Hungry genes?

Diets tailored to your genetic profile are being sold as the ultimate in healthy eating. But does the science add up, asks **Bijal Trivedi**

IT SOUNDS like the ultimate in personalised medicine: a tailor-made diet that controls your weight, optimises your health and reduces your risk of heart disease, cancer and diabetes. All you have to do to get one is hand over a couple of hundred dollars, take a simple genetic test, and wait for a personalised nutrition plan based on your genes to drop through your door.

Diet plans like this are widely available from private clinics, over the internet and, in the US, even in some supermarkets. Advocates claim they take the uncertainty out of grocery shopping and provide a guaranteed route to long-term health and fitness. Critics say the tests are at best misleading and at worst potentially harmful. I was simply curious. With my family history of heart disease, I wanted to know whether a diet tailored to my DNA could help me override my genes.

In theory, yes. All other things being equal, genetics is the reason why one person can eat a poor diet without serious health repercussions while in another person the same diet leads to high blood pressure, cancer or heart disease. This is the basis of nutrigenomics – the science of how the chemicals in food alter the regulation of genes and proteins, and how variations in certain genes might predispose people to troublesome gene-nutrient interactions and ultimately disease. Nutrigenomics is a relatively new science with genuine promise, but it has yet to yield many results of practical value. Even so, no sooner had nutrigenomics got off the ground than eager biotech companies began mining the results of newly published papers and translating them into over-the-counter tests. So does the science support such tests?

Each person has around 25,000 genes, many of which have several common variants. Some are linked to an increased risk of disease. The tests look at a handful of such genes to identify which variants the individual carries. If they have "bad" variants, the company offers advice on how nutritional and lifestyle changes could help counteract genetic flaws.

In 2001 the UK-based company Sciona broke new ground with the first such "nutrigenetic" testing service to provide personalised dietary and lifestyle advice. Nutrigenetics is the application of nutrigenomics – which looks at the genome in general – to the individual. However, the test soon drew criticism from the UK's Human Genetics Commission, and prompted the HGC's 2003 report "Genes Direct", which assessed genetics-testing kits sold directly to the public. The watchdog group GeneWatch UK also criticised the tests and called on major UK retailers to boycott the products.

The UK retail market soon collapsed, and Sciona focused on marketing the product to private health clinics, dieticians and nutritionists instead. The company relocated to Boulder, Colorado, in 2005, and began selling tests in the US via websites and genetic-testing companies; last year it sold about 18,000. Other companies sprang up offering the Sciona test, or something similar, for $100 to $1000.

The nutrigenetics industry has recently come under renewed fire, this time in the US. An investigation conducted by the US Government Accountability Office in July suggested that the type of nutrigenetic testing offered by four companies – Sciona, Genelex, Market America and Suracell – "misled consumers by making predictions that are medically unproven and so ambiguous that they do not provide meaningful information". The GAO report also criticised some companies for selling supplements supposedly tailored to a customer's genetic needs. These "nutraceuticals" cost anywhere

from $1200 to $1800 per year, yet according to the report they differed little from multivitamins available at the local pharmacy.

Despite this, I wanted to know whether I had gene variants that could increase my risk of broken bones, heart disease or cancer, and was intrigued by what the nutritional advice might be. Sciona provided me with its "Cellf" test, which is the most widely sold test of its kind, available at many online drugstores and shopping sites and sold by two of the four companies scrutinised by the GAO investigation. It looks at 19 genes that the company believes provide insights into heart and bone health, the body's antioxidant and detoxification ability, plus insulin sensitivity and inflammatory response. Market America also sells a test of the same genes, but under another name. I swabbed the inside of my cheek, completed a food and lifestyle questionnaire, and slipped both in the mail.

The good and the bad

Six weeks later I received my results. First, the good news. For the two genes related to antioxidant ability, which help destroy DNA-damaging free radicals, I have no "bad" variants. Of the three genes involved in detoxification I have versions that efficiently rid my body of noxious compounds.

Now the not-so-good news. My number one priority, according to the report, is bone health. The test screened for a total of seven variants, spread over four genes, each linked to bone problems. I tested positive for four potentially damaging variants. Two hinder absorption of calcium and vitamin D – ingredients critical for bone building – and the other two disrupt the process of dissolving old bone and creating new bone. It sounds to me like I'm a prime candidate for osteoporosis.

Sciona's advice: increase daily intake of vitamin D to 20 micrograms and omega-3 fatty acids to 3 grams, and exercise for 45 to 60 minutes at least five times per week. I get a pat on the back for getting enough calcium, my moderate caffeine consumption, and for my healthy body mass index.

