

## FEATURE

# PLAYING MATCHMAKER: FINDING PERSONALIZED APPROACHES TO SOLVE ALCOHOL PROBLEMS

*Researchers in the alcohol field are taking a personalized approach to understanding, preventing, and treating alcohol-related problems across the lifespan.*

**W**e've come to expect so much in our lives to be tailored to our personal preferences—from our music playlists, to our coffee choices, to our exercise workouts. Now, thanks to the concept of personalized medicine, health care options are beginning to follow suit. In the past, researchers developed medical treatments based on studies that determined what proportion of people with a particular disorder responded to various treatments for that disorder. Treatments with the highest proportions of positive responses were deemed best for nearly everyone. However, it has become clear that not every individual with a particular disorder responds to the same treatment in the same way. Much of how people respond has to do with individual genetic makeup, environmental influences, and their complex interactions.

Personalized medicine takes these factors into account. As in other areas of medicine, researchers in the alcohol field are taking a personalized approach to understanding, preventing, and treating alcohol-related problems across the lifespan.

As NIAAA fosters the development of new and more effective medications for dependence, learning more about which medications work best for whom is an important priority. New research is helping NIAAA to be more strategic about the medications tested, the way they are tested and designed, and how to determine the subpopulations of patients who are most likely to benefit from them. For example, information about an individual's subtype of alcohol dependence can guide treatment strategies and help predict which medications will be most effective for a given patient. (See "Alcoholism Isn't What It Used To Be" in *NIAAA Spectrum*, Vol. 1, Issue 1, September 2009.) Likewise, identifying individual genetic makeup can help predict who may respond positively to a specific medication. For example, sequence variations in genes linked to an increased vulnerability for alcohol dependence such as *mu* opioid receptor and dopamine D4 receptor have been associated with the efficacy of certain medications. A recent study showed that a particular gene (*OPRM1*) predicts which patients are likely to respond well to naltrexone, a medication for alcohol dependence.

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### *Learning more about which medications work best for whom is an important priority.*

Similarly, personalized information can help individualize alcohol treatment goals from patient to patient. Desired outcomes include abstinence for some and reducing heavy drinking to low-risk levels for others, depending on the individual.

Advances in pinpointing a connection between individual genetic makeup and environmental risk factors for alcohol problems also are contributing to the development of more effective prevention strategies. For example, previous studies showed that the short allele or form of

the 5-HTTLPR gene, which is found in over 40 percent of people, is associated with impulsivity, low self-control, binge drinking, and substance use. Recently, researchers at the University of Georgia found that a family-based prevention program designed to help adolescents avoid substance use and other risky behavior was especially effective for young teens with this gene variant. Investigators monitored the progress of 11-year-olds enrolled in a family-centered prevention program called Strong African American Families (SAAF) over 2 1/2 years, along with a comparison group. Some of the participants carried the

short allele variant and some carried the long allele. SAAF program participants with the short allele of the gene were no more likely than their long allele counterparts to have drunk alcohol, smoked marijuana, or been sexually active. They were half as likely as their short allele counterparts in the comparison group to have engaged in these risky behaviors.

Using information accumulated from studies like these, researchers and doctors can develop prevention and treatment programs that result in the most desirable outcomes. As our capabilities expand, we will close in on a time when developing an individualized treatment plan is as routine and targeted as creating a music playlist. ■

## PHOTO ESSAY: INPUT, OUTPUT, THROUGHPUT: HOW IS HIGH-THROUGHPUT TECHNOLOGY ADVANCING ALCOHOL RESEARCH?



The “addictions array” shown above is an example of high-throughput technology that enables researchers to study genes linked with a vulnerability to alcohol dependence, other addictions, mood disorders, and anxiety. “We need to conduct very large-scale DNA studies in different populations to understand links between various genes and alcohol use disorders or other clinical outcomes,” explains David Goldman, M.D., head of NIAAA’s Laboratory of Neurogenetics. This array and other high-throughput technologies make the job faster, easier, and cheaper.

