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PHARMACOGENOMICS SUPPLEMENT

One drug does not fit all

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The DNA sequence of all human beings is 99.9% identical. Why should we be interested in the 0.1% that differs from individual to individual? Because in a genome of three billion bases, even a tenth of a percent difference translates into three million separate "spelling" differences. And many of those spelling differences, which predict widely varying clinical responses to drugs, could be used to guide therapies. This is the basis for pharmacogenomics.

This supplement brings together articles that explore various aspects of pharmacogenomics and have been published in *Nature Biotechnology* over the past year. It is intended to capture some of the excitement that surrounds the area, present the rationale behind diagnostic-led treatment, and outline the commercial opportunities attendant with the move to individualized medicine. We are also publishing an original article based on a transcript of a roundtable discussion that took place at the BIO '98 International Meeting and Exposition in New York in June at which the likely impact of pharmacogenomics on drug development was debated.

As borne out by a spate of deals (over 15 since October 1997), both established biotechnology companies and startups anticipate significant revenue opportunities in this area. Companies are gearing up to collate proprietary collections of gene variants or to offer high-throughput sequencing services for profiling clinical trial participants. In tandem with the US federal initiative starting in October, three companies—Genset (Paris), Celera Genomics (Rockville, MD), and Incyte Genetics (Palo Alto, CA)—have also undertaken (or are preparing to undertake) systematic searches of the human genome for variants or single nucleotide polymorphisms (SNPs). Others have been busy acquiring, transferring, or licensing technologies for analyzing or detecting genetic variation.

The opportunities in diagnostics are particularly attractive, both for refining treatment regimens for existing drugs and, further down the line, for developing tests for use in tandem with "personalized" drugs. Already, diaDeXus (Santa Clara, CA) and Millennium Predictive Medicine (Cambridge, MA) have been spun out to develop molecular diagnostics, and Abbott (Abbott Park, IL), a market leader in traditional diagnostic kits, has staked its claim with a $20 million DNA diagnostics collaboration with Genset. These developments are important because they show that genomics companies were right to hold on to the diagnostic rights to their genes.

Apart from diagnostics, pharmacogenomics offers several other potential lines of revenue. An obvious advantage of profiling a population of responders and nonresponders in a trial is that new targets for future drugs may be discovered at the same time. In short, genes that predict nonresponse for one class of drug could represent targets for future drugs that will have no overlap with existing compounds. "Lazarus" programs—in which compounds that previously failed approval due to lack of efficacy or unacceptable toxicity are resurrected and used to treat genetically selected responders—represent another opportunity. Pharmaceutical companies will almost certainly discard these compounds—why try to rescue a failed compound when pipelines are overflowing with leads?—but smaller biotechnology companies may find the smaller margins sufficiently attractive to license them in.

While the business models look good, other issues remain unclear. First, it is not certain that genetic testing will streamline clinical trials. In some cases, it may make them even more expensive by adding a new layer of complexity. Clinical trials are designed to answer a few simple questions. Genetic profiling of a group of patients in a trial could turn up more questions than answers, and that is not what a drug company wants when it is spending millions of dollars. Second, for any drug potentially harmful to a subset of patients, the accompanying genetic test must be highly predictive and avoid false positives. Thus, diagnostic tests will have to become much more reliable. Finally, as with many other fields of biotechnology, there is a data gap. At present, vision outweighs data, and most of the technologies are unproven. The linchpin will be whether we can find genetic variants that are sufficiently penetrant—against a background of environmental factors, diet, age, and overall health—to justify the additional cost of genetic tests.

Examples can be cited to inspire confidence: There are differences in how people respond to Alzheimer's drugs depending on their *APOE* genotype; there are differences in the susceptibility of contraceptive users to deep vein thrombosis depending on Factor V Leiden polymorphisms; there are differences in cancer patients' responses to thiopurine chemotherapeutics depending on thiopurine methyl transferase polymorphisms. And the examples do not begin and end with humans: Probably the easiest way pharmacogenomics can be applied right now is to organisms simpler than humans—medically important bacteria and viruses. Gene chips are already being designed to profile HIV strains for use in guiding AIDS therapies, and other companies are working on ways of genotyping bacteria to more rapidly determine the correct type of antibiotic treatment to prescribe.

One drug certainly does not fit all. As genomics begins to reveal the genes involved drug response, drug companies can no longer afford to ignore the importance of genetic variation in human therapy. And at the end of the day, it may not matter whether more effective medicines result from diagnostic-led strategies designed to select patients who respond to therapies or from discovery strategies aimed at tailoring compounds that take into account target variability. Pharmacogenomics is here to stay because it means making medicines that are safer, better targeted, and more efficacious. And that makes sense for all involved: Drug companies, biotechnology companies, CROs, health payors, drug regulators, and, most important of all, patients.