Chapter 2
Personalized Medicine: Integrating Individual Exposure and Response Information at the Bedside

Diane R. Mould and Lawrence J. Lesko

2.1 Introduction

Historically, therapeutic agents were dosed using the same dose for all patients ("flat dosing"), sometimes dosed on body size (weight or body surface area, BSA), or adjusted based on key patient factors (covariates), such as degree of renal impairment. For some agents such as warfarin, the risks associated with both over and underdosing are substantial, and genetic markers can be used to refine the starting dose and the dose increments in order to safely achieve the international normalized ratio (INR) target range and subsequent clinical effect. However, owing to differences in tolerance such as with antineoplastic agents, or effects, such as with antihypertensive agents, adaptive dosing where doses are adjusted based on observed response ("adaptive dosing") is also used. Individualizing drug therapy, or tailoring the selection of both the drug and the dose for a specific patient, has been a long-held objective of physicians and other health-care providers. As stated in a recent review of the history of individualized medicine (Lesko and Schmidt 2012), "personalized medicine is an evolution, not a revolution."

Personalized medicine is expected to optimize the benefit and minimize the harm of medical interventions on a patient-by-patient basis. Thus, the goal of personalized medicine is to identify patient characteristics predictive of response to therapy and to use this information to provide a therapeutically optimal dose for each patient, or patient subgroups, based on their individual characteristics (Conti et al. 2010). Examples of patient characteristics that may affect drug exposure and response, and subsequently require individualization of treatment and dose include age, body weight, race, sex, organ function (e.g., hepatic and renal function), and various types of biomarkers, such as biochemical, disease markers, and genomic

D. R. Mould (✉)
Projections Research, Phoenixville, PA, USA
e-mail: drmould@pri-home.net

L. J. Lesko
Center for Pharmacometrics and Systems Pharmacology, University of Florida, Orlando, FL, USA

S. Schmidt, H. Derendorf (eds.), *Applied Pharmacometrics,* AAPS Advances in the Pharmaceutical Sciences Series 14, DOI 10.1007/978-1-4939-1304-6_2

markers. The goal of personalized medicine aligns well with that of population pharmacokinetic and pharmacodynamic (PK/PD) modeling, which includes identification of covariate factors that are predictive of heterogeneity and uncertainty in drug exposure and/or response.

The utilization of biomarkers for patient care decisions has been limited by the lack of decision-support tools for practitioners to facilitate integration of biomarker data with other patient specific information to generate a treatment recommendation (Zineh and Huang 2011). PK/PD modeling enables integration of multiple patient characteristics in a drug-specific framework, and recently has been combined with web-based applications that provide a user-friendly interface, or "dashboard" for including patient-specific inputs, updating the associated models, and summarizing and visualizing the data and model-based dose predictions (Barrett et al. 2008). Such dashboard systems have the potential to offer an improved and convenient means for health-care provider to tailor treatment for an individual patient, particularly for drugs with high variability in exposure or a narrow therapeutic window.

2.1.1 Current Dosing Paradigms

There are numerous approaches to developing dose regimens for therapeutic agents, but the most common are the "flat" dose (e.g., all patients receive the same dose), with dosing based on body size also being a common dose metric. In addition, dosing is often stratified based on covariates, such as genotype or organ function. Adaptive dosing, where doses are increased or decreased based on observed effect is also used.

One of the issues with the flat dose option is that the exposure and/or response to a given dose is often highly variable. This variability can arise from differences in the PK, such as in genetic subpopulations, that rapidly clear a drug, or can be due to differences in the PD related to a given plasma drug concentration. If there are factors, such as an effect of weight on clearance, then small patients will tend to be overdosed and patients with high weight will be underdosed using this dose adjustment strategy. Figure 2.1 depicts two hypothetical patients' response to the same dose of a drug. Depending on the therapeutically desired response, these patients may need to receive higher (in the case of the patient with a weaker response) or lower (in the case of the patient with a greater response) doses.