“Compared to our previous methods, the addictions array has allowed us to generate about 100 times more data at one-tenth the cost for each data point,” says NIAAA’s Colin Hodgkinson, Ph.D., who coordinated the multi-institution team that developed the array. It is based on a commercially available device, the Illumina GoldenGate array, which simultaneously mines the DNA of 96 individuals. The researchers customized the array to detect any of 1,350 possible variations in 130 genes linked with addiction and the related disorders of anxiety and depression. The array also can

detect 186 biochemical markers for ethnic ancestry, a variable that can confound genetic studies if not addressed.

In an important recent study, the addictions array helped to validate research showing that a particular gene (OPRM1) predicts which patients are likely to respond well to naltrexone, a medication for alcohol dependence. As this type of “personal genomics” research advances, this array and other high-throughput technologies hold great promise for bridging the gap between basic research and clinical treatment for alcohol use disorders. ■

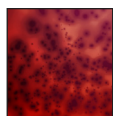
Article abstracts can be found here:

*Addictions Biology: Haplotype-Based Analysis for 130 Candidate Genes on a Single Array.* <http://www.ncbi.nlm.nih.gov/pubmed/18477577>

*An Evaluation of Mu-Opioid Receptor (OPRM1) as a Predictor of Naltrexone Response in the Treatment of Alcohol Dependence: Results from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) Study.* <http://www.ncbi.nlm.nih.gov/pubmed/18250251>

## FEATURE

## ALCOHOL AND CANCER NEWS



*Alcohol consumption is linked to cancers of the oral cavity, pharynx, larynx, esophagus, colon, rectum, liver, and female breast.*

An interdisciplinary working group convened in October 2009 by the International Agency for Research on Cancer (IARC) concluded that acetaldehyde associated with alcohol consumption is a Group 1 carcinogen. The IARC defines Group 1 agents as those for which there is sufficient evidence that they cause cancer in humans. The working group also confirmed the Group 1 classification of alcohol consumption and of ethanol in alcoholic beverages. A summary of the group's assessment appeared in the November 2009 issue of *The Lancet Oncology*. A complete write-up will be published in an upcoming volume of the *IARC Monographs*.

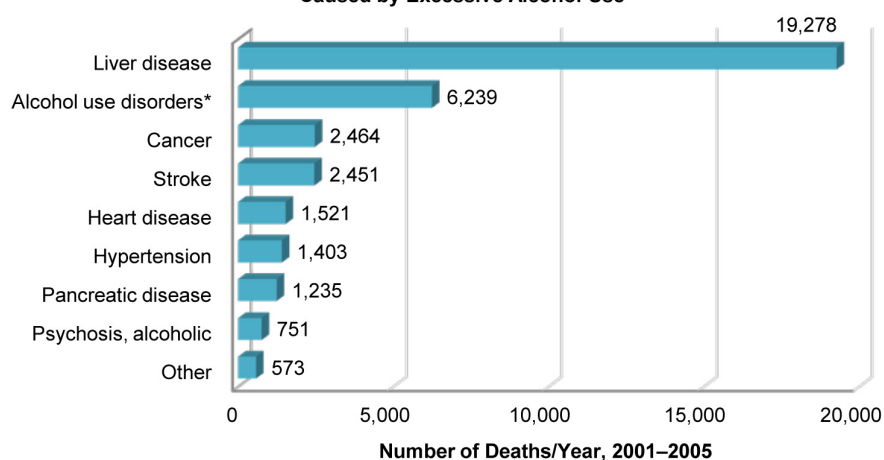
Part of the World Health Organization, the IARC brings together expert working groups to evaluate the evidence of the carcinogenicity of chemicals, occupational exposures, and lifestyle factors. Alcohol consumption is linked to cancers of the oral cavity, pharynx, larynx, esophagus, colon, rectum, liver, and female breast. Evidence linking alcohol to cancer of the pancreas is limited.

