The Chosen Genes:

Jews, Genetics, and the Future of Ethnic Medicine

by

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ABSTRACT

All humans have certain genes that cause or predispose them to various diseases. In the ideal medical future, scientists will have hyperfast gene analyzers able to sequence anyone's DNA in a matter of minutes. In that future, a patient could have his entire sequence of DNA screened for mutations that cause or predispose him to disease, and health care would be truly individualized to fit the genetic profile of each patient. But science isn't yet able to make this future a reality; DNA sequencing remains too time-consuming and expensive to allow for such completely individualized medicine. In the meantime, scientists have discovered a useful shortcut: race and ethnicity.

Many genes vary across racial and ethnic lines. Geography is linked to genetic variation, and people who have the same geographic ancestry are more likely, on average, to be genetically similar than people who do not. Although there is no gene for "race" or "ethnicity," many genes do occur in different ethnic groups at different frequencies. This means that doctors can use a patient's race or ethnicity — indicators of geographic ancestry — to make inferences about his genes, including his likelihood of developing specific diseases.

Today's Ashkenazi Jews are appealing research subjects because they are both genetically interesting and culturally willing. For the past half-century, Jewish communities have been getting the genetic scrutiny other populations can expect in the future. Such research has helped scientists make significant headway in diagnosing, treating, and preventing certain genetic diseases. But as the research studies continued, some Jewish communities began to worry about their implications. Lessons learned from the participation of American Jews in genetic research will be important for and applicable to many ethnic groups as the approach expands.

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It's an achingly cold December night — unseasonably so, the city's natives insist — and young Jewish couples from all over Chicago are pulling into the parking lot at Emanuel Congregation, a Reform synagogue set just yards from the freezing waters of Lake Michigan.

Their breath visible in the night air, they file into the brick building, into a colorful social hall adjacent to the sanctuary where services are held each Friday and Saturday. They head for a long banquet table, help themselves to food from a kosher buffet: fruit salad, deli sandwiches (a variety of meats, but, of course, no cheese), chocolate chip cookies. They settle around seven round tables. Conversation revolves around dating and marriage, what it's like to be young and Jewish in Chicago. Husbands get second helpings of cookies. Wives drop not-so-subtle hints about what they want for Hannukah.

And then everyone goes silent. At the front of the room, a young woman with curly brown hair launches into a presentation on the basics of human molecular genetics. From her place beside a large projection screen, Dania D'Achille explains that DNA, the genetic information contained in each cell of the human body, is merely a set of instructions the body uses to assemble proteins. With diagrams and drawings, D'Achille earnestly describes how we inherit these instructions from our parents, and what can go wrong if the body makes a mistake.

"You can have harmful gene changes that can lead to disease," says D'Achille, who spends her days working as a genetics counselor at Chicago's Children's Memorial Hospital. "By changing the structure of the gene in some way, that's going to change the structure of the protein." And that can cause diseases, disabilities, or birth defects.

After breezing through these basics with the nonchalance of someone who's done it many times before, D'Achille pauses and faces the room, asking the obvious question: "So," she says, "why are we here?"

After dinner, everyone will complete family histories and medical consent forms. Table by table, they will file into a room across the hall. They will roll up their sleeves and proffer their veins to lab technicians. They will switch naturally from asking how much blood will be drawn ("About two tablespoons") to asking whether the cookies offered afterward will be kosher ("Of course.") And, as the Chicago Center for Jewish Genetic Disorders wraps up its screening, the participants will be sent off with a tuft of gauze, a bandage, and a promise to hear in two to four weeks about the genetic destiny of their future children.

Though Jewish communities exist worldwide, many of today's Jews — who are largely descended from a small, insular founding population — exhibit remarkable genetic similarities. Historical events that wiped out large swaths of the world's Jews, coupled with cultural norms that largely discouraged the survivors from marrying outside the often isolated community, have helped created a gene pool with less variation than that of the general public. The result has been a shift in the frequency of certain genetic mutations, with some becoming more common and others becoming less so. These mutations include those that cause disease, which means that certain diseases are concentrated among Ashkenazi Jews — there are at least 18 diseases or disease variants prevalent predominantly among this group — while others are rare or nonexistent.

Each human being has certain genes that cause or predispose him to disease. In the ideal medical future, scientists will have hyperfast gene analyzers able to sequence anyone's DNA in a matter of minutes. In that future, a patient could have his entire sequence of DNA screened for mutations that cause or predispose him to disease, and health care would be truly individualized to fit the genetic profile of each patient. But science isn't yet able to make this future a reality; DNA sequencing remains too time-consuming and expensive to allow for such completely

individualized medicine. In the meantime, scientists have discovered a useful shortcut: race and ethnicity.

Scientists are discovering that many genes vary across racial and ethnic lines. Every population of humans that has been reproductively isolated for some period of time — and that means all humans — has developed its own genetic characteristics. People who have the same geographic ancestry are more likely, on average, to be genetically similar than people who do not. That means that doctors can use a patient's race or ethnicity — both of which are indicators of ancestry — to make inferences about his genes, including his *likelihood* of developing certain diseases. The result, in recent years, has been a decided push toward race- and ethnicity-based medicine, in which doctors and scientists use racial and ethnic groups not only to study disease, but also to treat it.

It's an approach that contains an enormous amount of both promise and peril — in differing proportions, depending on whom you ask. Examining the genetics of races or ethnicities presents an incredible shortcut for scientists trying to prevent, treat, and cure disease. But such research also sparks fears of discrimination and has prompted critics to pose many troubling "what-ifs?" What if genetic research on ethnic groups reinforces social stereotypes? What if genetic knowledge about differences in disease predisposition creates medical racial profiling, leading to insurance and workplace discrimination and widening health care disparities? And what if, in the face of all these concerns, it's not even good medicine?

But in at least one population, the hypotheticals can begin to be answered. For the past half-century, Jewish communities — because of their unique genetic heritage and their willingness to volunteer for study — have been getting the kind of genetic scrutiny that many other populations can expect in the near future. Those decades of experience with Jewish

communities suggest that, as scientists improve their ability to characterize and analyze the differences between human populations, medical breakthroughs will perpetually be pitted against their social ramifications.

"And that's the big ethical question in general: do we want to know something?" said Bob Pollack, the director of the Center for the Study of Science and Religion at Columbia University. "Can genetic information be toxic?"

Jews, Pollack said, are the canaries in the cave. If you want to know if the air is toxic, he said, look at genetics and Jewish communities.

Unveiling the genome

David Altshuler knows he's short. But the geneticist uses his stature to make a case for the importance of DNA.

"In America, height is about 90 percent heritable," says Altshuler, who stands on a wooden platform as he speaks. "Which is why my parents who are right here, can be blamed for my being short. Which is why I asked them to bring risers here, so I could be taller," he adds, to laughter from the audience. "I wanted to stack them actually, but they wouldn't let me."

Altshuler is speaking to the crowd that's assembled at the MIT Museum one November evening to hear about the latest advances in human genetics. He is trying to illustrate one of the central tenets of genetics: the more closely related you are to someone, the more similar you are to them genetically. In America, 90 percent of height variation is due to genetics, he says, as is 70 percent of the variation in body-mass index.

Altshuler, director of the medical and population genetics program at Harvard and MIT's Broad Institute, is a champion of the importance of DNA in human health and development. DNA influences not only physical traits, like height and weight, but also diseases — all diseases — he says. Yes, he acknowledges, environment and behavior affect health, but genetics invariably plays a role, in many cases a dominant one.

Altshuler is one of more than 200 scientists who contributed to the newly unveiled HapMap, a database of human genetic variation that scientists and doctors hope will speed the race to find genetic causes — and genetic cures — for a wide variety of medical conditions.

The entirety of the genetic code, called the genome, provides all the instructions necessary for human development. The genome is often compared to the text of a book. A sequence of DNA is composed of four different chemicals, or bases, which are abbreviated A, C, T, and G. Three of these bases in a row, known as a triplet, codes for a single amino acid, and a chain of amino acids makes up each of the body's proteins. So if each base that makes up DNA is a single letter, then the triplet of bases is like a single word — the smallest unit that conveys meaning — and an entire gene is a sentence or paragraph, composed of many different letters in a unique order. Changing a single letter of an English word, or adding or deleting a letter, can change the meaning of a word, sentence or paragraph, or simply produce nonsense. Similarly, a change in a single DNA base, called a mutation, can change the gene, altering the protein produced and possibly creating biological nonsense. Though some mutations, which arise naturally, are harmless, others can dramatically affect human health.

The HapMap is the sequel to the highly visible Human Genome Project, which aimed to map every gene in the human genome and sequence its 3 billion base pairs. Knowing the sequence of the entire human genome was considered to be, in an often-invoked metaphor of the

time, "the holy grail." The project was launched in 1990 by the U.S. Department of Energy and the National Institutes of Health, and a rough draft of the genome was completed in 2000. Subsequent work filled in the gaps, and by 2003, 99 percent of the human genome had been sequenced with 99.99 percent accuracy.

But for medicine, the human genome project was not the grail so much as it was the provisions needed on the quest for it. It would be inefficient — and prohibitively expensive — to examine the entire genome for a single mutation linked with one particular disease. Any two humans have 99.9 percent of their DNA in common, and it is this remaining 0.1 percent that accounts for any inherited differences between them — in height, hair color, or disease susceptibility. To search for a mutation that causes disease, then, the best approach is to look just within that 0.1 percent, for the few base pairs that might be different for diabetes sufferers than those without diabetes, for instance.

