

Up Close and Personal: Genetics and You



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6:00 – 7:30 p.m.**

The Joseph B. Martin Conference Center
Harvard Medical School
77 Avenue Louis Pasteur
Boston, MA 02115



HARVARD
MEDICAL SCHOOL

Up Close and Personal: Genetics and You

Moderator



Joseph V. Thakuria, MD, MMSc

Instructor in Pediatrics, MassGeneral Hospital *for* Children
Harvard Medical School

Speakers



Ting Wu, PhD

Professor of Genetics
Director of the Personal Genetics Education Project
Harvard Medical School



Robert C. Green, MD, MPH

Director, G2P Research Program
Associate Director for Research, Partners Center for
Personalized Genetic Medicine
Division of Genetics, Department of Medicine
Brigham and Women's Hospital and Harvard Medical
School

About the Speakers

Joseph V. Thakuria, MD, MMSc

Dr. Thakuria has background training in internal medicine and clinical and biochemical genetics with expertise in individualized interpretation of genomic and other -omic datasets. While still in clinical genetics training, he discovered a new syndrome of Wolff-Parkinson-White arrhythmia with developmental delay, along with the causative gene.

Since 2005, he worked as co-investigator and medical director of the Personal Genome Project (PGP) led by Dr. George Church – an HMS IRB approved study for enrollment of 100,000 participants for comprehensive sequencing, phenotyping, tissue collection, generation of individualized adult stem cell lines, and biobanking. He has been instrumental in developing GET (Genetic, Environmental, and Traits) Evidence, and Trait-omatic for automated analysis of whole genome and exome data. More recently, he and colleagues developed the Genome Parsing System (GPS), a genomic analyses tool for user-specified, project-customized, clinical bioinformatics. He has contributed to clinical genomic analyses published in several high-impact journals including Nature, Science, and Lancet.

Dr. Thakuria currently works as a staff physician in clinical and biochemical genetics at Massachusetts General Hospital and has been involved in NHLBI and NHGRI Working Groups developing consensus statements on the return of genomic results to research participants. He also reviews allocation of inpatient and outpatient resources for clinical genetic/genomic trials conducted system-wide across Harvard affiliated hospitals through his work with the Harvard Catalyst Clinical Research Center Protocol Review Committee.

Ting Wu, PhD

Ting (C.-ting) Wu is a professor of genetics at Harvard Medical School, where she directs a research laboratory focusing on chromosome structure, organization, and behavior and their relevance to gene activity and disease (homologyeffects.org). She is also director of the Personal Genetics Education Project (pgEd.org), which is dedicated to raising awareness of the benefits as well as ethical, legal, and social implications of personal genetics, keeping in mind the tremendous diversity of that public in terms of socioeconomic, cultural, ethnic, and religious status. pgEd employs a variety of strategies for reaching general audiences, including generating online curricular materials, leading discussions in classrooms, workshops, and conferences, developing a mobile educational game (Map-Ed.org), holding an annual conference geared toward accelerating awareness (GETed), and working with the world of entertainment (The Science and Entertainment Exchange of the National Academy of Sciences and Hollywood, Health, and Society) to improve accuracy and outreach.

Dr. Wu received her B.A. from Harvard University in Biology and her Ph.D. from Harvard Medical School in Genetics. She did her postdoctoral training at Yale University

and the Station for Natural Studies, after which she was appointed a Fellow in Molecular Biology at the Massachusetts General Hospital. She is now a professor in the Department of Genetics at Harvard Medical School.

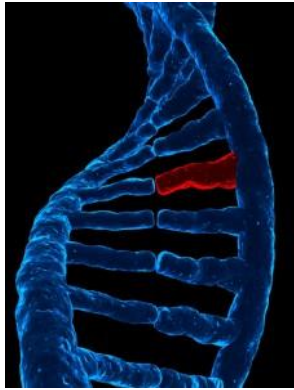
Robert Green, MD, MPH

Robert C. Green, MD, MPH is a medical geneticist and physician-scientist who directs the G2P Research Program (*genomes2people.org*) in translational genomics and health outcomes in the Division of Genetics at Brigham and Women's Hospital and Harvard Medical School.

Dr. Green is principal investigator of the NIH-funded REVEAL Study, in which a cross-disciplinary team has conducted 4 separate multi-center randomized clinical trials since 2000, collectively enrolling 1100 individuals in order to explore emerging themes in translational genomics. Dr. Green also co-directs the NIH-funded PGen Study, one of the first prospective studies of direct-to-consumer genetic testing services. He is principal investigator of the MedSeq Project, the first NIH-funded randomized trial to explore the use of whole genome sequencing in the clinical practice of medicine and co-directs the BabySeq Project, the first NIH-funded trial of sequencing in newborns. The MedSeq and BabySeq Projects utilize genome sequencing both in patients who are affected with hereditary disease and in those who are healthy, in order to study downstream impact on health, behavior and health care costs.

Dr. Green is currently associate director for research of the Partners Center for Personalized Genetic Medicine, a board member of the Council for Responsible Genetics and a member of the Informed Cohort Oversight Boards for both the Children's Hospital Boston Gene Partnership Program and the Coriell Personalized Medicine Collaborative. He was lead author of the recently published recommendations from the American College of Medical Genetics and Genomics for management of incidental findings in clinical sequencing.

Personalized medicine experiment details diabetes development



Patrick J. Skerrett, Executive Editor, *Harvard Health*

The term “personalized medicine” is still something of an abstract idea. In an audacious experiment, Stanford molecular geneticist Michael Snyder gave it a face—his own—and showed what it can do.

Snyder and a large team of colleagues first sequenced his DNA, revealing his complete genetic library. This information showed that Snyder was at increased risk for high cholesterol, coronary artery disease, basal cell carcinoma (a type of skin cancer), and type 2 diabetes. Next, they measured thousands of biological markers in Snyder’s blood every few weeks for two years.

During the average checkup or workup for an illness, a doctor will look at maybe 20 chemical or biological markers. This simple snapshot can be helpful. What Snyder and his colleagues did was akin to taking a 3D movie of his inner workings on a molecular level to observe how genes, the molecules that read and decode them (RNA), the proteins they make, and other substances work together during health and how they respond to illness.

The team saw how Snyder’s body responded to a cold at the very beginning of the study. Midway through, they watched as molecular changes wrought by a respiratory infection tipped him into full-blown diabetes. The work was [published in the journal *Cell*](#).

This intensive approach to health monitoring isn’t coming to your doctor’s office anytime soon. It’s an expensive process that takes a lot of time and technology, and the information it generates would overwhelm most people and their doctors. But it offers new ways to identify diseases and their triggers early, and offers a peek at how personalized medicine might someday work.

Diabetes connection

The study’s eyewitness account of the development of diabetes really caught my attention. Just before the study’s midpoint, Snyder was infected by the respiratory syncytial virus, which affects the lungs. About two weeks later, measures of his blood sugar regulation stopped looking normal. Then his blood sugar level began increasing. Three months later, Snyder was diagnosed with type 2 diabetes.

The lung infection prompted Snyder’s body to make various antibodies. That’s a healthy response to an infection. But it also made autoantibodies—antibodies that attacked his own proteins. One of the autoantibodies targeted a receptor on the surface of cells that latches onto insulin, a hormone that’s needed to usher glucose (blood sugar) into cells. Interfering with that receptor makes it hard for cells to absorb sugar from the bloodstream, a hallmark of diabetes.

I was diagnosed with diabetes six years ago, right after having a severe and persistent infection. The news was an absolute shock—I’m thin, active, eat a pretty healthy diet, and there isn’t any diabetes in my family.

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I've long thought that the infection caused, or at least triggered, my diabetes. There hasn't been much in the medical literature—until now—to back up my suspicion. The work by Michael Snyder and his colleagues won't do anything to help me control my blood sugar, but it does help take some of the mystery out of why I'm living with this condition.

