DAMES

Two Hospital patients, wearing 15th-century style dress danced to medieval music last Thurs., April 15, at a Medieval Day event organized by Recreation Therapy Coordinator Karen Zaremba.

Cohen receives Tyler Prize

ROBERT WARE



Abby Rockefeller Mauzé Professor Joel Cohen received this year's Tyler Prize on Fri., April 16, in Beverly Hills, California.

Joel E. Cohen, Abby Rockefeller Mauzé Professor and head of the Laboratory of Populations at The Rockefeller University, is attentive and pondering at the same time. He listens to questions with intensity, but when he talks he looks into the air as if his answers hover there. His office is compartmentalized into several spaces. One is social, with a sofa for visitors and a chair in front of a blackboard for himself; another is a work area with a desk well behind the camouflage of a tree-sized schefflera plant. Spend any time with him and you know that he is a pragmatist who, while congenial in all respects, assiduously maintains his daily work regimen. If you examine his day-to-day work, however, you realize that it is visionary without ignoring the past. Clearly, Cohen's dexterity is one of the keys to his success.

One of this year's two recipients of the Tyler Prize for Environmental Achievement, Cohen asks questions about humans, animals, plants and other organisms that span several sciences and many traditional disciplines. Though his work has many implications, and points constantly to the combination of economics, culture and natural events, it is best described as making connections between mathematics and biology.

For example, in December 1998, Cohen and molecular biologist Nina Fedoroff, a graduate of The Rockefeller University and now director of the Biotechnology Institute of Pennsylvania State University, organized a National Academy of Sciences Colloquium. They asked the question: Will there be enough time to develop and implement strategies that will permit the planet to feed and sustain its human population without profound economic dislocation and environmental degradation? The proceedings will be published as a book by the National Academy of Sciences in May.

His fascination with numbers dates at least as far back as junior high when he wrote a term paper about life insurance and noticed "a regularity in the fraction of people who will die at each age, even though an individual never knows whether he or she will die the very next day." His studies of human population dynamics began at Rockefeller in the 1970s with the observation that neither birth rates nor death rates were constant over time. This observation led to theoretical developments for which the Population Association of America awarded him its chief prize for mathematical demography. His travels in developing countries

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Fifth annual Cancer Research Fund symposium to be held next Thursday at RU

Associate Professor Marjorie Russel is one of the featured speakers at the Fifth Annual Cancer Research Fund Symposium, on Thurs., April 29

Former Runyon-Winchell Fellow Marjorie Russel, an associate professor in the Model lab, is one of the featured speakers at the Fifth Annual Cancer Research Fund Symposium, on Thurs., April 29, in Caspary Auditorium. Her talk, at 4 p.m., is entitled "Assembly and Extrusion of Filamentous Phage, a Specialized Form of Protein Secretion."

The symposium, which begins at 9 a.m., is hosted by the co-chairs of the Cancer Research Fund's Former Fellows National Committee: Nobel laureate Sidney Altman, Sterling Professor of Biology at Yale University, and Paul Talalay, John Jacob Abel Distinguished Service Professor of Pharmacology and Molecular Sciences at The Johns Hopkins University. Cutting- edge research will be presented to scientists, students and friends of the Fund. It is open to the Rockefeller community.

The speakers, who represent a range of disciplines in cancer research include David Botstein of Stanford University, Mark Ptashne of Memorial Sloan-Kettering Cancer Center, Joan A. Steitz of Yale University, Bernard Roizman of the University of Chicago, Stanley L. Falkow of Stanford University School of Medicine and Elliot Meyerowitz of the California Institute of Technology.

Since its founding in 1946, the Cancer Research Fund has been dedicated to supporting cancer-related research by young scientists working in the laboratory.

The Cancer Research Fund has a 21-member Scientific Advisory Committee

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Friday lecture cancelled

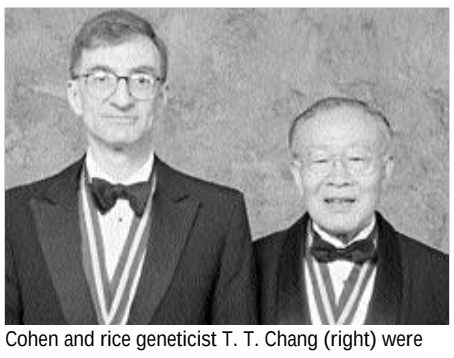
The Friday lecture for today (April 23) has been cancelled. The lecture series will continue next week when Robert Schreiber, of Washington University will discuss IFN-gamma and tumor surveillance.