The HapMap was an attempt to conduct that search for genomic *variation* on a large scale. Most genetic mutations are changes in just a single base, one letter, a change that is known as a single nucleotide polymorphism, or SNP. SNPs that are located physically close to each other on the genome are likely to be inherited together, in genetic chunks known as haplotypes. Haplotypes are interesting to geneticists for two main reasons. First, certain haplotypes seem to be correlated with disease, and second, haplotypes vary considerably from one population — geographic, ethnic, or racial — to another.

The HapMap project assembled a catalog of haplotypes, determining which chunks of DNA were most likely to be inherited as chunks and how common different versions of these chunks were in different populations. The project collected DNA from four different populations — European Americans, Japanese, Han Chinese, and the Yoruba of Nigeria — and catalogued

the groups' haplotypes. The project will allow scientists to determine which haplotypes are most characteristic of certain populations and to examine individual haplotypes for links to disease.

Think of disease as a crime, the mutation that contributes to it as the perpetrator. The map of the human genome provides the name and address of every person in existence — potentially useful information for tracking down the one or few criminals, but almost paralyzing in the vast amount of information it presents. The HapMap, on the other hand, Altshuler says, is a list of usual suspects, a place for scientists to begin their investigation.

Understanding the genetics of a disease is the first step in designing more effective treatments for it. Right now, drug developers rely mostly on trial and error. They hypothesize what target in the cell is involved in the disease, develop a molecule that interacts with that target, test the molecule in animal models, and then take it through many stages of human testing. It costs roughly $800 million to develop a drug, Alsthuler estimated.

"But most of that big number is due to failure," he said. "Most of the time you start down that path, and it turns out not to work in people or to have side effects. And the reason for that is it wasn't actually a very good target to begin with."

Altshuler hopes that once scientists understand what actually causes a disease at the molecular level, they will be able to design drugs that directly target the things in the cell that actually matter. The pharmacogenetic approach — in which scientists study how genetic variations influence responses to drugs — has already yielded some successes, particularly for cancer therapies. One example is the drug Gleevec, a cancer-fighting medicine approved in 2001. Gleevec doesn't work for everyone, but for leukemia patients whose cancer is caused by one specific mutation — the fusion of the BCR and ABL genes, a mistake that causes the body to produce an abnormal enzyme — Gleevec is remarkably effective.

But Gleevec was only possible once scientists pinpointed the specific genetic mutation that caused the leukemia. In this way, discovering the genes linked with disease will dramatically help the search for better treatments.

"It's very hard to develop treatments without actually having a clue what's causing disease," Altshuler said.

And one of the most effective ways to determine that is to focus on groups of people with genetic similarities. Even though the percentage of the genome that varies from person to person is a mere 0.1 percent, that still leaves 2 to 3 million nucleotides for researchers to sift through. The vast majority of those will be totally irrelevant to the disease in question.

So geneticists often study families, comparing family members who do have a disease, like cancer, with those who do not. Because family members share more genes than strangers do, some of the background noise is reduced, allowing scientists to narrow their search on the variations that might actually matter. (It's a lot easier to find one blue marble in a jar of red marbles than it is to find it in a jar of red, green, and yellow marbles.)

The same rationale also makes studying certain subpopulations — races and ethnicities, for instance — appealing. What interests geneticists about racial and ethnic groups is not their skin colors or physical features, but their geographies. What we think of today as "race" or "ethnicity" generally refers to a group whose ancestors once all lived in the same area of the globe. For long periods of time, populations in different parts of the world remained largely isolated from each other, allowing them to accumulate certain genetic changes and uniquenesses. For instance, scientists have discovered that a genetic mutation that increases the risk for Alzheimer disease occurs at significantly different frequencies among ethnic groups — with African Americans most likely to have it and Japanese least likely.

The result is that ethnic groups are useful to geneticists for two reasons. The first is that some diseases have become more concentrated in certain ethnic groups, making it easier to study sometimes rare diseases. Second, like studying families, studying ethnic groups minimizes the background genetic variation, allowing researchers to more easily identify genetic mutations relevant to disease.

Why is this gene different from all other genes?

The history of the Jews, especially a group known as the Ashkenazi Jews, makes them a genetically interesting population. Jews originated in the Middle East millennia ago. During the 9th century, small groups of Jews began settling in the Rhineland along what is now the border of Germany and France. They became known as Ashkenazi Jews, from the Hebrew word for German. (Jews who dispersed to the Iberian peninsula become known as Sephardic Jews, and those who spread throughout the Middle East became the Oriental Jews.)

A relatively few number of Jews made this migration from the Middle East, and over the next few centuries the population remained small. Stigma and outright discrimination against Jews was common in Medieval Europe, and periodic persecution kept the Ashkenazi population both small and insular. Jews, viewed as outsiders by Christian Europe, were usually segregated in ghettos. The Ashkenazim, as Ashkenazi Jews were collectively known, had also developed the Yiddish language, which created a linguistic barrier between them and the rest of the Europe. Furthermore, cultural values prevented most Ashkenazim from marrying outside their communities.

This insularity of Ashkenazi communities — a combination of force and choice — had distinct genetic effects. In the 14th century, the Ashkenazim began migrating east to Poland, and by the 16th century, the Ashkenazi population was concentrated in Poland, Lithuania, and Russia. But unlike other migrant populations, which got infusions from local communities as they populated new regions, the Ashkenazi Jews remained relatively insular, with little influx of new genes. Today's Ashkenazi population, estimated at 8 million people, can be traced back to a relatively small group of ancestors, whose genes were passed on to many descendants with little change along the way. That phenomenon is known as the founder effect.

The founder effect is often associated with another phenomenon called genetic drift.

"Drift deals with the fact that gene frequencies, by chance alone, will vary from one population to the next," said Harry Ostrer, a medical geneticist at New York University. "The variation will be greater for a small population than for a large population. So if a population has a relatively low breeding size for some period of time, it may see great fluctuation in gene frequencies."

Over many generations, this can result in a significantly different gene distribution than the one present in the general population. Among Ashkenazi Jews, the founder effect and genetic drift were amplified by a series of bottlenecks — times during which the population dwindled to small numbers — that resulted from the group's status as outsiders and inferiors.

Today's Ashkenazi Jews, who represent 60 percent of all the Jews worldwide and 90 percent of American Jews, are descended from a small number of ancestors, who rarely married outside their communities. The result is that, even as the population expanded, the gene pool remained relatively small. Certain genes — whether harmful, helpful, or utterly innocuous —

occur at much greater frequency among Ashkenazi Jews than in the general population, while others occur at a significantly lower frequency.

If these reasons have made Ashkenazi Jews scientifically interesting, a host of other cultural and social reasons have been at least as important in making Jews desirable research subjects. In the U.S., Jews tended to settle in urban areas, close to hospitals and major research centers. Futhermore, Jews have long had close ties to the medical establishment, and many researchers and scientists themselves are Jewish. And in Jewish communities, an emphasis on education and knowledge (particularly scientific knowledge), combined with the value placed on community service, provided a moral imperative to participate in genetic studies.

"It's a great laboratory of people in which to do genetic analysis," Ostrer said.

Ostrer, a mustached and bespectacled geneticist with dimples and an easy smile, has been studying Jewish populations for decades. He has an intense curiosity about human relatedness and the ability of genetics to reveal it. (For fun, he and his three children performed a genetic analysis to determine whether they were related to other Americans with the last name of Ostrer.)

From his office in NYU's Tisch Hospital, he juggles his projects. He oversees the work being done in the adjacent laboratory, where members of his lab busily study male sexual development or the genetics of prostate cancer. He still sees and counsels patients. And whenever he can steal an hour here or there, he works on another, more personal endeavor: a book about Jewish history and genetics. It's a story he's well equipped to tell. Ostrer has published papers on Tay-Sachs disease, Gaucher disease, cystic fibrosis, deafness, colorectal cancer, breast cancer, Canavan disease, Bloom syndrome, Usher syndrome, and familial Mediterranean fever, all among Ashkenazi Jews.

Over the second half of the twentieth century, researchers like Ostrer have done hundreds of studies on disease specifically in Jewish populations. In addition to the Ashkenazim, Sephardic Jews and Oriental Jews have their own genetic patterns. Other historically isolated populations — most notably, the Amish, Native Americans, Icelanders, and the Finns — have founder mutations, and these groups have also been studied. Even larger and more heterogeneous populations have unique sets of genetic mutations, and scientists have begun to examine them.

But Ashkenazi Jews remain a genetic goldmine, and interest in studying them, said Ostrer, who has a tendency to repeat himself when he is being especially emphatic, is "huge, huge, huge, huge."

Tay-Sachs: setting the stage

In 1952, in a community hospital in Brooklyn, babies kept coming in with the same bizarre symptom: a small, cherry-red spot in their eyes, surrounded by an opaque, milky white halo. These infants, who also had arrested physical and mental development, had come to take their places in a pediatric ward at the Jewish Chronic Disease Hospital. Though they could barely see, they were hyper-sensitive to sound. A medical student who indelicately lowered the side of a metal crib, causing a loud crash, once caused a ward full of the children to start having seizures.

The infants had Tay-Sachs Disease, a degenerative, metabolic disorder that was invariably fatal, usually by age five. The hospital was where the children came to be cared for until they died.

