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EDITORIAL

Precision Medicine: The Promise and the Paradox

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The practice of Clinical Medicine is a dynamically evolving paradigm. In its earliest era, medicine was intuitive – doctors relied on "experience" and heuristic assessment of signs and symptoms rather than scientific evidence.[1] Since the late 20th century, this has rightly been replaced by evidence-based medicine (EBM), with clinical trials and meta-analyses considered the height of empirical evidence. EBM has undoubtedly transformed population-level patient outcomes by fostering "best medical practices" supported by systematic medical research. Nonetheless, this system has an inherent limitation– evidence-based guidelines are formulated from mean results from a relatively homogeneous trial population, with the deliberate exclusion of heterogeneous characteristics.[2] Consequently, at the individual level in real-world settings, this often leads to heterogeneous outcomes such as poor responses or adverse events. This is due to inter-individual variation in genetics, lifestyle, environmental exposures, comorbidities or drug interactions.[3] It has become increasingly evident that treatment should be personalized, i.e.,it should target the patient with the disease, rather than the disease in the patient.

This has led to the 'treatable traits' approach – identifying and targeting clinically meaningful, measurable, and modifiable factors in each patient, including risk factors, comorbidities, and characteristic pathogenic biomarkers (such as markers of type 2 inflammation in asthma).[4] However, this only addresses traits at the macro level; to be truly individualized, medicine must also account for factors at the genetic and molecular levels. This is the crux of Precision Medicine.

The concept of precision medicine is not new; it was articulated by Sir William Osler who reiterated the importance of a patient-centric approach as opposed to a disease-centric one. PM has been driven by a rapid convergence of three major exponentially growing technological revolutions – genomics and other "-omics" technologies, the emergence of "Big Data", and machine learning and AI. The Human Genome Project accelerated the development of high-throughput sequencing and multi-omic technologies that could identify cellular molecules, including genes (genomics), RNA (transcriptomics), proteins (proteomics), and metabolites (metabolomics), as well as exogenous factors affecting gene expression (epigenomics). The dramatic reduction in cost and turnaround time of these technologies has made them more widely accessible, contributing to vast amounts of multi-omics data.[7-8]

Concurrently, there has been a surge in digital health data from electronic health records, wearable digital monitoring devices, and apps that record lifestyle and environmental data. On its own, this unprecedented mass of data has limited value and is difficult to interpret. Advanced machine le arning and artificial intelligence are indispensable for analyzing complex data, identifying patterns and associations, developing predictive models, and generating a clinically actionable algorithmic approach for patient-specific decision-making. The model works by constructing a "molecular profile" for each patient, providing biomarkers to aid personalized risk prediction, accurate diagnosis, personalized treatment protocols, treatment response prediction, and monitoring.[6-7]

The most advanced application of Precision Medicine has been in oncology, as malignancies are driven by genetic mutations. Molecular profiling of tumors can identify actionable genetic alterations such as EGFR in colorectal and lung cancers, ALK, ROS1, KRAS in lung cancers, HER2/ERBB2 in breast and other solid organ cancers, and BCR-ABL in myeloid leukemia, among others. Precision treatment is possible with anti-cancer therapies that specifically target cells with these mutations. This reduces injury to the surrounding normal tissue.[3-8] Circulating tumour DNA (ctDNA) assays now serve as non invasive diagnostic and monitoring tools, particularly when tissue samples are

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limited. These approaches have substantially improved overall survival in patients.

Precision medicine has also moved into the management of respiratory diseases. For patients with severe asthma, guidelines recommend profiling patients based on biomarker and clinical data. This is used to identify candidates with Type 2 inflammation, who are most likely to respond to biologic therapies targeting IgE (Omalizumab), IL-5 (mepolizumab, benralizumab), or IL-4/IL-13 (dupilumab) (GINA). In cystic fibrosis, the cornerstone of treatment is CFTR genotype-directed specific therapy (Murray).

Pharmaco-omics is another important component of precision medicine across all disciplines. This is based on the observation that genetic variants in drug-metabolizing enzymes and drug transporters significantly affect the pharmacokinetics, efficacy, and development of adverse effects of numerous medications. The Clinical Pharmacogenetics Implementation Consortium (CPIC) has issued prescribing recommendations for over 100 drug-gene pairs. Guidelines recommend screening for genetic variants to prevent severe adverse drug reactions, before certain drugs are prescribed (Landstrom AP, Circ., 2025; Roden DM, Lancet 2019). An important example is testing for TPMT/NUDT15 before prescribing azathioprine, to prevent severe myelosuppression. In patients with cardiovascular or cerebrovascular disease who require an antiplatelet agent, CYP2C19 genotype testing is recommended to guide antiplatelet drug selection. Loss-of-function genotypes indicate clopidogrel resistance; alternatives like prasugrel or ticagrelor should be chosen in these cases.[13] Studies have shown a strong association between the presence of the HLA B*15:02allele and carbamazepine induced Stevens–Johnson syndrome and toxic epidermal necrolysis in patients of South Indian descent.[15] Wider application of pharmacogenomics to individualize drug prescription can improve efficacy and reduce toxicity, but remains less accessible due to high costs.

A critical question is whether health policy in low- and middle-income countries should be population-based or personalized. The most important barrier is the lack of a dataset, as PM is only as good as the data driving it. Not only are electronic health records severely lacking, but genomic data from LMIC are underrepresented as well. The relatively higher cost of precision medicine technologies compared to conventional approaches and the reliance on folk healers are other barriers to the widespread implementation of precision medicine. Overall, population-based strategies may provide the most gains. In specific situations, however, particularly in hemato-oncology, precision medicine may perform better. It can perhaps be said that the application of precision medicine should itself be personalized. The promise of precision medicine is clear: better outcomes through better targeting. But the challenge ahead is ensuring this promise reaches every patient who could benefit.

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