

Forty years ago, doctors learned why some patients who received the anesthetic succinylcholine awoke normally but remained temporarily paralyzed and unable to breathe: They shared an inherited quirk that slowed their metabolism of the drug. Later, scientists traced sluggish succinylcholine metabolism to a particular gene variant. Roughly 1 in 3500 people carry two deleterious copies, putting them at high risk of this distressing side effect.

The solution to the succinylcholine mystery was among the first links drawn between genetic variation and an individual's response to drugs. Since then, a small but growing number of differences in drug metabolism have been linked to genetics, helping explain why some patients benefit from a particular drug, some gain nothing, and others suffer toxic side effects.

The same sort of variation, it is now clear, plays a key role in individual risks of coming down with a variety of diseases. Gene variants have been linked to elevated risks for disorders from Alzheimer's disease to breast cancer, and they may help explain why, for example, some smokers develop lung cancer whereas many others don't.

These developments have led to hopes—and some hype—that we are on the verge of an era of personalized medicine, one in which genetic tests will determine disease risks and guide prevention strategies and therapies. But digging up the DNA responsible—if in fact DNA *is* responsible—and converting that knowledge into gene tests that doctors can use remains a formidable challenge.

Many conditions, including various cancers, heart attacks, lupus, and depression, likely arise when a particular mix of genes collides with something in the environment, such as nicotine or a

fatty diet. These multigene interactions are subtler and knottier than the single gene drivers of diseases such as hemophilia and cystic fibrosis; spotting them calls for statistical inspiration and rigorous experiments repeated again and again to guard against introducing unproven gene tests into the clinic. And determining treatment strategies will be no less complex: Last summer, for example, a team of scientists linked 124 different genes to resistance to four leukemia drugs.

reveal which drug and dose will help them the most, but unlike asthma, drug response can be difficult to quantify biologically, making gene-drug relations tougher to pin down.

As DNA sequence becomes more available and technologies improve, the genetic patterns that govern health will likely come into sharper relief. Genetic tools still under construction, such as a haplotype map that will be used to discern genetic variation behind common diseases, could further accelerate the search for disease genes.

The next step will be designing DNA tests to guide clinical decision-making—and using them. If history is any guide, integrating such tests into standard practice will take time. In emergencies—a heart attack, an acute cancer, or an asthma attack—such tests will

To What Extent Are Genetic Variation and Personal Health Linked

But identifying gene networks like these is only the beginning. One of the toughest tasks is replicating these studies—an especially difficult proposition in diseases that are not overwhelmingly heritable, such as asthma, or ones that affect fairly small patient cohorts, such as certain childhood cancers. Many clinical trials do not routinely collect DNA from volunteers, making it sometimes difficult for scientists to correlate disease or drug response with genes. Gene microarrays, which measure expression of dozens of genes at once, can be fickle and supply inconsistent results. Gene studies can also be prohibitively costly.

Nonetheless, genetic dissection of some diseases—such as cancer, asthma, and heart disease—is galloping ahead. Progress in other areas, such as psychiatric disorders, is slower. Severely depressed or schizophrenic patients could benefit enormously from tests that

be valuable only if they rapidly deliver results.

Ultimately, comprehensive personalized medicine will come only if pharmaceutical companies want it to—and it will take enormous investments in research and development. Many companies worry that testing for genetic differences will narrow their market and squelch their profits.

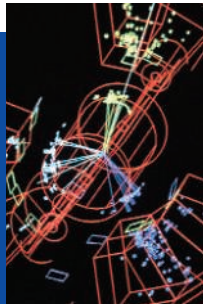
Still, researchers continue to identify new opportunities. In May, the Icelandic company deCODE Genetics reported that an experimental asthma drug that pharmaceutical giant Bayer had abandoned appeared to decrease the risk of heart attack in more than 170 patients who carried particular gene variants. The drug targets the protein produced by one of those genes. The finding is likely to be just a foretaste of the many surprises in store, as the braids binding DNA, drugs, and disease are slowly unwound.

—JENNIFER COUZIN

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Are there smaller building blocks than quarks?

Atoms were “uncuttable.” Then scientists discovered protons, neutrons, and other subatomic particles—which were, in turn, shown to be made up of quarks and gluons. Is there something more fundamental still?



CERN

Are neutrinos their own antiparticles?

Nobody knows this basic fact about neutrinos, although a number of underground experiments are under way. Answering this question may be a crucial step to understanding the origin of matter in the universe.

Is there a unified theory explaining all correlated electron systems?

High-temperature superconductors and materials with giant and colossal magnetoresistance are all governed by the collective rather than individual behavior of electrons. There is currently no common framework for understanding them.

What is the most powerful laser researchers can build?

Theorists say an intense enough laser field would rip photons into electron-positron pairs, dousing the beam. But no one knows whether it's possible to reach that point.



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