To learn more...

This information was prepared by the editors of the Harvard Health Publications division of Harvard Medical School. It is excerpted from our Harvard Health Blog, available at hvrld.me/ujWYp.

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Genetic testing for heart disease

What if a simple blood test could reveal with certainty your genetic predisposition for developing a serious, inherited form of heart disease? Would you take the test?

What if the test might reveal that you have a 50% increased risk of suffering a heart attack someday? Would you consider this knowledge worthwhile?

The advance knowledge that you will develop heart disease and the decisions you face when you acquire this knowledge are two of the issues inherent in genetic testing as it stands today. Researchers are also hard at work identifying specific genes and mutations (or variants) that play a role in the diagnosis, prognosis, and treatment of cardiovascular disease.

"Genetic testing is used for at least three purposes: to determine your risk for a common disease, such as heart attack; to know whether you have a gene variant that virtually assures you will develop a rare inherited disease; or to determine your response to, or side effects from, a particular drug," says Dr. Sekar Kathiresan, director of preventive cardiology at Massachusetts General Hospital and a professor of medicine at Harvard Medical School.

But in order for this so-called genotyping to be recommended, the information must be useful in helping with treatment decisions. "At this time, the value of genetic testing depends on your goals. For assessing risk of a common disease, like heart attack, I don't routinely offer genetic testing, because it's not clear that it helps with clinical decision-making at the present time," says Dr. Kathiresan.

Some answers are not helpful

Genetic tests look for the variants in a gene sequence that signal increased risk. You can have zero, one, or two copies of the variant. The more copies you have, the higher your risk. For example, there are about 30 sites in the DNA sequence that have been identified as increasing the risk of heart attack. If you carry more of the variants, your risk of heart attack may be twofold higher than those who carry fewer variants.

But what are you going to do with this information? Eat less? Exercise more? Stop smoking?

"We tell people to do these things anyway. It has not yet been shown that knowing they are at higher risk leads people to take better care of their health or helps doctors decide to treat you differently," says Dr. Kathiresan.

Medication response

Genetic testing can be useful in determining medication response. One genotyping success story involves clopidogrel (Plavix), a drug taken to prevent clots from forming inside a stent. Up to 30% of people have a gene variant that prevents their liver from activating the drug, putting them at increased risk for a clot-caused heart attack. A genetic test can tell whether a person has this gene variant.

"If you carry the variant, either the dose of clopidogrel must be raised, or you must be switched to a different antiplatelet agent, such as ticagrelor [Brilinta]," says Dr. Kathiresan.

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A similar test touted to reveal a genetic variant that prevents an individual from benefiting from statin therapy was widely embraced, until the claim could not be validated. However, another test that shows an increased risk of debilitating, potentially dangerous muscle pain in response to statins may have value. "The question is, should everyone be tested?" says Dr. Kathiresan.

When genotyping is useful

Genotyping may be more valuable for diagnosing inherited cardiac conditions controlled mainly by a single gene (called Mendelian diseases). In some of these diseases, there is a very good correlation between having the gene variant and having the disease.

At the Center for Cardiovascular Genetics at Beth Israel Deaconess Medical Center, Dr. Saumya Das and his colleagues screen people, usually young people, with a family history of early sudden death or inherited diseases such as Marfan syndrome, hypertrophic cardiomyopathy, dilated cardiomyopathy at a young age, or arrhythmogenic right ventricular dysplasia. Often, these people have abnormal electrocardiograms, a history of unexplained fainting, or atrial fibrillation that cannot be explained by normal factors.

"Sometimes we see a clear Mendelian factor in diseases such as long Q-T syndrome and Brugada syndrome—two problems of electrical conduction that increase the risk of sudden death—that manifest at an earlier age. Knowing someone has the gene doesn't mean the management of the disease will change, but it does increase the likelihood we can screen relatives for the disease," says Dr. Das, who is also an assistant professor of medicine at Harvard Medical School.

"As of today, genetic tests don't add much to common clinical variables," he says. "We feel that may change. In the future, genomics might well allow us to stratify young people who are at high risk of sudden death and allow us to intervene to prevent it."

To learn more...

This information was prepared by the editors of the Harvard Health Publications division of Harvard Medical School. It is excerpted from the September 2012 issue of the *Harvard Heart Letter*, available at hvrld.me/ujT54.

When to seek genetic testing for heart disease

Many kinds of heart disease run in families. Most of these, such as coronary artery disease, are influenced by multiple genes that interact in complicated ways. Thus, genetic testing has not yet proved particularly useful for these conditions. Heart problems caused by only one or a few genes are a different story.

For these conditions, genetic testing “is family testing,” says Dr. Carolyn Y. Ho, medical director of the cardiovascular genetics center at Harvard-affiliated Brigham and Women’s Hospital. “It is really for the benefit of the family at large to understand what is causing disease and to help identify those at risk.”

Gene-influenced heart disease

A number of heart conditions result from only one or a few genes that have powerful disease-causing effects. Examples include

- arrhythmogenic right ventricular dysplasia
- Brugada syndrome
- familial amyloidosis
- familial dilated cardiomyopathy
- hypertrophic cardiomyopathy
- Loeys-Dietz syndrome
- long QT syndrome
- Marfan syndrome.

Most of these diseases are passed from one generation to the next by way of dominant genes. This means that a person who inherits this gene from either parent will also have the disease—and that his or her siblings and children have a 50-50 chance of having it, too. A person carrying the genes for these life-threatening diseases may need to make major lifestyle changes and perhaps begin heart medications or even get an implanted device.

A family affair

Often an apparently healthy person will seek testing for a genetic heart disease after a family member has died of the disease. But that’s not the way it should happen. The first person in a family who should be tested is the person with the most serious manifestation of the disease. At Dr. Ho’s hospital, this “index” person would get comprehensive genetic testing. At present, this usually would not mean sequencing all the person’s genes, which would be very expensive (\$9,000 to \$10,000, Dr. Ho estimates). Instead, for less than half that cost (or \$1,000 to \$5,000), the test would look only at a panel of specific genes known to be linked to the person’s disease.

The reason for looking at the most affected person is to identify genes with the most powerful disease-causing effects. It’s possible that testing other family members may miss these important genes while identifying only those that make less significant contributions.

When comprehensive testing of the index person does *not* find a gene mutation known to cause that person’s disease—which happens frequently—it does not mean there’s no genetic disease in the family.

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“If that family has a genetic disease, but does not have a genetic mutation identified, they still have familial disease—we are just not smart enough in our current approach to understand what the cause of their genetic disease is,” Dr Ho says.

When comprehensive testing finds the genetic variation that caused disease in the index person, family members may—after counseling to prepare them for the results—undergo predictive genetic testing. These predictive tests are far less expensive (\$400 to \$900), as they only look for the specific gene variants linked to their relative’s disease.

“If we tested the index person and found what we think is a disease-causing mutation, we say, ‘Aha! Based on what we know about this mutation, we are quite confident it caused your disease.’ Now we can look at other at-risk family members to try to predict whether or not they are likely to develop the disease,” Dr. Ho says.

While the decision whether to undergo genetic testing is up to each individual, testing yields more information when results are available for multiple family members.

A positive predictive test shows that a person carries the disease-causing gene. It does not predict when—or even if—the disease will develop, nor does it predict disease severity. A person with a positive test will need follow-up care from a cardiologist, and his or her children should be examined as well. Those considering having children should consider their family planning options.

Testing negative for the heart-disease genes identified in a family member is good news. Those who test negative will not need intensive follow-up testing unless disease symptoms occur.

Cautions and concerns

“Our genes are complex traits, and are the end result of many biologic pathways,” says Dr. Ho. “We cannot test for all traits today because we do not know all the contributors that make them up. Disease could be caused by a family’s shared environmental factors, having nothing to do with genetics.”

