Short Communication

The Future of DNA Diagnostics

Gregory C. Critchfield

Myriad Genetic Laboratories, Inc., Salt Lake City, UT, USA

Over the next several years, DNA diagnostics will become more prominent in the management of patient care, and, more importantly, in the practice of predictive and preventive medicine. Four topics will be discussed: (1) What has been learned thus far from experience in DNA diagnostics? (2) What are the forces that will change DNA diagnostics in the future? (3) What kinds of genes will be important in future DNA diagnostic tests? and (4) What is the future of DNA testing? While some of the examples are drawn from BRCA testing, it should be strongly emphasized that the field of DNA diagnostics is much broader than any one area, and that numerous academic and industry groups are working to build the future for DNA diagnostics.

While DNA-based tests for a variety of conditions have been available for some time, the discovery of BRCA1 marked a milestone in that it was the first highly penetrant gene discovered in a disease that affects many individuals. As a result, global awareness grew rapidly of the potential of DNA diagnostics to alter medical practice. The potential changes, sweeping as they may be, provoked reactions among health care professionals and the public. For the first time, there was an important gene that could be targeted to cure disease in patients or even prevent disease in individuals not yet affected. Biomedical researchers began studying the biology of BRCA1 to take advantage of the new information in the treatment and understanding of disease. Because deleterious mutations in BRCA1 were discovered to place a large number of mutation carriers at a very high risk of breast and ovarian cancer, professional organizations developed guidelines regarding genetic testing, placing emphasis on identifying individuals truly at risk and advising individuals through genetic counseling about the benefits and limitations of the new information. Concerns about the misuse of genetic information about an individual prompted the passage of federal legislation in the United States, both in the areas of health insurance (Health Insurance Portability and Accountability Act (HIPAA)) and employment law (the American Disabilities Act (ADA)). Through contractual and other additional means, the individual’s rights to confidentiality and non-discrimination are further protected. To date, no case of genetic discrimination from BRCA testing has been reported.

As BRCA testing marks a change, it is indicative of why DNA testing will become more widespread. The power of genetic testing is the ability to transform familial risk into individual risk, where specific actions can be targeted to benefit individuals that carry clinically important mutations. Acceptance of susceptibility testing for breast and ovarian cancer is growing worldwide as a way to determine the individual risk and to design surveillance and therapies that will benefit these individuals.

For inherited disorders, germline mutations offer the best way to assess predisposition. The penetrance of the condition is very important in predicting the risks for mutation carriers. In some disorders, the distribution of mutations is simple, while for others it can be quite complex (such is the case for BRCA mutations). In some cases, the gene discovered will merely be “associated” with the condition, while in others it will be causal. Indeed there is also much work to be done in non-inherited, environmental and
unknown causes of disease. Even in such cases, the response to environmental stimuli probably come under genetic control, highlighting the need to study and understand the genetics involved.

The goal in biomedical discoveries is to change the world for the better. There is a process that occurs from the time that a gene is discovered until it has established clinical value. Indeed, to truly benefit society, the clinical value of the gene must be established. The process that occurs can be rapid for some discoveries but much slower for others. Factors that determine how rapid include whether the disorder is monogenic or polygenic, the kinds of technology necessary to demonstrate the presence/absence of important mutations, the ease with which appropriate phenotypes can be defined for study, and the length of time to develop important interventions based on the information. Currently, there is much activity among pharmaceutical companies to begin including genotyping as an entry criterion for patients in clinical trials. This trend is new and has been growing significantly over the last few years.

There are some axioms that underpin the process of turning a discovery into demonstrated clinical value:
1. For clinical value, all discoveries must pass through the developmental process.
2. It takes time to develop clinical value.
3. Inquiry into clinical hypotheses and education are key elements of the process.
4. To change the world, the discovery has to be translated into health care practice where many individuals benefit from the discovery.

![Diagram of BRCA1 and BRCA2 from discovery to standard of care](image-url)

Fig. 1. BRCA1 and BRCA2 from discovery to standard of care.
Figure 1 shows how BRCA1 and BRCA2 genes have moved from discovery to clinical recommendations. Note that the x-axis is time, with discovery occurring at the far left. Also note that several of the elements overlap one another. The diagram is meant more to be instructive than temporally exact. Once discovered, variability in a gene ("abnormalities") must be characterized. Following this, an understanding of the penetrance of disease and the characterization of the prevalence of important mutations begin. Another early activity in the process is the development and evaluation of a diagnostic test. Later, an evaluation of outcomes and interventions becomes very important. Then, evaluation of the cost-effectiveness of the testing in various populations becomes possible before recommendations for widespread screening are given. Finally, professional education and clinical recommendations take place.

