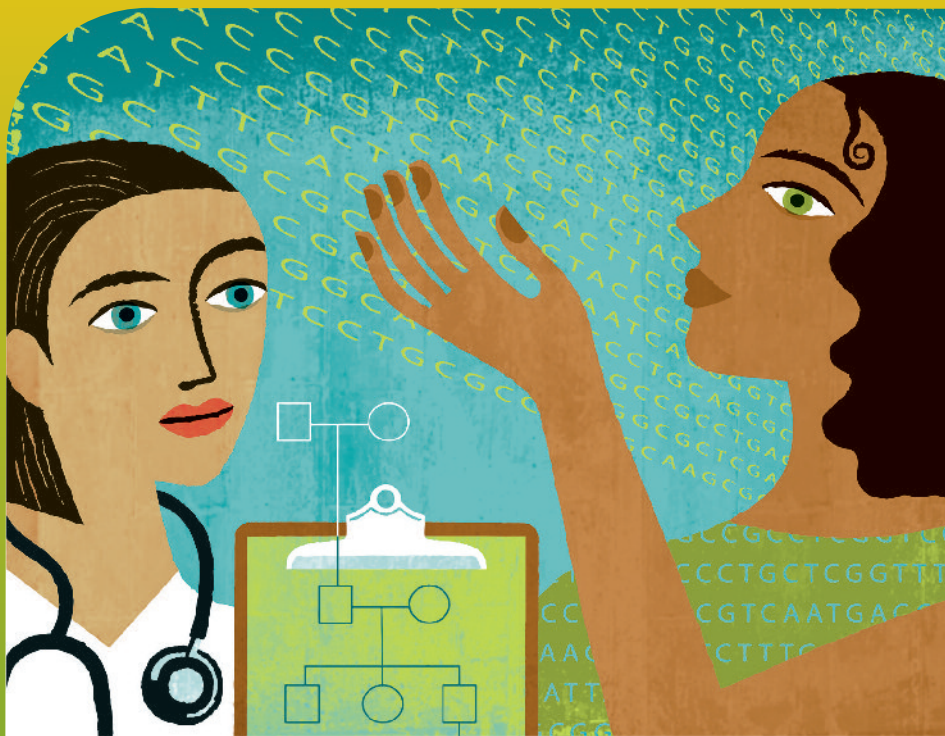


# Genome LIFE



## On the Front Lines

### *Efforts are Underway to Bring Genomic Medicine to a Clinic Near You*

Given the chance to peek at your genome and get a glimpse of what your future might look like – the heart attack you might suffer by 60 or the memory you're at risk of losing to Alzheimer's by 80 – would you take it? Would such a vision of the future embolden you to clean up your act or just fill you with dread? Or would you just shrug it off like so many of us seem to do when it comes to health advice and continue on your merry way?

Of course, genes are not destiny, and it follows that genome technologies won't serve as crystal balls. But our DNA sequence can already give us some pretty good hints at least about our risks for many diseases, from arthritis to glaucoma to heart disease. Researchers affiliated with the IGSP's Center for Genomic Medicine are busy trying to find out what exactly that predictive power might already mean for patients at Duke and beyond.

"It's a double-edged sword," said Alex Cho, an assistant professor of general internal medicine who is now testing the impact of genomic information on people predicted to be at high risk of diabetes through two Duke primary care clinics. "In some ways we wish genomics was more powerful. But if we did have the power to predict the future, some people would be absolutely terrified. The reality is we can use genomic information today in a way that it is not too scary as to be overwhelming, but could give people another reason to pay more attention to their health every day. Because in the end it is the accumulation of all of those little choices we make that pushes us in one direction or another."

### *Getting Off the Fence*

For patients in Cho's study, not making the right choices could mean going from higher than normal blood glucose levels (pre-diabetes) to a diagnosis of full-blown type 2 diabetes. Even without genomics, there are of course many diabetes risk factors, including weight, high blood sugar and family history. In many cases,

**On the Front Lines** (continued on pg 2) >

## INSIDE

<i>Little Fish, Big Science</i>	5
<i>Genomes For ALL?</i>	6
<i>The Evolution of Alzheimer's</i>	8
<i>GINA is in Effect</i>	10

## On the Front Lines (continued)

people can lower their risk of developing the disease in obvious ways, through changes in their diet and exercise habits. But the reality is, most of them don't.

"Even individuals without obvious risk factors – skinny, no family history, normal blood sugar – can get some signal of their baseline risk from genetic testing," Cho said. If an otherwise healthy person discovers they are at higher than average risk due to the 'bad genes' they carry, "it might encourage them to maintain healthy behaviors if they have them or – in the case of young people especially – to adopt healthier habits before it's too late."

With help from Duke physicians Scott Joy and Gloria Trujillo, Cho wants to know whether genomic information added to the list of traditional risk factors is enough to tip the balance in favor of a healthy lifestyle. The Duke team has already enlisted hundreds of patients at Joy's Pickett Road Clinic and Trujillo's Pickens Clinic in a study designed to find out.

"There was skepticism that our patients and providers wouldn't be interested in genetic testing, but we found they were actually all for it," said Trujillo. With that enthusiasm, she said it made all the more sense to test the value of

genomics in the primary care setting – to find out whether patients and their doctors would find it meaningful in practice to have a more complete picture of their diabetes risk.

### Building a Case

The researchers are using a commercially available test to screen the genomes of participants for four different single nucleotide polymorphisms or SNPs, common genetic variations that have known associations with type 2 diabetes. All of the patients receive a color-coded chart outlining their diabetes risk based on fasting blood sugar levels, family history and body mass index. Half will also get their genetic risk profile for the disease.