Tay-Sachs disease was first described by William Tay, a British opthamologist, in 1881, when he saw a one-year-old infant with the strange collection of symptoms. A few years later,

American neurologist Barney Sachs, unaware of Tay's findings, made a similar report about a young girl. Sachs elaborated on the disease in a series of papers, and by 1896 he had observed that Tay-Sachs clustered in families. What's more, he noted that nearly all of the 19 recorded cases of the disease had been "in Hebrews."

The Brooklyn hospital was open to all members of the community, but because the neighborhood where it was located was mostly Jewish, so, too, were the patients. Tay-Sachs was a rare, relatively unknown disease, but by 1954, the hospital unit had admitted 18 cases.

It was anecdotally obvious that Tay-Sachs had a prediliction for Jewish children, but when the exact prevalence was calculated, the numbers were stunning. The disease was determined to be *100 times as common* among Ashkenazi Jews as in the general population.

Perhaps no disease has become better associated with Jewish communities — or strikes more fear into the hearts of would-be Jewish parents — than Tay-Sachs disease. Children with the disorder fail to produce an enzyme known as hexosaminidase A, or hex-A, which normally breaks down fatty substances in the brain and other nerve cells. A deficiency of hex-A causes the body to accumulate these substances, killing cells until the central nervous system shuts down entirely. Children who inherit the disease look healthy at birth, but usually develop symptoms by six months of age and deteriorate rapidly. They lose muscular strength and motor skills, become blind, develop seizures, and eventually become paralyzed. They die from recurrent infections, pneumonia, or bodily wasting.

Tay-Sachs, like a number of the so-called "Jewish genetic diseases," is a single-gene, recessively inherited disorder. Every human child is born with two different versions of every gene — one from each parent. Each alternate version of a particular gene is called an allele. It is

this combination of alleles that helps determine which proteins the body builds, and, therefore, which traits — from eye color to deafness — a person possesses.

But not all alleles are created equal; some versions, called "dominant" alleles, take precedence over other "recessive" alleles. Traits associated with recessive alleles require two copies of the allele, one from each parent, to be expressed. For instance, a child must receive two copies of the Tay-Sachs allele — one from his mother and one from his father — to develop the disease. People with just one copy of the recessive Tay-Sachs allele are known as carriers; they remain healthy but can pass the disease on to a child. Each time two Tay-Sachs carriers have a child, there is a 25 percent chance the child will inherit both Tay-Sachs alleles and develop the disease. Among the general population, one in every 300 people are Tay-Sachs carriers. Approximately 1 in 30 Ashkenazi Jews are.

But in the 1950's, the only way to learn you were a Tay-Sachs carrier was to have a child who developed the disease. In 1957, five New York area couples who learned they were Tay-Sachs carriers in this tragic fashion banded together to form the National Tay-Sachs and Allied Diseases Association.

"At that point in time they did not know what the actual cause was of the disease," said Jayne Gershkowitz, the current director of the association. "They knew what it was called, they knew that it affected Jewish babies, they didn't know why, and they felt that they wanted to spare other families from going through the pain of what they were going through."

The new association held high-profile fundraisers and poured the money into research. Progress, when it finally came, was rapid. By 1969, scientists had discovered that the disease was a result of a hex-A deficiency. By 1970, it was possible to use amniocentesis to determine whether a fetus had Tay-Sachs. In the same year, another team of researchers reported that they

had developed a test that could determine whether someone was Tay-Sachs carrier by measuring his enzymatic activity.

The stage was set for Tay-Sachs screenings, and on May 2, 1971, the first public screening was held. More than 1,300 people were tested during the seven-hour screening, held in a synagogue near Washington, D.C. In the next year, eight more community screenings were held; about 7,000 people were tested and 250 carriers, including 7 carrier couples — in which both partners were carriers — were identified.

"It generated an enormous amount of enthusiasm within the Jewish community," said Ostrer, who ran his own public screening in New York in 1975. "It engendered a very strong sense of 'This is something that we can do as a people to prevent disease.'"

The characteristics of Tay-Sachs made it the perfect disease for genetic screening. It was an early-onset, fatal disease with no cure. It was governed by a single allelic difference that could be screened for with a test that was simple, accurate, and cheap. And a couple could actually *do* something about their test results, using them to make family planning decisions — whether it was to adopt, to use a sperm or egg donor, to use amniocentesis to make a prenatal diagnosis with the possibility of aborting an affected fetus, or to not have children at all.

The screenings were also successful because medical professionals worked directly with Jewish communities. Doctors and scientists partnered with Jewish organizations across the nation, asking Jewish leaders to help spread the message about Tay-Sachs screening.

"It was a real grassroots effort that focused on the American Jewish community," Gershkowitz said. "They went to the major metropolitan Jewish communities around the country and held these screenings. People lined up by the hundreds. It was scary. People knew what Tay-Sachs was."

In the next few decades, awareness of Tay-Sachs grew. By the year 2000, more than 1.4 million people, mostly Ashkenazi Jews, had been screened for the disease. The programs had identified 51,000 carriers, including 1,400 carrier couples. Those carrier couples went on to have a total of more than 2,500 healthy children through the use of various pregnancy and prenatal options. By the new millennium, the occurrence of live Tay-Sachs births among American Jews had decreased 90 percent.

"Our normal abnormal life"

Two and half years after they got married, Ken and Sherri Epstein had their first child, Jessica. Jessie, as they soon came to call her, was a sweet, happy baby, and Ken and Sherri wanted to have another. Sherri soon got pregnant again and announced the news at Jessica's first birthday.

On September 26, 1998, Sherri gave birth to her second daughter, Rachel. Even before she left the hospital, Sherri began to worry about her. "She would look like she was screaming her head off but no sound was coming out," Sherri said. It would take up to a minute for Rachel's larynx to actually push the sound out. But doctors reassured the Epsteins that everything seemed fine.

Once home, Sherri and Ken grew increasingly concerned. They could clearly remember Jessica's early development, and it soon became clear that Rachel's didn't mirror it. She couldn't make eye contact. Her head seemed bigger than normal. When Sherri went to wake Rachel from a nap, she would be in the exact same position she had fallen asleep in, without having moved

even a finger. And Rachel only slept four hours a day — non-consecutively — and spent the remaining 20 wailing.

Doctors brushed off their concerns. Until Rachel's four-month check-up. During the exam, the pediatrician held Rachel up, with her feet touching the floor. A healthy baby will bounce up and down when supported this way. Rachel just flopped over like a Raggedy Ann doll. The doctor finally conceded that something might be wrong. The Epsteins had Rachel evaluated by physical therapists and called a neurologist. But because Rachel's symptoms weren't life-threatening, they had to wait two months for an appointment.

In the interim, Ken and Sherri attended an Israeli street fair near Boston. There, they came upon a booth sponsored by the National Tay-Sachs and Allied Diseases Association.

Ken and Sherri had heard about Tay-Sachs. They're both Ashkenazi Jews and had known enough to get tested for it before Sherri's first pregnancy. Before getting tested, they talked about what they would do if they were both Tay-Sachs carriers.

"We said that we wouldn't want to burden society with a child that would be 100 percent needy for all of its life," Sherri said.

But neither had been a Tay-Sachs carrier. It wasn't until they stumbled upon the NTSAD booth at the street fair, and picked up a copy of a booklet called "What Every Family Should Know," that they discovered a whole constellation of disorders common among Ashkenazi Jews. Ken and Sherri hadn't known there was anything to worry about besides Tay-Sachs. They had met with a rabbi for pre-marriage counseling, and he had given them some pamphlets about the so-called "Jewish genetic diseases." But they had never looked at them. Marriage was supposed to be a happy time, and neither they nor the rabbi had wanted to dwell on statistically improbable hypotheticals.

On the car ride home from the street fair, Sherri began flipping through the booklet. She read through the list of Tay-Sachs symptoms, just to be sure. Nope, that didn't sound like Rachel. She flipped next to a description of Gaucher disease. That didn't sound right either. Then she read the symptoms for something called Canavan disease: big head, irritability, poor motor control. It all fit.

Canavan disease, the booklet said, was a recessively inherited genetic disorder, and 1 in 38 Ashkenazi Jews were carriers for it. When Rachel finally saw a neurologist, at six months old, a battery of tests confirmed what Ken and Sherri suspected: she had Canavan.

"That was the moment everything changed," Sherri said.

Canavan disease is a disease of the myelin, the fatty substance that coats the nerve cells in the brain and body. Myelin, which in the brain is known as the white matter, makes it possible for neurons to relay messages rapidly. Children with Canavan disease have a mutation in a gene that produces an enzyme known as aspartoacylase. Aspartoacylase usually breaks down an acid that can destroy myelin. Because Canavan children lack this enzyme, the acid gradually builds up in their bodies, ravaging the myelin.

The result is the deterioration of many nerve functions. Canavan children have trouble focusing their eyes, weak muscles, and gradually worsening mental function. They eventually lose all motor control, require, and develop silent but serious seizures. The disease progresses differently for all children, but it is always fatal. The neurologist said Rachel probably wouldn't make it past her fourth birthday, and Ken and Sherri spent the next year in mourning.

But Rachel is seven-and-a-half now, and the Epsteins are no longer preoccupied by thoughts of her death. They're too busy dealing with life.

It's a Sunday morning in February, and the Epsteins are embarking on their exhausting daily routine at their house in Worcester, Massachusetts. A fire is blazing in the fireplace. Jessie is simultaneously playing a handheld video game and watching T.V. Ken and Sherri are padding around the house in their pajamas, getting ready to wake Rachel. Ken disappears upstairs and re-emerges a few minutes later with Rachel in his arms.

