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Patient-oriented investigation in pharmacogenomics

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The big four areas for drug development include cancer, cardiovascular, psychiatric, and metabolic diseases. We hope that genomics will increase the relatively limited pipeline of new compounds. The expectation is that understanding the genomic underpinnings of the big four groups of common and complex diseases will lead to better therapeutics. However, are current approaches misdirected?

I believe so, because of the flawed assumption that understanding disease causation is the *sine qua non* of drug development. Considerable effort is directed at understanding etiology; however, the systems involved in disease causation may be unimportant to treatment and conversely, approaches that provide a therapeutic handle in complex situations might be entirely unrelated to etiology. Schizophrenia, a common and complex disorder of unknown cause, can illustrate this line of reasoning. It is now hypothesized that schizophrenia is a neurodevelopmental disorder. If that is the case, understanding the mechanisms underlying altered development may not be relevant to the treatment of adults. Instead, approaches to systems that underlie clinical presentation may be more fruitful. The misguided reductionism of recent years has made such clinically-based efforts unlikely to occur due to the current pressures in clinical investigation.

As research moves away from patients, investigators lose (or never gain) knowledge of the disease entities that are supposed to benefit from their labor. It is not possible to develop approaches to understand and treat the biology underlying disease presentation without being in constant contact with patients who suffer from the disease. If research grants do not cover work that requires direct patient contact, how can investigators gain such experience and develop the necessary insights? This is particularly true in complex disorders.

Genomic approaches conducted in dissociation from clinical research and aimed at dissecting fundamental causes of diseases are of course of great importance and should be vigorously pursued. However, such work may not bring about progress in the identification of new therapies. The dissection of clinical presentations, the insight gained from understanding subtle differences among cases, and the observation of serendipitous responses to unrelated treatments can only be achieved in the context of ongoing and active patient-oriented research. Drugs used to treat schizophrenia were intially developed as anesthetics and their antipsychotic effects were noted by astute clinicians. Likewise, antidepressants were initially developed as anti-tuberculosis drugs. This type of insight is not limited to historical cases. Understanding why male patients refused to return unused sildenafil after a cardiovascular clinical trial led to the development of a best-selling drug for impotence. In conclusion, insight from the clinic cannot be gained without a clinic—and 'clinic' in this case means well-funded, patient-oriented research operations that permit rigorous assessments of patients, clinical presentations, and patterns of expected and unexpected drug responses. Such a setting is increasingly different from today's highly pressured medical care environment in which clinical encounters are performed only if strictly needed, in the most abbreviated format possible, and reimbursed at the lowest possible amount. Clinical research efforts that are independent of patient care delivery are therefore necessary for the detailed understanding of disease presentations and treatment responses that should guide contemporary pharmacogenomics.

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