Next: heart health. The test reveals that I have variants in several genes that alter my body's ability to metabolise B vitamins – like folic acid, B_6 and B_{12}. These vitamins are important for maintaining low levels of homocysteine – high levels of which are a risk factor for cardiovascular disease. Also, my variants of the inflammatory-response genes can lead to "reactions that are too strong or inappropriate in their timing", according to Sciona, which could damage my cardiovascular system. I also have potentially problematic variants in genes that metabolise cholesterol and triglycerides, and another

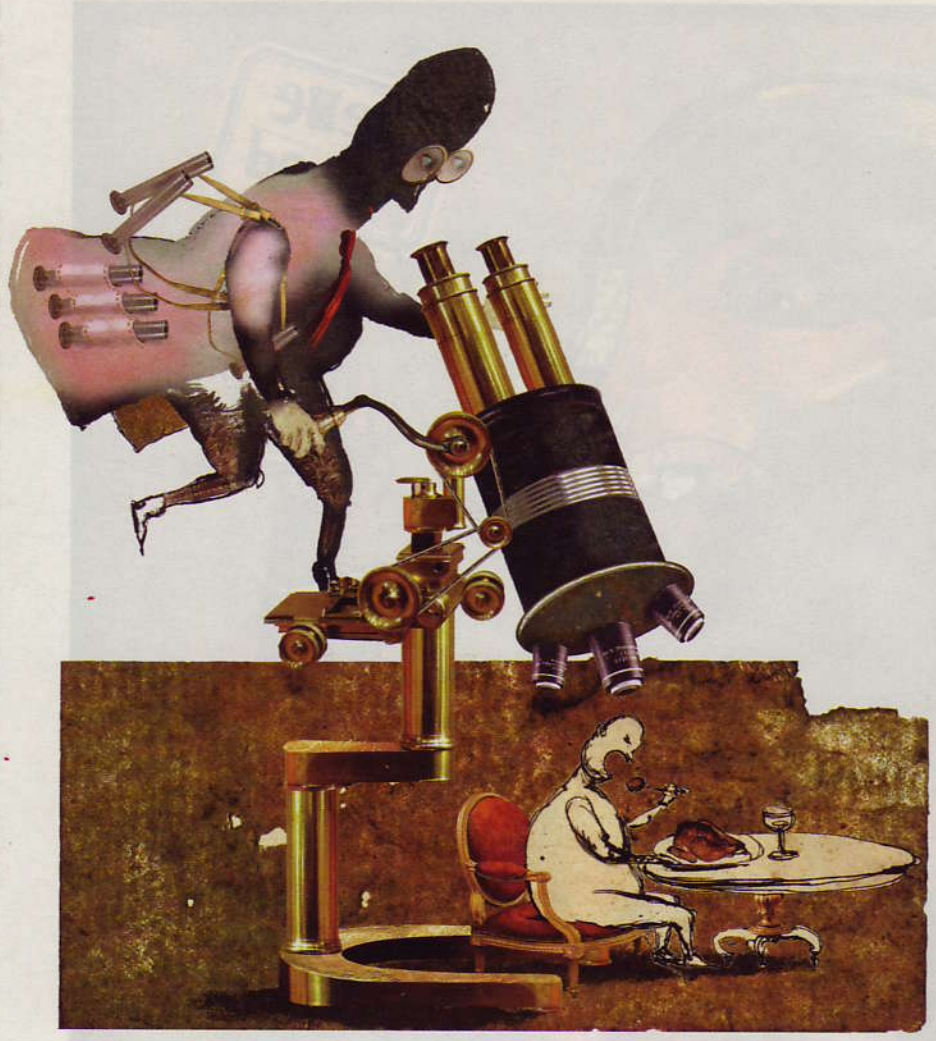
Out of control?

In the European Union, the US, Australia and Canada genetic testing is coming under increasing scrutiny, and governments are making efforts to standardise regulations. However, nutrigenetic tests are considered "lifestyle" tests, largely because they do not make clinical claims.

"The EU considers most genetic tests low-risk and thus exempt from independent pre-market review. This means that as long as the company can honestly state the technical accuracy of the test, the sale of the test and the advice offered is unregulated," says Stuart Hogarth, a research associate at the University of Cambridge who specialises in policy issues with genetic testing. In Canada and Australia there are even fewer controls. Nutrigenetic tests are reviewed for neither analytical nor clinical accuracy.

In the US, the majority of tests being offered are "home brews": companies receive genetic samples directly from physicians or consumers, do the analyses, and then issue a report. Historically, the Food and Drug Administration has not regulated these tests. "That means you don't have an evaluation of the clinical validity of the test," says Kathy Hudson, director of the Washington-based Genetics and Public Policy Center.

