

Plenary Address: Genetics, Pharmacogenomics, and Drug Safety

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Drug discoveries in recent decades represent major advances in our ability to combat disease. But according to Michael Hayden, this benefit comes at a high cost: “50% of newly approved therapeutic health products have serious adverse drug reactions (ADRs), discovered only after products are on the market.” Severe drug reactions include death (ADR is the fourth-leading cause of death in the United States), birth defects, disability, hospitalization, and life-threatening situations.

Every year, 26,000 children die of ADRs in the United States. The factors that put children at increased risk of severe ADRs include lack of testing in pediatric populations and lack of pediatric dosages. Pediatricians calculate dosages from those recommended for adults by correcting for children’s smaller masses. But—and this may be the most crucial observation—children are not simply small adults. A child’s metabolism is qualitatively different from that of an adult, and in the context of metabolizing drugs, this can make the difference between a safe drug dose and a lethal one.

ADRs occur in a minority of treated patients; removing drugs that have resulted in ADRs from the market leads to the suffering of more patients in that it deprives many of needed treatment. It is often not a drug itself that is unsafe but the interaction between a patient’s genetic constitution and the drug. That is where the Genetic Approaches to Therapy in Children (GATC) program comes in. The

program focuses on younger victims of ADRs, and its goals are to use genetic markers to predict when it is safe to administer particular drugs and to provide alternative treatments only to those at high risk for ADRs.

The first steps in the GATC program are to identify drugs that lead to severe ADRs and to discover potential genetic markers associated with them. The former is a challenging task because the vast majority of ADRs are unreported and controls are needed. To associate particular genotypes with an ADR, it is necessary to collect DNA from patients who were treated by the drug in question and did not manifest an ADR. To overcome those challenges, the world’s most extensive ADR-reporting system has been established in Canada. With the support of Canada’s federal government, GATC’s ADR surveillance network now encompasses more than 95% of pediatricians in Canada, 10 major hospitals serving more than 80% of Canada’s children, and all Canadian pediatric-oncology departments.

Hayden reported on findings pertaining to one of three widely used groups of drugs and two widely used drugs associated with severe ADRs: chemotherapy drugs (anthracyclines) that can lead to severe cardiotoxicity; a cancer drug (cisplatin), used for treating solid tumors, that can cause deafness; and codeine (found in Tylenol, for instance), which sometimes leads to infant death when taken by nursing mothers. In each of those cases, GATC researchers were able to identify mutations



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that account for many of the ADRs and that, if found in a patient, greatly increase the likelihood of a severe ADR.

Discovery of genotypic markers for an ADR is only the first step, which is followed by replication studies, pharmacokinetic mechanistic validations, and prospective clinical evaluation of suggested diagnostics. Once data from the studies lead to approval by regulatory agencies (such as the Food and Drug Administration), commercialization options can be explored and, with luck, will result in a product that is embraced by health-care systems and made available to the general public.

The new genomic era holds the promise of a revolution in therapy. Unfortunately, fulfillment of the promise is slow. For example, the gene for cystic fibrosis was discovered more than 20 years ago, but no therapies have been found yet. However, the situation may be changing. Michael Hayden and the pioneering research of his colleagues, including Bruce Carleton and the GATC program, are evidence that detailed knowledge of our genetic makeup can indeed be used to save lives and reduce human suffering. 🔥