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PRECISION MEDICINE: CURRENT STATUS, CHALLENGES, AND OPPORTUNITIES

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Commentary

Precision medicine, though a relatively new term, is not a really a new concept [1]. According to the Precision Medicine Initiative (PMI), precision medicine is an emerging approach for the treatment and prevention of diseases that takes into account an individual's genes, environment, and lifestyle. Among these intrinsic and extrinsic factors, this blog will focus on genetics.

Genetics has led to the identification of new drug targets and has improved our understanding of interindividual variability in drug exposure and/or response (safety and/or efficacy). In turn, this has led to the development and approval of therapeutic products that are tailored to an individual based on biomarker status to help identify the right treatment, right dose, or to monitor therapeutic response. About 25% of drugs that have been approved between 2014 and 2016 by the Center for Drug Evaluation and Research (CDER), FDA are considered as precision medicines [2]. A number of these precision medicines have been co-approved with companion diagnostics to help identify patients who should receive the therapeutic product [3]. A recent trend is the codevelopment and approval of complementary diagnostics that can aid in determining an individual's relative benefit/risk. Some recent examples of precision medicines and companion/complementary diagnostics are listed in Table 1. Among products regulated by Center for Biologics Evaluation and Research (CBER) in 2017 are two chimeric antigen receptor (CAR) T cell therapies as well as the first gene therapy to treat cancer.

Table 1: Some recent examples of precision medicine approvals

Generic Name	Indication and Diagnostics Information [a]
eteplirsen	Treatment of rare genetic disease, Duchenne muscular dystrophy (DMD) with DMD gene mutation amenable to exon 51 skipping
atezolizumab	Complementary diagnostic for bladder cancer and non-small cell lung cancer (NSCLC): Ventana PD-L1 (SP142) assay
rucaparib	Treatment of deleterious breast cancer gene (BRCA) mutation (germline and/or somatic) positive ovarian cancer Companion diagnostic: FoundationFocus CDxBRCA Assay
nusinersen	Treatment of rare genetic disease, spinal muscular atrophy (SMA)
ribociclib	Hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer
niraparib	Complementary diagnostic for the treatment of ovarian cancer: BRACAnalysis CDx
deutetrabenazine	Dose modifications for CYP2D6 poor metabolizers in Huntington's chorea
cerliponase alfa	Treatment of rare genetic disease, ceroid lipofuscinosis type 2 (CLN2) also known as tripeptidyl peptidase 1 (TPP1) deficiency
midostaurin	Fms-like tyrosine kinase 3 (FLT3) mutation-positive acute myeloid leukemia (AML) Companion diagnostic: LeukoStrat CDx FLT3 Mutation Assay
brigatinib	Anaplastic lymphoma kinase (ALK)+ NSCLC
durvalumab	Complementary diagnostic for the treatment of urothelial carcinoma: Ventana PD-L1 (SP263) Assay

Note: [a] List includes new molecular entities (small molecules and biologics) that use biomarkers to identify patient population or identify appropriate dose of the drug. The original new drug application (NDA) or biologic license application (BLA) was approved between July 2016 and June 2017 by CDER, FDA. The labeling was last accessed in June 2017. Refer to individual drug labels for additional information.

The ultimate goal of precision medicine is to provide a more individualized treatment. In order to facilitate development and utilization of precision medicines, it is essential to address the existing challenges and take advantage of the opportunities at hand. Some of these challenges and opportunities include:

- Addressing the unmet need: Many of the precision medicine approvals are in oncology, antivirals, and rare diseases. Though our understanding of the genomics of many common chronic diseases has improved, we don't yet have a good understanding of the disease process (e.g., Alzheimer's) to translate the use of biomarkers in drug development to facilitate identification of successful drug targets, disease progression, or patient selection.
- Increasing diversity: Increased effort to recruit participants from underrepresented populations for genomic studies and clinical trials is still a long way away from achieving its goal. Because genetic factors for disease and drug response can vary across racial/ethnic populations, the extent to which the results observed in European ancestry will apply to more diverse populations is unclear [4].
- Evidence based data interpretation: As genomic data is being used for clinical decision making, there is a need to address inconsistencies in the interpretation or classification of genetic variants. This makes data-sharing and transparent documentation crucial.
- Return of genetic data: In the era of whole genome-sequencing and patient-centered drug development, return of genetic information back to the patients, especially incidental findings is still a challenge that needs to be addressed [5].

- Harnessing big data: Large- and small-scale research efforts have led to the generation of vast amounts of genotype and phenotype data. To harness the potential of big data, facilitating data connectivity (e.g., electronic medical record with multi-omic data including genomic, proteomic, metabolomic, and microbiomic) is essential as a lot of this data exist in silos. Challenges related to data collation, standardization, harmonization, management, interpretation, and privacy need to be addressed.
- Adopting innovative trial designs: Recent public-private partnerships have led to an uptake in umbrella (different targeted agents targeting different biomarkers in the same tumor type) and basket (single targeted agent targeting specific biomarker(s) irrespective of tumor type) trials. Though these trial designs have their own challenges, they hold the promise of creating certain efficiencies related to cost, resources, and patients.
- Building partnerships: In the past few years, non-traditional, cross-sector partnerships are being formed to promote innovations in the healthcare sector. Multiple stakeholders including patients, clinicians, academic researchers, biopharmaceutical industry, device developers, technology companies, payers, and regulatory agencies should come together with aligned interests to fulfil the vision of a patient-centered precision medicine.
- Training: Training the next-generation clinical pharmacologists is crucial as they would be working in multidisciplinary teams and will be handling an array of data from traditional and emerging disciplines (e.g., pharmacometrics, genomics, biomarkers, bioinformatics, etc.). Organizations like ASCPT play a pivotal role in this regard. Networks and Communities within ASCPT promote interaction among members with different expertise and interest, thereby promoting growth in the fields of clinical pharmacology and translational medicine.

In the recent years, incorporating genomics- and modeling-based approaches have led to successful drug development programs. This can be target-related (such as development of targeted anti-sense oligonucleotides and rational combinations of targeted therapies) or ADME-related (such as dosing recommendations for belinostat, eliglustat, and aripiprazole lauroxil [6]). The multi-disciplinary nature of clinical pharmacology puts us clinical pharmacologists in a unique position to embrace the opportunities and address the challenges by incorporating model-based and genomics-based drug development strategies to facilitate the discovery, development, regulation, and utilization of precision medicines.

References

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