Future of Pharmacometrics: Predictive Healthcare Analytics

Quantitative clinical pharmacologists have made great strides into drug development, regulatory science, and patient care. The access to digital data, that was previously unavailable, opens new avenues for us. We are at the cusp of a great revolution that can propel us into predictive analytics.

State of the Art

We started our journey as clinical pharmacologists with pharmacokinetics (PK), physiologic-based PK (PBPK) and gradually expanded to time course of pharmacologic effect (pharmacodynamics). Pharmacometrics, as we know it, encompasses disease, drug and trial modeling to support drug development and regulatory decisions.[i] More recently, PBPK has made a come-back into drug development to support drug-drug interaction projections. The need for discovering novel targets triggered the need for systems biology modeling (referred to as quantitative systems pharmacology, QSP).

During its inception, pharmacometrics was used primarily to summarize (description) PKPD data. Today, we are able to employ pharmacometrics to support approval of products without additional efficacy trials or which were not possible to be approved otherwise. By using PBPK, we are able to waive in vivo PK trials particularly for assessing drug-drug interactions. Lately, QSP is being explored by scientists in preclinical and early clinical phases to project likely pharmacologic activity or clinical outcomes. Such applications can be construed as 'predictions' out of the range of the observed data.

We have been able to prove a value-add to drug development decisions. Modeling groups in pharmaceutical companies and regulatory agencies have grown larger and enjoy more organizational clout. As a community, we are flourishing! However, the growth rate of modeling and simulation is reaching a plateau.[ii] [iii] In my opinion, organizations are not increasing investments at the same rate as 10 years ago. It is time for us to think about the next big thing for our community.

Future Opportunities

The type of input data and the applications of quantitative clinical pharmacology approaches has evolved. The ability to acquire patient data using digital technology has fundamentally changed the type of questions we can answer using quantitative approaches. The single-most important advance being the Electronic Health Records (EHR). Mobile and telemedicine technologies enable monitoring of patients more frequently to preempt and mitigate risks.

The applications of quantitative clinical pharmacology have also evolved from a descriptive nature to a predictive nature. Using modeling and simulation, we can waive in vivo studies for drug-drug interactions and efficacy studies. Future lies in predictions where there may be sparse or no data.

More innovative approaches such as QSP and machine learning are being added to our armamentarium, 'Clinical Pharmacology' continues to be the principal foundation that binds us together. Figure 1 depicts an integrated view of the different sub-specialties of clinical pharmacology. The different sub-specialties are shown as pillars standing on the foundation of clinical pharmacology. The goal of the different quantitative approaches all the way from discovery to hospital setting remains to be the prediction of desired and undesired effects in a patient or group of patients. Clinical pharmacology constitutes of different types of scientists with expertise in different sub-specialties ranging from disease expertise to innovative quantitative approaches such as DeepNLME. We have scientists who possess indepth knowledge of the disease area. This expertise is critical when considering endpoints, trial designs, biomarkers and patient management characteristics. Pharmacometrics, PBPK and QSP provide the necessary support via translational modeling through the continuum of drug development. The contributions of these approaches are well documented. Statistical modeling entails empirical approaches to analyze discrete data (e.g. logistic regression, parametric hazard modeling) and modern designs such as Bayesian adaptive trials. Throughout the drug development process, the probabilities of technical, regulatory and commercial successes are constantly estimated. Decision analyses, powered by clinical trial simulations and scenario-planning, provide a structured basis for decision-making (e.g. go/no-go, trial design).

One of the most promising areas for quantitative clinical pharmacology applications is individualization of patient care through Clinical Decision Support systems (CDS). The focus so far has been solely on drug development, whose goals revolve around averages. However, in a clinical setting, individual patients are treated. Another related area relevant to this setting is comparative effectiveness. It is impractical to conduct empirical head to head trials for a new treatment versus existing treatments. The availability of EHR data ('Real World Data') in conjunction with the randomized trials during drug development enable us to provide individualized recommendations for each.[iv] [v] The spend on healthcare delivery is orders of magnitude larger than a typical R&D budget. Investing in the individualization of patient care could provide us exceptional growth opportunities. The availability of disease domain expertise (via Clinical Pharmacists) is an advantage to us in developing and implementing CDS.

Finally, digital data could be available as a voice recording, video, image, social media clip, gene sequence or a lab value.[vi] We need tools to convert these diverse sources to signals. Data scientists play a crucial role in processing these data. These signals could be driven by a mixture of known and unknown mechanisms. QSP is at one end of the spectrum where models are proposed based on biology. Machine learning is at another end of the spectrum which relies completely on large empiric observations. Further, machine learning by itself is bound to fail in healthcare. The scientific modeling (second pillar in Figure 1) together with machine learning (called 'DeepNLME') is a more effective means of supplementing the valuable mechanistic knowledge with machine learning.[vii] That is, the mechanistic exposure-HbA1c modeling can be extended to clinical outcomes such as cardio-vascular risk using machine learning. The machine learning portion can then be converted into a set of differential equations for future use.

