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Editorial

Clinical Decision Support Tools for Precision Medicine

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There is universal agreement that germline genetic sequence variants affect an individual's susceptibility to a variety of diseases, disease complications and effectiveness of some treatments. The problem is the unique variability in genetic sequence variants between each human being.

There is also general agreement that current Western Medicine has major limitations. (1) Two major problems are (a) the approach of using case-control population studies linked to evidence-based medicine (EBI) to select the best treatment for individual patients, and (2) disease nomenclature that is based on the appearance of affected tissue (pathology diagnosis) or combinations of signs and symptoms (i.e. syndrome diagnosis).

These two problems with the Western Medicine paradigm make it nearly impossible to determine the etiology of complex disorders where multiple factors that, by themselves are neither necessary or sufficient to cause disease, and where multiple pathogenic disorders result in identical tissue pathology and/or syndromes. As a result, targeted treatment effectiveness is tagged with a *number needed to treat* (NNT) factor, while "more effective" treatments target down-stream consequences of the true pathogenic factors, such as dampening the inflammatory response or managing pain and stress disorders.

Artificial Intelligence (AI) and Deep Learning (DL) are two computer-based tools that have been used in attempts to crack the code of the high variability in human diseases experience and responses to treatment. They are highly effective in pattern recognition when the data is highly structured and reproducible, such as digital images. The fatal flaw of these approaches for complex disorders is GIGO, *garbage in, garbage out*. The "garbage in" is electronic health records that are populated with Western Medicine definitions of diseases (e.g. ICD-10 codes) and depend on complex associations. The results are typically replicating what we know or seeing computer "hallucinations" – true associations within a training set that are, in fact not biologically true.

Precision Medicine is an alternative to the paradigm of Western Medicine that was built on the 19th century Germ Theory of Disease. The goal is to give right treatment to the right patient at the right time. This requires that many genetic variants and other risk factors must be considered in the context of an individual person.

One of the first areas of Precision Medicine to be recognized as being highly valuable is pharmacogenetics (PGx). Indeed, the FDA recognizes over 200 drugs that are affected by genetic variants in drug metabolizing and other genes and has provided strong recommendations for altering standard prescriptions to ensure that prodrugs are activated to provide utility and active drugs are cleared to prevent toxicity. In this issue we highlight insights on the PGx of beta-blockers (page e9-e13), as there is evidence of altered drug metabolism, but consensus guidelines are lacking. Unfortunately, most physicians do not use PGx to guide treatment, resulting in significant effects on cost and toxicity to patients.(2)

Precision Medicine is also gaining use in oncology. Here, genetics testing focuses on tumor genetics to guide treatment rather than the patient. This is proving to be a major step forward and brings an awareness of the possibility of precision medicine to the treatment of complex diseases.

To understand the pathophysiology of an individual patient requires an *engineering approach* rather than a statistical one. All the factors must be organized by specialized cell and systems and then studied under dynamic conditions of activation and stress. No physician can accurately compute the effect of all the variables that interact in sequential, parallel, multiplicative, inhibitory or conditional ways under dynamic conditions – nor calculate the effect of one or more interventions in an individual patient. Representative cell, organ and multi-system models are needed with simulated outputs under various input conditions. While this type of engineering approach is being developed, it remains out of the reach of most physicians.

A major requirement of the Precision Medicine paradigm must be *clinical decision support* (CDS) tools. While various tools have been available to help in clinical decision making (e.g. a clinical decision pathway), precision medicine requires CDS systems with the capability to leverage data and observations that are otherwise unobtainable or uninterpretable by humans.(3) The limitations are not ones of comprehension, but of speed and accuracy. The physicians must have confidence that the clinical recommendations (not instructions) are based on systems that they understand at a working level, and that the results can be traced to known levels of evidence.(4) However, for uncommon or complex clinical conditions, there are typically not enough patients – or too long of a disease process to run adequately powered clinical case-controls trials. In this case, the practicing physicians may refer the patient to an expert consultant or learn what an expert consultant would do if they had a patient like the one that is being evaluated by the practicing physician. It is this latter scenario that is critically needed for managing common complex disorders that are plagued with unexpected responses to treatments or unusual complications. In this case a CDS system can provide a reasonable perspective that, within the practicing physicians experience and knowledge base, is useful in making a good decision.

Precision Medicine is the future. But excellent CDS systems are required for the implementation of new insights into the cause and cure of complex chronic conditions. It is a goal of the *SMART-MD Journal of Precision* Medicine to structure articles to serve future needs of sophisticated CDS platforms and tools.

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