The Impact of New Technologies on the Science of Clinical Care and Drug Development

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Advances in molecular medicine, genomics, imaging, pharmacometrics, and clinical research have generated a wealth of new methodologies expected to improve the safety and efficacy of pharmaceutical therapeutics by explaining variability in patient response to therapy. The ultimate goal is to utilize new information to optimize therapy for individual patients—that is, treating patients with the right dose of the right drug at the right time—to maximize benefit and minimize risk.[1] Terms such as *personalized, individualized,* or *stratified medicine* are used interchangeably to describe this concept. Identification, qualification, and approval of patient factors predictive of efficacy or safety are typically performed by academic researchers, drug developers, and regulators during drug development or postapproval. Using the information for individual patient care is the prerogative of the clinical care provider, who must be equipped to collect, organize, and interpret the large volume of patient-centric information.[2] Ensuring consistent and efficient utilization of data remains a challenge, requiring multidisciplinary collaboration and communication between scientists and clinicians working in academia, drug development, regulatory organizations, and clinical care settings. We provide a multidisciplinary perspective on the current state of new technologies and opportunities for greater utilization of targeted, individualized drug therapy from the Pharmacoimaging, Pharmacogenomics, and Pharmacometrics focus groups affiliated with the CPTR (Clinical Pharmacology and Translational Research) section of the American Association of Pharmaceutical Scientists (AAPS).

ADVANCES IN IMAGING TECHNOLOGIES: PHARMACOLOGY IS NOW "VISIBLE"

For over 40 years, imaging has significantly added to noninvasive clinical assessment of disease and determining therapeutic success. The impact of imaging cannot be understated in such successes as cancer identification, measures of tumor efficacy (tumor kill) or cardiac performance (glucose utilization), identity of brain and endocrine disorders, improved surgical targeting, and many other advances. The nonclinical imaging laboratory is now a practical add-on for drug/biologics development, extending capabilities beyond the limitations of analytical chemistry and clinical laboratory services. Many scientists ask, "How can I employ imaging in my work?"

In the 1990s, applications of polymerase chain reaction (PCR) in gene mapping, cloning, and protein expression helped define pathologies in terms of molecular processes, which has led to many innovations in tracking disease. Heat map arrays are images of gene expression which can inform an investigator using regional pattern recognition as a quantitative tool. *Modern medicine* has thus morphed into *molecular medicine* because of advances in molecular biology, tracer-labeled chemistries, computational physics, and material sciences. Imaging used to mean the view through the microscope in the 1800s; it then became the view on photosensitive film. Now an image is not simply a two-dimensional picture but rather information about time, space, and depth of signal intensity, the sum of which provides quantitative information within the image.

Real-time visualization of pathology using molecular imaging probes has given us a theater to watch drug or biologic pharmacodynamics. Imaging can noninvasively track the kinetics of a probe's localization, metabolism, and elimination, thus defining a disease process quantitatively. Table 1 describes how biomarkers are being used in clinical imaging and how they can be *predictive, prognostic, diagnostic,* or *dosimetric*. Diagnostic positron emission tomography (PET) tracers as biomarkers include C-11 ß-CFT (a dopamine agonist for presynaptic reuptake assessment) and C-11 Raclopride (for D2 postsynaptic receptor function). Both are clinically used to assess presumptive dopamine-rich regions and diagnose the onset of Parkinson disease. These agents are also useful in diagnosing early onset Parkinson disease initiated by the use of improperly synthesized amphetamine as a street drug, which may contain a toxic byproduct, MPTP. The clinical utility of other PET tracers for confirmation of Alzheimer disease has led to two clinical agents: C-11 PIB and F-18 Florbetapir. Both of these probes provide quantitative images showing the extent of amyloid deposition in the brain, which correlates to dementia. While these agents can confirm extensive involvement of amyloid, current efforts to detect early onset of amyloid deposition and allow for therapeutic intervention to halt the neuropathy are yet to be realized.

