SPECIAL REPORT

Cardiovascular disease gets personal

Gene-association studies hint at better ways of treating the leading cause of death, but capitalizing on them is proving to be a slow and difficult process. **Erika Check Hayden** reports.

As personalized cancer treatment edges into the clinic, doctors and scientists are hoping that cardiovascular disease — the world's top killer — will be next to benefit from genomics.

An avalanche of studies has linked genetic variants to various cardiovascular conditions and to patients' responses to commonly prescribed drugs. First up could be genetic guidance for the anti-clotting agents warfarin and clopidogrel, followed by testing for genetic variants responsible for conditions such as atrial fibrillation, a heart-rhythm abnormality that is a leading cause of stroke.

Doctors caution that there is a long way to go before the hints raised by gene-association studies translate into solid evidence that genetic variants can improve clinical practice. "I would hope that cardiovascular disease would be one of the next leading areas of personalized medicine, because it has such an enormous impact on public health," says Christopher Granger, a cardiologist at Duke University Medical Center in Durham, North Carolina. But "we're at a primitive stage right now," he says.

Warfarin exemplifies some of the promise and pitfalls of personalized medicine. The drug is commonly used to prevent clotting in patients who have atrial fibrillation and other conditions, yet the dose needed varies from patient to patient; if it's not precisely right, it can trigger fatal haemorrhaging. In 2007, after studies found that variants in two genes, *CYP2C9* and *VKORC1*, account for up to half of the reason why patient response differed, the US Food and Drug Administration (FDA) changed the labelling to suggest that doctors consider using genetic tests to guide dosing.

Yet studies have failed to show that such tests help improve patient outcomes. In 2007, for instance, a trial of 206 people reported that using information about a patient's genetic variants to guide their dosing regimens didn't lessen the risk that patients on warfarin would develop unsafe levels of clotting proteins¹. And this January, another group reported that genetic testing wouldn't save money if done in all patients prescribed the drug, partly because it still costs hundreds of dollars to determine the genetic variants of each patient².

The US National Heart, Lung and Blood Institute in Bethesda, Maryland, is now sponsoring a larger clinical trial to test the usefulness of

Cardiovascular conditions are the leading cause of death worldwide.

genetically guided warfarin dosing. But as Eric Topol, director of the Scripps Translational Science Institute in La Jolla, California, says: "Warfarin was kind of the poster adult for pharmacogenomics, but it's really lost favour."

He and other doctors now see greater potential instead for clopidogrel, marketed by Bristol-Myers Squibb of New York and Sanofi-Aventis of Paris as Plavix. Clopidogrel is given to fight clotting, including in patients who have already had a stroke or heart attack. The drug, second in the world in global sales, is converted in the body into an active form that inhibits the pro-clotting protein P2Y12. But it, too, can cause haemorrhages.

In December, three groups reported that variations in the *CYP2C19* gene were associated with an increased risk of cardiovascular events in patients on clopidogrel^{3–5}, and a poor ability to convert clopidogrel into its active form⁴.

And last month, the FDA approved a new drug, prasugrel, which is a more potent inhibitor of P2Y12 but also carries a higher risk of bleeding. It is conceivable that patients who have the genetic variants associated with poor response to clopidogrel might instead be

treated with prasugrel, says Matthew Price, an interventional cardiologist at Scripps Clinic/Green Hospital in La Jolla.

Misunderstood

Predicting the overall risk of cardiovascular diseases is proving even more complicated than treating them with genetically targeted drugs. Many genome-wide association studies have been done, but few have uncovered variants that, on their own, boost the risk of cardiovascular disease very much. And taken together, the variants discovered so far still don't explain most of the genetic risk of various diseases.