Dosing based on body size is a common approach. However dosing on a mg/kg basis often results in subtherapeutic exposures in low weight patients, particularly pediatric patients (Anderson and Holford 2013; Xu et al. 2013) because the relationship between drug clearance and weight (if it exists) is rarely linear due to the differences in the ratio of clearance organ size to overall body weight. This finding has been confirmed for many compounds, including infliximab (Xu et al. 2012; Fasanmade et al. 2011). The US Food and Drug Administration (FDA) has written a guidance document for industry on dose selection for the minimum recommended dose for first time in humans (FTIH) studies (Guidance 2014) that suggests selection of initial doses based on body weight (e.g., mg/kg) in order to scale exposure observed in nonclinical studies to safe levels in humans. While this document is

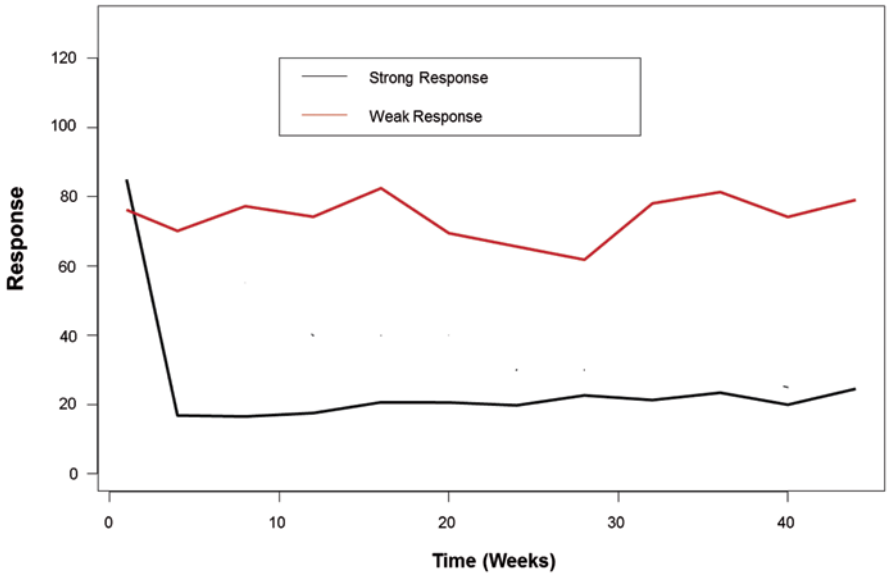

Fig. 2.1 Examples in differences between patients in response to a specific dose. In this figure, two hypothetical patients were administered the same dose of drug with the goal of lowering the measured response indicator. The patient response represented by the *black line* is a patient with a strong response while the patient whose response is represented by the *red line* has a weak response. Thus the latter patient may need a higher dose or a different treatment for their disease

not specifically aimed at providing guidance for dose selection, many marketed monoclonal antibodies (mAbs) are labeled for dosing on a mg/kg basis. A recent review (Mould and Green 2010) found that only three of 26 marketed mAbs had a clearance that was linearly related to weight, eight were dosed on a mg/kg basis and two of these had no weight effect identified on the clearance. Doses based on BSA are similarly problematic. Egorin published a review on BSA-based dosing for antineoplastic agents (Egorin 2003). The variability in exposure with this dosing approach is not always improved as compared to "flat" dosing.

A stratified dose approach where flat doses are administered over specified ranges of body weight, or over and under a given mg/kg weight, is often the best way to ensure appropriate dosing when body size impacts clearance, and may be particularly relevant for pediatric patients (Xu et al. 2013). This approach has the benefit of reducing the overdosing and underdosing seen with flat dosing and dosing based on body size, either weight or BSA.

Some compounds such as epoetin (a biologic agent used to treat anemia) are dosed based on specific hemoglobin measurement. The dose algorithm is complex however, and although the approach works well to control hemoglobin, the complexity of the dose strategy can give rise to dose errors, and dose adjustments takes time to determine. Computer-based dose support has been shown to improve the percentage of patients staying within the target range of hemoglobin, often with a lower dose than the manual adjustment provided (Ho et al. 2010), and with substantially increased staff efficiency without having a negative impact on safety

(Miskulin et al. 2009). Thus, computer-guided dosing may have a substantial impact on optimizing patient management of their therapies.