There’s no way to predict heart disease when complex genetic traits are just one of a family’s many risk factors. In these cases, even when there’s a family tendency toward heart disease, the only thing to offer people is the same advice they already should be following for optimum heart health. And Dr. Ho notes that there’s little evidence that genetic testing in these cases makes it more likely a person will follow this advice.

To learn more...

This information was prepared by the editors of the Harvard Health Publications division of Harvard Medical School. It is excerpted from the October 2013 issue of the *Harvard Heart Letter*, available at hvrld.me/ujT54.

Shared genes link depression, schizophrenia, and three other mental illnesses

Howard LeWine, M.D., Chief Medical Editor

Internet Publishing, Harvard Health Publications

Five seemingly different mental health disorders—major depression, bipolar disorder, schizophrenia, autism, and attention deficit hyperactivity disorder—may be more alike than we think. A groundbreaking new study has identified a handful of genes that are shared by people with these disorders. This work could help find new and better ways to diagnose and treat mental illness.

Back in 2007, researchers from 19 countries formed the [Psychiatric Genomics Consortium](#). Since then, the group has analyzed DNA from 33,000 people with major depression, bipolar disorder, schizophrenia, autism, or attention deficit hyperactivity disorder and another 28,000 without one of these disorders. In the group with mental illness, four regions of the genetic code carried the same variations. The team's report, published [in *The Lancet*](#), was led by [Dr. Jordan Smoller](#), director of psychiatric genetics at Massachusetts General Hospital and professor of psychiatry at Harvard Medical School.

Two of the affected genes help control the movement of calcium in and out of brain cells. That might not sound like much, but the movement of calcium is a key way that brain cells communicate. Subtle differences in calcium flow could cause problems that, depending on other genes or environmental factors, could eventually lead to a full-blown mental illness.

What's next?

We've known for years that some major mental health conditions run in families. This is especially true for bipolar disorder, major depression, and schizophrenia. Scientists are making progress in identifying genes associated with certain mental illnesses, but they still have a long way to go. The work reported in *The Lancet*, for example, won't immediately help clinicians either diagnose mental illness or give individuals a warning that they are at risk for it. That's because the genetic variants the researchers discovered are weak risk factors for the five diseases.

"Each one of them, by themselves, still accounts for a small amount of the risk," Dr. Smoller told the [Boston Globe](#). "The fascinating thing is there might be such variants that cross our clinically-distinct syndromes."

There are many paths to mental illness. But the Psychiatric Genomics Consortium report offers tantalizing hints that bipolar disorder, major depression, and schizophrenia—and possibly autism and attention deficit hyperactivity disorder—may not be so distinct after all, but could be different manifestations of the same underlying disorder. This could change the way we view mental illness and open the door to more effective therapies. And who knows—this work could even open up paths to preventing mental illness.

To learn more...

This information was prepared by the editors of the Harvard Health Publications division of Harvard Medical School. It is excerpted from our Harvard Health Blog, available at hvrld.me/ujWYp.

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Test for ovarian, endometrial cancers

Every year, nearly 70,000 women in the United States are diagnosed with ovarian and endometrial cancers, and about one-third of them die. Researchers at Johns Hopkins University have developed a test they say can detect ovarian and endometrial cancers from fluid taken during a routine Pap test. The new test—called PapGene—analyzes DNA from ovarian and endometrial cancer cells that have been shed into the cervical fluid.

In a study published in *Science Translational Medicine*, the PapGene test accurately detected all of 24 (100%) endometrial cancers and nine out of 22 (41%) ovarian cancers. The authors of the study called their test a “promising step” toward a broad screening tool for ovarian and endometrial cancers. However, the research is still very preliminary.

The PapGene test needs to be evaluated in larger groups of women and fine-tuned for accuracy before it can be widely used as a diagnostic tool. Until ovarian and endometrial screening tests become available, women need to know their cancer risks and call their doctor if they experience symptoms such as pelvic pain or bloating, abnormal vaginal bleeding, and unusual fatigue.

To learn more...

This information was prepared by the editors of the Harvard Health Publications division of Harvard Medical School. It is excerpted from the April 2013 issue of the *Harvard Women's Health Watch*, available at hvr.d.me/ujZmP.

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Colorectal cancer genes identified

Colorectal cancer is the fourth most common cancer in both men and women. Over the past 20 years, scientists have identified a number of genes that make people more vulnerable to this cancer. Some genes are inherited from a parent. Some genes are mutated long after a person is born, with the mutations leading to cancer. A huge new study published in the journal *Nature*, involving over 150 researchers from many different institutions including Harvard Medical School, examined genes from colorectal cancers and from healthy tissue of the same people. The study identified many new genetic changes that appear to be involved in causing colorectal cancer. Cancer therapy is moving from the use of chemotherapy (drugs that kill cancerous cells, but also injure or kill healthy cells) to new drugs that target only cancerous cells. Each of these newly identified genetic changes is a target for drug therapy.

To learn more...

This information was prepared by the editors of the Harvard Health Publications division of Harvard Medical School. It is excerpted from the October 2012 issue of the *Harvard Health Letter*, available at hvrld.me/ujZBY.

Gene mutation key to aspirin's benefit in people with colorectal cancer



Howard LeWine, M.D., Chief Medical Editor

Internet Publishing, Harvard Health Publications

At age 113, aspirin is still going strong. Once known mainly as a pain reliever and fever easer, research over the past few decades has shown it can help prevent heart attack and stroke. Now a new Harvard-based study suggests why taking aspirin helps some—but not all—people with colorectal cancer. It could lead to routine

genetic testing for people with this common cancer.

[Back in 2009](#), Dr. Andrew T. Chan and his colleagues at Harvard-affiliated Massachusetts General Hospital found that people diagnosed with colorectal cancer who took aspirin on a regular basis tended to live longer than those who didn't take aspirin. Later studies confirmed these findings. Aspirin only worked for some people, though, so Chan and a larger group of researchers set out to learn why.

As is true for other types of cancer, colorectal cancers are not all genetically the same. They have different gene variants and different amounts of proteins. In the 2009 study, people with extra amounts of an enzyme called prostaglandin-endoperoxide synthase-2 (PTGS2) had a particularly longer survival if they used aspirin. Higher-than-normal amounts of PTGS2 permits colon cancer cells to thrive. Aspirin blocks the action of PTGS2, slowing tumor growth.

PTGS2 is hard to measure, so the team conducting the new study used a related gene called PIK3CA. A mutation that makes this gene more active than normal boosts PTGS2 levels. In the new study, only three of 66 (4.5%) men and women with colorectal cancer who were taking aspirin died over more than a decade of follow-up, compared with 26 of 95 (27%) who weren't taking aspirin. The results were published in the [New England Journal of Medicine](#).

New options

This new discovery about response to aspirin in people with colorectal cancer could dramatically change treatment for some. If the results are confirmed in a randomized trial, people with colorectal cancer may be automatically tested to see if they have the PIK3CA gene mutation. Those who do—about 15% to 20% of people with colorectal cancer have this mutation—may be advised to take aspirin to prevent the spread of their cancer after surgery.

Aspirin is also being investigated as a possible way to prevent colorectal and other cancers. As I [wrote in this blog](#) a while back, aspirin is a promising but as-yet unproven option for preventing colorectal, stomach, and breast cancer.

For now, here are the best ways to prevent colorectal cancer:

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- Have a colonoscopy once every 10 years to look for polyps and to have them removed.
- Stay physically active and dedicate time to exercise each day.
- Don't smoke. Use alcohol in moderation or not at all.
- Maintain a healthy body weight.
- Eat a diet rich in fruits and vegetables, and choose whole-grain products that provide more fiber instead of foods made from highly processed grains.
- Get enough vitamin D through sunlight, diet, and supplements if you need them.

