

Broadening Genetic Tests in the Consumer Market

Several Companies Boldly Venture into Uncharted Waters

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Genetic testing was a hot topic at the 57th meeting of the American Society of Human Genetics (ASHG), which took place in San Diego in October. Over 1,000 genetic tests are now available clinically, and hundreds more are under development. The tests aim to diagnose or predict diseases linked to genetic conditions.

Typically, an individual test analyzes a single gene for mutations or changes in copy number. Whereas Mendelian diseases have clear links to single gene mutation, multifactorial traits are influenced by numerous genes at various loci. The general consensus is that diagnostics based on profiling of multiple genes may result in large public health benefits by increasing the probability of correct prediction of risks and clinical outcomes.

The relative contribution of the individual mutations to the onset of complex diseases is yet to be completely elucidated, but extensive association studies are now under way.

The Rotterdam Study is an example. It is a large prospective cohort study being undertaken in Europe by Erasmus MC, University Medical Centre in Rotterdam (www.epib.nl/ergo.htm). The study aims to genotype more than 10,000 samples and to cross-reference the genetic information with over 1,500 physiological parameters. The data will serve as a model for predicting the development of several late-age diseases including neurological, cardiovascular, endocrine, locomotor, and ophthalmological conditions.

Some researchers strongly believe that more genes need to be identified to predict the risks for any single complex adult-onset disease. Environmental influence may add an additional hard-to-calculate variability. Despite these concerns, profiling of SNPs in the entire human genome for clinical diagnostics may soon become a reality.

While high-throughput sequencing remains a distant option, profiling using SNP chips is a relatively affordable solution. Already dozens of so-called certified service providers are able to deliver whole-genome genotyping based on **Illumina** or **Affymetrix** genotyping chips. Lists of these service providers can be found at www.illumina.com/pagesnrn.ilmn?ID=69 and www.affymetrix.com/support/service_providers.affx.

Direct-to-Consumer Approach

While these services and the resulting data are certified for research use only, the same methodology could be used to collect data for the purposes of clinical diagnosis. At ASHG, **Navigenics** (www.navigenics.com) unveiled its strategy to use an individual's genetic information to deliver risk assessment of developing a number of adult-onset diseases such as Alzheimer, diabetes, and cardiovascular disease.

Since primary care physicians remain largely uneducated about forefront advances in genome profiling, and because there are few genetic counselors able to interpret such complex sets of data, Navigenics chose a direct-to-consumer (DTC) approach. DTC genetic testing has gained prominence and controversy over the past several years.

"We believe that everyone has the right to access their genetic information without third-party intervention," said Dietrich Stephan, CSO at Navigenics. "Every human disease has a genetic component. By identifying that component and by delivering actionable information we could alter the history of the disease. Early treatment, change in lifestyle, diagnostic course prediction—these measures could push back the onset of disease by years."

Navigenics will use the Affymetrix® Genome-Wide Human SNP Array 6.0 featuring 1.8

million genetic markers including more than 906,600 SNPs and more than 946,000 probes for the detection of copy number variation. The chip covers close to 90% of the 3 million SNPs identified by the HapMap Consortium (another 7 million are yet to be identified).

The actual typing data will be interpreted based on the known published stable associations with diseases. The probabilistic risk assessment will also take into consideration family history and other environmental risk factors gathered during the application process. The company emphasized the use of stringent control metrics to achieve a correct call rate greater than 99% and the ability to compute additional SNPs not represented on the arrays.

“Our genetic counselors are versed in probabilistic risk assessment, and they are able to explain risk estimates to consumers and primary care providers,” noted Dr. Stephan.

Communication with consumers would take place via a secure web portal to protect confidentiality. Participants may also request to have their data deleted from the company’s databases, however, Navigenics advocates donation of the data for research purposes. “Our vision is to improve health outcome on population bases,” added Dr. Stephan. “We believe that our service could lessen disease impact by providing early mitigation strategies.”

Whole Genome Typing

“We are still in the very early days of whole genome typing,” said Greg Lennon, cofounder, SNPedia (www.snpedia.com). “There are still significant scientific limitations to our ability to derive actionable knowledge from this data. Even though chips can characterize thousands or millions of SNPs, very few of the SNPs—less than 2,000—are known today to have medical significance.”

SNPedia originated as a free online forum for sharing information about SNPs and their disease associations. The user-driven format, analogous to Wikipedia, enables researchers to directly input and edit data. The SNPedia website provides cross-references between SNPs originating from different methods and possesses substantial information about SNPs not represented on either of the leading chip platforms.

“As we accumulate information about individual SNPs, we foresee that it will be easier and easier to find common associations between them and thus to predict their cumulative effects,” continues Dr. Lennon.

“SNPedia creates a bridge between individual research and global forums. We hope that our virtual meeting space will bring together experts in different clinical areas who can start building disease models based on curated collections of SNP information from around the world.” SNPedia provides the infrastructure for accumulation of knowledge that could eventually transform clinical practices.

Although it is generally agreed that little actionable information can be derived from the human genotyping today, companies focused on clinical diagnostics frequently visit SNPedia. As the direct-to-consumer genomic profiling continues to grow, average consumers will be able to form SNPedia forums around common genetic variations. Comparison of individual genotypes could help to subdivide the patients currently grouped under the same disease umbrella, to stratify populations based on their response to medications, or to aid those lacking family history.

“No matter how valuable this information potentially is, without an appropriate regulatory framework consumers are at risk of receiving data of dubious quality, of misinterpretation of the results, or of being misled by unproven claims or benefits,” cautioned Gail Javitt, J.D., Genetics and Public Policy Center Johns Hopkins University (www.dnapolicy.org).

“What’s missing is an independent external evaluation of analytical and clinical validity of genetic tests,” said Javitt. Errors in genetic testing can have tragic consequences; the errors

could multiply in cases of diagnostics based on assaying multiple individual SNPs. Genetic testing laboratories are not required to participate in externally administered proficiency testing programs. Therefore, consumers must rely on each lab's self-assessment for information on consistency and reliability of their services.

In 2006, after years of protracted regulation development, the Centers for Medicare and Medicaid Services, vested with overseeing the quality of clinical laboratories, inexplicably rejected the implementation of CLIA to strengthen the standards for genetic testing. The renewed hope for enhancements to CLIA may come from the recently posted draft report titled "U.S. System of Oversight of Genetic Testing". The report was prepared by the Secretary's Advisory Committee on Genetics, Health, and Society, and it contains a comprehensive map of the steps, structures, and regulatory policies needed to oversee genetic and genomic tests.

"Another issue for DTC genetic testing is interpretation of genetic information," continued Javitt. "Few patients have access to genetic expertise, especially for complex multifactorial conditions. In the absence of qualified genetic counselors a patient would have difficulties determining if the information provided by testing was supported by available evidence."

While the American public overwhelmingly supports a law forbidding genetic discrimination by health insurers and employers, the Genetic Information Non-discrimination Act is stalled in the Senate. This delay means that the uncertainty surrounding genetic discrimination continues, and may negatively impact businesses like Navigenics.

"We are yet to see how the general public will react to personalized diagnostics based on global knowledge about the genome." Uncertainty regarding how tests are regulated and whether privacy of the information is protected could further impede the future of personalized genetic medicine," concluded Javitt.

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