COHEN, continued from page 1

led him to write, among other things, the popular 1995 book, *How Many People Can the Earth Support?* For it, Cohen was the first winner of the Nordberg Prize "for excellence in writing in the population sciences," given by the Population Council in 1997. In his laboratory at Rockefeller he also studies disease from the perspective of its effects on population.

Cohen has a knack for choosing unlikely but meaningful projects, then describing them. Over the years he has offered vibrant analogies and pithy metaphors to help explain his research. In a 1997 interview he said, "Mathematical concepts can help illuminate the essential core of complex situations, just as X-rays reveal the skeleton of a complicated body." This year he described his work in yet another manner: "Mathematics is a railway track, and the other sciences (demography, epidemiology, ecology, population genetics) are the freight which run on the track. Without the track the other sciences don't go anywhere, but without the freight, the track is only possibility." In a 1996 article that reviewed possible approaches to dealing with population problems, Cohen described a "Bigger Pie," (more technology to save the planet), "Fewer Forks," (voluntary reductions in fertility to slow population growth, and less consumption per person) and "Better Manners" (less inequity between men and women, rich and poor; more rational economic policies for the use of common resources like water and the atmosphere).

How Many People Can the Earth Support? won Cohen major recognition for his work in population studies. It also established his commitment to quality-of-life issues that cannot be resolved through mathematics alone. In this regard, Cohen figuratively rubs elbows



ROBERT WARE

Cohen and rice geneticist T. T. Chang (right) were corecipients of the Tyler Prize this year.

with this year's Nobel laureate for economics, Amartya Sen, whose work on famines addresses the issues of poverty and gender inequities. "I have great admiration for [Sen's] work and for him as a person," Cohen remarks when reflecting on the parallel between his work and Sen's.

Cohen has completed another book since 1995, on stochastic matrices. A stochastic matrix is a mathematical tool that presents a collection of discrete probability distributions. More simply, the matrix is a rectangular grid, with columns of fractions, each column adding up to 1. In their book, *Comparisons of Stochastic Matrices with Applications in Information Theory, Statistics, Economics and Population Sciences,* Cohen and his colleagues J. H. B. Kemperman and G. Zbaganu developed novel means of working with sets of these tools.

The Tyler Prize, administered by the University of Southern California, is the premier international award honoring achievements in environmental science, environmental protection, and the environmental aspects of public health. Cohen is not the first RU scientist to win the Tyler Prize. In 1976 René Dubos won for his books and articles, which provided a new perspective on the interaction between environment and humanity. Other famous Tyler recipients include the eminent Harvard biologist Edward O. Wilson, primatologist Jane Goodall and former U.S. Surgeon General C. Everett Koop.

"Winning the Tyler Prize was a complete surprise," says Cohen. He's grateful that President Emeritus Torsten Wiesel nominated him, although Cohen confesses he resisted preparing the necessary materials for a while. Modesty was the reason. Reflecting on the announcement he comments: "It is very unexpected but nice to be honored in this way."

Cohen is thinking a lot about education right now. While he studies probability, patterns and population prediction he maintains that our best option for ensuring the quality of the future is through education. He adds, with emotion, "We waste so much potential in not educating kids." He gave the entire $100,000 of his share of the Tyler Prize money to endow a scholarship fund at The Cranbrook School in Bloomfield Hills, Mich. This school gave him a full scholarship when he could not afford to go there as a high school student. The fund honors the memory of his parents, Hymen Ezra Cohen and Alice Cohen. The criteria for a student to be supported by his fund are simple: financial need, outstanding academic achievement and exceptional creativity in any field.

"Guardians of the future" is how Alice C. Tyler, co-founder with her husband, John Tyler, of the Tyler Prize referred to its recipients. Cohen certainly matches this description. And he protects what lies ahead by frequently looking back. In 1995 he quoted John Stuart Mill, writing in 1848: "A population may be too crowded, though all amply be supplied with food and raiment. It is not good for man to be kept perforce at all times in the presence of his species. A world from which solitude is extirpated ....is a very poor ideal." Whether he is vividly describing his work or enjoying a few well-earned moments of solitude, Cohen's accomplishments count significantly toward the future.

MEDIEVAL, continued from page 1

and exercise, outdoor activities, sports and recreation. Rather than treat the programming as a checklist, my curriculum offers a 'concept mapping' approach." In other words, Zaremba still offers the standard recreational therapeutic activities, but some of them are under the aegis of examining medieval culture, surrealism or women's folk arts.