When alcohol is consumed, it is first metabolized into acetaldehyde, a chemical similar to formaldehyde, which causes DNA damage and has other cancer-promoting effects. Aldehyde dehydrogenase 2 (ALDH2) is the main enzyme responsible for breaking down acetaldehyde into

acetate, a non-toxic metabolite in the body. Many people of East Asian descent have an inactive variant of the ALDH2 enzyme. When individuals with the inactive variant drink alcohol, acetaldehyde accumulates in the body and puts them at elevated risk for alcohol-related cancer. As pointed out recently by NIAAA researchers, heavy alcohol consumption greatly increases the risk for esophageal cancer among such individuals, and greater awareness of this risk among affected individuals and their doctors could have important implications for cancer prevention. (See "Alcohol 'Flush' Signals Increased Cancer Risk" in *NIAAA Spectrum*, Vol. 1, Issue 1, September 2009.) ■

## CHARTICLE: DRINKING TOO MUCH CAN KILL YOU QUICKLY . . . OR SLOWLY

**Estimated Annual Deaths in the United States from Chronic Diseases Caused by Excessive Alcohol Use**



\*Note: Deaths from alcohol use disorders included 2,382 from alcohol abuse and 3,857 from alcohol dependence, which is typically the more chronic of the two conditions.

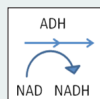
Excessive alcohol use causes an estimated 79,000 deaths per year in the United States. Most people are unaware that close to half of these deaths (approximately 36,000 annually) result from chronic alcohol-related illnesses rather than acute causes such as motor vehicle crashes and falls. Unlike other drugs, alcohol disperses in all body tissues and therefore has the potential to harm many organ systems. The chart at left shows a variety of conditions linked with drinking too much, along with the estimated average number of alcohol-attributed deaths each year. In the cancer category, the top alcohol-related deaths are from cancer of the liver, head and neck, esophagus, and female breast.

Source: *Alcohol-Attributable Deaths Report, Average for United States 2001-2005*, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention.



## NEWS FROM THE FIELD

## MOLECULE REPAIRS ALCOHOL METABOLISM ENZYME



*A recently identified molecule called Alda-1 activates the defective enzyme.*

A n experimental compound repaired a defective alcohol metabolism enzyme that affects an estimated 1 billion people worldwide, according to research supported by NIAAA. Published January 10, 2010, in the advance online edition of *Nature Structural and Molecular Biology*, the finding suggests the possibility of a treatment to reduce health problems associated with the enzyme defect.

“We recently identified a molecule called Alda-1 that activates the defective enzyme, and in the current study, we determined how this activation is achieved,” said the study’s senior author, Thomas D. Hurley, Ph.D., professor and associate chairman of biochemistry and molecular biology at Indiana University School of Medicine in Indianapolis. Initial investigations of Alda-1 were led by co-author Daria Mochly-Rosen, Ph.D., professor of chemical and systems biology at Stanford University School of Medicine.

After alcohol is consumed, it is first metabolized into acetaldehyde, a toxic chemical that causes DNA damage.

Aldehyde dehydrogenase 2 (ALDH2) is the main enzyme responsible for breaking down acetaldehyde into acetate, a nontoxic metabolite in the body. It also removes other toxic aldehydes that can accumulate in the body.

About 40 percent of the East Asian population and many people of East Asian descent throughout the world carry a variant of the ALDH2 gene that produces an inactive form of ALDH2. When individuals with this variant drink alcohol, acetaldehyde accumulates in the body, resulting in facial flushing, nausea, and rapid heartbeat. In addition to its link to increased cancer risk, the inactive form of ALDH2 also reduces the effectiveness of nitroglycerin, a drug used to treat angina.

In a series of experiments that examined the interaction between Alda-1 and the defective ALDH2 enzyme, Dr. Hurley and his colleagues found that Alda-1 restored the structure of the inactive enzyme. The normal, active form of ALDH2 creates a catalytic tunnel, a space within the enzyme in which acetaldehyde is metabolized,

explained Dr. Hurley. In the defective enzyme, the tunnel does not function properly. Alda-1 binds to the defective enzyme in a way that effectively reopens the catalytic tunnel and thus allows the enzyme to metabolize acetaldehyde.

“The manner in which Alda-1 binds to the structure of ALDH2 provides us with powerful insight into the relationships between activators and inhibitors of this crucial detoxifying enzyme,” says Dr. Hurley. “This insight will lead to the modification of Alda-1 to improve its potency, and also opens up the possibility of designing new analogs that can selectively affect the metabolism of other molecules that are detoxified by aldehyde dehydrogenase.” ■

The article abstract can be found here:

*Alda-1 Is an Agonist and Chemical Chaperone for the Common Human Aldehyde Dehydrogenase 2 Variant.*  
<http://www.ncbi.nlm.nih.gov/pubmed/20062057>

## NEWS FROM THE FIELD

## THE VINE THAT ATE THE SOUTH MAY HELP ALCOHOLICS CURB CRAVINGS



*Daidzin, one of the active ingredients in kudzu, inhibits ALDH2.*

The kudzu plant, nicknamed the “vine that ate the South” for its fast and wild growth throughout the southeastern United States, may help

alcoholics curb their desire to drink. Aside from being a pesky weed, kudzu is the main ingredient in a Chinese folk medicine used for 1,000 years to treat alcoholism.