Imaging technologies such as magnetic resonance and optical imaging (i.e., MRI/MRS and functional MR, bioluminescence, fluorescence, self-illuminating quantum dots) and other nonvisible light and nonionizing radiation platforms have made imaging a practical and safe clinical tool. Surgeries are safer and more effective with technologies such as monoclonal

antibodies with luminous tracers, which can reveal tumor borders, metabolic borders, tumor-specific expressions, and even nerve fibers and vessels transiting through tumors. Using these tools in real time can save normal tissues, such as revealing a hidden nerve and protecting it from inadvertent excision.

The advanced imaging addition of quantitation is key to imaging's clinical success. Using imaging in drug/biologics development and in the clinical world as potential companion diagnostics is why imaging is no longer simply a "picture." We now have an image with three-dimensional

information that is clinically important in a patient's personalized medical needs. We are shifting from the formalism of the pharmacology and toxicology pathways of the last century to a profoundly revolutionary formalism of personalized medicine. The wide array of imaging platforms and probes now available, along with imaging platform improvements in resolution and computational speed for large data compilations, has opened an enormous new potential for targeting therapy to the individual patient and confirms that pharmacology is indeed becoming "visible."

GENOMIC MARKERS WITH POTENTIAL FOR INDIVIDUALIZING THERAPY

Mechanisms underpinning a disease and a drug's mechanism of action have to be addressed in the context of inter-individual variability to identify biomarkers predictive of efficacious or adverse responses in patient subgroups. Antiviral drugs demonstrate the important role of genomic biomarkers in personalized medicine since viral genotypes as well as genetic variations in humans influence the response to therapeutics. For example, different response rates are observed in patients with chronic hepatitis C (HCV) upon treatment with peginterferon alfa and ribavirin, depending on the HCV genotype and on the genotype in the single nucleotide polymorphism in the region upstream of the IL-28B gene (a host gene). Knowledge accrued with genomic biomarkers has also helped in the development of targeted therapeutics such as trastuzumab in oncology. This drug has a higher likelihood of success in a subpopulation of breast cancer patients who overexpress the HER2 protein, because the drug is designed to bind to the HER2 receptor and impacts downstream signaling pathways. Cancers are being defined by their molecular drivers, and targeted therapies are being developed based on genomic biomarkers.

Safe use of a therapeutic is an important consideration in regulatory approval and clinical decision making. Drug safety is evaluated in preclinical studies and clinical trials. However, a drug may be inefficacious or toxic in a minority of individuals. This may be due to variation in genes encoding drug metabolizing enzymes/transporters or proteins involved in the drug's mechanism of action; either may result in underexposure to the drug, and thus lower or no efficacy, or increased exposure to the drug, and thus toxicity or adverse events. It is important to understand the genetic diversity and the resulting phenotypes of these enzymes before prescribing a drug known to be influenced significantly by such variation. A classic example is warfarin, where genetic variations in the metabolizing enzyme CYP2C9 and in VKORC1 involved in warfarin's mechanism of action are important considerations in identifying the right dose for the patient.

Table 1. Biomarker Classes for Imaging Biomarkers: Examples of Clinical Use
Many imaging systems are now available, and these examples are not intended to be exhaustive but rather to describe a marker class. Table is adapted from Moyer and Barrett.[3]