Rachel, who is still sleepily waking up, has a head full of fine, copper hair, green eyes, and her parents' fair skin. She is wearing her pink pajamas and has sleep in the corner of her eyes.

Ken holds Rachel for a few minutes before putting her in her wheelchair and wheeling her into the dining room. He goes into the kitchen and comes back with a syringe full of a grayish liquid. He lifts up Rachel's shirt and pushes the liquid in through a plastic "button" that leads to Rachel's stomach. After feeding her, Ken lifts her from her wheelchair and carries her into the next room to change her diaper.

"It's tough to not have her on the forefront of our minds almost all the time," Ken says.

Rachel's eyes wander, but she can make momentary eye contact. Rachel can't talk, but she can smile and laugh and understand things her parents say to her. She can't stand or sit on her own or even support the weight of her own head, but she can raise her arms and hands to about chest level.

Rachel's needs and demands have become routine. She has to be monitored all the time in case she has a seizure, so Ken and Sherri have hired a night nurse so they can sleep. They bathe Rachel in a special chair because she can't support herself. She takes seven medications a day. A plastic bowl of syringes for Rachel's feeding tube lives alongside the regular pots and pans on the kitchen counter.

"This is our normal abnormal life," Ken said.

The Epsteins have learned to cope by having a sense of humor — one that took their friends a while to get used to. Ken often carries Rachel around the house, and as she's gotten bigger, he occasionally misjudges the width of doorways or his distance from walls, and Rachel's head sometimes brushes up against them. "Oh no!" he'll joke. "She'll never walk again!" Or: "At least there's no brain damage."

But they've lost a lot, too. Sherri and Ken fight seemingly constant battles with their insurance company and spend huge proportions of their income on health care. Their friends are saving for their children's college educations or buying vacation homes, but Ken and Sherri can't even go on vacation because they can't find a caretaker who's not afraid to watch Rachel.

"What have I gained?" Ken asks. "A wonderful, beautiful family. What have I lost? A lot. This is not something I'd wish on my worst enemy. It's not normal for a young couple to know that we're going to outlive one of our children."

Beyond Tay-Sachs

The Tay-Sachs myopia that persisted for so many decades is beginning to give way. There are now ten genetic conditions that are commonly screened for among Ashkenazi Jewish couples: Tay-Sachs disease, Canavan disease, cystic fibrosis, familial dysautonomia, Bloom syndrome, Fanconi anemia group C, Gaucher disease type I, mucolipidosis type IV, Niemann-Pick disease type A, and DFNB1 sesorineural hearing loss. These disorders are wide-ranging in their effects, from the anemia and bone fractures of Gaucher to the fatal neurodegeneration of

Niemann-Pick. But all are remarkably more common among Ashkenazi Jews than the general population. Gaucher is the most common of the set, with as many as 1 in 12 Ashkenazi Jews carrying one copy of the disease allele.

Carrier screening programs, like the ones sponsored by Chicago's Center for Jewish Genetic Disorders, are usually targeted at young couples planning to conceive. The Center's programs screen for four diseases: Tay-Sachs, Canavan disease, cystic fibrosis, and familial dysautonomia. As D'Achille explains the statistics and the probabilities to the group assembled at Congregation Emmanuel in December, one young man asks a question that takes all the abstract talk of inheritance patterns and makes it personal.

"With a group this size, what percentage will end up being carriers?" he asks.

D'Achille hesitates, then looks around the room. "We have about 45 people here, so with a group this size, you'd expect at least one carrier for each condition," she said. "Possibly more."

Many screening programs maintain strong ties with Jewish communities. When the Chicago center was first developing its screening programs, it worked closely with the city's rabbis. The center developed what it called "Mazel Tov" (the Hebrew words used to bestow congratulations, on the occasion, for example, of a marriage or birth) packets, which contained information about Jewish genetic disorders, and had rabbis distribute them to young couples.

But Jewish communities are not monolithic, and different programs have emerged to serve different needs. In New York, the Orthodox community has developed a program known as Dor Yeshorim. Among Orthodox Jews, aborting a fetus with a genetic disorder is not acceptable, nor is choosing not to have children at all. Dor Yeshorim, founded in 1983, is a screening program designed to prevent engagements or marriages between two carriers.

For the recessively-inherited, single allele disorders, carrier screening is a model that works well. The Chicago center runs four screenings a year; since the program began in 2002, it has screened more than 500 young adults, about 8 percent of whom turn out to be carriers for one of those four diseases.

And interest is growing.

"We've had more and more people calling over the years," D'Achille said. "All of our programs are usually full. I think it's becoming more and more — I hate to use the word popular — but I think word of mouth has a lot to do with it. The Jewish community is pretty small and people, especially young people, seem to be talking about it with their friends."

The programs are expanding, too. As the genetic basis of the so-called "Jewish genetic disorders" have been identified, new tests are being added to screening panels. The American College of Obstetrics and Gynecology, which sets standards for obstetrical and gynecological care, has issued formal recommendations that all Ashkenazi parents-to-be be screened for at least Tay-Sachs, Canavan disease, familial dysautonomia, and cystic fibrosis. Most labs offer, and recommend, even more tests for Ashkenazi Jews.

"We have been adding diseases pretty steadily since the 90's," said Randi Zinberg, director of the genetic counseling program at the Mount Sinai School of Medicine, which currently offers an Ashkenazi screening panel that includes nine genetic diseases. "In the early 90's, it was pretty much only Tay-Sachs. Then we added cystic fibrosis, Gaucher, Niemann-Pick. We will be continuing to add to the panel."

Mount Sinai's labs test "a few thousand" people a year for one or more of the diseases on the Ashkenazi Jewish panel, Zinberg said. And screening is happening for people of other backgrounds, too; Mount Sinai offers all couples screening tests for genetic diseases based on

their ethnicities. Tay-Sachs, for instance, is also remarkably common in French-Canadian and Cajun populations. About 1 in 12 African Americans are carriers for sickle-cell anemia. Cystic fibrosis is prevalent among Northern Europeans. The blood disease beta-thalassemia is common among Middle Eastern, North African, South Asian, and Mediterranean populations, including Sephardic Jews. Indeed, Sephardic and Oriental Jews each have their own sets of common disorders.

Among people of every ethnicity, "screening now is starting to become more common. I think people are starting to see it as a standard part of reproductive care," Zinberg said.

Increasing complexity, increasing concern

The field of genetics has proceeded far past the days of the single-gene, recessively inherited disorders. Today researchers are exploring the genetics of diseases with far less straightforward inheritance patterns, particularly cancers.

A major breakthrough in cancer genetics came in 1994, when researchers discovered a gene that, when mutated, predisposed women to breast cancer. It was the first step toward understanding the molecular basis of the disease, but the discovery had limitations. The gene, named BRCA1, appeared to have an almost endless number of possible mutations. Because women could have any one of many mutations in the BRCA1 gene, screening for mutations was difficult.

But scientists soon came to notice an anomaly — some of the Jewish families that had donated DNA to the BRCA1 study had the exact same mutation. Was it possible that many other

Ashkenazi Jews shared it? The cooperation of Jews in genetic screening programs made it easy to search for the mutation on a wide scale. Tens of thousands of American Jews were being tested for Tay-Sachs a year, and they were providing blood and cell samples for the screenings. Researchers mined this genetic resource, using samples that were originally collected for Tay-Sachs testing to search for the BRCA1 mutation.

In 1995, researchers announced that announced that 1 in 100 Ashkenazi Jews had the exact same BRCA1 mutation, which increased the risk of breast and ovarian cancer. It was a staggeringly high percentage for a single cancer mutation.

The finding made headlines in almost every major newspaper. But often these headlines, and those about subsequent related studies, were misleading or inflammatory. Some made reference to a "Jewish gene" or referred to Jews as "mutant-gene carriers."

The study caused growing concern among some Jewish communities, particularly in Boston. In 1995, Jane Matlaw, the director of community relations at Boston's Beth Israel Deaconess hospital, began receiving phone calls from Jewish women wondering if they should be tested for a BRCA1 mutation. Matlaw wanted to be able to respond to these questions, so she organized a meeting with Boston's cancer researchers, health care providers, and Jewish community and religious leaders.

It was not a consensus-building meeting. It became clear the researchers wanted to mobilize the city's Jewish residents to participate in follow-up studies on BRCA1, said Judi Hirshfield-Bartek, a breast cancer nurse who attended the meeting.

Hirshfield-Bartek, herself an Ashkenazi Jew, was immediately wary. "'Whoa, wait a minute," she recalled thinking. "'Why do we even need to do that? And what's the benefit? Will our very genetic makeup be used to discriminate against us?'"

It became clear that other women shared the concern, so Matlaw and Hirshfield-Bartek organized a community forum at a Boston synagogue. Eight-hundred and fifty women showed up. Hirshfield-Bartek posed a question to the group: Would this research be to the benefit of mankind or to its detriment? This was not Tay-Sachs, which invariably occurred if the mutations were present and was invariably fatal. These were *predisposition* mutations, which may or may not ever actually lead to cancer. And there were no federal genetic privacy laws to protect women who tested positive for a BRCA1 mutation from employment or insurance discrimination.

A group of women worried about the implications of the research banded together. Officially, they became the Jewish Women's Coalition on Breast Cancer, but they called themselves "the loudmouth women," Hirshfield-Bartek said. They urged Jewish women not to be tested for BRCA1 mutations in the absence of a family history of breast cancer and refused to participate in follow-up studies.