To learn more...

This information was prepared by the editors of the Harvard Health Publications division of Harvard Medical School. It is excerpted from our Harvard Health Blog, available at hvrld.me/ujWYp.

Genes and the relaxation response

Exciting new research from the Benson-Henry Institute for Mind Body Medicine at Massachusetts General Hospital suggests that the simple act of eliciting the relaxation response (and thereby dialing back the stress response) temporarily changes the activity of certain genes in ways that may benefit health. For starters, it switches off genes associated with chronic inflammatory responses. Many experts believe these inflammatory responses stress the body, possibly contributing to a host of chronic ailments, such as heart disease, inflammatory bowel disease, and diabetes. At the same time, it switches on genes linked with a variety of functions: the use of energy in the body, the release of insulin (which helps regulate blood sugar), the maintenance of telomeres (protective end-caps on our chromosomes that erode with age until a cell dies), and the functions of the tiny cellular powerhouses called mitochondria. The researchers speculate that the latter may create energy reserves that help the body counter oxidative stress that can harm cells.

For this study, the researchers recruited two small groups of healthy subjects: long-term practitioners of techniques like yoga, meditation, and repetitive prayer that elicit the relaxation response; and novices who hadn't used these techniques. The novices were tested initially after listening to a health education tape—this allowed them to serve as a control group. They then learned a sequence of relaxation response techniques, which they practiced for 20 minutes a day, guided by a CD, over eight weeks. This sequence included diaphragmatic breathing (also known as breath focus), body scan, mantra repetition, and mindfulness meditation.

To gauge the changes in gene activity, the researchers obtained blood samples from both groups immediately before a single relaxation response session, immediately afterward, and 15 minutes afterward. While the long-term practitioners had the most profound changes in gene activity, the group with eight weeks of training also experienced significant changes in gene activity compared with results they'd posted as complete novices.

These results build on an earlier study conducted by the Genomics Center at Beth Israel Deaconess Medical Center and the Benson-Henry Institute for Mind Body Medicine that had similar results—it found changes in the activity of genes controlling how the body handles free radicals, inflammatory processes, and cell death. Once again, greater changes were seen in the long-term practitioners than in the novices.

Aiming for lasting benefits

Gene activity isn't altered forever by yoga or repetitive prayer. One lesson gleaned from these studies is that the relaxation response must be regularly elicited in order to make beneficial changes persist. Additional research needs to be done to learn whether similar changes occur in people who use relaxation response techniques to help treat stress-related illnesses. Already, studies examining the effects of relaxation techniques on hypertension, inflammatory bowel syndrome, and multiple myeloma are under way.

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Cancer

Cancer is not a single disease, but many diseases. What they have in common is the uncontrolled spread of abnormal cells. Currently, there is no evidence to suggest that stress causes cancer by itself. But whether long-term stress may play a role by tampering with immune defenses is a question that bears closer scrutiny. One theory about how cancer develops suggests that cancerous changes in cells occur frequently for a variety of reasons, but the immune system recognizes the cells as aberrant and destroys them. Only when the immune system becomes ineffective are the cancer cells able to multiply. Since chronic stress can hamper the immune system, this might affect the body's ability to head off the uncontrolled proliferation of cancerous cells.

Can stress management help?

It's too early to say whether managing stress affects the risk for various cancers. But there are promising hints. In 2008, Dr. Dean Ornish, president of the Preventive Medicine Research Institute in Sausalito, Calif., published a pilot study in the *Proceedings of the National Academy of Sciences*. The study participants were 30 men with early-stage, nonaggressive prostate cancer who had opted for "active surveillance" of their condition rather than medical treatment. They all agreed to follow Dr. Ornish's program, which combines a healthy low-fat diet with exercise, stress reduction techniques, and increased social support (which also reduces stress). In such a study, it's impossible to tell how great a role any of the four lifestyle interventions played individually. But the collective effect was impressive.

After the men had followed the program for three months, an oncologist analyzed biopsy tissue taken from each of the men upon diagnosis and compared it with a second tissue sample taken after the three-month trial and found major changes in gene "expression"—that is, the activity of various genes. Across the board, the changes were of the type that can help protect against cancer and other major diseases. A total of 48 protective genes had become more active, including the "secreted frizzled-related protein" gene, which is a tumor suppressor. By contrast, 453 genes that promote inflammation, heart disease, and cancer were tamped down, including the RAN and SHOC2 genes, which are classified as tumor promoters. It was the first time anyone had shown that lifestyle changes may positively affect the genes involved in cancer. Of course, it's a long way from there to concluding that stress management can help prevent either the initiation or progression of cancer. Many more studies of greater size are needed.

At present, an interesting new line of inquiry is opening at the Benson-Henry Institute for Mind Body Medicine into multiple myeloma, an incurable cancer that affects blood cells. Certain gene changes found in multiple myeloma appear to be the opposite of gene changes evoked when healthy people elicit the relaxation response regularly. Thus, it's possible that the relaxation response might beneficially act on pathways altered by multiple myeloma. The researchers are currently enrolling participants with asymptomatic changes in their blood cells that sometimes progress to multiple myeloma. The results remain to be seen.

To learn more...

This information was prepared by the editors of the Harvard Health Publications division of Harvard Medical School. It is excerpted from our Special Health Report *Stress Management*, available at hvrld.me/ujZT2.

Will it help to get gene testing for Alzheimer's if it runs in my family?



DEAR DOCTOR K:

Alzheimer's runs in my family. Will it help to get gene testing for this disease?

DEAR READER:

Family history is indeed a risk factor for Alzheimer's. If you have a parent or sibling with Alzheimer's, you're more likely to develop the disease than someone who does not have a close relative with this condition.

Genetics is most important in families with a history of early-onset Alzheimer's (occurring between ages 30 and 60). The early-onset form accounts for less than one percent of all Alzheimer's cases, but in most people with early-onset disease, the cause is one of several altered, or mutated, genes that the person has inherited from a parent.

Several genes responsible for early-onset Alzheimer's have been identified. They are called APP, PSEN1, and PSEN2. If someone inherits one of these mutated genes, it is very likely (but not certain) he or she will develop the disease.

Testing for these genes is costly and is not usually covered by insurance. At this time, there is no treatment proven to prevent or slow the onset of Alzheimer's disease. However, some people want to know if they have one of these genes so they can use that information in planning for their future.

If one of my parents had developed early-onset Alzheimer's, I would have wanted to know if I had inherited the gene. If so, I might have planned my career and my non-professional life differently. Fortunately, my parents did not develop this disease.

You also may choose to be tested. For you, like me, perhaps bad news is better than living with uncertainty. Or you may want the opportunity to enroll in trials for experimental treatments.

Everything I've said so far applies only to *early-onset* Alzheimer's disease. Most cases of the disease start after age 60. We know of just one gene that is a reasonably strong predictor of this more typical form of Alzheimer's: APOE. People who inherit two copies of the APOE4 type of the APOE gene are at much higher risk for developing Alzheimer's compared with people who have no copies of the gene.

However, most authorities do not recommend getting tested for the APOE4 gene. That's because the gene does not provide a solid answer. If you inherit two copies of the gene, you may still avoid Alzheimer's. And if you inherit no copies, you may still get it. Nevertheless, some people want to know if they are at increased risk. I have not had myself tested for this gene.

Human genetics has developed enormously in the past 30 years. In the 1980s, few scientists imagined that we would discover the structure of every human gene in their lifetime, or even their children's lifetime. But we have. And we have identified thousands of genes that are linked to particular diseases.

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Genetics and You

Longwood Seminars, March 20, 2014

However, this information has not yet led to many highly accurate predictions of what diseases a person is at high risk for, or to many cures. In tomorrow's column, I'll explain why.