Zaremba, who joined the Rockefeller Hospital staff in 1996, says the two other workshops she has scheduled won't be quite so elaborate as Medieval Day. However, the input of patients will largely determine the scale of the projects. Patients generally learn of Recreational Therapy from the floor nurses, who encourage them to browse Recreational Therapy's video and book libraries. "Everyone comes to check out the videos," Zaremba explains. "Once patients arrive on the fourth floor suite, they are surprised to find what a range of activities and comfortable space we provide."

MICHAEL DAMES

Recreation Therapy Coordinator Karen Zaremba, a.k.a. the Duchess de Rocque, added a medieval twist to conventional recreational therapy last week.

Potpourri

Tree spraying

The spraying of trees and shrubs throughout the campus will take place Sat., May 1, starting at 4 a.m. and continuing until 10 a.m. In case of bad weather, the alternative date for spraying will be Sun., May 2, starting at 4 a.m. Plant Operations recommends that you close your windows, shut off air conditioners, stay out of direct contact of the drift and keep pets inside. If you have any questions, call James Sullivan, x8001.

Faculty off-campus talks

Professor Alexander Tomasz and Assistant Professor John McKinney spoke at the American Museum of Natural History on Mon., April 12. The program, entitled "Bacterial Infections and New York City," was the 1999 Harold C. Neu Symposium of the New York Society for Infectious Diseases.

Professor A. James Hudspeth spoke at the Society for Neuroscience Symposium "Neuroscience 2000: A New Era of Discovery" held at the National Academy of Sciences in Washington, D.C. on Mon., April 12. The audience consisted of neuroscientists, members of Congress, government officials, leaders in education and medicine and CEOs of companies with connection to brain research. He then continued on to give the keynote address for the 1999 Association for Chemoreception Sciences Annual Meeting in Sarasota, Fla. on Wed., April 14. Last month, on Wed., March 24, he gave a briefing on hearing and deafness to the Congressional Biomedical Research Caucus on Capitol Hill in Washington, D.C. This is a forum where members of Congress and their staffs can interact directly with researchers who have led the world in scientific discoveries.

AwardsCorner

Huaxi Xu, an assistant professor in the Laboratory of Molecular and Cellular Neuroscience headed by Paul Greengard, recently received a research award from the American Health Assistance Foundation ($200,000 over two years) for studying the molecular and cellular mechanism by which estrogen reduces Alzheimer's beta-amyloid protein in neurons.

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and a nine member Scholar Review Panel, both of which are composed of leading scientists. The committee reviews applications from many promising young investigators in the nation's leading laboratories and awards postdoctoral fellowships and scholar awards each year. Only those scientists whose applications survive the rigorous scrutiny and review process are recommended for awards.

The full amount of any grant to the Cancer Research Fund is used for cancer research. In fiscal 1998, the Fund invested more than $4.8 million in 141 young men and women beginning their careers as Damon Runyon-Walter Winchell Fellows. The Fund also established a new award program in 1995. As a result, the Fund is now providing another $900,000 annually for grants to nine Damon Runyon Scholars, selected from among outstanding junior faculty throughout the United States.

For luncheon reservations, please contact Sarah Caddick at (212) 697-9588.

Constr uction update:

The construction schedule for the Bridge/Plaza project for the week of Mon., April 26 will include:

1. Complete removal of stone panels from RRB.
2. Demolition of the stairway from the loading dock to the Plaza.
3. Site work in the parking lot east and south of the Weiss Building.
4. Mechanical and telecommunication relocation in the 2nd floor of Weiss.
5. Core drill work on the second floor of the Scholar's Residence

Planning and Construction hopes these activities will have minimal effect on everyday activities of the campus.

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Putting the brakes on cancer, Part 1 of 2

President Levine discusses insights from the *p53* tumor suppressor gene

On Tues., April 13, President Arnold J. Levine spoke to the RU Council, an advisory group of leaders in business and industry, education, law, finance and many other areas. His talk was entitled "Putting the Brakes on Cancer: Insights from the p53 Tumor Suppressor Gene." Below are excerpts of his remarks, which will be reprinted in two parts.

I want to begin with a prologue. What I've learned in teaching is that it is best to start off with a message, repeat it frequently throughout the talk and then end up with the message. Now, my message is: "Fidelity is a good thing." But I'm going to end by pointing out what Lewis Thomas once told us: that too much fidelity is not a good thing.