The researchers then assess the effect of this additional information on the patients by asking them questions about their diet and exercise, both before and again three months after testing. They will also examine the patients after a year – measuring weight, waist circumference and blood glucose values – to see whether their health has changed, for better or for worse. Now a year into the project, the researchers are just starting to crunch the first numbers.

"The interesting thing is that there are no data on the effect that any of this information has on patients at risk of developing diabetes," said Cho. "We want to use genetic information to build a case for the patient that motivates them to change their lifestyle. So we can look at how a patient fares on each of our measures, one-by-one, and relate what that tells us about their risk for type 2 diabetes. Then if everything is moving in the same direction, this genetic information just further solidifies our case."

Trujillo says she often considers how the results of such genetic testing would affect how she manages her own patients.

"I like to think of it in terms of this three-generation family that I take care of with various stages of diabetes," said Trujillo. "I don't have genetic information on them, but I sure wish I did. Now would testing them change my intervention? I don't think it would because I am being as aggressive as I can, but it might change what they do for themselves."

In the next phase of the study, the researchers will arm patients with knowledge of their genetic risk plus additional tools to lower that risk over time – things like health coaching and nutritional counseling – to see if that gets even better results. They also plan to add in genetic markers for cardiovascular disease risk as an added incentive to exercise and eat better.

### Future Medicine

The diabetes trial is just a piece of a much larger effort at Duke to introduce genomic medicine into clinics across the health system in a gradual and systematic way.

"At Duke, we recognize that tailoring advice and treatment to each patient is the future of medicine, and we intend to be on the leading edge," says Victor Dzau, Chancellor for Health Affairs and CEO of the Duke University Health System. "Understanding an individual's risk factors for disease is one aspect of this 'personalized medicine', and genomics will be an important part of that understanding. In fact, it already is for some diseases."

## Sample Risk Profile

Yellow = average risk; Purple = increased risk; Red = highly increased risk

**Fasting Glucose** ("Sugar") Your fasting blood sugar (glucose) was 101 mg/dL. This means that you are "**pre-diabetic**," which puts you at High Risk for diabetes.

- You should probably see your doctor to follow up this test result.
- 1 out of 4 people with a blood sugar this high get diabetes in the next 3 to 5 years.

**Family History** You have 0 first degree relatives with diabetes and 0 second degree relatives with diabetes.

**Body Mass Index** (BMI) Your (BMI) is **23.5**, which is **normal**.

**Genetic Testing** ("DNA") **Based on the genes tested, you are at increased genetic risk for diabetes.**

- You have 6 of 8 possible higher-risk DNA changes tested for in four genes linked to higher diabetes risk.

**Why Diabetes Prevention is important**

- Diabetes is a serious disease.**
- Leading cause of blindness, kidney failure, and amputations in U.S.
  - Increases your risk of heart attack, nerve pain, digestive problems.

**But diabetes can be delayed or even prevented.**

Each participant in the diabetes trial receives a color-coded chart outlining their risk for the disease.

**“The reality is we can use genomic information today in a way that it is not too scary as to be overwhelming, but could give people another reason to pay more attention to their health every day.”** —Alex Cho

Geoff Ginsburg, director of the IGSP's Center for Genomic Medicine, likes to think of the Pickett Road Clinic and the Pickens Clinics, together with The Duke Executive Health Program and other sites, as part of a larger R & D unit that tests new technologies around personalized and genomic health care and, based on the evidence, either optimizes them for distribution to other Duke clinics or rejects them.

The Duke Executive Health Program was an obvious place for IGSP researchers to pilot the use of full genome scans in the clinical setting, according to Lori Orlando, who directs the program. Executive Health patients tend to be a uniquely motivated group, Orlando notes, so if personal genome services don't work for them, they aren't likely to work for Duke patients in other clinics who tend to be less health conscious. In addition to a yearly physical, patients at Duke Executive Health receive a personalized fitness, nutrition and stress management regimen. Now they can get a genome scan from the personal genomics company Navigenics as well.

“We have always been willing to include new technologies on a trial basis to see if they improve the health of our patients,” Orlando said. “So it is sort of a natural experiment for us, to see if adding a genomics assessment to our menu of services would help patients stick to the recommendations we make for avoiding disease down the road.”

The Navigenics Health Compass test scans almost one million SNPs, including ones with associations to 26 different health conditions. Only a handful of patients have signed up for the \$999 test in the last year, and it is still too early to tell if those who do perceive their genomic information any differently from other types of risk information.

Even for this well-educated and professional group, pouring through the more than 100-page test report from Navigenics can be overwhelming. Julianne O'Daniel, an associate in research within the IGSP's Center for Genomic Medicine and a practicing genetic counselor, walks patients through their results over the course of an hour. She says the program is set up so that patients receive their genomic information not in isolation, but as an add-on to other risk factors, including family history.

“We do that because we believe that testing and family history on their own give an incomplete picture,” said O'Daniel. “The testing is a very narrow look; it only provides information about specific gene variants that are known, so it is only as good as our current knowledge. Family history is a very broad look; it is

only as good as our recollection and it only tells us about conditions that have expressed or shown up, which we know are both a combination of genetic and environmental factors.”

O'Daniel says that regardless of whether Duke Executive Health patients are at increased or decreased risk for a particular condition, it's often the first time they've thought concretely about the magnitude of their risk for different health conditions and what they might do about them. For instance, someone might have an average risk for heart attack, but that still means their lifetime risk is a whopping 35 percent.

### *Family Matters*

While those investigations into genomic testing are underway, Ginsburg says his virtual R & D unit plans to roll out the electronic family history tool now offered to patients at Duke Executive Health to clinics across the Duke Health System.

“It just seems like we would be jumping the gun if we were to try to provide complex genetic and genomic information without first getting the fundamentals of something more basic, like family history, in place,” said Ginsburg. “I think that another benefit of this effort is that it helps us understand how to frame risk in the context of a lot of other things that are going on with these patients, both in their medical as well as their personal lives.”

