History of the Terms “Pharmacogenetics” and “Pharmacogenomics”

As explained by de Leon (2009) and others, the term pharmacogenetics was reportedly coined in 1959 and was used for many years in reference to genetic differences in pharmacokinetic factors, particularly metabolic enzymes. This history may have something to do with how the FDA continues to define pharmacogenetics, although this is just speculation. Not until the 1990s did the term pharmacogenomics enter the scientific literature. Before then, most research on genetic difference (not just in drug response but with respect to most phenotypes) was limited to differences in DNA sequence. Not until genome-wide technologies emerge and advance did research on the underlying genetic differences in drug response begin to really expand beyond focusing on DNA sequence variation. Even then and now, most of the focus is still on specific DNA sequences, although genome-wide technologies are often used as a first step toward identifying those sequences.

Not to confuse the semantics even more, but as mentioned in Chapter 4, some scientists have begun speculating on whether epigenetic mechanisms might also contribute to drug response, leading to coinage of the terms pharmacoepigenetics and pharmacoepigenomics.

1.2. The Promise of Pharmacogenomics

In the popular and trade literature, the goals of pharmacogenomics are often viewed as being: (1) to improve the clinical use of drugs (by increasing benefit-risk ratios); and (2) to reduce the time and cost of clinical drug development. However, it's not at all clear that the latter goal is really an achievable goal, at least not in the near future. In fact, as discussed in Chapter 4, utilizing a PGx strategy in the clinic could actually increase the time and cost necessary for bringing a drug to market. Here, the goal of PGx is viewed very simply: to make better drugs. In so doing, drug-makers might not necessarily reduce the time and cost of clinical drug development, but they will definitely improve their long-term returns on investment (ROI).

What Making Better Drugs Means

Not all drugs work for all patients. Any given drug works in some patients but not others. Likewise, all drugs cause adverse drug reactions (ADRs) in some patients but not others. Making better drugs means (1) improving effectiveness, and (2) improving safety (i.e., reducing adverse drug reactions). Reaching these goals require, first, identifying
The Science Behind Warfarin Dosing: Still Building the Evidence Base

Charles S. Eby, MD, Associate Professor, Departments of Pathology & Immunology and Medicine, Washington University School of Medicine (St. Louis, MO), explained at the CHI conference in Montreal that two major sources of variability account for warfarin’s wide, unpredictable therapeutic dose:

1. Acquired sources of variability
   a) Age, body mass
   b) Smoking
   c) Liver disease
   d) Vitamin K status
   e) Medications/nutritional supplements

2. Genetic sources of variability
   a) Pharmacokinetics: People with CYP2C9*2 and *3 SNPs/alleles have reduced warfarin metabolism and therefore require lower warfarin doses.
4.6. Impact of Technology on Pharmacogenomics

All of the experts interviewed for this report agreed that technology is not the obstacle it was before the days of the Human Genome Project. By the mid to late 1990s, technologies were available that allowed for rapid parallel genetic testing (i.e., the simultaneous testing of multiple genotypes). By the early 2000s, the industry was abuzz with talk about reaching the $1,000 genome. Since then, genetic testing and in particular DNA sequencing technology has advanced even further. Most experts seem to think that even if technology poses a problem, it is not nearly as problematic as the other scientific and methodological challenges that PGx poses.

Advances in DNA Sequencing

That said, during his presentation at CHI, Bernard Prigent, MD, MBA, Vice President and Medical Director, Pfizer Canada, argued that the only way for PGx to reach its full potential is to rely on rapid advances in DNA sequencing technology and a step-wise reduction in the cost of full-genome sequencing. To this end, NIH launched programs in 2004 to accelerate the development of sequencing technologies and reduce the cost of whole-genome sequencing, with the initial goal of reducing the cost of producing high-quality genome sequences to $100,000. Ultimately, the goal is to reduce that cost to $1,000 or less—low enough for whole-genome sequencing to become a routine part of medical care. In August 2008, the NIH announced that the National Human Genome Research Institute (NHGRI) had awarded more than $20 million in grants to ten different teams of researchers dedicated to developing new technologies that can meet this goal. Prigent predicted that the cost of whole-genome sequencing will drop to $1,000 by 2014.