2.1.2 Definition of a Dashboard

A dashboard is a user interface that, like a dashboard in a car, organizes and presents information so that is easy and quick to read and interpret. Software packages that integrate information from multiple components into a unified display are referred to as dashboards. For example, patient management dashboards might obtain information from electronic medical records, laboratories, and through clinician and patient input and present it as though it all came from the same source. Hewlett Packard (HP) developed the first dashboard system, which began as a tool for customizing Windows desktops. Called "Dashboard," the HP product was later acquired by Borland and then a company called Starfish (Dashboard 2014).

"Dose calculators" have been in existence since the late 1950s, although the majority of these early systems were to calculate radiological doses (Sivyer 1959). Until recently, the computational needs of individualized dosing were limited, although the application of Bayesian forecasting has been shown to result in therapeutic improvements. For example, application of Bayesian-based dosing substantially increased the number of patients whose trough phenytoin levels were within the target range (63.6% of the phenytoin troughs from the Bayesian forecasting group, compared with 34.0% in the conventional dose adjustment group) (Tobler and Mühlebach 2013). One of the earlier dashboard systems in clinical use focused on antineoplastic dosing for pediatrics (Barrett et al. 2008), and the number of dashboard systems has grown over time.

A related topic that will not be covered in detail here is the emergence of computerized clinical decision support systems (CDSS). Papier (2012) defined these as "an interactive system allowing input of patient-specific information and providing customized medical knowledge-based results via automated reasoning, for example, via a set of rules and/or an underlying logic, and associations." These systems generally are not based on an underlying population model but embody collected clinical expertise which is compared to a patient's symptoms using methods such as rule-based or fuzzy logic algorithms (Domínguez Hernández et al. 2013). Like dashboard systems, they are a growing area of research seeking to maximize the use of prior knowledge for an individual patient.

2.1.3 Relationship to Population Models

Dashboard systems are generally built around a population model (Mould and Upton 2012). The population model is essentially an embodiment of the current state of knowledge about the PK or PD of a drug and generally includes three key components:

1. The structural (base) model (e.g., a one-compartment PK model) that provides a (ideally) mechanistic description of the time course of a measured response.

2. Stochastic (probability) models that describe the distribution of unexplained variability in the observed population, such as between-subject variability (BSV) or residual variability (RUV).
3. Covariate models that quantitate the influence of explainable factors such as demographics or disease on individual time course of the response.

The dashboard system is intended to be a user-friendly system for accessing the model to forecast exposure or response for an individual patient, with the predictions of the model refined by incorporating information about each individual patient into the model. The greater the size and diversity of the database used to construct the underlying model, the greater the chance that the model will be able to return useful and accurate individual predictions for most patients. However, it should be recognized that there are limitations to forecasting using population models. The underlying assumption is always that a particular population model will continue to describe data from a patient into the future, and that the model captures all important sources of variability (both explainable and unexplainable). When the underlying assumptions do not apply to a given patient, the model predictions have the potential to be in substantial error. For example, a given model of drug PK may have been appropriate for a patient in the past, but if the patient has a cardiac infarct (with major reductions in cardiac output with a subsequent impact on drug clearance), the forecast concentrations from the model may be substantially underestimated.

2.2 Individualized Forecasts

There are two main mechanisms by which individual data can be used to refine the predictions of a population for a particular patient. These are via covariate relationships identified during the model building process, and by Bayes updating on model parameters based on individual data. Figure 2.2 shows an example of how both methods can work together to improve the forecast for an individual patient.

2.2.1 Covariate Effects

Covariates (e.g., age, sex, renal function) modify the value of a model parameter (e.g., clearance, CL) depending on the value of the covariate (e.g., body weight on CL in Fig. 2.2). The inclusion of a covariate relationship in a model will generally imply that the model provides a better description of the data and that the unexplained BSV of the associated parameter is reduced. Thus, covariate factors effectively convert unexplainable variability to explainable variability at the population level, and reduce the uncertainty in the values of the model parameters for individual patients for whom covariate values are known (Fig. 2.2). However, depending on the drug and the dataset used to develop the model, the contribution of covariates to reductions in unexplainable variability can vary from nothing (i.e., no covariates identified) to modest or substantial contributions. When no covariates are found, this implies that