"We were really challenging the status quo," Hirshfield-Bartek said. "We said, 'No. In Boston we're not going to do that. We're not going to just line up and let you take our blood.' The Jewish community as a whole has always been supportive of research. But this was a little different."

More was to come. That same year, researchers discovered a second gene involved in breast cancer, which they named BRCA2. It turned out that one particular BRCA2 mutation was also common among Ashkenazi Jews. Subsequent studies revealed that more than 2 percent of Ashkenazi Jews had certain BRCA1 or BRCA2 mutations, which increased their risk of breast and other cancers.

In 1997, a Johns Hopkins researcher accidentally discovered a mutation that predisposed Ashkenazi Jews to colon cancer. The mutation, he calculated, was present in 6 percent of American Ashkenazi Jews — about 360,000 people — making it the most common cancer-related genetic mutation ever discovered in any ethnic group.

By the time the colon cancer finding was announced, even scientists were acknowledging the worries some Jews were beginning to express. In an editorial in the September 1997 issue of *Nature*, the issue in which the colon cancer study appeared, the editors wrote: "One of the profound ironies of modern science is that no social group is better equipped either in its ability to provide reliable, ordered health data or in its capacity to interpret its genetic and medical implications than the Jewish community. At the same time, no group has greater reason to be wary of the way in which such implications can be misused."

Hadassah, the largest women's Jewish organization in the U.S., promptly took up the cause. Worried that Jews would become part of an "insurance underclass," Hadassah began what would turn into a years-long campaign to get Congress to pass genetic privacy and anti-discrimination laws.

There was also palpable concern about another, less overt kind of discrimination. The Jews, if you weren't reading the genetic news carefully — and sometimes even if you were — seemed to be being branded as a "diseased" population.

"Jews have been overstudied," said David Jones, an MIT historian of science who is writing a book on the history of race-based therapeutics. "A high percentage of the genetic disorders we know about have been studied in Ashkenazi Jews. If you just read a book on genetic disorders not knowing the background you'd think, 'Oh my god, what's wrong with this group?'"

"The fallacy of biological Judaism"

At two minutes after seven in the morning, Bob Pollack barrels in through the door of Congregation Ramath Orah, an Orthodox synagogue in New York's Upper West Side. He grabs a prayer book, heads for a pew on the men's side of the sanctuary and quickly sheds his parka and fleece hat. Pushing up his shirt-sleeves, he dons a prayer shawl and yarmulke, and fastens tefillin, Jewish prayer boxes, to his arms. By five minutes after the hour, he's ready to join a few dozen congregants for shacharit, the daily morning worship service.

Fifty-five minutes later, after a few words with the rabbi, Pollack emerges into the cold morning. Though the sky is finally light, Pollack's work day doesn't start for another two hours. So over a breakfast of a bagel with cream cheese, fruit, and coffee, he explains what's wrong with the whole idea of "Jewish genetics."

""There is the tacit acceptance that the Jewish population is a genetic group," he says. "That's a mistake. It's a deeply serious political mistake, and it's a very queer genetic mistake."

Pollack has a bushy salt-and-pepper beard and eyes that focus intensely when he is talking about something he feels passionate about, which he often is. His lips curl into a slight smile when he's recounting a scientific or religious claim he finds particularly preposterous, which he often is. As the founder and director of Columbia University's Center for the Study of Science and Religion, Pollack expertly straddles the worlds of scientist and lay person. (He's written more than 100 articles for peer-reviewed scientific journals, in addition to op-eds, reviews, essays, and books for the public.)

As an undergraduate at Columbia, Pollack studied physics, but he switched to biology in graduate school. ("I wished to be a physicist," he said. "And then I found that to study physics

was necessarily to become involved in grants that had a military content, and I felt uncomfortable with that.") After a post-doc at New York University, he ran a lab at Cold Spring Harbor for several years before returning to Columbia as a biology professor. In 1982, he was appointed the dean of Columbia College, becoming the first Jewish dean of an Ivy League College.

Pollack found the world outside the lab to be an open and expansive place and searched for ways to stay connected to that world after his deanship ended in 1989. For a while he went back to the lab, but in 1999 he founded the Center for the Study of Science and Religion. Outspoken and seemingly tireless, Pollack has a deep concern for the social and political implications of what happens when the work done inside scientific laboratories reaches the world outside them.

As a biologist, Pollack understands why the genetics of Jewish populations interests scientists. But he thinks genetic studies of Jews are accompanied by a raft of problems. He worries that studies of diseases in Jews, or any other minority group, might confirm prejudices about them by implying that they have "weak DNA." But even more than that, he thinks studies of Jews as a group will only reinforce the misconception that Jews are somehow genetically, biologically different from everyone else.

"The fact that Ashkenazic Jews have a high frequency of single-gene differences driving single-gene diseases sets the implication that the normal background allele distribution is also restricted, that there are 'Jewish genes,' " said Pollack, who wrote an article in 2003 called "The Fallacy of Biological Judaism."

In some cases, he says, it's Jews themselves who cling most fiercely to notions of biological difference. Many Jews are raised with the idea that there is a special Jewish soul, or

that they are Jewish not because of their Jewish teachings and learnings, but because they are born Jews, because they are born different, he says. Those, he says, "are beliefs that are not founded in biology. That's a shock to many Jews, who would cling to a Tay-Sachs allele as a sign that it's not true. That's how desperately they hold on to biological Judaism."

Pollack is particularly scornful of a study published last year that used the selective advantage argument to explain the high frequency of Tay-Sachs and related disorders among Jews. This study suggested that being a carrier for Tay-Sachs was associated with high intelligence, particularly numerical intelligence. The study attempted to use this logic to both explain the high frequency of Tay-Sachs among Jews and to assert that Jews were more intelligent than other populations — and that there was a biological basis for this supposed difference. The study provided little empirical data to support its claims, and Pollack — and most other scientists — largely dismissed it as bunk. But Pollack was troubled by the positive reaction it received among some Jews. The response of some Jews, he said, was " 'See, I told you we're different, I told you we're smarter, I told you we're genetically Jewish.' What would you do if this were the case? Would you say, 'Thank God I'm Jewish — Tay-Sachs is a risk but at least I'm smart' "?

He finds those lines of thinking, whether they come from within the Jewish community or without, to be troubling. In fact, he finds the whole endeavor of doing genetic research on America's minority communities to be fraught with problems. He says we're simply not ready to handle the consequences of our ever-expanding genetic knowledge and strongly indicts scientists for failing to do their part to ensure society is ready for the genetic information they seem to be churning out daily. In America, he says — with its virtually non-existent genetic non-

discrimination laws, privatized medicine, and history of racism and prejudice — having genetic data about large numbers of people is downright dangerous.

He returns to his metaphor of Jews as the canaries. "The canary in the cave is that we have been pegged as different for thousands of years," he said. That's the canary. Every technology for picking up difference picks us up as different. There's still people walking around with numbers on their arms because of that. So we are here to teach the risk to people who may think it's the golden day of medicine, that as soon as we get the information we should use it. Our experiences say how it's used can be toxic. Our ancestors keeled over in the cave because of the bad biological air. So we're here to say, 'That can happen to you.' "

The specter of the past

In 1972, Harvard evolutionary biologist Richard Lewontin published a famous article called "The Apportionment of Human Diversity." In it, he examined genetic variations in seven different population groups — using his terms, Caucasians, Black Africans, Mongoloids, South Asian Aborigines, Amerinds, Oceanians, and Australian Aborigines — and came to the remarkable conclusion that 85 percent of human genetic variation was due to differences within populations and not between them. In later years, Lewontin would famously illustrate the point by remarking that if all the humans on Earth became extinct except for the Kikuyu tribe in Kenya, the repopulated planet would have 85 percent of the genetic diversity it has today.

Lewontin's conclusion — that race accounts for very little genetic variability and is therefore of "no social value" and "virtually no genetic or taxonomic significance either"— dominated for the next thirty years, said David Jones, the MIT historian of science. Partly it was

because scientists didn't really have the tools or technology to analyze the problem more carefully. But partly, it was because the issue was intensely political, too hot to handle.

History provided reason enough for caution. There is a long record of assertions of biological difference between humans who looked different. In 1758, Carl Linnaeus, who developed the binomial classification system we use to classify all living organisms today, proposed two different categories for white and black humans: *Homo sapiens europaeus* and *Homo sapiens afer*, respectively. Linnaeus would later divide humans into four categories, based on color and geography: white Europeans (*europeanus*), red Americans (*americanus*), yellow Asians (*asiaticus*), and black Africans (*africanus*). Eventually, this classification resulted in a hierarchy of races, with Europeans at the top.

In the following century, eugenics was born. The father of the modern eugenics movement was Francis Galton, a cousin of Charles Darwin. Galton used Darwin's ideas about selection and evolutionary fitness to develop his ideas about using selective breeding to improve the human race. Through encouraging the "most fit" people to reproduce and discouraging the "least fit" from doing so, Galton explained how we could improve the stock of the human race, much as a breeder could do with dogs or horses.

In the early 20th century, interest in eugenics expanded in the U.S. and Europe. Many U.S. states enacted laws that forbade undesirables from marrying, and some eugenicists even advocated sterilizing the "unfit," a term that primarily referred to the diseased, the disabled, immigrants, and the poor. Ideas of racial purity were closely tied to eugenic arguments, which were usually racist, anti-Semitic, anti-feminist, classist, and more.