MARKER CLASS	DEFINITION	EXAMPLE
Predictive	A biomarker available before a drug or action is applied to a target.	MRI: In Multiple Sclerosis the brain exhibits physical changes in the white matter structures related to water relaxivity (the magnetization of water hydrogen can be detected as emission of radiowaves).
Prognostic	A biomarker available after a drug or action is applied and which predicts a subsequent increase in risk of injury or change in pathologic state.	PET/SPECT: C-11 ß-CFT uptake in dopamine-rich regions of the substantia nigra is significantly reduced following exposure to the neurotoxin MPTP, a byproduct of improper chemical synthesis of methamphetamine.
Diagnostic	A biomarker available at the time of symptoms (pathology) or following a drug or action on a target.	PET: C-11 PIB and F-18 Amyvid serve to measure amyloid deposition in the brain of suspected Alzheimer disease patients. PET and SPECT: Imaging of suspected lung cancer with standard uptake value (SUV) of >5 using F-18 FDG, or ischemic myocardium viewed as cine gated images where regional uptake and wall motion are measured. Optical: Bioluminescence/Ultrasound/MRI/PET/SPECT/Thermal: Blood flow changes; metabolic changes; shape changes; etc. fMRI : rCBF (regional cerebral blood flow) in regions of the brain during thought or physical movement—using BOLD (blood oxygen level dependent) techniques to localize flow change from a stroke.
Dosimetric	A biomarker available after a drug or biologic imposes an action applied on a target and which a response can be related to the dose (or proportionality of an action) relative to a negative control.	Imaging: Microscopy: Chromosomal aberrations (dicentrics) using microscopic imaging (radiation dosimetry). MRI: Apparent diffusion (weighted) coefficient MRI in tumor responses (necrosis) to chemo- and radiotherapy. SPECT: Application of In-111 for cell trafficking white blood cells recognizing changes in tissues, i.e., cytokines to elicit natural killer cell proliferative dose response following chemo- or radiotherapy.

Genomic markers can help predict susceptibility to rare life-threatening conditions. For example, an individual who tests positive for HLA-B*1502 and is treated with carbamazepine is likely to develop Stevens-Johnson syndrome, a potentially fatal adverse event. Thus, the U.S. Food and Drug Administration (FDA) has added a warning to the label that "patients testing positive for the allele should not be treated with carbamazepine unless the benefit clearly outweighs the risk." Additional examples of genomic biomarkers included in drug labels are available at the following website and highlight the potential for improved patient therapy with use of biomarkers to predict safety and efficacy: www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm

The advent of novel and emerging technologies such as next-generation sequencing is making the transition from research tool to clinical tool possible and holds great potential to identify the basis of Mendelian diseases, a previously unattainable goal using traditional methodologies. Future potential includes truly personalized medicine in rare diseases, utilizing family history and genetic information from family-based studies through identification of causal genetic alterations. Increased availability of electronic health records with individuals' genetic information will enable easier access to, and utilization of, patient information in clinical decision making.

DASHBOARDS: APPLICATION OF PK/PD MODELING WITH PATIENT-SPECIFIC DATA

The goal of personalized medicine aligns well with population pharmacokinetic and pharmacodynamic (PK/PD) modeling objectives, which include identifying factors predictive of heterogeneity in drug exposure and/or response, and is a key component of the paradigm of model-based drug development (MBDD). Using biomarkers for patient care decisions has been limited by the lack of decision support tools for practitioners to integrate such data with other patient-specific information to generate a treatment recommendation.[2] PK/PD modeling enables integration of multiple patient characteristics in a drug-specific decision-support framework and has recently been combined with Web-based applications that provide a user-friendly interface, or dashboard, for including patient-specific inputs, updating PK/PD models, and visualizing the data and model predictions.[4] Dashboard systems offer an improved, convenient means of tailoring treatment for individual patients, particularly for drugs with high variability in exposure or a narrow therapeutic window. Applications similar to dashboards, where clinical trial data are seamlessly integrated with PK/PD models, may be advantageous as platforms for facilitating decisions within a MBDD framework and overcoming some of the hurdles in implementing MBDD.

DASHBOARDS IN CLINICAL CARE

The recent escalation in health care costs is partly explained by longer life expectancy and inefficiencies in health care, particularly for patients with chronic conditions. Effective clinical decision support tools will help address this challenge.[5] The medical care system is not always equipped to collect and manage the volume and complexity of new patient-centric information, resulting in a disconnect between advancing science and its practical application. Thus, the next major improvement in medical care will be the way data are accumulated, processed, and applied.[6] For example, IBM's Watson of *Jeopardy* fame is being evaluated as a diagnostic tool at the Memorial Sloan Kettering Cancer Center. The application of systems like Watson should improve efficiency in the clinic and help avoid the tendency to rely too heavily on a single piece of information, anchoring bias—an important component of misdiagnoses.