Adapted from the U.S. Surgeon General's "My Family Health Portrait," the tool includes questions not just about patients' and their family's medical history, but also their social history, their background and their expectations about health care. That way, the information they receive about their health and their risk for diseases like heart disease and cancer can be delivered in a truly personalized way.

Family history has also been the emphasis of another of Ginsburg and Orlando's endeavors known as the Genomedical Connection, a \$12 million partnership between the IGSP, the Moses Cone Health System in Greensboro, and the Center for Biotechnology, Genomics and Health Research at UNC-Greensboro. In the initial phases of the project, researchers assessed the base-



*As a first step, an IGSP-led "R & D unit" plans to roll out a family history tool in Duke clinics.*

**“It is the current environment in primary care that you get ten minutes with your doctor and that is not enough to promote healthy behaviors. I think that as the pressure in the patient population builds, the system will evolve to include genomics, but only time will tell.”** —Lori Orlando

line understanding of genetics and genomics in the community and among physicians in Guilford County and then developed a series of Continuing Medical Education modules to provide information on diseases that have a strong family history component.

In the second phase, they created a family history tool called MeTree, which doctors at three community clinical practices have begun to use in the last few months as part of their routine visits. The researchers plan to assess two things – how much influence family history has on physician decisions and how well patients understand the concept of risk. In the next phase, they would like to see how the addition of a health risk assessment tool and genomic testing, for conditions such as colon cancer, breast cancer and blood clots, affects doctors and their patients.

“Once we determine which elements have the most impact, we can start designing the infrastructure and standardizing the process so that the tools can be incorporated into all medical practices,” said Orlando.

### *Clearing the Way*

Right now, one of the biggest obstacles to clinical genomic testing is demonstrating that it's a worthwhile thing to do. There is still no solid evidence to show that genomic information is going to change how people live their lives or impact how physicians make care recommendations. And that's exactly why the IGSP is investing its time and resources so heavily in these efforts and in thinking through the ways medicine would need to adapt to make genomics part of standard clinical care.

“The infrastructure – how to run the tests, who gives the results, how to communicate health risks – all of that is still undecided,” said Orlando. “I think that [genomic information] is going to be a very useful tool, but I believe that creating an infrastructure that can be standardized and spread to other clinics is not going to be as easy as it should be. Family history isn't even routinely practiced, and we all know that is helpful for identifying people at risk and treating them accordingly. It is the current environment in primary care that you get ten minutes with your doctor and that is not enough to promote healthy behaviors. I think that as the pressure in the patient population builds, the system will evolve to include genomics, but only time will tell.” ▶

## Testing, Testing, 1, 2, 3...

Last spring, the IGSP created a formal committee to advise the Duke Health System about which of the growing list of genetic tests on the market should be routinely offered to Duke patients. The Genetic Testing Advisory Committee – or GTAC (an acronym that conveniently mirrors the four bases of DNA) – is a multidisciplinary group with members from molecular diagnostics, clinical informatics, human resources, oncology, cardiology, pediatrics, primary care and pharmacy.

**“I haven't heard of another medical center that is doing anything like this,”** said Geoff Ginsburg, who, along with Scott Joy, established the committee. **“I imagine most health systems wait for a decision to be made by the FDA or insurance companies rather than making it themselves. But by doing so, we will be on the cutting edge, and leading rather than following. We will also have the opportunity to package genetics and genomics in an educational framework, to teach physicians about why this or that test is important, how to order it and what the results mean.”**

First on their agenda are pharmacogenomic tests, those that guide the choice and dosing of prescription medications. So far, the committee has already met to discuss genetic testing for the blood thinner warfarin (Coumadin) and the anti-clotting drug clopidogrel (Plavix). Joy says the committee evaluates the tests on everything from their analytic validity – how accurate and reliable the test is – to their clinical or personal utility – what an individual has to gain from the test.

**“Personal utility is a very powerful aspect of genetic testing,”** said Joy. **“With this genetic testing people think – ‘Wow, that's me, that's my DNA, that's something I can't change' – but there are things you can change. It is a different way to look at controlling your health, and hopefully it can make a difference.”**

# Little Fish, Big Science

## *Zebrafish Aid Researchers in Quest for the Genomic Causes of Disease*

The zebrafish population at Duke is about to boom. It turns out those puny, striped fish (they get their name honestly) that dart around many a household aquarium are ideal specimens for unraveling disease. New Duke faculty member Nico Katsanis thinks that zebrafish may hold the key to tackling some of the biggest obstacles facing genome scientists today.

The challenge is this: genome technologies have made it a snap to generate sequence data and identify spots in the genome where one person might differ from the next. But the ease of sequencing has now far outstripped scientists' skill in identifying medically important variations. As a result, researchers sometimes get stuck "data gazing." Or they may focus in too early on certain genes based on what they already know or think they know, potentially missing big or unexpected discoveries in the process.

"I think that can be dangerous, because you no longer look at the big picture but instead use a narrow genetic model to try to sort out which mutations might be relevant to the disease or trait you study," Katsanis says.

As director of the Center for Human Disease Modeling, a new School of Medicine entity, Katsanis intends to narrow down the hundreds of potential leads that genome studies can turn up to a short list of prime suspects in a less biased way. He likes to think of his new center as an "an intellectual hotel" where people can come to mull over and work together to solve problems they have found intractable by other means.