To learn more...

This information was prepared by the editors of the Harvard Health Publications division of Harvard Medical School. It is excerpted from our "Ask Doctor K" website, askdoctork.com.

Will studies of our genes change medicine and improve our lives?



In yesterday's column, a reader asked whether she should be tested for genes linked to Alzheimer's disease. Today, I thought I'd give you my view on the larger question: Will studies of our genes change the practice of medicine and improve our lives?

My answer: During my career, progress in human genetics has been greater than virtually anyone imagined. However, human genetics also has turned out to be much more complicated than people imagined. As a result, we have not moved as rapidly as we had hoped in changing medical practice.

I graduated from medical school in the late 1960s. We knew what human genes were made of—DNA—and we were beginning to understand how genes work. We had even identified a handful of genes that were linked to specific diseases. We assumed that disease resulted from an abnormality in the *structure* of a gene.

If I had asked any biologist on the day I graduated, "Will we ever know how many genes we have, and the exact structure of each gene?" I'll bet the answer would have been: "Not in my lifetime, or my children's lifetime."

They would have been wrong. Today we do know those answers. Indeed, some diseases are caused by an abnormality in the structure of genes. In fact, sometimes it is very simple: one particular change at one particular spot in just one particular gene leads to a specific disease. Sickle cell anemia is an example.

Unfortunately, with most diseases it's far from that simple. The first complexity: Most diseases are influenced by the structure of *multiple* genes, not just one. Examples are diabetes and high blood pressure.

The second complexity: Many diseases are explained not by an abnormal gene structure, but by whether genes are properly turned on or off. Most cancers fall into this category.

What do I mean by that? Every cell in our body has the same set of genes. Yet, a cell in our eye that sees light is different from a cell in our stomach that makes acid. Why? Because different genes are turned on in each type of cell.

Similarly, if a gene with a normal structure is not properly turned on or off, a cell can malfunction — it can become diseased. Whether a gene is turned on properly is proving to be a more important cause of disease than we once imagined.

The third complexity: We have 10 times as many bacterial cells living on and inside our body as there are cells in our body. And the genes of those *bacterial* cells—not just the genes in our own cells—affect our health, perhaps profoundly. Bacterial genes may play an important role in obesity, heart disease, even autism spectrum disorders.

Up Close and Personal

Genetics and You

Longwood Seminars, March 20, 2014

So, am I discouraged about whether progress in human genetics will improve our lives? To the contrary, I'm more convinced than ever that it will. We are already seeing earlier and more accurate diagnosis and prognosis and improved treatments.

And just as 40 years ago very few would have imagined what has been achieved by 2014, very few today can imagine what will be achieved in the next 40 years.

To learn more...

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HarvardMedicine

The following article is from *Harvard Medicine* magazine's autumn 2013 edition. Additional content can be found online, please visit: <http://harvardmedicine.hms.harvard.edu/>

Legacy

Secrets packed away in a family's genome are increasingly being found—and discussed

by David Cameron

Photo: Tetra Images/Corbis

Joseph Thakuria was facing an impasse.

He stood at a whiteboard in a conference room where a group of patients, all members of an extended family, sat around a table. They had come to him out of desperation. For generations, seemingly healthy family members in the prime of life had, without warning, died of a thoracic aortic aneurysm. The indiscriminate nature of the affliction was shaking the psychological well-being of the family tree. No one knew where they stood. Doctors were out of ideas. As a last-ditch effort to find answers, this band of relatives had come to Thakuria, a medical geneticist at Massachusetts General Hospital.



Using the investigatory skills that specialists like Thakuria are known for, part science and part detective work, he and his colleagues solved the mystery. Careful and intensive genome sequencing had fingered the causative mutation.



While knowing the identity of the genetic culprit would not point to a cure, it would allow physicians to screen family members. Those in the clear could breathe easy, while those bearing the DNA signature could take preventive measures.

GOOD COUNSEL: Medical geneticists like Joseph Thakuria work with patients and their families as they learn of heritable conditions uncovered in analyses of the genetic information contained in their chromosomes.

Photo: Jennifer Sarbahi

Thakuria ushered the family into a conference room to explain all this—and to give each of them the option to be tested for the mutation. More than a dozen members of this extended family listened, rapt, as Thakuria described the diagnosis buried in their genes. Then, he asked each of them the million-dollar question: Do you want to know?

“Not everything in genetics is 100 percent certain and predictive the way it was for this particular family,” says Thakuria, who also is an instructor in pediatrics at Mass General. “But there really is no correct answer to this question.”

One by one, members of the family agreed to be tested. Then one said “no.” He preferred to continue receiving annual echocardiograms rather than knowing which genetic cards he’d been dealt.

His relatives thought he was nuts. Each of them took him to task, insisting that there was only one sane answer to the question. Dodging the genetic test was simply not rational. In the hope of breaking the tension, Thakuria jumped in.

“I tried to explain that this was like deciding what to do with lottery money,” he says. “It’s different for everybody. There’s no right or wrong.”

The individual stuck to his decision, and, in the end, everyone was right. But what should medicine do when the patient is a family and the diagnosis implicates generations?

A Change of Pace

Over the past decade, the science of genetics has accelerated at a rate that makes Moore’s Law look like a slacker. Thanks to advances in technology platforms like microfluidics, printing out a patient’s genetic code could soon become as routine as taking blood for a cholesterol test.

As Thakuria and his colleagues continue to incorporate more in-depth genomic sequencing into the clinic, researchers will need to grapple not only with a whirlwind of information, but also with patients and doctors who will struggle over how to interpret the results.

In short, the world of genetics is undergoing a revolution. But like all major cultural and technological insurgencies, the attendant issues raise a host of medical, social, ethical, and even psychological concerns.

Take Thakuria’s foray into family therapy. Decades ago, the majority of known genetic disorders were rare, and often chromosomal. Today researchers know of nearly 5,000 such disorders. Not more than a decade ago, medical geneticists relied on physical examinations and phenotypic clues, while genetic testing yielded only the crudest data, confined primarily to single gene analyses and to locating large structural rearrangements, such as the extra chromosome that causes Down syndrome or the string of nucleotide repeats associated with Huntington’s disease.

But the clinical use of genetic testing has now caused an information surge that the medical establishment is struggling to manage. Today, a person can spit into a tube, send the sample to any number of direct-to-consumer companies and, for as little as one hundred dollars, receive a

scan of genetic markers—known variations in DNA that can be used to identify a person, species, or disease—that indicates susceptibility to conditions such as Alzheimer’s disease and prostate cancer.

When We Talk About Genes

Joan Stoler knows well the complexity of translating genetic information to the layperson. For years, Stoler, an HMS assistant professor of pediatrics at Boston Children’s Hospital and program director of the Harvard Medical School Genetics Training Program, has been working with patients and families as they wrestle with the fact that they carry a potentially troublesome genetic mutation.



Joan Stoler
Photo: Tracy Aiguier

One problem she and others in her profession confront is that for many conditions there is no definitive test. The binary precision of the genetic condition found in the family Thakuria was counseling isn’t the norm. What’s more, if genomic information has been increasing by an order of magnitude each year, so has our appreciation of a gene’s complexity. Sure, a gene may be turned on or off—but it may also simply be dimmed. Or the gene itself might be fine but one of its regulators may have gone rogue. For unknown reasons, a genetic alteration that may result in a calamitous deformity in one person might cause a physiological blip in another.

In other words, as our knowledge increases, the one gene-one protein pedagogy becomes almost quaint.

Stoler, however, must explain the subtleties we do know about to her patients, finding ways to bridge the knowledge gap, and, often, a cultural gap.

“For a couple from China, who often have only one child, learning of a genetic defect is a tremendous blow,” she says. “One mother, from Central America, thought the mutation her child carried occurred because when she was pregnant she wore red during an eclipse. Some blame coffee. Part of my job is simply to educate patients about what this all means. I try to drive home that each of us has something that we can pass down to our children.”