If the cost of whole-genome sequencing does in fact drop to $1,000 per genome by 2014, Prigent further predicted that between 2014 and 2019, as many as 50% of oncology drugs would be targeted by tumor genomics, 20% of chronic disease drugs would be linked to genomic profiling, and PGx-based risk profiles would be available for cardiovascular disease. By 2020, pre-symptomatic diagnostic and preventative treatment techniques would be available for chronic diseases. Therapies would deliver efficacy rates as high as 80–90%, and the healthcare system would experience a dramatic decline in medical expenditures due to a reduction in drug-induced serious adverse events (SAEs).
Pharmacogenomics: Delivering on the Promise

PharmGKB: The field of pharmacogenomics is facilitated by advances in genotyping technology, standardized ontology, and access to clinical biometric data, among other things. Efforts are underway to address logistical impediments to the advancement of the field of pharmacogenomics and its use in predicting drug response and disease susceptibility. They include improved technology associated with a reduction of costs for genotyping, forums to establish working nomenclature (e.g., the Pharmacogenetics Ontology Project), and efforts to collect large amounts of biometric data on patients under treatment in order to identify and track genotype-phenotype relationships.

For example, despite the increased accuracy of warfarin dosing by using an algorithm, application of the algorithm was not cost effective,\textsuperscript{103d} and medical insurance coverage for genetic testing lags behind scientific discoveries. However, a number of initiatives between private firms and healthcare providers are teaming up to use the knowledge of pharmacogenetics in drug treatment and diagnosis (e.g., El Camino Hospital Genomic Medicine Institute\textsuperscript{103e}). Over time, the barriers between scientific discovery and the clinical application of pharmacogenetics and pharmacogenomics will diminish and the full benefits of the field will be realized.

5.2. A Perspective on Pharmacogenomics Based on Interviews With 60 Industry Executives and Key Opinion Leaders

Interview with Philip Ma, PhD
Director, McKinsey & Company (Palo Alto, CA)

Dr. Ma was senior author on a recent “Perspectives” article in Nature Reviews Drug Discovery,\textsuperscript{104} “The microeconomics of personalized medicine: today’s challenge and tomorrow’s promise.” The article describes the authors’ (all of whom are affiliated with McKinsey) perspective on personalized medicine based on interviews with payers (eight payer executives from both private payer companies and the Centers for Medicare and Medicaid Services), regulatory experts (eight regulatory experts from the DHHS, FDA, and National Institute for Health and Clinical Excellence; two attorneys with legal expertise spanning FDA regulation law), pharmaceutical and diagnostic company executives (20 biopharmaceutical executives and 13 diagnostic company executives), academic opinion leaders (six researchers from leading academic institutions), and venture capitalists (three from leading firms focused on molecular diagnostics investments). Most of the following interview with Dr. Ma pertained to the outlook described in this paper.
See Chapter 3 for a discussion of this question. It appears that most companies are now collecting PGx information during clinical development. It is unclear, however, how they use that information. As Dr. Roses indicated in his interview (see Chapters 3 and 5), a growing number of companies are beginning to utilize an efficacy PGx approach to drug development, which means collecting PGx information early and often. Dr. Ma, in his interview, said that most companies are collecting PGx information for efficacy, not safety, reasons. But some of the responses below suggest that safety PGx is just as, if not more, prevalent than efficacy PGx. Again, see Chapter 3 for a discussion on safety vs. efficacy PGx.

6.2. Pharmacogenomics in Drug Development

Note: Respondents had the opportunity to answer questions 11–17 only if they indicated in question 10 that their organization collects PGx information during clinical development.

Question 11: Is genotyping done because preclinical or other evidence suggests that it should be done, or is it done for a broad range of genes and not necessarily for any particular reason?

<table>
<thead>
<tr>
<th>Response</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>It is done only when there is a reason to suspect that genotype might matter</td>
<td>50%</td>
</tr>
<tr>
<td>It is done for a broad range of genes</td>
<td>50%</td>
</tr>
</tbody>
</table>

n = 20

Source: Insight Pharma Reports’ Pharmacogenomics Survey—March/April 2009