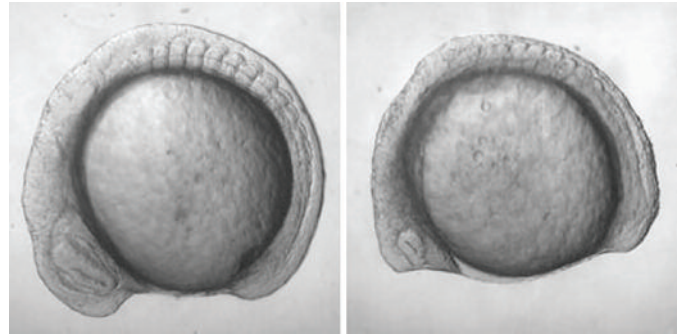
"Nico's combination of expertise in human genetics and zebrafish is unique and he is a very interactive person," said Ken Poss, an associate professor of cell biology and fellow zebrafish guru. "I think he will make things happen here."

### *Blinders Off*

Katsanis is drawn to challenges. In graduate school he mapped and cloned candidate genes for Down's syndrome, but ultimately found the work too mainstream for his taste. When his postdoctoral advisor asked him to tackle a virtually unknown and hard to crack disease – Bardet-Biedl Syndrome (BBS) – Katsanis jumped at the chance. BBS is a rare genetic disorder that affects a variety of different organ systems, resulting in obesity, visual impairment, mental retardation and kidney problems. It took what Katsanis described as an "atrocious" two and a half years before they uncovered the first gene for the disease.

"Every hypothesis I had about the syndrome was wrong, but the truth was more exciting," said Katsanis. "It has taught me to try as hard as I can not to pigeon-hole myself and to just let the science take me where it takes me. I have to tell you, it has been a hell of a ride."

Lately, the science has led him to analyze every single disease variant reported in BBS patients – about 150 in all – and examine their function in zebrafish. The results have been surprising. In twenty percent of BBS patients, it takes a combination of three mutations to manifest the disease.



*Just 24 hours after fertilization, a zebrafish embryo with disease-linked genes suppressed (right) already shows developmental defects.*

"We have had blinders on for a long time, but I now know that if you take those blinders off and look at the data objectively you come up with new ideas," said Katsanis. "We have a far more precise – not fully accurate – but far more precise notion of the disease architecture from doing this model-free experiment. And I am willing to bet – in fact, I am betting my entire career – that this is going to be an approach that will be useful for many other problems of clinical relevance."

### *Something's Fishy*

Katsanis' new center can handle organisms from worms to flies, but he chooses to focus his own efforts on zebrafish, whose transparent bodies make it easy to observe their inner workings as they develop – craniofacial malformations, heart defects, aberrant signaling pathways and all. Because zebrafish share 70 percent of their genes with humans, they can also be "humanized," meaning that the fish version of a gene or set of genes can be replaced by their human equivalents.

Katsanis' team uses specially designed strings of nucleotide bases – As, Ts, Cs and Gs - to mask specific gene messages in zebrafish embryos. At the same time, they insert a normal or mutated human version of the gene. In that way, they can see how those human variants affect development – this fish is growing a tail, this one is not; this fish is making a cortex, that one is not. They can even watch as molecular-level events unfold in real time. The center expects to generate zebrafish with hundreds to thousands of gene variants per month.

Ultimately, Katsanis hopes to encourage a shift in the approach to complex disease all the way down to the level of personal genomes.

"I think that in the future, we should be able to gaze at someone's genome and make a pretty strong argument about what is going to happen and what is going to be helpful to them," said Katsanis. "I am sure that you or I have random mutations throughout our genomes, but they could have nothing to do with any medical problems that you or I develop. The question is what variation is relevant to the problems you are interested in." ▶



## Genomes For ALL?

### *The Genome Revolution Has Hit Home for Some, But Time Will Tell Where it Takes the Rest of Us*

It's 2010, a new decade, and a good time for making predictions about what the future might hold. IGSP Investigator and self-proclaimed "Genomeboy" Misha Angrist has one: he foresees a day not so far off from now when whole-genome sequencing is considered as routine as newborn genetic screening is now and when it's as cheap as a cholesterol test.

That's pretty remarkable when you consider that scientists only released the first drafts of the reference human genome in the year 2000. It was an achievement Francis Collins, then director of the National Human Genome Research Institute, ranked at the time as "up there with going to the moon." In 2003, that first draft was made "final," and a couple of years after that, human genomes really started getting personal when Craig Venter and James Watson became the first individuals to have their complete genomes fully sequenced and made publicly available.

Today, full genome sequencing has become all but routine, at least in some research settings. As David Goldstein, director of the IGSP's Center for Human Genome Variation has noted, their Genomic Analysis Facility can churn out the equivalent of a

Human Genome Project every week. For anywhere from \$48,000 to \$68,500 and dropping, those with the means can purchase their own complete genome sequence from one of several direct-to-consumer companies. And for less than \$500, 23andMe will scan anyone's genome for all the common variations (or SNPs) it contains. The widespread appeal of such services may still be in doubt. The Icelandic personal genomics company deCODE declared bankruptcy in November, and the 23andMe went through a recent round of layoffs, despite the fact that more than 30,000 people have already signed up for 23andMe service.

As we ring in this New Year, the human genome is near the top of many of the decade's top ten lists, including ABC News' list of "top medical advances." Yet it's hard to ignore the fact that we still understand very little about how the variations in our genomes relate to meaningful differences among us in disease risk, and truly genomic medicine is still finding its way into the clinic only selectively and slowly (see cover story in this issue).

No matter where you sit on the issues raised by the new genome technologies or what value you

place today on any one person's sequence, it's clear that the Genome Revolution is barreling along and that personal genomics is here. In part, this is a simple reflection of how cheap DNA sequencing really has become. The company Complete Genomics recently published genomes they sequenced for around \$1700 apiece in reagent costs. Nevertheless, exactly how, when or why we will get to the point of genomes for all is so far anyone's guess.