A study published in the November 2009 issue of *Alcoholism: Clinical and Experimental Research* investigated a new compound that works much the same way

## THE VINE THAT ATE THE SOUTH MAY HELP ALCOHOLICS CURB CRAVINGS, CONTINUED

as one of kudzu's active ingredients. This information may help scientists develop new drugs to combat alcoholism.

Researchers led by Ivan Diamond, M.D., Ph.D., University of California at San Francisco, based their work on two premises demonstrated by previous studies. The first is that people are less likely to drink heavily or become alcoholics if they lack aldehyde dehydrogenase 2 (ALDH2), an enzyme that breaks down alcohol in the body. A deficiency in ALDH2 can cause a substance called acetaldehyde to build up. An accumulation of acetaldehyde triggers a "flushing reaction" in drinkers, with symptoms that can include nausea, headaches, and a racing pulse. An accumulation of acetaldehyde also alters

the metabolism of dopamine, which could reduce the desire to drink. The second premise is that daidzin, one of the active ingredients in kudzu, inhibits ALDH2.

Diamond and his team developed a synthetic substance called CVT-10216, modeled after daidzin, but designed to be even more effective at inhibiting ALDH2. They tested it in various rat models using a variety of experimental paradigms. Rats who received CVT-10216 not only drank less, but had reduced alcohol cravings.

By monitoring the rats' blood and brain chemistry, the researchers explored possible mechanisms that caused these cravings to wane. One possibility is the effect on the dopamine system. During

alcohol intake, CVT-10216 prevents increased levels of dopamine from accumulating in the nucleus accumbens, an area of the brain that perceives drinking in positive or reward terms. Stabilizing this brain chemistry may be the key to CVT-10216's innovative potential.

Since alcohol-dependent rats can model some of the addictive behaviors seen in humans, this new research may help develop new drugs to treat the root causes of addiction and relapse. ■

The article abstract can be found here:  
*Suppression of Heavy Drinking and Alcohol Seeking by a Selective ALDH-2 Inhibitor.*  
<http://www.ncbi.nlm.nih.gov/pubmed/19673742>

## NEWS FROM THE FIELD

## CAN DRINKING DURING PREGNANCY AFFECT KIDS' BEHAVIOR?



*Australia-based research supports the notion that fetal development is vulnerable to alcohol exposure throughout pregnancy.*

Research points to a possible link between drinking during pregnancy and behavioral problems in children. Australia-based researchers polled a random sample of more than 2,000 mothers at 3 months post-partum on their pregnancy drinking habits. By following up with these same mothers after 2, 5, and 8 years had elapsed, the researchers were able to gather data on the behavioral trends in their children.

According to the analysis published in the January 2010 issue of *Addiction*, children whose mothers drank moderate to heavy amounts of alcohol during early pregnancy suffered from anxiety, depression, and inexplicable aches and pains at higher rates than children whose mothers drank little to

no alcohol while pregnant. Children whose mothers drank moderate to heavy amounts of alcohol in the second and third trimesters were more likely to exhibit aggressive behavior than children whose mothers drank less or abstained. As the amount and frequency of drinking increased, the risk for behavior problems in the children went up as well. The study defines moderate drinking by mothers as three to four drinks per occasion, and up to seven drinks per week.

These results support the notion that fetal development is vulnerable to alcohol exposure throughout pregnancy. That's why pregnant women generally are cautioned to abstain from alcohol completely.

