Clin Chem Lab Med 2003; 41(4):610–614 © 2003 by Walter de Gruyter · Berlin · New York

Roundtable

Pharmacogenetics: From Bench to Bedside

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Introduction

F. W. Frueh

In this roundtable discussion, we will try to point out some of the necessary issues which bring pharmacogenetics from the research laboratories into the clinics, and, in particular, point out the actions required by various different entities involved in this process. Now, I thought that everybody will show pictures of Santorini, so I thought to show something else which is appropriate to launch this discussion (showing a Greek salad). The reason I'm showing you this is that genetics, including pharmacogenetics, is something that we are exposed to daily. But by looking at the genetic code, at the molecular level, we are now able to convey information to the patient, which so far we were not able to, and which can bear significant ethical consequences. However, everybody is, for instance, talking freely about their cholesterol level, and nobody thinks twice that this information contains genetic information. The lesson is that, as scientists and physicians, we have a lot to do to educate patients about the meaning and impact of everyday genetics.

Financial aspects

A study done by Decision Resources this year shows that genetic testing is accounted for by 10% pharmacogenomics- and 90% disease susceptibility-based assays. It is expected that this ratio will change dramatically over the next 5 years. The current market is estimated to be 100–110 million $ and is expected to grow to almost 1 billion $ over the next 5 years. This will only happen if we succeed to translate what we are talking about today into clinical reality. I'm somewhat surprised how Decision Resources were able to come up with this number because I assume it to be really difficult to predict the success we will or will not have in this respect. Now, as we have heard during the last few days, I would like to distinguish between two things: first, testing for disease genetics, and second testing for "pharmacogenetics". The most important differences between these two aspects are the ethical and social implications: with pharmacogenetic tests we are not telling somebody that he will die within the next 5 years, but rather that he is susceptible to develop side effects when taking a given drug and that it might be advisable to use this treatment rather than alternative one.

Adverse drug reactions

Pharmacogenetics related to drug metabolizing enzymes is what we know best and I would like to follow the nice presentation of Dr. Oscarsson with some additional comments in this context. Although we know a lot about these enzymes, not much has been done to transfer this knowledge into clinic applications. An incentive to do so can be found by looking at these randomly collected numbers: about 30 years ago, 28% of hospitalized patients had adverse drug reactions, 6 years later, 17% of hospitalized children had adverse drug-attributed events, a pretty large number. In 1994, the first extensive study on adverse drug reactions showed that more that 2 million people had serious adverse drug reactions in hospitals. Consequently, these numbers make adverse drug reactions the 6th leading cause of death, with associated costs of about 76 billion $ in 1995. A recent study shows an increase in these costs to about 177 billion $ for 2000.

Therefore, from the perspective of healthcare providers, there must be a large financial incentive to prevent adverse drug events from happening. That this is a "real world" problem is confirmed by the fact that drugs are regularly taken off the market because they are not safe. Two major reasons why drugs are removed from the market are hepatotoxicity and QT segment prolongation (a measure for ventricular repolarization). Hepatotoxicity due to mutations in drug metabolizing enzymes, about which we already have a substantial amount of knowledge, is linked to adverse drug reactions, QT prolongation is being investigated and we slowly start to understand its implications with respect to adverse effects.

Current routine applications

We heard today two wonderful presentations on HER2 testing and HIV genotyping. These are currently the