### *Destination Unknown*

"We have only a very small inkling" of how all of this will play out, says Angrist, one of the most open early adopters of personal genomics as one of the first 10 participants in Harvard's Personal Genome Project. "It's still really early. We've been conditioned to expect things to happen immediately, and I'm as guilty as anyone. But it took decades to adopt cholesterol screening. We've known that there's a strong genetic component to the response to warfarin, but we still haven't made up our minds whether genotyping patients who need blood thinners is a good idea. So this will take time."

Like any new technology, personal genomics will have to gradually seep into the general consciousness. In the meantime, some people at least want their genomes "done," even if much of the information within them is hard to interpret or without any obvious use.

Angrist has had the results of his genome scan in hand, packaged and interpreted in several different ways, for some time and has openly puzzled over their meaning. "Do bad versions of four risk genes for multiple sclerosis add up to four times the risk?" He'll tell you he's learned some other, more comforting tidbits: for instance, he carries a variant that makes him more likely to respond to some anti-depressant drugs.

For some, that kind of information might not seem like quite enough, but Angrist thinks personal genomics companies are onto something. People have been slow to catch on to what their genes might mean for them. Direct-to-consumer companies are shaking things up and making the genome relevant in ways that clinical genetics just hasn't.

"I think HIV patients who have found out they



“**Serious consideration about how to handle the practical and ethical implications of such predictive power should begin now.**”

—David Goldstein

are sensitive to abacavir or people with two APOE4 alleles who want to make plans for an eventuality of Alzheimer’s disease or amateur genealogists [who have learned something about who their ancestors were] will tell you they’ve gotten their money’s worth,” Angrist said. “It would be presumptuous to say that everyone is going to run out and get a SNP chip, but that day is coming. We’re still handicapping when it will come and what will be most useful to whom.”

### *What’s in Your Genome?*

Bob Cook-Deegan, director of the IGSP’s Center for Genome Ethics, Law & Policy, would tend to agree, even if he isn’t necessarily so gung-ho himself. Personal genomics is personal after all, and so far he hasn’t found a reason compelling enough for him to submit his DNA for scanning, even if he is a bit curious about his APOE genotype.

He predicts whole genome scanning will make its impact first for those who might today have a reason to get targeted (and relatively expensive) genetic testing, for genes that predispose people to breast or colon cancer, for instance. Ultimately, as whole genome sequencing becomes more and more accessible and genome scientists learn more about what it all means, he says the pool of potential customers will only expand. In the end, it might not take all that much for many of us to make the leap.

“When there is at least one piece of information of value to everybody, we’ll all have a reason to get it,” Cook-Deegan says. And when that day comes, he doesn’t think we’ll want to go to a doctor for our sequence. “It may not be medical information we’re after,” he said. “We might want to find a relative we didn’t know about; it might be something we haven’t even thought of yet.”

Even if the information we seek is health-related, our reasons for wanting it might not be the ones

typically thought about in a clinical context, adds director of the IGSP’s Center for Genomic Medicine Geoff Ginsburg.

“Personal utility is an important emerging concept,” Ginsburg says. “Genomic test results might influence our life agenda, our financial life, or plans for retirement. There are a whole series of issues not measured in the health system that may play into the value people attribute to their genomic information, particularly if they are subscribing outside of the doctor’s office.”

Ginsburg is convinced of this in part given that his own scan turned up something he hadn’t really anticipated – a greater than average risk for type 2 diabetes. He says that insight motivates him, or at least reinforces his commitment, to sticking to a healthy diet and exercise routine.

Still, if you ask IGSP Investigator Susanne Haga, it may be quite some time before personal genomes really become a mainstream commodity. She points out survey results showing that more than 20 percent of people still say they’ve never heard of genetic testing, personal genomics aside. The public at large may understand something about the notion of heredity, but the very subject of genetics still seems to intimidate many people more than it motivates them.

“I don’t think price is the bottleneck,” Haga says. “It’s lack of awareness.” That hurdle won’t be overcome until it becomes a lot more obvious than it is now how the information in our genomes can be valuable, beyond telling us what we all already know: to eat right and exercise, she says. Even once it does, some people, and likely Haga herself, may still opt out for fear that their genomes might do little more than provoke anxieties.

“Even if it were free, I don’t think I’d take it,” Haga says. “Every little thing would worry me, even though it’s probably nothing.”

### *My Genome and Me*

Angrist, of course, is at the other end of the spectrum. In October, he became one of the elite few, and the first at the IGSP, to gain access to the sequence of his entire genome, thanks to a research project led by the Genomic Analysis Facility and Goldstein’s team. So far, that added information has inspired more awe than answers.

IGSP Associate Investigator Dongliang Ge ran the sequence through a software program he developed to uncover more than 100,000 SNPs “that have never been seen before,” Angrist said. That is to say, they aren’t included in any publicly available database, and Goldstein’s group hadn’t seen them in any of the other genomes they’ve sequenced so far.

“That to me is staggering,” Angrist said. “It’s not because I’m unique or extraterrestrial or anything; it’s simply stark evidence as to how few genomes we’ve done.”

What exactly will genome scientists uncover in this next decade as they sequence more and more human genomes, and how might their findings change the way we see ourselves and live out our lives? Perhaps only time can tell, but as Goldstein wrote in the journal *Nature*, some forecasts for the year 2020 are now all but certain.

“Over the next decade millions of people could have their genomes sequenced. Many will be given an indication of the risks they face. Serious consideration about how to handle the practical and ethical implications of such predictive power should begin now.” ▶

### **Personal genomics group forming**

A new IGSP working group on personal genomics is aimed at those with an interest in direct-to-consumer services and the transition to full-genome sequencing. The first meeting of the new group is February 10th. If you would like to get involved, sign up for the working group listserv online at <https://lists.duke.edu/sympa/info/personal-genomics>.