Individual dose adjustments to achieve safe and efficacious exposure are also needed for drugs with a narrow therapeutic index that are codeveloped with a therapeutic-drug-monitoring assay, an idea used since the early 1990s.[7] Using Bayesian forecasting to achieve concentrations within a specified therapeutic window has been shown to substantially increase the number of patients whose trough phenytoin levels were within the target range (63.6 percent of the phenytoin troughs from the Bayesian forecasting group, compared with 34.0 percent in the conventional dose adjustment group).[8] The ability to accurately adjust a patient's dose to achieve a specified endpoint could substantially shorten the time needed to identify appropriate doses for more thorough clinical evaluation.

Although complex dose recommendations may be necessary for safe and effective treatment, they require a lot of time. However, software-guided dosing has already been shown to effectively control doses for individual patients and to increase efficiency in clinics.[9] Individualized adaptive dosing using PK models has been undertaken[10] but was a labor-intensive process prior to using dashboard systems. Several dashboard systems already exist[4,11] to improve dosing in pediatric patients. Clinical use of such systems is still limited because of a lack of familiarity with the approach, ineffective communication to practicing clinical staff on the use and benefits of such systems to facilitate decision making,[12] and the resources required to use modeling to fully individualize treatment.

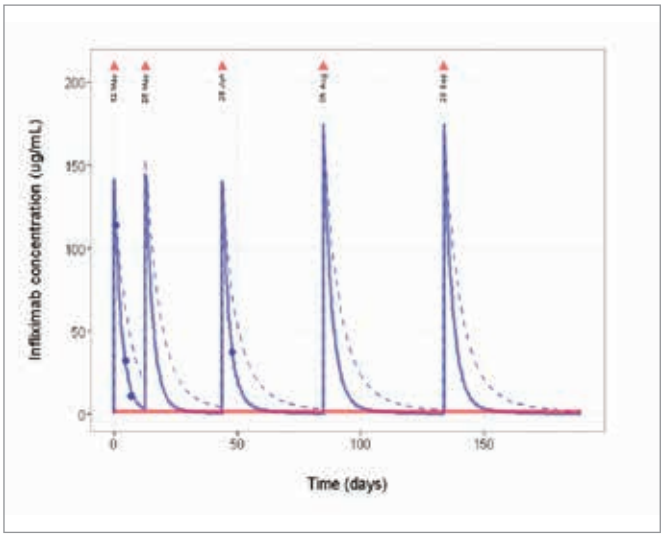
Recent publications have underscored substantial variability in patient exposure and response when biological therapeutic agents are administered at the labeled dose,[13,14] supporting the need to individualize the dose to account for this variability and ensure safe and effective treatment.[15,16] Suboptimal exposure is related to the development of anti-drug antibodies (ADA) and loss of response (LOR). Adjusting the doses of these biological agents to maintain effective concentrations is not intuitive and can take time. The benefits of using a dashboard system can be shown in an external in silico evaluation of an infliximab dashboard system using data from two clinical trials in 79 patients

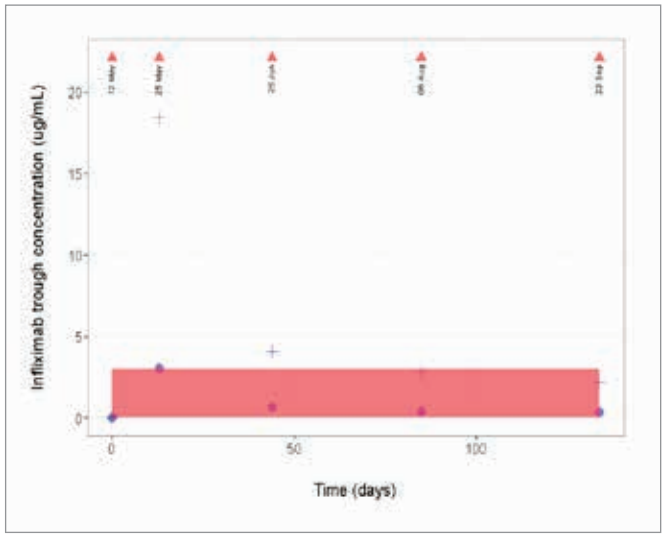
with moderate to severe ulcerative colitis. Reductions in time to optimal dose were seen with all patients when the dashboard was used, with the reduction in time to find appropriate doses being dependent on disease severity. Patients with more severe disease generally took longer (4 to 20 weeks) for optimization without the dashboard. Importantly, the dashboard identified LOR owing to suboptimal dosing before the clinician saw it and adjusted the dose. The results for a severely ill patient are summarized in Figure 1. The goal was to identify doses that would maintain trough blood levels of infliximab