According to the study's lead author, Colleen O'Leary, M.P.H., of the Telethon Institute for Child Health Research, alcohol's unpredictable risks are reason enough for extra caution. "Not every smoker gets lung cancer despite being at higher risk—and in this case, not every child will be affected by prenatal exposure to alcohol. However, it is important that women have this information about increased risk so that they can make informed decisions to give their child the best start to life." ■

The article abstract can be found here:  
*Evidence of a Complex Association Between Dose, Pattern and Timing of Prenatal Alcohol Exposure and Child Behaviour Problems.* <http://www.ncbi.nlm.nih.gov/pubmed/19922516>

## NEWS FROM THE FIELD

## CAN DRINKING POLICIES KEEP RISKS AT BAY?



*Public health benefits may be found in limiting the concentration of both “on-premises” and “off-premises” alcohol outlets.*

Neighborhoods where many alcohol-selling establishments operate in close proximity to each other tend to have higher incidences of alcohol-related violence and aggressive behavior. In collaboration with the Task Force on Community Preventive Services, scientists at the Centers for Disease Control and Prevention and other experts in research, practice, and policy worked together to select and review recent research addressing this topic. Their findings, published in the December 2009 issue of the *American Journal of Preventive Medicine*, suggest that effective policies limiting how many alcohol outlets can exist in a given area may help reduce these alcohol-related problems.

Public health benefits may be found in limiting the concentration of both “on-premises” outlets where alcohol is consumed where purchased and “off-premises” outlets where alcohol is purchased for consumption elsewhere, such as at home. The researchers explain that people tend to congregate in areas where there are many places to buy alcohol and consume it on-premises, like bars, restaurants, and ballparks. When these people drink excessively, they may become aggressive or violent. With respect to off-premises outlets, like convenience stores, grocery stores, and liquor shops, a higher density of outlets may increase excessive consumption by decreasing the effort needed to get alcohol.

The authors conclude that reducing the number of alcohol-selling outlets in a given community can make alcohol harder to access and perhaps more expensive, thereby reducing adverse alcohol-related consequences like violence and aggression. ■

The article abstract can be found here: *The Effectiveness of Limiting Alcohol Outlet Density as a Means of Reducing Excessive Alcohol Consumption and Alcohol-Related Harms*. <http://www.ncbi.nlm.nih.gov/pubmed/19944925>

## NEWS FROM THE FIELD

LOOKING TO SOBER UP?  
CAFFEINE IS *NOT* THE ANSWER

*Drinking caffeine to combat alcohol’s numbing effect on thinking and judgment actually leaves drinkers even more open to risky behavior.*

The conventional wisdom that a strong cup of coffee can sober you up after too much drinking is about to become obsolete. A new study suggests that drinking caffeine to combat alcohol’s numbing effect on thinking and judgment actually leaves drinkers even more open to risky behavior.

Researchers from Temple University administered caffeine and alcohol—separately in some experiments, together in others—to lab mice. The mice received enough alcohol to inebriate them. They also received the caffeine equivalent of one to eight cups of coffee. The researchers tested the mice’s changes in anxiety

levels (as indicated by how much time a mouse spent in the open area of a maze), movement, and ability to learn while under the influence of various combinations of the two substances.

Mice that received alcohol alone ran around more, but felt less anxious and had more difficulty learning than control mice. Mice that received just caffeine felt more anxious, but moved and learned more poorly than control mice. When mice

*All evidence points to serious risks associated with caffeine–alcohol combinations.*

received both alcohol and caffeine together, they were less anxious but had the same difficulty learning as mice that received alcohol alone. As a result, these mice were still unable to dodge what they knew were dangerous areas of a maze.

Thomas Gould, Ph.D., who co-conducted the research published in the December 2009 issue of *Behavioral Neuroscience*, believes the results have broad implications for human alcohol and caffeine consumption.

The researchers concluded that consuming caffeine and alcohol together may make a drunken person feel more alert, but the combination will not make the person any less impaired. In fact, the effect is quite the opposite. As a result, drinkers who wrongly believe they can offset the effects of alcohol with caffeine make poor decisions. These are the very decisions that lead to problems such as drunk driving and drinking enough to require medical care.