# The Evolution of Alzheimer's Disease

*Discovery Based on Evolutionary Analysis May Narrow Alzheimer's Genetic Risk Prediction to Five- to Seven-Year Window*



On the list of things in the human genome that many people might choose not to know about, it could be argued that the APOE gene, and especially the APOE4 variant, is somewhere near the top. That's, of course, because of the association of APOE4 with a greater risk that the symptoms of late onset Alzheimer's disease will set in earlier, at least in those unlucky enough to carry two copies of the variant.

James Watson – one of the first people to have his entire genome sequenced and made publicly available – famously redacted (or at least attempted to redact) his APOE genotype because he has a family history and didn't "want to know unless [he could] do something about it."

That's not to say that many in a similar position, including participants of the recently published Risk Evaluation and Education for Alzheimer's disease (REVEAL) study, wouldn't make the opposite choice. The REVEAL results led researchers (including the IGSP's Bob Cook-Deegan) to conclude that disclosure of APOE genotype information to adult children of patients with Alzheimer's disease doesn't lead them to become any more anxious or

depressed. And, for some people, doing "something about it" could simply mean opting for long-term care insurance.

And now it appears that a new result from Allen Roses, an IGSP member who directs the Deane Drug Discovery Institute at Duke, may be poised to make the situation all that much better or worse, depending on your point of view. His group has evidence that a gene next door to APOE, called TOMM40, can be highly predictive of not only the risk of developing Alzheimer's disease, but also the approximate age at which the disease will begin to manifest itself.

## Size Matters

That means that in place of the somewhat abstract lifetime risk for developing Alzheimer's that APOE status provides, a test including TOMM40 may predict the age of Alzheimer's disease development within a five- to seven-year window, at least among people over the age of 60, according to Roses.

"It now looks fairly clear that there are two major genes – APOE and TOMM40 – and together they account for an estimated 85 to 90 percent of

the genetic effect [on Alzheimer's]," Roses said. "If borne out through additional research, a doctor could evaluate a patient based on their age, their APOE genotype and their TOMM40 status to calculate an estimated disease risk and age of onset."

"This will be really exciting if it can be replicated in diverse groups of people," said Duke's Kathleen Welsh-Bohmer, director of the Joseph & Kathleen Bryan Alzheimer's Disease Research Center and a collaborator on the research. "It has tremendous potential to help us determine who is at the highest risk of developing Alzheimer's disease."

Roses led the Duke team that first uncovered the association of APOE4 with the risk and lower age of onset for Alzheimer's disease back in the 1990's. That discovery is arguably one of the most confirmed genetic associations for any complex disease. But he now suspects that APOE4 might not have been found at all back then if it weren't for its close proximity to TOMM40. "If someone gets APOE4 from their mother and APOE3 from their father, they also get TOMM40 as a linked caboose," Roses said.

Everyone has an APOE gene in one of three flavors, designated by the number of the variant, E2, E3 or E4. TOMM40, on the other hand, comes in many forms that vary by the number of so-called poly-T repeats in one of the gene's non-coding regions.

As it happens, the APOE4 version is almost always attached to a long version of TOMM40. APOE3, on the other hand, can be found in association with either a long or short version of TOMM40.

Roses' data show that, if someone carries a short version of TOMM40 attached to APOE3, then that person has a better chance of getting Alzheimer's disease very late, after age 80. But if it's a long TOMM40, they have a better chance of getting the disease earlier. Roses' concludes it is the overall length of the TOMM40 gene that is apparently critical in determining your most likely fate when it comes to Alzheimer's disease.

### Tracing Evolution

The findings also bear on the recent debate over genome-wide association studies (GWAS) and the apparently small risk typically associated with common disease variants that turn up in those studies. GWAS identify what amount to single letter "typos" (known as single nucleotide polymorphisms or SNPs) in the genomes of one group of people versus another, pointing the way to the genes responsible for particular diseases or other traits. In the past, the signal from GWAS of Alzheimer's disease in the APOE-TOMM40 region had been attributed to APOE. But now it seems there are two genes in that region that bear responsibility.

Others had recognized the link between TOMM40 and Alzheimer's risk before, Welsh-Bohmer explained, but it was generally interpreted

as an artifact of its physical linkage to APOE. The new work "solidifies" a role for TOMM40 in its own right, she says.

Roses' TOMM40 discovery was made by deep sequencing the portion of the genome near the APOE gene in patients with and without late-onset Alzheimer's disease. To make sense of those sequences, he then did something that is routine in the case of evolutionary biologists studying the relationships among species or perhaps viral strains, but not so routine in the study of human genetics and genomics; he applied a phylogenetic approach to identify the relationships – essentially the genealogy – of the region, including many different versions of the TOMM40 variant, and the order in which they arose over the course of time.

"Genome-wide screening maps blocks of DNA where common variations occur, but it doesn't tell you anything about the fine structure," Roses said. "We conducted a phylogenetic analysis to explore the evolution of the DNA and to see what changes took place on the backbone of other changes."

Two major groups fell out of that evolutionary analysis: one characterized by long versions of TOMM40 (with anywhere from 19 to 39 poly-T repeats) and another with short TOMM40 variants (with just 14 to 16 poly-T repeats). Those two evolutionary groups separate people with a greater risk of getting Alzheimer's disease early from those who have a lower risk. Roses stressed that he will need to repeat his analysis of the TOMM40 region and its relation to Alzheimer's disease in people of different geographic origins and ethnicities.

"It's cool to see that the phylogenetic method can be useful in this really applied way," says Greg Wray, director of the IGSP's Center for Evolutionary Genomics.

What's interesting about the problem, Wray says, is this: you have a strong variant – APOE –

that explains a lot of the variation in risk for Alzheimer's disease, but nearby there is a second variant that also plays a role. "The question is how do you separate the effects of two closely linked variants – how do you tease that apart? Gene genealogies are one approach."