BRCA1 was discovered in 1994. A rigorous high quality test was not available until 1996. Continued study of penetrance is taking place. The evaluation of several important interventions and outcomes is much of the work performed participants in this Demonstration Programme with their collaborators. Countries are at different stages in this process, depending on their medical systems and their technological capabilities. Indeed, the ability to use BRCA information depends on much more than simply being able to generate data: it is one of many important elements used to manage families with inherited risk.

The future of DNA diagnostics will be driven by two main factors: (1) technological advances, and (2) the choice of diseases that will be studied. Technological forces that will be important include continued miniaturization — just as in the computer industry. From this will emerge chip and mass spectrometric applications as the technical problems are solved. Key in any future diagnostic development is bioinformatics, the ability to manage information and to interpret the large volumes of data that are generated in analysis. Complex (and realistic) models will be developed as a part of the technological advances to allow better, earlier and more complete diagnoses.

The choice of diseases will also be a driver of change. The areas that have the most impact are those that cause the greatest degree of suffering to society and individuals. For example, both public and private sources currently fund investment in the areas of prostate cancer, cardiovascular disease, diabetes, asthma, osteoporosis, obesity and mental disorders. The promise of biotechnology is to be able to cure, and better yet, to prevent these disorders. That promise still remains to be realized.

Let us look into the crystal ball, but remember that “he who lives by the crystal ball eventually eats glass.” Predictions are risky. The timelines become even more inexact as we project further down the road. Nonetheless, let us permit some speculation about what the future of DNA diagnostics might be, in light of our current understanding and shaped by what we predict the drivers of change to be. Just as it was virtually impossible 25 years ago to predict the existence of the wonders of the Internet, the world of DNA diagnostics will undergo significant changes during the next quarter of a century. All consultants point out that DNA diagnostics will fractionally consume more health care funds, with the result that the treatments will be better targeted and more efficacious. This means that significantly more developments will need to take place as we link discovery to clinical intervention and outcome. Industry pundits also point out that we are on a fast track for scientific development.

Globally, there will be continued rapid advances in DNA diagnostic technologies in first world countries. As this happens, the cost of testing will decrease. Eventually this will also spread to developing countries. There will be a “threshold effect”, when a technology is perfected and becomes cheap enough that it can be disseminated to less developed countries. The cell phone analogy is an interesting one here.

Education — both of professionals and of the public — is a key activity as scientific advances occur. This is a major responsibility of people working in the field of clinical genetics, since
there will always remain very important limitations to technologies. We need an informed public in order that there be understanding of genetic issues and so that better public and private decisions can be made in this area. We will need better-educated clinicians so that decisions are made with the most current and complete information. The education of the public can help us to drive home the importance of family history in assessing risk, the fact that families — not simply individual patients — are at risk for familial diseases and can help support each other in working through the challenges of facing these conditions.

Therapeutics will focus increasingly on prevention. What can a person at risk do to modify his/her risk for a disease? Medicine will be more personalized and predictive. Vast quantities of information will be available from multiple data sources. Complex biological models will be used to integrate the information and make it available to the decision process for the person. Drug selection will eventually be highly individualized. DNA diagnostics will allow prediction of who will respond, or who should not be given a drug because they have a genotype that is likely to predispose to a toxic reaction. This kind of medicine will more cost-effective: i.e. lower costs and better efficacy.

Over what period of time might these things occur? Here is a very rough timeline:

Within 5 years: Many of the major genes in highly prevalent diseases of humankind will be discovered. The clinical utility of these genes will begin to be developed. Continued miniaturization and technological evolution will occur.

Within 10 years: The beginning of the development of more detailed knowledge of biology will take place. The initial integration of the knowledge will take place. The first new drugs arising from gene discovery will emerge. The first clinical and mass spectrometric technologies will begin to be widely distributed.

Within 15 years: Pharmacogenomic information will be integrated in a way that it can be used to benefit patients. The first early predisposition gene chips will be developed.

Within 20 years: Widespread genetic testing will be in practice. Whole-life risk profiling will occur, where the goal will be to establish risk and to prevent the major diseases of mankind. There will be a variety of earlier “wellness intervention” available, again, with emphasis on prevention. Many technologies will be available to do this.

Within 25 years: The 2024 meeting of the Familial Breast Cancer Demonstration Project will take place in Heidelberg. A lecture will be given on the history of DNA diagnostics. The concerns and hope for the future will have been pioneered by many participating in the present programme. The foundation will have been laid. DNA diagnostics will have changed the world.