These lines of thinking culminated in the horrific eugenic programs of Germany's Nazi regime. State programs in Germany rewarded Aryan couples who had children and sterilized or

euthanized the mentally and physically disabled. Jews, in particular, were victims of the Nazi obsession with racial hygiene. The Nazis were not the first to view the Jews as members of a distinct biological race. In the Middle Ages Jews had become viewed as "diseased" by Christian Europe, and in later centuries Jews were thought to have flatter feet than gentiles did — a reference to the devil's hooves.

But the Nazis put conceptions of biological "Jewishness" to new and unimaginable ends. Jews, they believed, could be identified by a characteristic posture, forehead, brow, nose, eyes, and ears. And in case this left any doubt about who was Jewish, the Nazis forced Jews to wear yellow stars on their clothing. Worried that the Aryan "race" would degenerate if Jews were allowed to reproduce without restriction, the Nazis killed 6 million Jews — in addition to other undesirables such as Gypsies and homosexuals — during the Holocaust. Among Jews opposed to the current research on Ashkenazim, the Nazi eugenic programs loom large.

Pollack, for one, isn't shy about invoking the Nazi analogy. He thinks that chapter of history is utterly relevant to today's genetic research and is incredulous that, given the history of Nazi eugenics, modern Jews have been so willing to believe in ideas of biological difference.

"There's a failure of Jewish communities to understand the misuse of the notion of the gene — to allow themselves to be called a homogenous genetic population for the sake of the marketing of genetic tests and designer drugs," he said. "That isn't the same as wearing a yellow star, but it's close enough to give me the creeps."

Indeed, history shows Pollack's fear that genetic screening could lead to discrimination is certainly not unwarranted. In the early 1970's, at the same time Tay-Sachs screening programs were getting underway, so were screening programs for sickle-cell anemia, a recessively inherited blood disorder common in African Americans. The programs were poorly designed and

rife with misinformation; sometimes carriers for the sickle-cell trait were not distinguished from those who actually had the disease. What's more, the mass screening programs led to insurance and employment discrimination — including discrimination by the U.S. military. By 1972, African American leaders were already calling the screenings racist and equating them with the rebirth of eugenics. Not long after they began, the screenings were all but abandoned.

After eugenics

After the Holocaust, eugenics rapidly fell out of fashion, and social scientists began to argue that race was merely a social construction. When Lewontin, a biologist, lent his professional weight to the argument that differences between races were negligible, social scientists viewed it as the scientific validation they'd been waiting for, said Jones, the scientific historian. Race, the popular consensus became in the 1970's and in the decades after, was nothing more than a superficial and biologically irrelevant distinction society had created between people who looked different.

The power of this belief was evident in the response to scientific attempts that threatened to topple it. In 1993, shortly after the Human Genome Project was launched, a group of scientists established a related project. While the Human Genome Project set out to map the vast swaths of DNA that are shared by all humans, this project, called the Human Genome Diversity Project and run out of Stanford University, aimed to map the 0.1 percent of DNA that varies among humans. The project, which planned to collect DNA samples from different human populations around the world, was based on the assumption that these populations would have important genetic differences.

The project became hugely controversial. Anthropologists claimed that the project was based on antiquated notions of race, worried that it would exploit indigenous peoples, and claimed that it evoked "colonialist" modes of thinking. Many worried that the data generated would lead to biological conceptions of race and, subsequently, racism. Indigenous rights groups feared that scientists would patent DNA sequences they discovered in native populations. Conspiracy theories ran rampant — ranging from the concern that some governments would deny people rights based on genetic tests for "race" to the idea that the entire project was actually a covert U.S. military project launched in an attempt to design racially-targeted biological weapons.

The project eventually collapsed under these political and social pressures, Jones said. But it was only abandoned temporarily; the HapMap, one of the project's descendants, seems positioned to finally provide the tools for more closely examining the genetic variation among people. Lewontin's 85 percent statistic has held up over the years, but so has another observation he made: about 6 percent of human genetic diversity is explained by race. (The remainder is explained by differences between populations within a race.)

"There were always people who were arguing against the idea that race was biologically unimportant. They weren't able to do much, for scientific and political reasons," Jones said. But improving genetic technology and computational power has lowered at least the scientific barriers. "Now they've been very carefully mapping that 6 percent."

Scientists agree that there is no "race" gene, but some are beginning to attack Lewontin's argument that the genetic differences between races are superficial and irrelevant. In a 2003 article called "Human genetic diversity: Lewontin's fallacy," British statistician A.W.F Edwards critiques Lewontin's logic. Lewontin looked at one genetic marker at a time and found that very

little of the variation at each marker was due to race. But the human genome can provide information at a higher level. We end up looking the way we do, as both individuals and members of various populations, not because of any single nucleotide or gene, but because of all of them taken together. Whatever biological basis there is for race, Edwards argues, exists in the combination and correlation of all these genes and traits.

The fact remains that two people whose ancestors are from the same geographic region will, on average, be more genetically similar than two people whose ancestors are from different ones. Now, some of these differences are actually being applied to treatment choices. In a 2004 article called "Will tomorrow's medicines work for everyone?" biologists Sarah Tate and David Goldstein noted that between 1995 and 1998, 15 new drugs came with a statement that mentioned racial or ethnic differences in response. At least 29 medicines had been documented as having substantially different effectiveness or safety in certain racial or ethnic groups. Though some of this difference may be due to environmental factors, the evidence for a genetic basis for the difference is, in some cases, strong.

Of these 29 substances, one, a drug called BiDil, has spurred much of the recent race-based medicine debate. The FDA rejected BiDil, which is used to treat heart congestion, in 1997, after a mixed-race trial failed to demonstrate that the drug was more effective than a placebo. But when scientists looked at the data more carefully, they discovered that BiDil had been more effective for the blacks in the trial than for the whites. The drug company joined with the Association of Black Cardiologists to sponsor a new trial — this time to test the drug's effectiveness specifically in blacks. The drug proved so effective, reducing mortality in as many as 43 percent of patients, that the trial was halted early so that the patients who had been receiving the placebo could start getting the real thing. In June 2005, the FDA approved BiDil,

but with a stipulation: it was only for self-identified 'black' patients. It became the first drug ever to be approved for use specifically in one racial or ethnic group.

What's in a name: race as proxy

This winter, Pollack discussed genetic diseases and genomic medicine on a New York public radio program. A doctor called into the show, telling Pollack about the promise of race- and ethnicity-based medicine. The doctor related a story about a commonly prescribed anti-asthma medication. This particular asthma medication, the doctor said, had been shown to cause a fatal reaction in some black children. Therefore, the doctor argued, the medicine should be prescribed only to white children. When Pollack pressed him for hard numbers, the doctor said that 1 in 5 black children had a serious adverse reaction to the drug, while only 1 in 10 white children did.

Pollack was incredulous. "So I said, 'What you're saying is, 4 out of 5 black kids are going to be deprived of a medicine that would work, and 1 in 10 white kids is going to be given a medicine that could kill him?" he recounted. "And you don't have any idea what the allelic differences are and you're not interested in that. So why is that good medicine?"

The doctor was using race to infer patients' genetic makeup. But it's not skin pigmentation or facial features that have anything to do with the disease, it's the other genetic variants that have popped up in particular races and ethnicities. Skin color and hair color are phenotypes — the physical trait expressed — but what medicine really cares about is genotypes — a patient's actual combination of alleles. That means that even though basing medicine on

race or ethnicity may produce better results than basing it on nothing, it will always produce some mistakes.

Pollack understands the appeal of pharmacogenetics and even thinks it has promise. The approach, he said, makes sense: determine whether a disease is a result of a mutation in a single gene, develop a drug that compensates for that gene's lost function, screen patients for that mutation, and give the drug only to them. He'll happily list success stories, examples when that approach has worked. Gleevac, the leukemia drug, is one. Another was the development of an AIDS treatment based on the discovery of a genetic variant that naturally protects against the disease. "Of course," he said, "they have nothing to do with race."

That, he believes, is where science has gone wrong. The rational approach assumes that people know their own genotypes, which most don't. "So what you look for are socially acceptable markers for genotypes," he said. He pauses. "They're all wrong. Because they're all associated with multi-genic phenotypes. Race is the classic one. Ashkenazic Judaism is another one. What do you mean by Jewish? What do you mean by black? If you have the gene and the allele why aren't you talking about that rather than the social construct?"

Such inexactness will undoubtedly have medical consequences. Allele frequencies do differ across populations — racial, ethnic, geographic — but only rarely are certain alleles confined solely to one population. Race or ethnicity then merely becomes an over-simplified stand-in — or a "proxy," "shorthand," or "flawed surrogate," depending who you ask — for a much more complicated pattern of genetic variation. Not all blacks will have whatever genetic variant makes BiDil an effective therapy (researchers haven't yet been able to identify what genes might be involved), but some whites almost surely will. Eventually, scientists and doctors will be able to use genetic screening to determine exactly which patients will benefit from BiDil,

regardless of their race. In the meantime, however, making race a proxy for genetics will inevitably mean giving BiDil to some people who won't benefit from it and keeping it from some people who might.

"What starts out as rational pharmacogenetics attached to a single gene, a single mutation, becomes racial profiling through the marketing of a drug whose mechanism is unknown," Pollack said. "The sale of drugs to African Americans and not to whites, is to imply a genetic difference by that single gene difference, which is crazy. And fits a social structure which is crazy. So when BiDil emerges, it sounds like a favor to black people. It is in fact a continued insult of a difference which is presumptively biologically deep when it's in fact biologically shallow and culturally deep."