“The bottom line is that, despite the appeal of being able to stay up all night and drink, all evidence points to serious risks associated with caffeine-alcohol combinations,” said Dr. Gould. ■

The article abstract can be found here:  
*Effects of Ethanol and Caffeine on Behavior in C56BL/6 Mice in the Plus-Maze Discriminative Avoidance Task.* <http://www.ncbi.nlm.nih.gov/pubmed/20001110>

## NEWS FROM THE FIELD

# MARRIAGE AND PARENTHOOD MAY PROTECT AGAINST STRESS-INDUCED HARMFUL DRINKING



*Terrorism-related stress may be less likely to cause harmful drinking in individuals who are married or have children.*

**S**tress is a known risk factor for harmful drinking, and that includes stress resulting from terrorist attacks and terrorism-related fears. However, terrorism-related stress may be less likely to cause harmful drinking in individuals who are married or have children. This finding was published in the December 2009 issue of *The Journal of Nervous and Mental Disease*.

Researchers studied the effects of terrorism-related stress on drinking behaviors using a long-term survey that began in 1996. Survey respondents were initially drawn from 2,492 employees at a midwestern university and were surveyed before and after the 9/11 terrorist attack. Respondents estimated their number of alcoholic drinks per day and their frequency of drinking for escapism, drinking to intoxication, and binge drinking.

Married individuals were less likely than unmarried individuals to have terrorism-related stress lead to harmful drinking behaviors, such as frequently drinking to intoxication and binge drinking. Individuals with children showed a similar protective effect against terrorism-related stress prompting drinking to intoxication. However, this protective effect against terrorism-related stress leading to binge drinking was found only in men with children; women with children were not less likely than women without children to binge drink due to terrorism-related stress. ■

The article abstract can be found here:  
*Terrorism, Distress, and Drinking: Vulnerability and Protective Factors.*  
<http://www.ncbi.nlm.nih.gov/pubmed/20010027>

## 5 QUESTIONS WITH...

# DAVID GOLDMAN, M.D., CHIEF OF NIAAA'S LABORATORY OF NEUROGENETICS

- 1. We hear a great deal about genetics in many areas of health research. Why is this field so important for the study of alcohol use disorders?**

Genetics research is critical to our understanding of the most fundamental questions about alcoholism—who among

our family, friends, and neighbors are most susceptible to developing alcohol problems, and how can we help them?

We've made enormous strides in identifying the traits that signal a predisposition to alcoholism, which can help us intervene earlier—and more effectively.

Perhaps more important, genetics research has shown that it is not always a simple path, so we need to learn how genetics are linked to addictions in both direct and indirect ways. Some genes, for example, are directly related to how the body metabolizes alcohol and the degree to which drinkers' endorphin levels rise. Others are related





*Dr. David Goldman*

indirectly—through stress, anxiety, and personality disorders, for example—which often lead people to self-medicate through alcohol. Some genes are related

to general risk-taking behaviors, which are also linked to alcohol use disorders. And some genes even serve as protective factors, particularly among those who are highly sensitive to the nausea and dizziness that can accompany drinking.

Learning more about the complex relationships among all these genetic factors—and the environmental effects that trigger them—is essential to finding ways to help the millions of people affected by alcohol use disorders.

**2. In a 1989 interview, you discussed your work, at the time, of identifying biomarkers for alcoholism, with the eventual goal of identifying the genes that produce them. Looking back 20 years later, are you satisfied with how the field has progressed?**

Yes, I'm satisfied to a degree. As a scientist, you always want the rate of discovery to be faster than it is, but I do think we've made a number of important advances in several areas.

First, early studies of biomarkers—including alcohol-induced flushing, alcohol response, and brain imaging responses—have led to current studies of the genes themselves. This type of study, conducted on what is sometimes called an intermediate phenotype, has pointed to roles of genes in particular mechanisms, such as stress response, that are important in alcoholism, other addictions, and other psychiatric disorders.

Second, the studies in animal models have led to advances in the basis of alcoholism in humans, particularly in gene-environment interaction studies where it is powerful to be able to control the environment.

And finally, on an overall basis, we have learned the importance of several genes that determine stress resilience or whose effects are modified by stress, and even that endocrine context matters. Those genes include neuropeptide Y, the serotonin transporter, and monoamine oxidase A.

Because of these developments, I believe we have a much better handle now on what we know about the human genome and where we need to go in order to build upon that knowledge. I also think we've helped reach a point where genetics research can help inform clinical work, which is, of course, the ultimate goal of our investment.