Jose Ordovas, director of the Nutrition and Genomics Laboratory at Tufts University in Boston, supports the idea of personalised nutrition but is concerned that the current batch of nutrigenetics tests is too much, too soon. Without regulation, he cautions, jumping the gun could wipe out public support and damage the reputation of the entire field. "We are very, very early in the game," he says.



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in a gene that alters blood flow, which can adversely affect "tightening of your blood vessels". Nowhere does the report say I'm at increased risk of a heart attack, but reading between the lines I feel like a time bomb.

The final segment of Sciona's report covers insulin sensitivity. In four of the five genes tested, I have variants that make my fat cells less efficient at removing sugar from my blood and storing it in the cells. That means insulin resistance, which has been linked not only to type 2 diabetes but high blood pressure and heart disease as well.

While all this sounds quite alarming Sciona's advice on how to deal with these risks seems comparatively mundane: eat more foods rich in B-vitamins and antioxidants like vitamins A, C and E, and increase the amount of omega-3 fatty acids; decrease my glycaemic load (how much sugar I pour into my blood) and eat more fibre and whole grains; cut down saturated fats and cholesterol; exercise more. The advice hardly seems personalised but Rosalynn Gill-Garrison, co-founder and chief scientific officer of Sciona, assures me the intake goals are calculated based on my particular genetic make-up.

Paranoid that my bones are disintegrating and my arteries narrowing I seek a second opinion. Jose Ordovas, director of the Nutrition and Genomics Laboratory at Tufts University in Boston, provides reassurance. "The genetic component [of a complex disease] is split among 10, 20, 50, 100 genes or more, and you are being tested for one," he says. "Remember, you can go wrong with one of your genes but you may be blessed with another set of genes that compensate."

Robert Nussbaum, chief of the medical genetics division of the Institute for Human Genetics at the University of California, San Francisco, puts it even more bluntly. "I don't think it is information worth having... I wouldn't trust any of it," he says. "Testing negative [for certain variants] doesn't mean that you are not going to develop these diseases; testing positive doesn't mean that you will. If I was asked by a patient what would I recommend based on this test, bottom line: eat right."

So if feeding my genes is as simple as eating healthily and laying off the fat and sugar, what good has it done me to find out about specific variations? According to critics of such tests, not much. Nussbaum says that the science behind the tests is often far from conclusive – and may be based on single studies that have never been replicated.

One example is California-based Consumer Genetics's "caffeine metabolism test", which went on the market in November. The test is based on a paper published in March 2006 in *The Journal of the American Medical Association* (*JAMA*). It reported that depending on what version you carry of the gene *CYP1A2*, which codes for the caffeine-metabolising enzyme cytochrome P450 1A2, you are either a "rapid" or "slow" caffeine metaboliser. According to the *JAMA* report, higher caffeine intake is associated with increased risk of heart attack only in people with slow caffeine metabolism. Within weeks of publication, Consumer Genetics announced on its website that it would offer a caffeine metabolism test and give results within three days.

Hannia Campos, a nutritionist at the Harvard School of Public Health and a co-author of the *JAMA* paper, says that she was shocked when she discovered the findings had been translated into a genetic test. "I couldn't believe it. I thought it was a joke." She says the findings need to replicated and confirmed before they are used to guide people.

What's more, the tests lack clinical validity, says Nussbaum. That is, the gene variations that the companies are testing have a pretty low "positive predictive value", meaning that even among people who carry a "bad" variant, only a small percentage actually go on to develop the disease. "None of these genes is going to kill you," says Ordovas. "It might put you at 5 or 10 per cent higher risk than somebody [without the variant], but that's it."

Proof of the pudding

In comparison, a family history of heart disease, especially the early-onset form, has been shown to increase risk 100 to 500 per cent, says Howard Levy, a physician and medical geneticist at Johns Hopkins University in Baltimore, Maryland. "Family history is the biggest thing missing from what this company has to offer." he adds.

More to the point, says Levy, even when the associations between genes and disease are fairly robust, it is far from clear whether increasing intake of specific nutrients will lower the risk. Take, for example, variants of the *MTHFR* gene and heart disease. Of the genes tested in the Cellf test, all the researchers I contacted agreed that this had the strongest association; individuals carrying the variation known as C677T had higher levels of homocysteine, which is associated with an increased risk of heart disease.