And that's the connection he sees between Ashkenazi Jews and African Americans. Both groups have a history of being stigmatized or marginalized. For both groups, this discrimination often came in the guise of a scientific basis of difference or "otherness." Now, both groups are again allowing themselves to be told by science that they are biologically different. (Many African Americans heralded BiDil, which they said would finally help to equalize their unequal burden of heart disease.) And medicine's treatment of both groups as genetically unique, Pollack said — ranging from screening for Tay Sachs to prescribing BiDil — has sent the message that race and ethnicity are appropriate proxies for genetic difference and a reasonable basis for decisions about medical treatment.

"But it's irrational, dangerous, stupid, and wrong," Pollack said. "Otherwise, it's fine."

And it goes beyond just the burden of the sometimes intangible consequence of social stigma. It's easy to imagine very concrete inequities that could result from a race- or ethnicity-based approach, and that is, unsurprisingly, a favorite pastime of its critics.

"Suppose BiDil were developed as a drug that had shown benefit largely or exclusively in self-described European American populations," said Mark Rothstein, a bioethics and law professor at the University of Louisville. "Can you imagine what happens when some African American or Asian American goes to the doctor and says, 'I just read that there's this new drug that might be more effective in treating my cardiovascular disease,' and the doctor says, 'Well that's just for white people'? We're on the road to getting to that point."

Rothstein said he worries about the day when television drug commercials begin, "Are you Hispanic? Do you have diabetes? We have come up with a drug that's just for you!"

It might seem like an exaggerated speculation, but it's not far off base. Take, for instance, the full-page magazine advertisement the National Gaucher Foundation ran in 2005. Gaucher disease, which has the highest carrier rate of all the genetic diseases prevalent among Ashkenazi Jews, is a recessively inherited genetic disorder that causes bleeding and bruising, bone problems, and an enlarged liver and spleen. The foundation's ad features a large photo of a woman with her eyes half closed and her head resting on her arm. "If you often feel tired, it could be anemia," the large text at the top of the ad reads. "If you're Jewish, it could be Gaucher Disease." Only the fine print at the bottom of the ad gets around to mentioning that although it's most common among Ashkenazi Jews, "Gaucher can affect anyone." (Nor does the ad initially make any distinction between Ashkenazi Jews, who are at heightened risk, and Oriental and Sephardic Jews, who are not.)

"I don't know if we've done a good job anticipating this," said Rothstein, who began an NIH-funded study of the social and ethical implications of pharmacogenomics in 1998. "In the late 90's, I saw that this was coming down the road. I thought that it was time to look into these problems before they materialized. And unfortunately they've materialized."

There's also concern about a deeper sort of discrimination. If drug companies have to invest money to research, develop, and test drugs for many different populations, some worry that the companies will be most inclined to do that for populations best equipped to pay for the final product. Not all populations will be as well-connected to or trusting of the medical establishment as Ashkenazi Jews have been, and research may not get as far in these communities. Studying each racial and ethnic group separately seems almost destined to produce inequities.

Yet, it may still be a productive strategy. Basing treatment on race or ethnicity, will, on average, be more effective than basing it on nothing at all. And proponents of pharmacogenetics almost universally say that race and ethnicity are merely being used temporarily. When knowledge and technology improve, they say, race and ethnicity will gradually fade out of the equation, and medicine will become truly individualized — based on the exact genetic profile of each patient. That ultimate goal, Jones said, seems to be pretty benign.

"The stuff with race seems to me less benign," Jones said. For him, it's not that there are too few reasons to use race in medicine — it's that there are too many reasons not to. "There are just so many problems. Part of it's just a historical reflex. The standard now shouldn't be to use race if we think it might be useful. We should only use race if we have to."

"The gifts of the Jews"

Some people would argue that we do have to — that we have learned things from studying Jewish communities, for instance, that we would have discovered no other way. The concerns have been real, but so, too, have the successes.

There have been successes for Jewish communities, which have made genetic screening an accepted part of family planning. Ashkenazi Jews are also among the first populations to benefit from genetic screening, including breast cancer screening tests. An African American woman could be screened for the BRCA mutations, but her results may not mean very much. A negative result could mean that she has no genetic predisposition to breast cancer. Or it could simply mean that she has a different BRCA mutation, perhaps one that is common among African Americans but that researchers have not yet identified.

There have also been success for medicine as a whole, Ostrer said, advances that stem from research on Ashkenazi Jews but will benefit all communities.

"What are the gifts of the Jews?" Ostrer asks, leaning back in his chair and clasping his fingers together on top of his head. He can go on and on. "The sheer discoveries for one thing. Some of the discoveries really wouldn't have been made if the diseases hadn't occurred in Jews. Familial dysautonomia, Tay-Sachs disease. Tay-Sachs disease wouldn't have even been on the map if it hadn't been a Jewish disease. Bloom syndrome, for which, really the majority of patients are Jewish. Canavan disease. The development of large-scale genetic testing programs, which originated with Tay-Sachs. Enzyme replacement therapy," which has proved to be the most effective treatment for diseases like Gaucher, which leads to spleen, liver, and bone problems and is caused by an enzyme deficiency. "If Gaucher disease hadn't been so prevalent among Jewish populations we wouldn't have enzyme replacement therapy."

The concern that the research will stigmatize Jews or mark them as different is "legitimate," Ostrer said, but "it really hasn't found its way into the mainstream." Ostrer says he has had no trouble recruiting Ashkenazi Jews to even large genetic studies. Surveys of his

patients have revealed that they seem to support and want whatever genetic disease testing is available.

Work with Ashkenazi Jews also taught researchers valuable lessons about how to bring genetics to the communities that are affected by it. Education and genetic literacy are vital. So is working with leaders and organizations within the community — rabbis played as large a role as doctors in bringing genetic screening to Jews. Any genetic test offered should be sensitive, specific, and accurate, and the message about what the results mean should be clear. Today's guidelines for genetic screening are largely based on these lessons from working with American Jewish communities, Ostrer said.

And still more successes, and more research projects, are expected. "Once you know about genetic susceptibility then it leads to secondary studies to identify genetic modifiers and environmental interactions," Ostrer said.

Ostrer and the members of his NYU lab are currently working on studies of susceptibility to prostate cancer among Ashkenazi Jews. A Johns Hopkins researcher is studying Ashkenazi Jewish families with a history of schizophrenia and bipolar disorder; more than 5,000 Jews from more than 1,200 families have already been enrolled. This winter, research at Albert Einstein College of Medicine uncovered a genetic mutation linked to Parkinson's disease in Ashkenazi Jews.

Although research on Ashkenazim has been going on for decades, the pace, Ostrer said, is definitely not slowing down: "No, not at all, not at all, not at all, no."

The genomic future

Genomic medicine isn't slowing down either. In fact, it's absolutely inevitable. Knowledge about the genetics of medicine has been increasing rapidly, and scientists do not have a tendency to ignore knowledge. By 1989, scientists had used hereditary studies to locate four genes that were linked with disease, according to the National Human Genome Research Institute. By 1998, they had located more than 100.

"There is this remarkable change in the ability to study DNA," Altshuler said. "Five years ago, we could maybe detect one one-millionth of a person's DNA variation in a single experiment. Today we think we can get 80 or 90 percent in a single experiment. There's this tremendous opportunity to study genes."

It's inconceivable that scientists would not use this ever-expanding knowledge for medicine. In 2005, a group of scientists at a National Human Genome Research Institute meeting predicted that in a mere ten years, a person may be able to get his entire genome sequenced for $1,000. Genetic knowledge will affect the way medicine prevents, diagnoses, and treats disease.

In this ideal future world, still many years away according to most geneticists, everyone will have their genomes sequenced. Those predisposition and disease-causing genes we each carry? We'll know what they are. And once we know, presumably at a young age, we can start our preventative programs. Mutation that predisposes you to breast cancer? Yearly mammograms. At risk for heart disease? A special diet and exercise regime. Some scientists are already exploring a field known as nutrigenomics, in which diets are individually prescribed based on each person's genetic profile.

Altshuler is both hopeful and realistic about the future. In the next three to five years, he predicts more discoveries about the genetic causes of disease, followed by "tremendous efforts" to turn that knowledge into practical new medical diagnostic and treatment tools. "It ain't gonna happen in a year-and-a-half," he said. "But that doesn't mean we shouldn't be excited." Genomics, Altshuler says, may prompt a revolution on the order of the one that swept medicine a century ago, with the discovery of antibiotics.

For years, researchers have been hopeful about a treatment known as gene therapy. If disease is caused by the disruption of the gene's function, doctors can either treat the disease by compensating for that lost function — what most traditional medicines do — or by somehow repairing or replacing the gene — what gene therapy aims to do. In gene therapy, copies of the functioning gene are inserted directly into a patient's body, where the gene then begins to perform its normal function. Rachel Epstein, for instance, was one of ten children to participate in a gene therapy trial for Canavan disease. In May 2003, doctors drilled six holes into her skull and inserted functional genes for aspartoacylase, the enzyme her body had been missing. The genes traveled to Rachel's brain cells and began manufacturing the enzyme, which in turn, helped to limit the build-up of the acid that had been ravaging her brain. The therapy vastly improved her functioning, her parents say, and subsequent tests revealed that her acid level had decreased. Gene therapy has been slow to take off because of some safety concerns and public relations disasters, but researchers still have great hope for it as a treatment for hereditary disease. But of course, progress in gene therapy depends directly on progress in understanding the genetic causes of disease. Gene therapy for Canavan became possible only after researchers had pinpointed the exact mutation, and genetic product, involved.