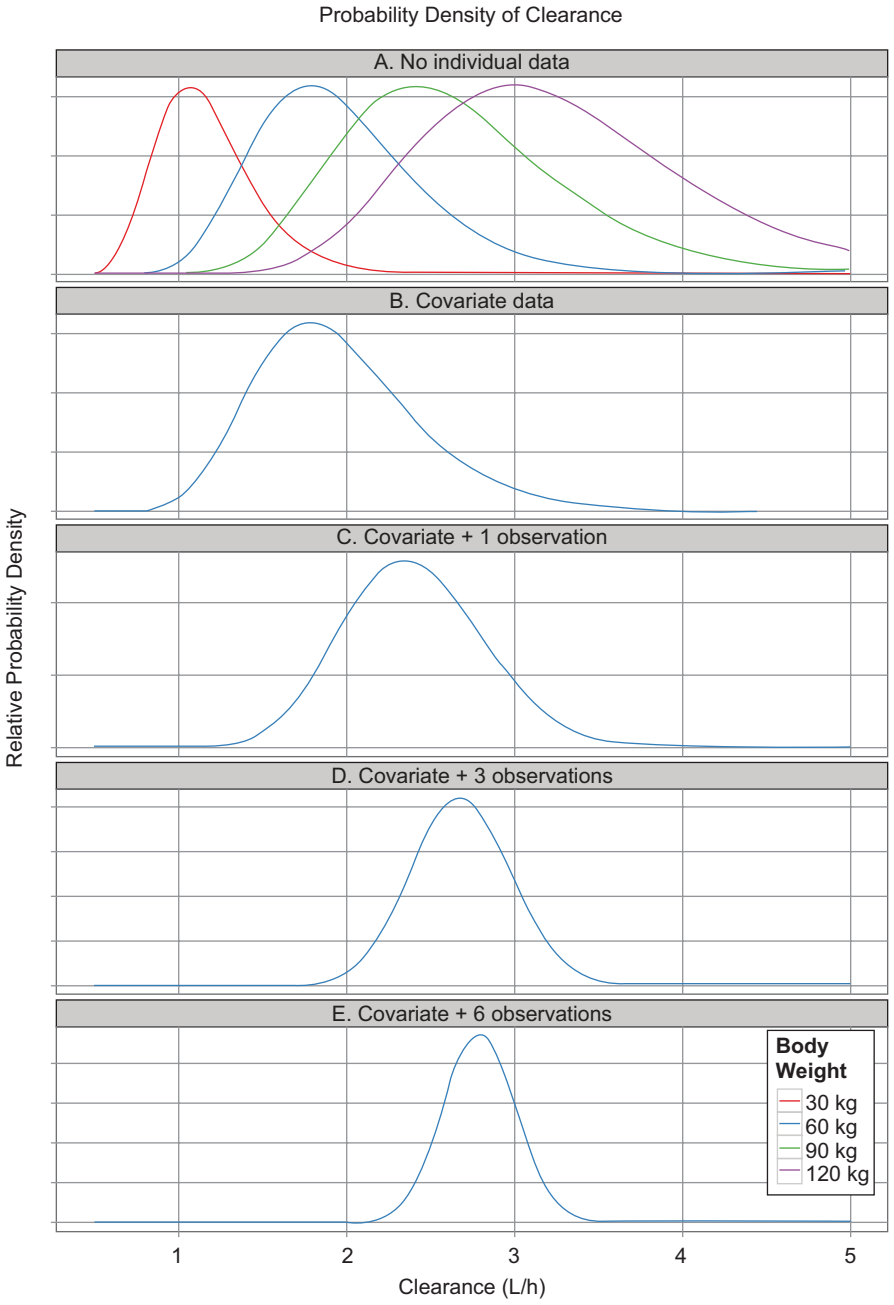

Fig. 2.2 An example of the contribution of individual data to Bayes forecasts. Below is an example model to determine steady-state drug concentration (C_{ss}) of a chronically administered drug: C_{ss} = DoseRate/(CL*(WT/70)$^{0.75}$). CL is a log-normally distributed population parameter with a population value of 2 L/h and BSV of 25%. Patient body weight (WT) is a covariate affecting

the factors causing variability between patients have either not been identified, were not possible to measure in sufficient numbers of individuals, or were not available at all in the analysis dataset. It is important to note that the ability to identify predictive covariates is dependent on both the method used to evaluate the data (Wählby U, Jonsson EN, Karlsson MO. Assessment of actual significance levels for covariate effects in NONMEM. J Pharmacokinet Pharmacodyn. 2001; 28(3):231-52) and the approaches used during modeling (Mould and Upton 2013). However, even when covariates are identified, many agents still have considerable unexplained variability, which limits the use of patient covariates in individualizing dosing.