**3. What are some specific ways that genetics research can help in the prevention and treatment of alcohol use disorders?**

Genetics research has raised awareness that the main reason alcoholism runs in families is genetic predisposition. All of us are at some risk for alcoholism and other addictions, but awareness of familial risk can be valuable to people who, because of their family history, are at higher risk but who want to avoid problems they have witnessed in their relatives.

Clearly, we are a long way from having sufficient genetic markers to warn people of risk, and also it is likely that the use of such markers would be complicated, for example, by the need to understand gene-environment interactions. One prevention tool at our disposal is the knowledge that 500 million people worldwide carry a deficiency of the aldehyde dehydrogenase gene. These individuals flush after drinking and have a higher risk of upper gastrointestinal cancers; however, they can prevent most of those cancers by reducing, or stopping, their consumption of alcohol.

With regard to treatment, genetics gives us the key to match the best therapeutic plan with the best candidate. In the past, clinicians have had to rely, to some degree, on trial and error in applying pharmacological and psychological interventions. Now, we know a great deal more about which medicines are likely to work for which patients—based on genetics profiles.

Take the drug naltrexone, for example. For many patients, it's not particularly effective. However, rather than abandoning its use, ongoing research is showing that this drug, which is used in combination with psychotherapy, is very effective with alcoholics who have a particular genetic variation in one of their opioid receptors. So it is highly effective with roughly a quarter of all patients in treatment.

Breakthroughs like this are helping us learn how to match specific treatments to a patient's genotype—saving time, money, and—ultimately—families and lives.

**4. While genetics research is constantly evolving, are there any new developments in the field that you're particularly excited about?**

Yes: our work in imaging genetics is particularly useful. This has had the effect of tying genetic variation much more directly to the processes the genes are altering—for example, the effect of stress-related genes on brain stress responses. A genomics technology that is very important is the new ability to sieve the genome with arrays of a million (or more) genetic markers, which recently led to the identification of a gene involved in nicotine addiction. And alcoholics often smoke, so the connections are becoming clearer.

Looking ahead 5 to 10 years, we expect that we will learn even more about the complexities of the human genome, particularly as it relates to alcohol. One area that seems particularly promising is deep sequencing—a process for uncovering rare and uncommon variants. Most of the gene



variants we know about so far are common variants, but much of the variation that influences human behavior is rarer. Deep sequencing also allows us, for the first time, to measure the impact of the environment on the genome. This is one of the steps that ultimately is needed to understand gene-environment interactions.

## 5. What would you be doing if you were not at NIAAA?

I suspect I would still be a scientist, in which case I would be somewhere else at NIH, which is probably the best place in the world for a scientist to work. However, before I was a researcher I was a physician. On a day-to-day basis there was nothing that I have ever done that was more rewarding, challenging, and occasionally heart-wrenching than helping my patients and their families. ■

## ADDITIONAL NIAAA RESOURCES

*If you enjoy the NIAAA Spectrum, visit <http://www.niaaa.nih.gov> for other NIAAA alcohol research and education products.*



**Alcohol Alert** (<http://www.niaaa.nih.gov/Publications/AlcoholAlerts>) is NIAAA'S quarterly bulletin that disseminates important research findings on a single aspect of alcohol abuse and alcoholism.



**Alcohol Research & Health** (<http://www.niaaa.nih.gov/Publications/AlcoholResearch>) is NIAAA's quarterly, peer-reviewed scientific journal.



**Rethinking Drinking** (<http://rethinkingdrinking.niaaa.nih.gov>) is NIAAA's newest resources where individuals can evaluate their own drinking patterns.



**College Drinking—Changing the Culture** (<http://www.CollegeDrinkingPrevention.gov>), created by NIAAA, is your one-stop resource for comprehensive research-based information on issues related to alcohol abuse and binge drinking among college students.

## ABOUT US

*NIAAA Spectrum* is NIAAA's first-ever webzine. With engaging feature articles, short news updates, and colorful graphics, *NIAAA Spectrum* offers accessible and relevant information on NIAAA and the alcohol research field for a wide range of audiences. Each issue includes feature-length stories, news updates from the field, charticles and photo essays, and an interview with an NIAAA staff member or alcohol researcher. *NIAAA Spectrum* is published three times a year.

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