In addition to helping design new treatments, genomics may eventually help doctors better determine which of the "old-fashioned" treatments, like prescription medicine, will be most effective. Last year, the FDA approved a gene chip that can identify mutations in two genes involved in drug metabolism. Based on the variants that the chip detects, patients can be classified as poor, intermediate, extensive, or ultra rapid metabolizers. People who metabolize drugs more slowly than normal are at risk for drug overdoses and toxic side effects if the drug builds up in the bloodstream. Such patients should be prescribed lower doses of drugs, while fast metabolizers, whose bodies rapidly break down medicines, may need higher doses for drugs to be effective. Though drug metabolism does vary among ethnic groups, the guesswork of trying to infer metabolism from the patient's ethnicity is eliminated because scientists have been able to identify the actual genes involved. The chip has already come into limited use by physicians.

"Five years from now — well maybe not five years from now but 15 or 20 — there will be a million of these chips," Jones predicts. In the ideal system, he said, all patients would be tested for the genes that regulate drug metabolism. Whenever a doctor prescribes a drug, he could look up the results of the patient's genetic screen to determine if the patients is a poor metabolizer, for instance, and should be started on a lower dose. Ethnic screening would never be involved.

The approach can also be used to manage specific side effects to certain drugs. Last summer, the FDA approved a new acne medication, but required that patients being prescribed it first be tested for a genetic mutation that could cause serious anemia as a side effect.

But if anything is clear about genetic medicine, it's that it won't be enough to just have all the information — we still need to think seriously about what we will do with it. The early data already illustrates the difficulties. Last year, DeCode Genetics discovered a genetic mutation

that increased the risk of heart attacks. The mutation is present in 30 percent of European Americans, but just 6 percent of African Americans. But, among those who do inherit it, the mutation increases the risk of heart attack only 16 percent in European Americans but a whopping 250 percent in African Americans. What should a doctor do with this information, then? Should he screen his white patients, who are more likely to have the risk-raising mutation? Or should he screen his black patients, who are less likely to have the mutation but more likely to suffer from it if they do?

Such conundrums may multiply as genetic and genomic studies yield more complex statistics and probabilities. In the end, Jones thinks, doctors will still be best off taking the cautious, empirical, and equitable approach they do now. Start everyone on a low dose and increase it if necessary. Screen the patients who have other risk factors for heart attacks. He doubts genomics will prompt a radical paradigm shift in medical treatment — at least for everyone.

"About 20 years from now they're going to have this vast amount of data, and what it all means is that 9 times out of 10 we treat patients the same way we're treating them now," he said. "The typical patient responds the same. If a black person and white person come into your office, 90 percent of the time, which is pretty good, you should treat them the same. The question is what to do about that other 10 percent."

Jones is certainly not alone in questioning whether genomic medicine will truly have the magic bullets some scientists have been advertising. But whether it ultimately succeeds or not, "I'm sure the experiment will happen," he said.

Race is already beginning to give way to ethnicity, and that, too, will eventually dissolve. But the social concerns, effects, and fears may not disappear as readily. Even if ethnicity based

medicine is only temporary, scientists need to address these social concerns head-on. Otherwise the research may be stopped in its tracks, before producing anything useful.

"If we lose sight of the hope that we might be able to help people with terrible diseases, then we sort of get confounded by all the bad things that might happen," Altshuler said.

And in the end, if its promises are borne out, the real potential in genomic medicine will not be in its ability to make ever-finer distinctions among populations, but in its ability to improve the baseline level of care for individuals. All of them.

"Are you sure you're not Jewish?"

Two months after Rachel Epstein was born, the American College of Gynecologists and Obstetricians officially recommended that all Ashkenazi couples be screened for Canavan disease. ACOG recommendations that Ashkenazi couples be screened for certain genetic disorders have helped reduce the number of children born with these disorders.

Stories about Tay-Sachs usually focus on the 90 percent decrease of live Tay-Sachs births in the Jewish community. In 2003, the headline for a *New York Times* story on Tay-Sachs carrier screening read, "Using Genetic Tests, Ashkenazi Jews Vanquish a Disease." But the disease has not been vanquished. In part this is because Tay-Sachs is an autosomal recessive disorder, which means the recessive disease allele is likely to silently persist in the population for generations to come. But in part, the failure to vanquish Tay-Sachs has had something to do with its identification as a "Jewish genetic disease."

"When you use that term, then those genetic diseases become Jewish, and only Jewish," said Gershkowitz, noting that although Tay-Sachs does occur, though more rarely, in the general population. "It's a label. And I think that the people who are Jewish take notice, and others don't. And they say, 'Oh, this doesn't affect me.'"

Gershkowitz's office at the NTSAD headquarters in Brighton, Massachusetts is piled with stacks of papers. The filing cabinets lining the walls are full, and the overflow fills boxes on the floor, the tops of cabinets, the windowsills. Many of the posters and pamphlets talk about screening for the constellation of disorders that are common in Ashkenazi Jews. But inside the filing cabinet, Gershkowitz has a folder that says, "French Canadian." And another labeled "Black Families."

Over the years, the profile of the traditionally "Jewish" genetic diseases has been changing, especially as Jewish communities have become more savvy about testing. The NTSAD gets calls from all over the world — Mexico, Jordan, Sri Lanka — and many are not from Ashkenazi Jewish families.

The NTSAD celebrates its 50th anniversary next year. As the association, which features the Jewish Star of David in its logo, commemorates its half-century of work, it's trying to strike a balance between serving Jewish communities and expanding out past them.

"It's a double-edged sword, because these diseases are pan-ethnic," Gershkowitz said. "So while you want to make sure that people who are in a high-risk population such as Ashkenazim, to know about them, you want people to realize they don't only occur in people who have an Ashkenazi background."

Gershkowitz dreams of the day when universal carrier screening will become possible, allowing all couples, not just high-risk ones, to be screened for Tay-Sachs and other disorders.

She has a seemingly endless number of stories about doctors who have failed to get past the proxy problem — when the rough category of self-reported ancestry becomes a stand-in for genetics.

Gershkowitz relates the story of a husband and wife, neither of whom were Jewish. They had a child — a "beautiful little boy, just beautiful," Gershkowitz said. But his development was slow and the parents could tell something was wrong. Specialists ran a battery of tests, and the results were pointing toward Tay-Sachs. But the doctor was hesitant to make the official diagnosis. "He couldn't believe what he was seeing," Gershkowitz said. " 'If they're not Jewish, how could this be?' It actually delayed the diagnosis." Some parents of Tay-Sachs children, Gershkowitz said, have even brought wrongful-birth suits against doctors who failed to mention genetic screening.

Gershkowitz pulls out some of the pamphlets and educational materials the NTSAD has issued over the years. As she flips through them, she tells the story of each child pictured. She points out a picture of a toddler with a mess of brown hair and big, brown eyes. "This is a Hispanic boy with Tay-Sachs. Not Jewish." She flips to the next brochure, which pictures blond infant named Nickolas Duvall. "Here's another little boy with Tay-Sachs. Not Jewish."

She turns to the next booklet, pointing out a photo of a father holding his infant son. She's still incredulous about how doctors treated him. "When you have an Asian couple come in with a child with Tay-Sachs, and they look right at the father who's Chinese, and they say, 'Are you sure you're not Jewish?' And the father, who's Chinese, says, 'I'm sure,' and he himself is a physician — I mean, it's absurd," Gershkowitz says. "What difference does it make? Don't look at the guy who's Chinese and ask him if he's Jewish. Diagnose his kid and see what you can do for him."

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INTERVIEWS

Much information for this thesis came from personal and telephone interviews with the following individuals.

David Altshuler: Director of the Medical and Population Genetics Program at Harvard and MIT's Broad Institute. Public talk at MIT Museum, 15 November 2005.

Dania D'Achille: Genetics Counselor at Chicago's Children's Memorial Hospital; Genetics Counselor at Chicago Center for Jewish Genetic Disorders. Telephone and Personal Interviews.

Sherri and Ken Epstein: parents of Rachel Epstein, child with Canavan disease. Telephone and Personal Interviews.

Jayne Gershkowitz: Executive Director, National Tay Sachs & Allied Diseases Association. Personal Interview.

Judi Hirshfield-Bartek: co-founder of Jewish Women's Coalition on Breast Cancer; Nurse Coordinator at the Breast Care Center at Beth Israel Deaconess Medical Center. Personal Interview.

David Jones: Assistant Professor, MIT's Program in Science, Technology, and Society. Personal Interview.

Mark Levin: an oncologist who has written on Jews' participation in genetic studies. Telephone Interview.

Jacob Lindenthal: creator of "The Lindex: A Database of the Disease Experience of American Jews;" Professor, Department of Psychiatry, New Jersey Medical School. Telephone and Personal Interviews.

Karen Litwack: Director, Chicago Center for Jewish Genetic Disorders. Telephone and Personal Interviews.

Harry Ostrer: Professor of Pediatrics, Pathology and Medicine, New York University Medical Center. Personal Interview.

Robert Pollack: Director of the Center for the Study of Science and Religion at Columbia University. Telephone and Personal Interviews.

Mark Rothstein: Director of the Institute for Bioethics, Health Policy and Law at the University of Louisville; author of *Pharmacogenomics: Social, Ethical, and Clinical Dimensions* (2003). Telephone Interview.

Randi Zinberg: Director, Genetic Counseling Program, Mount Sinai School of Medicine. Personal Interview.