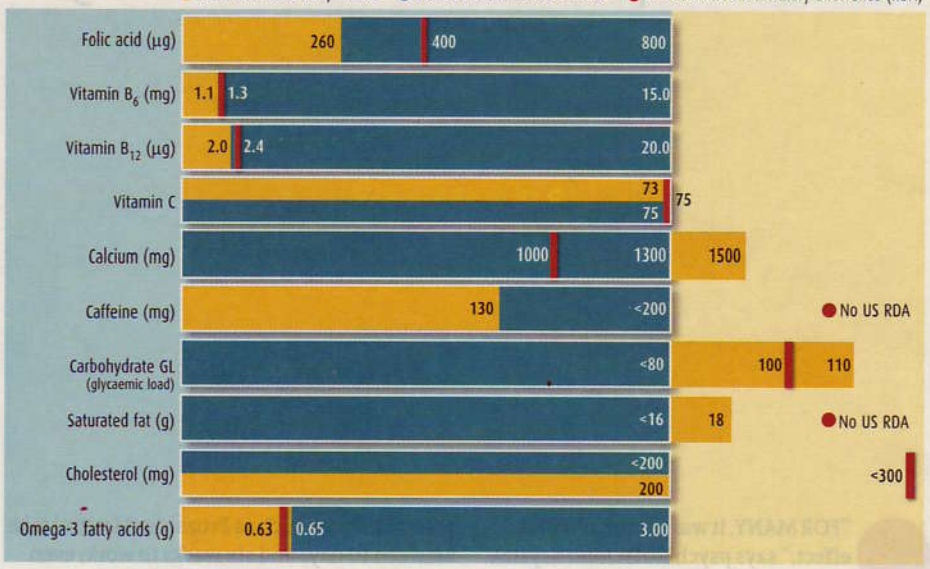
It is also known that folic acid and vitamins B_6 and B_{12} lower homocysteine levels. Sciona and Genelex both advise people to consume more B vitamins if they test positive for potentially problematic variations in the *MTHFR* gene. But two studies published in *The New England Journal of Medicine* in April reported that, although supplements of B vitamins could lower homocysteine levels, this did not reduce the risk of heart attacks in patients with vascular disease.

In fact, says Philip Wood, director of the genomics division at the University of Alabama at Birmingham, no studies have demonstrated that any nutritional supplementation would actually overcome a genetic variation and reduce the risk of a complex disease. "That would require clinical trials... and those studies haven't been done."

Howard Coleman, CEO of Genelex, disagrees. "There needs to be a symmetry between the level of proof and the risk associated with something," he says. "The clinical-trial standard is the standard you need to have if you are going to give somebody a dangerous drug. Remember, this is just a harmless test. [Dietary interventions] are helpful but can do no harm."

FEEDING MY GENES

Author's current intake of key nutrients compared with the US dietary recommendations and Sciona's advice, based on the results of a "neutrigenetics" test performed by Sciona



> "What would I recommend based on this test? Bottom line: eat right"

While he acknowledges that the conclusions are "not medically proven in the sense that there's been clinical trials done", he disputes the GAO's notion that the advice is worthless. "An expert in this area... may say it is too soon or that it is not worth the money but they won't say it is worthless. We are at the early stages of this – we are playing Pong and transitioning to Pac-Man."

Sciona's Gill-Garrison is also confident about the tests. "If we claimed we were going to make you live 100 years or prevent the development of a particular disease, I would agree with them, but on the other hand if we are providing personalised info to help you control cholesterol levels because of particular sensitivities you have based on your genetics – absolutely there is enough information."

Genelex connected me with Carolyn Katzin, a Los Angeles-based certified nutrition specialist, for a personal consultation and interpretation of my genetic results. Genelex usually charges an additional couple of hundred dollars for this service, a total of $525 for the test plus consultation.

Katzin's analysis differed from Sciona's by ignoring the food questionnaires, which she says are not accurate indicators of nutrient intake, and instead asked about family history before focusing on my genes. She offered much the same nutritional advice as Sciona, however – eat more of this, less of that, take a good multivitamin, add specific supplements, and "be careful with salt and avoid too many packaged or processed foods". Her knowledge of my family history, though, did lead her to suggest, after seeing my mixed bag of gene variants, that I check my levels of homocysteine, HDL and LDL cholesterol, triglyceride and C-reactive protein – all of which have been linked to cardiovascular disease risk – the next time I get a physical.

One of the major criticisms about nutrigenetics testing is that it may induce complacency in people who find they have "good" genes and panic in those who find theirs are "bad". The information is certainly difficult to ignore when it's there in black and white. But good genes or bad, discussing family history with a physician and taking a few blood tests will probably give you a similar or more accurate snapshot of your current health – and without the hefty price tag. That is exactly what I'm going to do. Now if I can just get an appointment... ●

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