Stoler often finds herself trying to explain the basic concepts of cells, chromosomes, genes, and proteins through an interpreter. In these situations, she goes visual, using charts, drawings, tic-tac-toe boards, and whatever analogies she can to inform those she is working with.

In a way, experts like Stoler play the traditional role of gatekeeper. They collect and interpret the genetic data, and then decide the best methods for educating the patient. But as genetic testing becomes increasingly democratized, how will the role of gatekeepers shift?

Green's Genes

Robert Green is an expert in moving genetic discoveries into genomic medicine. He has investigated and deciphered the nuances of many genomes, including his own.

Like Thakuria and Stoler, Green, an HMS associate professor of medicine at Brigham and Women's Hospital and director of the G2P (genomes2people) research program, is a medical geneticist. In addition to treating patients, he oversees a research program that can best be described as translational genomics. Green and his research colleagues use sequencing technologies to diagnose some of the more obscure conditions. But Green's discipline is complicated by some hazy intricacies. To illustrate this, he references his own genetic blueprint.

A full sequence of Green's genes turns up a few million variations, 109,000 of which could initially be considered medically relevant. Of these, computational analysis predicts that approximately 11,900 have an effect on a protein. Further analysis to find the variations that are uncommon, and thus more predictive of disease, leaves only 1,800. When this remnant is processed through a database of known genetic diseases, only 16 rare mutations are left.

Each of these 16 mutations could be alarming without clinical context. One of them, for example, is in the gene that causes Treacher Collins syndrome, a dominant condition resulting in severe facial deformities at birth. But here's the thing: Green doesn't exhibit a single feature of Treacher Collins. Which brings up yet another dilemma in the world of genetic diagnosis: There is no clear consensus on what defines a pathogenic mutation—and the race to package and sell translational software to patients and doctors may only add to the confusion.

"There's a powerful narrative in play that genomics will reveal all of our medical secrets, and that we all will benefit from genome sequencing," says Green. "But there are many questions to be answered before genomics is routine, particularly in healthy individuals. Can we validate the interpretation of disease risks so that we know what the genome is telling us? Will genetic information improve people's health? How often is it misunderstood? Can it be dangerous?"

There is, in fact, a great deal of angst in the medical community about how an increasing glut of genetic information will affect patient behavior, and that is precisely what Green and his colleagues are studying.



UPON REFLECTION: A full sequencing of Robert Green's genome revealed 16 mutations that, without the benefit of clinical context, could be considered alarming.

Photo: Gretchen Ertl/Redux Pictures/The New York Times

Over the past decade Green has been the principal investigator for the REVEAL study: Risk Evaluation and Education for Alzheimer's Disease. For this project, researchers randomized participants to receive information regarding their genetic susceptibility to Alzheimer's.

"The study was run just like a clinical trial, except the drug we dispensed was genetic information," says Green.

The group measured potential patient harm in terms of anxiety, depression, and distress, eventually publishing in the *New England Journal of Medicine* that participants experienced a minimal and temporary rise in distress when they learned they were at an increased risk for Alzheimer's disease. Some of their subsequent behaviors were positive, such as better diet and more exercise; other behaviors were debatable, such as purchasing unregulated dietary supplements online. One striking finding: participants who learned that they were at increased risk reported increasing their long-term care insurance coverage.

For another set of participants, however, Green disclosed risk for heart disease along with the Alzheimer's risk and found that when people learned they were at risk for both conditions, they were, counterintuitively, less distressed.

"Our preliminary data suggest that learning about multiple risks, particularly if one of them seems preventable, is actually less distressing," he says.

In a separate study, Green and his group surveyed roughly 1,800 individuals who had received medically relevant genetic information through a direct-to-consumer company. When asked who they would present this information to, the respondents indicated overwhelmingly that they planned on discussing it with friends, family, and colleagues, and, in some cases, their family doctor. But few planned to discuss their results with a genetic specialist.

"As genomics enters the mainstream of medicine and society, regular physicians will have to learn to cope with this information about their patients," says Green. "Genetics is becoming democratized in a big way."

Green's newest studies are NIH-supported ones that will explore genomic sequencing in the medical care of adults and in newborns. Ultimately, this work anticipates a future where genomics data are available for every clinical visit.

Until then, medical geneticists are in the trenches with families excavating the uncertainties of inherited disease. Thakuria has continued to follow his family of patients. The good news is that, since availing themselves of genetic testing, no one in the family has died from the condition: screening and medical intervention has fended off what once seemed certain.

The kind of detailed sequencing that improved the family's options, however, is still reserved for extreme abnormalities. Thakuria, however, thinks that one day genomic sequencing will become a preventive measure, like mammograms and colonoscopies. If that occurs, family discussions of

the results of genetic testing may lose some of their emotional freight. Then again, given family dynamics, maybe not.

David Cameron is director of science communications in the HMS Office of Communications and External Relations.

The following article is from *Harvard Medicine* magazine's autumn 2010 edition. Additional content can be found online, please visit: <http://harvardmedicine.hms.harvard.edu/>

Dilemmas of Destiny

Genetic predictors of disease can raise thorny ethical issues.

by Ann Marie Menting

Lila* was only in her twenties when she learned that she could be at increased risk for breast cancer. A genetic test had revealed that her mother carried a mutation signaling a heightened risk for the disease. But Lila opted to live with uncertainty—and the hope it engendered—a little longer. She wouldn't test, but she would be vigilant, opting for frequent mammograms.

At age 34, Lila, now the mother of two small children, learned she had breast cancer. Personalizing her treatment would require genetic testing. This time she consented. The procedure verified the mutation and revealed another detail: her tumor flourished with exposure to hormones.

“She knew the mutation increased her risk for a second cancer, so she chose bilateral mastectomy,” says Judy Garber, an HMS associate professor of medicine at Dana–Farber Cancer Institute and Brigham and Women's Hospital. But because the tumor was hormone-receptor-positive, Lila faced another decision: take drugs to cut her hormone levels, or have the source of those hormones, her ovaries, removed. She chose the surgery.

Garber, who directs the Cancer Risk and Prevention Program at Dana–Farber, describes Lila's decisions as aggressive for a young woman, even one burdened with a mutation promising a lifelong threat of cancer. Could her choices have been driven by her desire to remain a mother to her children for as long as possible?

Judy Garber

Rick Friedman

Rick Friedman Collection Corbis

“Oh, of course,” says Garber, adding softly, “For young mothers, that's often the issue.”

Lila's story underscores how genetic diseases thread throughout a family and how decisions made by individuals—to test, to treat, to disclose—are fraught with difficulties and emotions that can strain,



and sometimes break, family ties. The reach of genetic diseases goes beyond the individual, often visiting ethical dilemmas upon a patient's entire family.

Over the past three decades, genetic testing and its offspring—personalized medicine—have matured; tests for more than a thousand diseases are now available. Yet while the ability to identify genetic signposts for patients allows doctors to recommend screening, offer preventive surgeries, and fine-tune drug treatments, that same ability delivers unsettling futures to those with genetic evidence of diseases that as yet have no cure, such as Huntington's disease, cystic fibrosis, hemophilia, and Alzheimer's disease.

Often, patients and doctors become entangled in such issues as how to best share at-risk information, access treatment options, and weigh decisions about hidden threats to the young and unborn. And sometimes these issues mushroom, becoming quandaries for society as a whole.

It's a Family Affair

Patients rely on physicians to deliver medical news directly and in confidence, good or bad. Medicine's growing ability to plumb a person's genetic information, however, can challenge this expectation.

"People are accustomed to keeping some details private," says Ting Wu, an HMS professor of genetics and director of the Personal Genetics Education Project. "But genetic information is explicit; it speaks to pedigree."