Now, what do I mean when I say: "Fidelity is a good thing?" Today, as we walked around, as we worked, as we thought, a billion cells in our body duplicated themselves. To do that, it takes a blueprint, and we all know what that blueprint is. Oswald Avery here at Rockefeller University in 1944 taught us that the blueprint that directs the division of a billion cells a day is made up of the chemical DNA, deoxyribonucleic acid, and like any bit of information, it is encoded in some way. If you were talking about computer tapes, the information would come to us in 0s and 1s; in Morse code, it's dots or dashes. And so, too, the genetic code. The information in our blueprints is a four-letter code.

We use just the first letters of the four chemicals that make up DNA: A, T, G or C. So A-A-A means something in the big computer tape that we have in duplicating our information. To duplicate the information, we have to take A-A-A and duplicate it one more time, and then separate the two copies into two cells. And when I talk about fidelity being a good thing, I mean A-A-A making A-A-A and nothing else, because when it makes A-T-A, that's a mutation, that's a change, that's a mistake. And so a big part of life is fidelity.

We have three billion bits of information in our chromosomes, so there are three billion As, Ts, Gs and Cs in a defined sequence that need to be copied faithfully. And when it fails, that's a mutation. That's the prologue: We want to be faithful, but as Lewis Thomas said, not too faithful.

Now, let me take you back historically to the time when I was a graduate student at the University of Pennsylvania, from 1961 through 1966. My passion was that I wanted to understand what caused cancer in human beings, and we knew very little.

In 1911 Peyton Rous, working at the Hospital here at Rockefeller, discovered a virus in chickens that caused cancer, and in 1934 Rockefeller's Richard Shope discovered another virus that could cause cancer in rabbits. And so one thing we knew in 1961 was that in some animals, like chickens and rabbits—and now we know in kittens—cancer can be spread by viruses; in some cases it is even an infectious disease. That means it's transmitted from one kitten to another in a litter so the whole litter gets leukemia all at once. But cancer is not usually an infectious disease in humans. So in 1961 we knew there was some disconnect between what we had gotten from the grandfathers of science and what we knew about human cancer.

We had one other fact in 1961, one other observation which the epidemiologists gave us: the people who watched the incidence of cancer around the country, around the world, and tracked all the variables. One of the variables was age; what is the age at which people acquire cancer for the first time? You can do the experiment of just plotting up age versus the incidence of cancer, the rate at which people get cancer.

Cancer is by and large a disease of the elderly. At 55 to 60 years old, the cancer rate starts increasing; between 60 and 70, the rate per 100,000 goes way up; it only peaks at about 70 to 75 and declines slightly in older age. Now, how do you explain a curve like that?

Well, Lewis Thomas had a hypothesis. When I was a student, Thomas put forward the hypothesis called "immune surveillance," which means that our immune system is taking care of us and eliminating tumors all the time. He said that the rate at which you get tumors is the same over your lifetime, whether you are one year old or 70 years old. And the reason for the curve is that when you are young, the immune system takes care of you, and it kills off all the tumors. But the immune system decays as we get old.

On Tues., April 13, President Levine spoke to the RU Council about the *p53* tumor suppressor gene.

At 55 to 60 years old, the cancer rate starts increasing; between 60 and 70, it goes way up, peaks about 70 to 75 and declines slightly in older age. Now, how do you explain a curve like that?

That's not a bad hypothesis. We know that as we get older our immune system isn't as good as it once was, so his hypothesis explained the curve; that was what was good about it. But there are a couple of experiments of nature that knocked his hypothesis out of the box. The first was the "bubble boys." These are the young children born with no immune system, who have to live in bubble chambers to keep infectious diseases away from them. They don't get tumors. The same thing was found in mice that were born without immune systems; they don't get tumors at any higher rate than mice with immune systems. So immune surveillance, even though it was a good hypothesis, had a lot of contradictory evidence, and we didn't accept that as a good idea.

Over the decades of the '70s and the '80s, we learned that the cancer curve looks the way it looks because of mutation—because of being a little less faithful than we'd like to be in duplicating our own genetic information. That happens at a constant rate over our lifetime, so by the time we're 10, we may have accumulated a mutation in a particular cell. And by the time we're 20 we may have a second mutation, and by the time we're 35, a third; and by the time we are 50, a fourth; and by the time we are 60, a fifth. And as these mutations accumulate in a single cell, they come together and they make a constellation of mutations, which trigger the uncontrolled growth of cells and cancer. So the first mutation is not sufficient to cause cancer, the second is not sufficient, the third is not sufficient; the fourth starts the process. To cause cancer, mutations need to accumulate over a lifetime.