Figure 1: A comparison of conventional adaptive dosing and dashboard-guided dosing

CONVENTIONAL DOSING

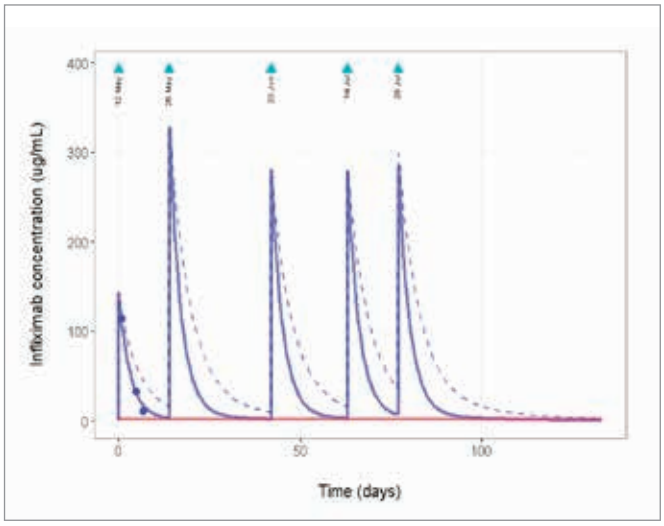
The patient is an ulcerative colitis patient with severe disease, managed with infliximab, which is available as 100 mg increments, and dose is typically rounded up to use the entire vial. After the induction doses (which were started at 6.8 mg/kg [500 mg] owing to the severity of disease), the dose was increased to 8.3 mg/kg (600 mg) every 4 weeks, rather than the labeled 8-week interval. The C-Reactive Protein reduced to 30 mg/L and the patient's condition improved to moderate disease activity. A final dose adjustment was made to increase the dose to 11 mg/kg (800 mg). The patient now became ADA positive, further complicating treatment. Plots show the predicted time-course of infliximab concentrations (solid line, left) and the concurrent infliximab trough concentrations (filled circles, right).

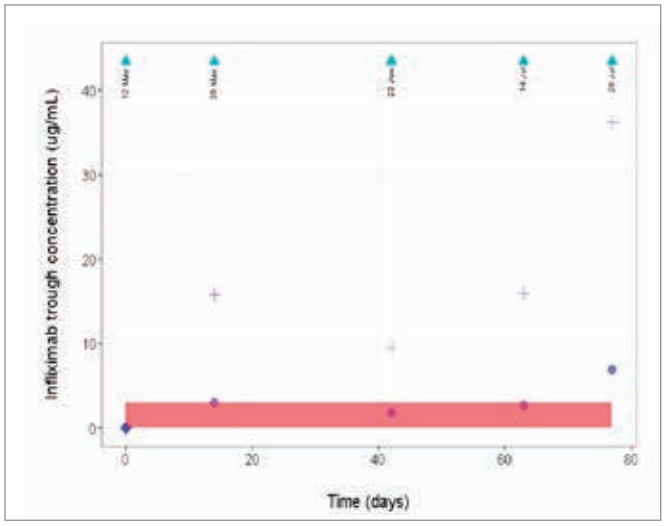




DASHBOARD-GUIDED DOSING

The first dose was given as per the conventional dosing scenario, and observed concentration data from that patient's first dose were fit. The remaining information is projected from the dashboard, which used collective information from other patients to make better prediction and suggested a dose of 10 mg/kg (700 mg), administered every 4 weeks, as being appropriate. All troughs but the second are at target, so time to appropriate dose regimen was found in 2 weeks as compared to 20 weeks for conventional dose selection. Plots show the predicted time-course of infliximab concentrations (solid line, left) and the concurrent infliximab trough concentrations (filled circles, right).