For instance, last January, US researchers aimed to improve risk prediction of cardiovascular disease by adding information about a genetic variant associated with coronary artery disease and diabetes to other risk factors, such as smoking, cholesterol levels and family history of heart attack. The variant, found on chromosome 9, had formed the basis of a genetic test sold by deCODE Genetics in Reykjavik, Iceland. The team found that genotyping the variant did not improve the ability to predict

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whether the 22,129 women in the study would develop heart disease⁶. “Our study didn’t show very much change [in risk-prediction ability], especially over the risk score that had family history in it already,” says Nina Paynter, team leader and an epidemiologist at Brigham and Women’s. “I was a little bit disappointed.”

Since Paynter’s study began, however, many more genetic associations with cardiac risk have been reported, and companies such as deCode, Navigenics of Foster City, California, and 23andMe of Mountain View, California, now sell tests that purport to assess heart-disease risk using combinations of these variants. Paynter’s group is evaluating multi-variant genomic tests, as is the independent Evaluation of Genomic Applications in Practice and Prevention initiative set up by the US Centers for Disease Control and Prevention in 2004, which is expected to issue recommendations on their use this autumn.

Other groups have already examined genomic tests for diabetes, which greatly increases the risk of heart disease and stroke. Last year, for instance, three groups published studies examining whether a number of variants associated with diabetes could predict a person’s risk of developing this disease^{7–9}. All found that the variants added little to the predictive value of known diabetes risk factors, such as obesity, smoking and family history.

In addition, the way these genomics tests are reported can be confusing to consumers. Companies update consumers’ risk profiles as new variants are discovered, but because each new variant changes a person’s risk so little, variants added to a risk profile can cancel out previous ones.

A team led by Cecile Janssens of Erasmus Medical College in Rotterdam, the Netherlands, showed this by studying the same diabetes-associated variants analysed in the 2008 risk-prediction studies¹⁰. When genotypes of 17 of these variants were added to an existing risk profile based on variants of *TCF7L2* — a gene whose variants confer a substantial increase in risk of common forms of diabetes — 34% of the patients’ risk profiles changed, for example, from high to low or low to high. When data about patients’ age, sex and body mass index were added to the profiles, 29% changed risk categories, and 11% of the participants reverted to their initial risk category.

Patients hoping to use their genotyping results to motivate healthy lifestyle changes might thus be confused when their disease risk changes multiple times without any action on their part, Janssens says: “Our studies show that

these products are not ready for prime time.”

Cardiologists hope that will change, and see some promise on the horizon in specific cardiovascular diseases.

Last month, for instance, two research teams published studies that linked variants in the *ZFHX3* gene to atrial fibrillation^{11,12}. Two years ago one of the same groups published variants adjacent to a separate gene, *PITX2*, that almost doubles the risk of atrial fibrillation¹³. Drugs and monitoring can be used to treat the condition, and might help prevent the roughly one-third of strokes that have no known cause. So atrial fibrillation could serve as an early example of genomic risk prediction, Topol says.

“To be able to zoom in on the probable cause of a stroke by genomics, and then institute a much more intensive heart-rhythm monitoring programme, would be a whole new path that we didn’t have months or even a year ago,” he says.

But even if the tests are proven useful, they may still have a limited impact on patient care — at least at first. Granger says that doctors already have various risk-prediction tools that work, but don’t use them effectively. For instance, patients with higher levels of the protein complex troponin, an indicator of heart-muscle damage, do better on certain treatment strategies. But, Granger says, they are no more

likely to get those drugs for various reasons, including that family doctors are not as familiar with the cardiac literature. “Part of our challenge is that we’ve already got some information that could help us better customize medicine to patient risk, and we tend not to be doing that in practice.”

Remedying that problem will require more physician education — and some knockout examples of genetic profiling aiding medicine, as seems to be happening in cancer. “Maybe we need a couple of major success stories of the benefit of using genetic variants for treatment of disease, and I think we’re getting some of those,” Granger says. Cancer drugs may be blazing the trail for personalized medicine, but cardiovascular drugs may not be far behind. ■

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