### Prevention is Worth a Pound of Cure

The Deane Institute team now plans to validate their findings through a prospective clinical trial designed to test TOMM40's predictive value over a five to seven year window in people over the age of 60. Those who are classified as high risk based on their TOMM40 status will also be randomized into a clinical trial of a drug that may help prevent or delay the onset of Alzheimer's symptoms.

Even if a preventive medicine were to put a small dent in the incidence or slightly delay the onset of Alzheimer's symptoms, it could be very significant, Roses says. After all, the prevalence of Alzheimer's disease is predicted to quadruple worldwide by 2050 to more than 107 million cases, meaning that one out of every 85 people will be living with the disease. It has been estimated that delaying disease onset by just one or two years will decrease the disease burden 40 years from now by some 10 to 20 million cases.

The strategy applied to Alzheimer's might also help crack other diseases as well. As Roses explains in a perspective piece on the subject, "In the evolutionary history of other complex diseases, multiple evolutionarily-linked variants within a genomic interval... may determine risk of disease. ...Phylogenetic approaches may provide a powerful mechanism for capturing the effects of disease susceptibility variants."

Wray concurs. "APOE was one of the early cases that convinced everyone to do GWAS," he says. Now it appears there is more to the story, and Alzheimer's disease probably isn't unique in this way. "There will likely be more examples." ▀

“It will really be exciting if we can replicate this in diverse groups of people. It has tremendous potential to help us determine who is at the highest risk of developing Alzheimer's disease.” —Kathleen Welsh-Bohmer

# GINA is in Effect

## *Federal Law Protects Against Genetic Discrimination in Health Insurance, Employment*



Those undergoing genetic or genomic testing can now breathe a little sigh of relief. The Genetic Information Nondiscrimination Act (aka GINA), which was signed into law in 2008, went into full effect in December although policy experts are still waiting for final regulations to be issued.

GINA prohibits group and individual health insurers from using genetic information to determine an individual's eligibility or premiums. It also prohibits employers from using genetic information in decisions about hirings, firings, job assignments and promotions. In addition, GINA limits the kinds of genetic information that a health insurer or employer may collect. GINA has been widely celebrated in the genomics community as an essential ingredient for ushering in the new era of genomic medicine and the growing personal genomics industry.

Lauren Dame, associate director of the IGSP's Center for Genome Ethics, Law & Policy, spoke with *GenomeLIFE* about the new protections, the challenges they present to wellness programs, and their significance as genomic information becomes more widespread in the coming decade.

***Q: What is GINA meant to accomplish and what do you see as challenges under the new law?***

**A:** GINA has a difficult task. It's trying to stop people from using genetic information to discriminate, but genetic information is getting broader and broader all the time. Almost every health issue has some kind of genetic element. In our current health care system, insurance companies try to set premiums based on the costs they anticipate, and they have been allowed to do that. GINA now says there is one slice of information they can't use.

Under GINA, "genetic information" is broadly defined to include family medical history. This means that if I had a heart attack, that's not genetic information. But if my mom or grandmother had a heart attack, that *is* my genetic information even though there is no genetic test. Family medical history is considered genetic information and that is an important part of the law. Many state laws protect against discrimination based on genetic information, but not family history, and that leaves an enormous loophole. If a health insurer is allowed to use family history, it really scoops up the entire medical record. GINA gets rid of that loophole.

***Q: GINA was passed into law back in 2008, but the interim regulations under the law only became available more recently. What are some of the key elements of those regulations?***

**A:** The regulations are important for explaining what key phrases in the law mean – for example, as defining "genetic information" to include family medical history. This definition has led to heated discussions about the effect of GINA on wellness programs and health risk assessments (HRAs). The number of health plans or employers with wellness programs is increasing, and it's common to ask about family medical history as part of HRAs. Now, as soon as they do that they are collecting "genetic information," which is prohibited by GINA under certain conditions. As a health insurer, you can't collect genetic information before enrollment or in connection with enrollment – this means a health insurer would have to limit the HRA questions during these periods. You also can't ask for genetic information at any time for underwriting purposes, and under GINA, the definition of "underwriting" is very broad, and can include a financial break or incentive – a common element of wellness programs to encourage individuals to participate. Because all of the final regulations have not been released yet, there is still a lot of uncertainty about how the details of GINA will affect workplace wellness programs.

***Q: As you bring up, there has been a lot of talk about the fact that some wellness programs, as currently run, might be in violation of GINA, and there are complaints from those affiliated with those programs that the new law will result in a decline in participation. What is your take on that?***

**A:** I come from a civil rights and patient advocacy background and there is always tension in crafting anti-discrimination laws in such a way as to prevent use of the information in a bad way, but to allow use in a good way. It's rare, if not impossible, to craft a rule that draws the line at exactly the right spot.

Members of the business and insurance communities who want to do wellness programs and say GINA hampers that effort are correct. It does make that more difficult, but it has to be acknowledged that if they collect genetic information for a good reason, it could also be used for a bad one. If you introduce an exception, then that becomes the loophole that eats up GINA. The fact that GINA now prohibits some wellness program strategies, however, doesn't mean wellness programs are doomed. The administrators will have to make changes in light of GINA, and after a period of some uncertainty, they will develop new strategies to promote the goals of wellness programs, without collecting sensitive genetic information.

**Q: By all accounts, genetic discrimination has not been a pervasive problem. Given that, why is GINA important?**

**A:** It's probably true there have not been a lot of cases of genetic discrimination, but that doesn't lead me to conclude there's no reason for concern. Most people still don't have a lot of genetic information in their records to be used – the average person probably hasn't had a genetic test, so there may not be much genetic information available to be used against him. Of the information that is out there, it might tell you something like you've got an increased risk of heart disease in your 70s, which probably isn't particularly useful to a health insurer or employer. On the other hand, some kinds of genetic information can be more meaningful to an employer – if I know I may develop Huntington's disease in my 50s and an employer is deciding whether they should send me or another employee to an expensive training program, you could imagine how that genetic information about me might be used.