Ting Wu

**Photo by Stephanie Mitchell
Harvard News Office**

Wu notes that while patients might seek genetic testing as a means of customizing their treatment and prevention strategies, others—particularly at-risk family members—may be less amenable to testing and the possibility of news of an incurable condition.

"Patients realize that information can sometimes be used in a way that hurts someone," says Wu. "That possibility—and that fear—can present a slippery slope: The more we learn, the more information we have to use, properly or improperly."

How deeply those details penetrate family defenses can be found in a story Wu cites of a 23-year-old woman who chose to be tested for Huntington's disease. The young woman's grandfather had been ravaged by the rare brain disorder for three decades, a maternal aunt had tested positive for it, and she was now witnessing a cousin's debilitation. Her mother, however, refused to test and became embattled with her daughter over the issue. Undeterred, the young woman went ahead with her plans. She learned she carried the gene—as did her mother, by

implication. Her mother severed their ties, unable to forgive her daughter for inflicting upon them both what she viewed as future-robbing news.

A Fine Line

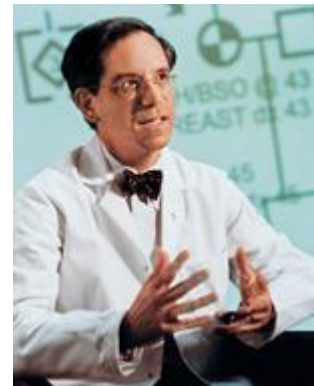
Kenneth Offit '81, chief of the Clinical Genetics Service at New York City's Memorial Sloan-Kettering Cancer Center, has seen the difficulties that disclosure can bring to families. "When it comes to handling the results of genetic testing," he says, "health professionals must respect the boundaries imposed by the ethical practice of medicine by encouraging, but not coercing, patients to share their news with family members." But when the patient can't meet that responsibility, the custodianship of genetic information—and the duty to warn—may be left to the physician.

Kenneth Offit

Photo courtesy of Memorial Sloan-Kettering Cancer Center

"Two decades ago, a breast cancer patient we'd enrolled in a study of the genetic risks of certain cancers died before learning she had a mutation linked to her cancer," Offit recalls. "We needed to tell her daughters of their own risk—but we didn't know their locations."

Offit called the woman's mother to explain his need to contact her granddaughters. She rejected his plea and ignored his follow-up letter. Years later, after she had died, the daughters found a letter that Offit had written—and showed up at his clinic. One daughter tested positive for the mutation and began regular screening.



Offit once told this story to a group of lawyers to illustrate how he had tried to fulfill his duty to warn. Terse, unsettling comments followed. One lawyer chided him for failing to hire a private detective, find the daughters, and tell them their risks. Another frostily said she would have offered to represent the daughters should they have developed breast cancer before they were notified and elected to sue.

Open House

Physicians aren't the only ones tussling at the ethical edges of genetic testing. Patients, too, wrestle with such dilemmas. They share test results to warn siblings and cousins, help adult children make childbearing decisions, or explain their medical care to others. But patients also withhold information to avoid causing alarm and to notify only those relatives at greatest risk. Information sharing may hit additional barriers, both real and perceived, such as geographic distance, adoption, and stigma.

Disclosure requires a middleman when the patient is very young. Parents must act on behalf of newborns, children, and adolescents whose genetic disorders may not manifest until adulthood. "We often avoid testing children unless it's absolutely necessary," says Joseph Thakuria, an

HMS instructor and clinical geneticist at Massachusetts General Hospital. “We worry about how testing can negatively affect this population.”

Thakuria, who trains medical students and house staff as well as genetic counselors, says that his worries about stigma and self-concept sometimes begin with the parents. “It’s not unusual for one to say to the other, ‘It’s from your side of the family.’ Usually it’s said half-jokingly, but I always try to nip that thought in the bud.”

He does so by sharing a fact: We are all carriers. Geneticists estimate that each of us has 6 to 25 genes that, under the right conditions, could trigger a disorder or disease in a person or in his or her offspring. Understanding this helps move parents away from shock, guilt, and grief and into proactive postures, such as joining a support group, learning about treatments and interventions, and safeguarding their child’s quality of life.

Protective Services

Protecting quality of life for all who undergo genetic testing has gained legal ground in recent years. Worries about institutional discrimination that might deny medical coverage, employment, and equitable access to the benefits of personalized medicine have been eased in the United States by provisions forged in the Genetic Information Nondiscrimination Act, or GINA, and in the recent health care reform legislation.

Since 2008, GINA has accorded genetic information the same privacy protections that the Health Insurance Portability and Accountability Act, or HIPAA, has provided to medical data. GINA has also prohibited genetic discrimination by health insurers and employers.

GINA does not, however, affect life, disability, or long-term care insurance. Nor does it prevent insurers from determining eligibility or rates based on a person’s gene-linked disease or disorder that has already manifested. And while GINA mandates payments for tests for mutations linked to diseases such as breast cancer and colon cancer, it doesn’t require coverage for preventive interventions

Health care reforms signed into law in 2010 may help flesh out just what personalized medicine can and can’t deliver. The reform act creates an independent Patient-Centered Outcomes Research Institute charged with examining the use and comparative effectiveness of medical products and services within groups differentiated along traditional lines—such as race, sex, and age—as well as new ones distinguished by genetic and molecular characteristics.

Society’s acceptance of personal genomics will surface in its laws, says HMS geneticist Wu. Preimplantation genetic diagnosis, for example, which screens for genetic diseases in embryos used for in-vitro fertilization, may come under scrutiny. Studies have found that parents see an advantage to this screening procedure if it means they can avoid receiving a prenatal diagnosis requiring them to consider terminating a pregnancy. But others fear that choosing an embryo based on its genetic makeup is mere prelude to selecting for gender, IQ, and eye color—in short, a slide toward eugenics.

For Wu, education is the right response. “We need to understand the social, legal, and ethical outcomes of our decisions,” she says. “When we know the issues surrounding genetic testing, we’ll consider carefully before judging the decisions of others. For when we categorize others, we categorize ourselves.”

*The patient’s name has been changed.

Ann Marie Menting is editor of Harvard Medicine.

Researchers to Sequence Genomes of Newborns

Randomized trial is the first to explore the benefits and risks of genome sequencing in newborns.

By TOM LANGFORD

September 5, 2013

Parents of some Boston-area newborns will have a rare opportunity to have their baby's DNA completely analyzed as part of the first-ever randomized trial to explore the benefits and risks of genome sequencing (reading the entirety of a person's DNA) in this age group.

The five-year study will assess the baby's risks of future diseases and how that information affects the baby's medical care, and the relationship between the parents, baby and baby's pediatrician.

The study is funded by a \$6 million grant from the National Institutes of Health to [Brigham and Women's Hospital](#) and [Boston Children's Hospital](#). It will be led equally by [Robert C. Green](#), Harvard Medical School associate professor of medicine at Brigham and Women's Hospital and [Alan Beggs](#), the Sir Edwin and Lady Manton Professor of Pediatrics at Boston Children's Hospital.



Families who volunteer could have their baby's genomic data available as a resource to aid in the baby's medical care. Image courtesy of Brigham and Women's Hospital

"This first-of-its-kind study will accelerate the use of genomics in clinical pediatric medicine by creating and safely testing novel methods for integrating sequencing into the care of newborns," said Green, a medical geneticist in the Division of Genetics at Brigham and Women's Hospital and director of the [Genomes2People Research Program](#).

"We will implement and study a futuristic goal: that genomic information examined shortly after birth can serve as a resource throughout infancy and childhood to inform clinical care and identify appropriate and timely interventions," he said.

Beginning in early 2014, the study will enroll 480 newborns and their parents in order to compare outcomes that occur when genomic newborn sequencing is added to the conventional newborn screening that babies currently receive.

