Drug Safety in the 'Omics Era'

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Adverse drug reactions (ADRs) are a top 5 leading cause of mortality in the United States [1] and reports continue to rise worldwide. The current drug safety paradigm puts heavy emphasis on identifying new problems in approved drugs. This is evidenced by significant financial investment in the FDA Sentinel Initiative (http://www.fda.gov/Safety/FDAsSentinelinitiative/ucm2007250.htm) that captures ADRs through electronic medical record integration among other sources. Unfortunately drugs that receive black box warnings or are withdrawn are not identified until months or years after approval when a large population has been exposed. While the Sentinel Initiative offers increased capture of ADRs, it continues to struggle to identify low incidence ADRs, does not adequately emphasize prevention, and fails to focus on the mechanism by which ADRs occur.

Various omics techniques (pharmacogenomics, pharmacoproteomics, transcriptomics, epigenomics, and metabolomics) have aimed to identify associations between patient factors and ADRs. Highly predictive omics screens to prevent ADRs have been elusive. Ultimately all drug effects, therapeutic and adverse, have a combination of omics mechanisms. Failure to acknowledge upstream and downstream molecular contribution represents a fundamental limitation in drug safety research.

Given the small well-controlled cohorts studied in premarketing trials, it is no wonder that we fail to predict ADRs in the heterogeneous population ultimately exposed to an approved drug. Researchers focusing on a single omic association are destined for the same failure when the findings are applied to large heterogeneous patient populations. While the single omics paradigm minimizes the effect of background noise, it also importantly limits our ability to apply findings in the real world. We cannot reasonably expect efficient ADR prediction with this reactive paradigm.

Proactive population based screening for ADRs, paired with mechanistic determination, is an approach far more likely to decrease future drug warnings and withdrawals. Large heterogeneous cohorts must be studied; every ADR, regardless of the incidence, must have a mechanistic evaluation through a systems biology approach. This approach requires a fundamental refocus on populations rather than small cohorts. It requires the establishment of a data warehouse that is widely available to researchers. Ultimately the Sentinel Initiative may serve as an excellent repository for clinical data; linkage to omics data will be essential to perform proactive mechanistic ADR evaluation. We must view all ADRs as preventable.

Pairing population level ADR identification with omics data will allow determination of population risk and ultimately mitigate individual risk.

References

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