**Q: Some have said that GINA is primarily important as a means of reassuring people that they can get genetic testing in a clinical or research setting without fear of discrimination. Do you agree?**

**A:** The reassurance GINA provides is very important. There is ample evidence that people are concerned about genetic discrimination and that people worry about research participation. The law can't prevent all discrimination, but it certainly helps. For instance, there are people out there with a strong family history of breast cancer who have forgone genetic testing out of fear of discrimination, and that's really a shame. Now GINA is offering protection for those people.

It is important to note, however, that GINA only protects in the case of health insurance and employment – not disability insurance or long-term care insurance or use by any other entity. As more and more people get their genome sequenced and more entities get the idea that DNA can be used for something, GINA won't offer complete protection.

**Q: GINA has been called the "first civil rights bill of the new century." Given your civil rights background, how do you place GINA within this context?**

**A:** To the extent civil rights laws over time have been aimed at ensuring people are treated equally and as individuals evaluated on the basis of their qualities and abilities, not on stereotypes or generalizations – whether those are defined by skin color or a genetic mutation – GINA is a part of that effort. Because we don't have the same widespread background of genetic discrimination, it will not have as dramatic an impact. But GINA's impact may be to stop genetic discrimination before it really gets started; once discrimination is built in, it is hard to eradicate it. Wellness programs are popping up all over the place and they ask for all sorts of private medical information. Before that takes off too much, it makes sense to have rules about what you can and can't do with that information and how it should be handled and collected.

## Equal Employment Opportunity is THE LAW

Private Employers, State and Local Governments, Educational Institutions, Employment Agencies and Labor Organizations

Applicants to and employees of most private employers, state and local governments, educational institutions, employment agencies and labor organizations are protected under Federal law from discrimination on the following bases:

**RACE, COLOR, RELIGION, SEX, NATIONAL ORIGIN**

Title VII of the Civil Rights Act of 1964, as amended, protects applicants and employees from discrimination in hiring, promotion, discharge, pay, fringe benefits, job training, classification, referral, and other aspects of employment, on the basis of race, color, religion, sex, or national origin. It also prohibits religious discrimination where the action or omission does not impose undue hardship.

**DISABILITY**

Title I and Title V of the Americans with Disabilities Act of 1990, as amended, protect qualified individuals from discrimination on the basis of disability in hiring, promotion, discharge, pay, fringe benefits, job training, classification, referral, and other aspects of employment, and also require reasonable accommodation to the known physical or mental limitations of an otherwise qualified individual with a disability who is an applicant or employee, "unless such individual is not qualified to perform the essential functions of the job in question because of his or her disability."

**AGE**

The Age Discrimination in Employment Act of 1967, as amended, protects applicants and employees 40 years of age or older from discrimination based on age in hiring, promotion, discharge, pay, fringe benefits, job training, classification, referral, and other aspects of employment.

**SEX (TWINS)**

The Equal Employment Opportunity Commission (EEOC), 1400-600-4000, will investigate and attempt to resolve your complaint. If you are unable to resolve your complaint through EEOC mediation, you may file a lawsuit in court.

**GENETICS**

Title II of the Genetic Information Nondiscrimination Act of 2008 protects applicants and employees from discrimination based on genetic information in hiring, promotion, discharge, pay, fringe benefits, job training, classification, referral, and other aspects of employment. GINA also restricts employers' acquisition of genetic information and strictly limits disclosure of genetic information. Genetic information includes information about genetic tests of applicants, employees, or their family members; the manifestation of diseases or disorders in family members (family medical history); and requests for or receipt of genetic services by applicants, employees, or their family members.

### Duke Meets GINA

**In accordance with GINA, Duke has posted notices to assure employees that they are protected from discrimination on the basis of their genetic information.**

**"We have taken steps to ensure that all of our benefit programs,**

**services and employment practices are in compliance with the new act," said Kyle Cavanaugh, vice president for Human Resources.**

**Cavanaugh had been following GINA for several years at it wended its way through Washington. He said there was never any concern that genetic information was being used inappropriately at Duke. The new law led to only minor adjustments in Duke's Prospective Health Program, such that the health risk assessment at this time no longer requests information about family health history, he said.**

**The GINA requirements apply to all private, state, and local government employers with 15 or more employees.**



**The Institute for Genome Sciences & Policy**

Duke University  
CIEMAS  
101 Science Drive  
Box 3382  
Durham, NC 27708  
www.genome.duke.edu



**Genomes@4: Engaging diverse perspectives on the Genome Revolution**

**M a r c h**

**Not just another seminar series! The IGSP invites you to our series, "Genomes@4," held every other Wednesday (at 4 o'clock, naturally) this spring from March 3 through April 21. This is an opportunity for all IGSP faculty, collaborators, students and any other interested parties at Duke to hear presentations and engage in discussions on various topics relevant to the genome sciences, ethics and policy.**

- 3 Geoff Ginsburg**, *director of the IGSP Center for Genomic Medicine*, will present "The Human Genome, Personalized Medicine and Duke" *in Bio Sci 111*.
- 17 Jim Evans** *in the genetics department at UNC-Chapel Hill* will present "Genomic Analysis in Clinical Medicine: Too much information or not enough?" *in Bryan 103*.
- 31 Tom Schulz** *from the Duke University Marine Lab* will present "Environmental Genomics" *in Bryan 103*.

**A p r i l**

- 7 Anil Potti**, *an IGSP Investigator in the department of medicine*, will present "Markers and Modulators of Radiation Sensitivity" *in Bryan 103*.
- 21 Rick Kittles** *in the department of medicine at the University of Chicago* will present "The Role of Diverse Populations in Personalized Genetic Medicine" *in Bryan 103*.