Considering the above tenets, the following are the strategic goals for the success of Predictive Healthcare Analytics.

Develop Holistic & Integrated Vision for Predictive Analytics to Drug Development
Pharmacometrics, PBPK, QSP, Statistical Modeling and Decision Analysis should develop a common vision for the application of modeling and simulation to drug development. The focus should be on predictive analytics – so drug development can be disrupted. These approaches can own the estimation of the probability of technical success and play a key role in formulating the probability of commercial success. The vision should also include an updated definition of basic skillset for clinical pharmacologists.

Develop 10 CDS Applications
Clinical pharmacologists and clinical pharmacists should come together in developing 10 CDS applications by 2030. This is a unique opportunity for academic clinical pharmacologists. It might not be an overstatement to state that only academic scientists can drive this innovation. They have the access to hospital data, patients and the ability to conduct clinical trials. In an era of limited research funding, academic institutions can view this is a entrepreneurial opportunity to fuel research and training. In fact, a consortium of academic institutions to take advantage of each other's strengths might be a prudent strategy.

Cross-train 100 Scientists in Drug Development
The advent of newer approaches (e.g. QSP, DeepNLME) brings scientists outside of drug development into clinical pharmacology. While they bring invaluable innovation, they can also benefit from the vast drug development experience of others. This preamble applies to all new recruits into clinical pharmacology. Academic training is mostly on techniques, and not on the application of modeling to real-world problems. Each organization should commit to cross-train 2 eligible scientists per year in drug development by providing dedicated time to participate in routine developmental activities (e.g. writing an IND, protocol, product strategy, developing a target product profile, writing a label). Creating a critical mass of such 'drug development scientists' is crucial for the growth of opportunities for that sub-specialty.

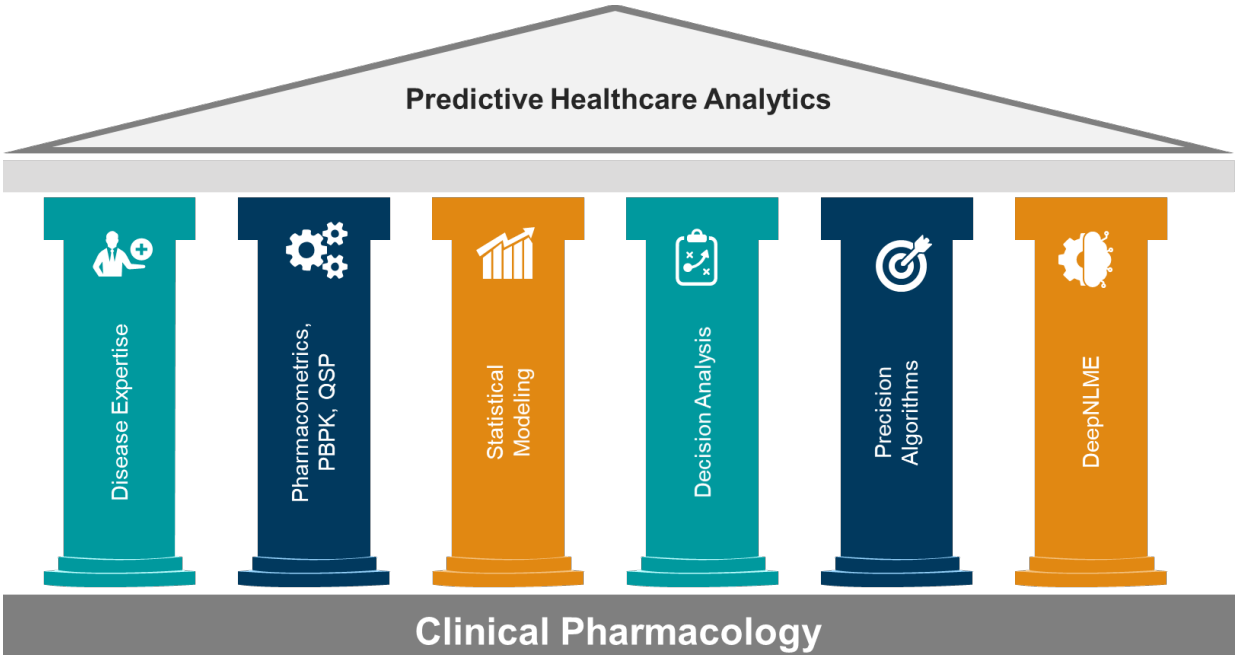

Figure 1 Integrated vision for Predictive Healthcare Analytics.

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