That's the hypothesis. And, in fact, the hypothesis makes a prediction that's really testable in people born with a mutation. What happens if you inherit a mutation through the fertilization of sperm and egg, and then the mutation is present in every cell of the body ahead of time? You have one mutation you're born with, and you only need three more. You get cancer at a younger age. There are multiple cancers in some families, and some people even get more than one cancer if they've inherited a mutation. In fact, we can test that hypothesis. We can see what happens if people inherit mutations.

A very important event happened in the '70s for us in the molecular biology revolution; we learned how to go into chromosomes and take out genes to test whether they were altered in cancer cells, or whether the patient inherited a gene that predisposed him or her to cancer. We learned how to clone a gene, in the jargon of the molecular biologist, and we learned how to sequence the As, Ts, Gs and Cs to get at the information to see if it was mutant or normal.

Now, this is what happens when many mutations lead to cancer. We have a group of normal cells with no mutations, and as they duplicate, a mutation arises in one of them; it's the first mutation. And then that cell divides and makes two and so on, and they all share this mutation. Then one of them gets a second mutation in the same cell, in the same chromosomes, but a second independent mutation. Then it happens a third time, and a fourth. At that time, there is a conversion of these cells to a malignant cancer. That's the hypothesis we're going to test at the cellular level. Let's look at an organ where cancer arises: the colon. It may take four independent mutations accumulating over a lifetime to evolve into colon cancer. In a normal colon, the muscle cells are underneath, and a membrane separates the stromal cells from the epithelial layer *(see illustration below)*.

The first sign of an abnormal growth in the intestine is a benign tumor that starts to grow. The normal cells start to grow and they pucker out and form an early adenoma, a benign tumor. And this continues to grow to intermediate size, and finally to a very large adenoma. (This is why physicians do scanning of the intestine to look for these polyps, because they are the precursors of the carcinoma.) The malignant tumor breaks through this membrane into the muscle tissue, spreads and metastasizes. This is a true carcinoma.

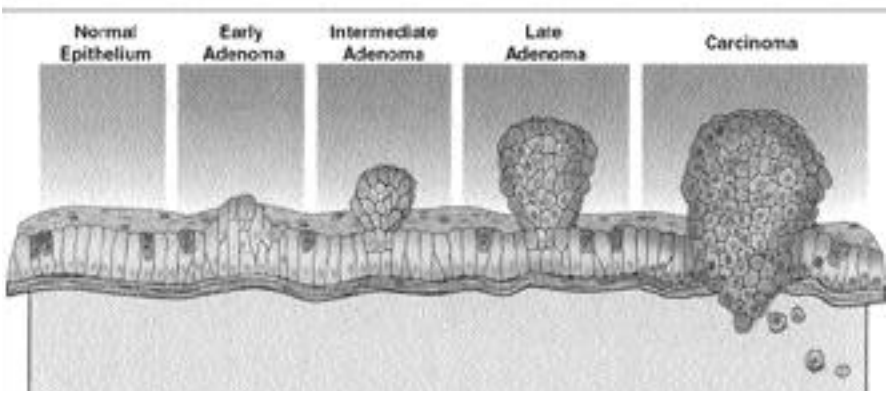
We can take cells from the four stages and extract the genes from the chromosomes of those cells and ask: "Have they mutated? And do they have four different mutations, three different mutations, two different mutations, one mutation, no mutations?" That would test the hypothesis.

And here's what Bert Vogelstein found when he did the experiment: in an early adenoma, a little polyp, there was a mutation in the gene called *APC*. Then, in our intermediate polyp, there was a mutation in an oncogene called *Ras*. And then in late adenoma, we would find mutations not only in *APC* and *Ras* but also in a gene for something called the TGF-β receptor. TGF-β is a hormone that prevents growth. When the receptor is wiped out, you get active growth.

The final transition, from benign tumors to carcinomas, occurs with a mutation in the gene that we found, the *p53* gene. And this is why the *p53* gene seems so seminal, so critical to everyone, because it stands at this terrible transition between benign tumors, which are under control, and malignant tumors, which are out of control.

In next week's issue of News&Notes, *part 2 of President Levine's talk will explain* p53*'s role in putting the brakes on cancer*

The Evolution of Colon Cancer



Four stages of colon cancer development are shown above. Scientists are able to take genes from each stage of the cancer's progression, as well as from normal cells, to test for mutations.

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