The volunteers, healthy newborns from Brigham and Women's Hospital and infants from Boston Children's Hospital's Neonatal Intensive Care Unit, will be divided into two groups. One group will receive conventional state-mandated newborn screening, the other will receive conventional screening and genome sequencing.

Researchers will collect and analyze the genomic sequences, which may include information on potential causes of any birth defects, predispositions to future medical conditions and predictions about responses to certain drugs, and will return that information to parents and pediatricians to evaluate the medical, psychosocial and economic outcomes.

“These analyses will help illuminate the full spectrum of benefits and risks associated with genome sequencing of newborns,” said Beggs, director of the [Manton Center for Orphan Disease Research](#) and a professor of pediatrics and scientist in the Division of Genetics at Boston Children’s Hospital.

This research project follows the start of a similar NIH-funded study at Brigham and Women’s Hospital, the [MedSeq Project](#), which is the first NIH-funded randomized clinical trial to study the integration of whole genome sequencing into the practice of adult medicine. The Manton Center at Boston Children’s is a multidisciplinary center for research into the causes and prevention of rare “orphan” diseases that is working with [Claritas Genomics](#) to develop genomic testing to enhance pediatric health.

Beggs said, “Synergies between the MedSeq Project, the Manton Center, and this newborn sequencing project we are calling the BabySeq Project will help us discover how best to integrate genomic sequencing into medical care to benefit all adults, children and their families.”

Enrollment in the study will begin after researchers receive approval from their institutional review boards.

In addition to Green and Beggs, the project will be co-led by a multidisciplinary team of investigators in pediatrics, neonatology, genetics, psychology, ethics and newborn screening.

Adapted from Brigham and Women's Hospital [news release](#).

Painting Genomes

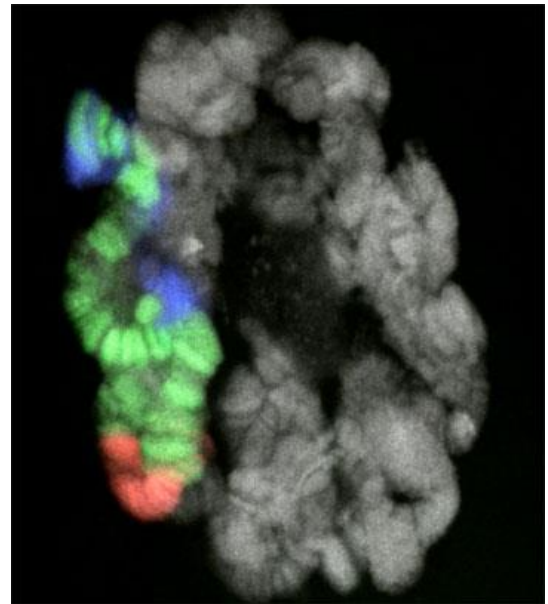
‘Oligopaints’ allow researchers to design and produce probes for virtually any sequenced region of any genome

By ELIZABETH COONEY, Harvard Medicine News
December 13, 2012

Oligopaints show a multicolor banding pattern in chromosomes. The method allows higher resolution at a lower price.

Image courtesy of Brian Beliveau, Eric Joyce and Nicholas Apostolopoulos.

Sequencing genomes, from simple organisms to creatures as complex as humans, produces a torrent of information. That flood will likely grow as advances in technology continue to push down the cost of generating genetic data. But the ability to study the chemical nature of DNA has outstripped the ability of researchers to actually look at chromosomes — organized packages of DNA — and to see their position in the nucleus. How chromosomes are folded or stretched is critical to gene expression, with implications for congenital abnormalities as well as cancer.



A new tool promises to change the imbalance between what can be sequenced and what can be seen. “Painting” the genome with renewable, highly specific fluorescent probes offers a low-cost yet high-resolution method with the potential to improve genetic diagnosis in the doctor’s office and basic research in the lab. A team led by [Ting Wu](#), HMS professor of genetics, described the method they call “Oligopaints” in a paper published online this week in [Proceedings of the National Academy of Sciences](#).

“There have been some fantastic technologies that have given people a molecular handle on how chromosomes are folded — these involve looking at millions of cells at once,” Wu said. “What people are also hankering for is single-nucleus resolution where they can see every nucleus for itself. That’s where we need this kind of technology to complement advances in sequencing.”

For a long time scientists used chemical stains to view chromosomes in the nucleus. But they need to see chromosomes with greater precision in order to detect which chromosome they are looking at and understand how it is arranged in the nucleus, regardless of whether it’s intact or broken.

After chemical staining came chromosome paints based on genetic sequencing. They made use of a technique called fluorescent in situ hybridization (FISH) to light up chromosomes, but to date the method has been both laborious and expensive. Wu’s lab has focused on making probes that lower the cost by using easily made oligonucleotides — short, single-stranded DNA

sequences — that they believe will better hug the chromosome, yielding a cleaner signal and better revealing chromosome structure and positioning.

These Oligopaint probes contain as few as 32 bases of homology to the genome and can target any sequenced region of the genome along a chromosome, compared to the 100 bases or more of other methods, which Wu believes can result in the probes bunching up among themselves and therefore generating a less than optimal signal. Each Oligopaint probe carries single-fluorophore primers, meaning it lights up at only one point, which should allow for greater precision in super-resolution microscopy and image interpretation.

One of the Wu lab's goals is to make chromosomal analysis as inexpensive as a blood test. Such a test could potentially be used to screen newborns for congenital abnormalities or to guide treatment for cancer patients. The lab has thus far been working in fruit flies and human cell lines, but the principle could apply to any organism, including humans.

In the past, testing a single 50-kilobase region — a small fraction of the entire genome — could cost \$25 or more. The same region costs anywhere from 10 cents to \$1.50 using Oligopaint probes, Wu said. The trick is to design commercially available oligonucleotide libraries that are then amplified after adding primers purchased with fluorophores attached to them. Advances in DNA synthesis have dropped the price of oligonucleotides, an opportunity seized by the Wu lab.

The proof of principle provided in the paper is “a huge event,” said [R. Scott Hawley](#), American Cancer Society Research Professor at the Stowers Institute for Medical Research in Kansas City. He was not involved in the study.

“This will change the way we do things in my lab,” said Hawley, who studies cell division in *Drosophila* chromosomes. “We’ll be able to follow chromosomes in a way we’ve never been able to follow them before: more efficiently, easily and elegantly.”

[Kim McKim](#), a professor of genetics at Rutgers University who also works in *Drosophila*, is eager to use Oligopaint probes. He also played no part in the study.

“Can’t wait to get them,” he said. “Having a tool like this, which allows one to specifically examine the positions of a specific chromosome in a cell, is incredibly valuable.”

This work was supported by National Institutes of Health/National Institute of General Medical Sciences Grant 1R01GM085169 and Pioneer Award; a Broad Institute SPARC Award; a Cox Program Award from Harvard Medical School; an NSF Graduate Fellowship; an NIH/National Cancer Institute Ruth L. Kirschstein National Research Service Award; an NIH Centers of Excellence in Genomic Science grant; NIH Grants 5R42GM097003 and 1R43GM093579 for the development of the oligo synthesis technology; and Grant 1S10RR028832-01.

For More Information

If clicking on a link below does not take you to the website, please copy and paste the URL into your browser

National Human Genome Research Institute

<https://www.genome.gov/>

Personal Genetics Education Project

<http://www.pged.org/>

Partners Healthcare Center for Personalized Genetic Medicine

<http://pcpgm.partners.org/>

Personal genetics kits (interview with Robert Green)

BBC News

<http://www.bbc.co.uk/programmes/b03pmbj4>

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The Boston Globe

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The Associated Press

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Do inventors get enough respect in science? (features Ting Wu)

Boston.com

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