(filled blue circles) above the assay limit of quantitation (the broad red line). *Conventional Dosing* represents the actual course of management and disease with changing disease status and covariates. In this test, dashboard-guided dosing used data from the first dose, and subsequent dosing was based on what the software predicted for the same patient given available information. For all subjects, the initial doses selected by the dashboard were very similar to the final doses ultimately selected by the clinician, but the time to stable disease control was reduced.

In addition to advancing patient care, improved individualized dosing using dashboard systems provides potential advantages to drug manufacturers as well as to payers such as health insurance companies. When fewer patients develop ADA and subsequent LOR, the resulting reduced rates of discontinuation or switch to other therapies may increase utilization of the manufacturer's drug. Improved accuracy of dose adjustments may substantially reduce reimbursement costs of these expensive therapies by precluding use at doses higher than those needed for maintaining target concentrations. Consistent with this potential advantage of dashboards, a recent evaluation found individualized infliximab dosing reduced treatment costs compared to conventional dosing.[17]

DASHBOARDS IN DRUG DEVELOPMENT

The continuing need for more efficient and effective approaches to drug development is highlighted by recent estimates of the enormous development costs for each new drug approved ($4 billion to $11 billion).[18] Applications similar to dashboard systems, where PK/PD models and clinical trial data are integrated for seamless model updates and visualization for better and faster decision-making, could be valuable tools for successful implementation of MBDD. Drug development dashboard systems may be utilized in a manner similar to that in clinical practice when individualization of dose is required during a clinical trial. Such trial designs may include adaptive designs where models are used to forecast the likely outcome of dosing a specific patient with a given dose, and the dose is adjusted according to prespecified criteria, such as a target concentration or effect.

Several considerations must be made to implement adaptive designs. In its draft guidance,[19] FDA classifies adaptive designs into well-understood designs (e.g., typical group sequential designs) and less-understood designs (e.g., adaptive dose finding and two-stage phase 1/2 [or 2/3] seamless adaptive designs). Although adaptive designs offer flexibility, more flexibility may result in classifying the study as a less-understood design. With such studies, statistical inference is often difficult to obtain, leading to the use of adaptive designs in early "learning" (e.g., phase 1 and 2) clinical trials. For example, consider a phase 1 dose escalation study to evaluate a new antineoplastic agent where the primary objective is to determine the maximum tolerated dose. Generally, there are two choices for dose escalation: an algorithm-based traditional dose escalation rule design or a model-based continual reassessment method (CRM) design. CRM designs typically utilize traditional statistical models of dose and toxicity to step through a predetermined dose range and can be linked via dashboard systems to select doses based on PK/PD models, emulating existing dashboard systems in clinical use.[4] In the CRM trial design, the next enrolled patient will be assigned to the dose that is close to the estimated maximum tolerated dose from the updated PK and PD models, which incorporate the individual patient's demographic, PK, and PD information. Dashboard-driven CRM designs can incorporate dose escalation/de-escalation and stopping rules, which can be updated as more information is gathered.

CONCLUSIONS

The shift from empirical drug development to MBDD requires early, proactive planning; dynamic access to multisource data; quantitative knowledge integration; multidisciplinary collaboration; and innovative, impactful application of pharmacometrics focused on enhancing quantitative decision making.[20] Similarly, the shift from conventional empirical dose adjustments in the clinic will require access to the models developed and used during drug development. The barriers to implementation for both applications are similar: a need for more effective communication and a change in the way we think about health care. Consideration of new technologies and biomarkers (including genomic and imaging biomarkers) is also critical for advancement of personalized medicine.

REFERENCES

References for this article can be found with the December 2013 *AAPS Newsmagazine* online extras at www.aaps.org/NewsmagDec13.

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