2.2.2 Bayes Update of Models with Individual Data

Most of the currently available software packages for individualizing therapy utilize Bayesian methods to help predict future response to a given dose regimen. In general, such software packages use a mixture of Bayesian updating, Bayesian forecasting, and Bayesian model averaging. Bayesian inference is a method in which Bayes' rule is used to update the probability estimate for a hypothesis as additional data are obtained. Bayesian updating is particularly important in the dynamic analysis of data collected sequentially over time.

Bayesian updating uses a model that not only describes the time course of exposure and response but also includes terms describing the unexplained (random) variability of exposure and response. It involves applying a "prior" (which is called a prior because it reflects the underlying information derived from previous evaluations) to form the underlying hypothesis. The prior distribution is the distribution of the parameter(s) before any new data are observed and is usually developed in a separate analysis. The prior therefore is the series of mathematical models describing exposure and response following administration of a drug. The sampling distribution is the distribution of the observed data conditional on its parameters. This is also termed the likelihood, especially when viewed as a function of the parameter(s). The marginal likelihood (also called a "posterior") is the distribution

---

CL via an allometric relationship, where the standard body weight is 70 kg. DoseRate is the average steady-state dose rate—set at 10 mg/h, proportional residual error for the model was 20%. We wish to forecast the clearance of the drug (so that individual C_{ss} can be estimated). *Panel A* shows the probability densities for CL for the case where no individual patient information is known (densities are normalized to the same peak value for clarity). There are a variety of possible distributions for CL, depending on the unknown body weight of the patient. *Panel B* shows the distribution of CL with covariate data. The patient has a weight of 60 kg, eliminating other candidate distribution curves. *Panel C* shows the distribution of CL with covariate data and a single observation of C_{ss} in the patient. In this case, C_{ss} was found to be 4 mg/L, which was lower than the expected value of 5.6 mg/L for a 60-kg subject. The distribution therefore moves to the right, reflecting higher individual clearance and becomes narrower, reflecting more certainty about the individual patent value of CL. *Panels D* and E show the distribution of CL with covariate data, and 3 and 6 observations of C_{ss} in the patient, respectively. Note that as more individual data are available, the uncertainty in the distribution of CL reduces (i.e., the distributions are narrower) via Bayesian learning. Adapted from Mould DR, Upton R, Wojciechowski J. Dashboard Systems: Implementing Pharmacometrics from Bench to Bedside. AAPS J ePub June 2014 with permission

Table 2.1 The balance between the prior and the data

Factors that favor the prior	Factors that favor the data
Few data points	Many data points
High residual error	Low residual error
Low population variability	High population variability

of the observed data marginalized over the parameter(s). Thus, Bayes' rule can be applied iteratively. That is, after observing data, the resulting posterior probability can then be treated as a prior probability, and a new posterior probability computed from the next set of new evidence. This procedure is termed Bayesian updating or sometimes "Bayesian learning" (Gill 2008).

However, rather than estimate the parameters for the model based solely on the patients data, Bayes' theorem is implemented to balance the contribution of new data and prior knowledge in the estimation of the model parameters for the individual (see Table. 2.1). Thus, a single data point in an individual is given less weight in the fitting process if it deviates substantially from what has happened before, but is given more weight as additional data points support the finding. Similarly, a parameter value is given less weight in the fitting process if it deviates substantially from the prior values inherent in the population model (see Fig. 2.2). From a Bayes perspective, the interpretation of a data point is seen to have contributions respectively from the truth (the underlying process, described by a model), the errors (intraindividual, interindividual, interstudy, residual, etc.), and the prior knowledge:

$$\text{data} = \text{truth} + \text{error} + \text{prior knowledge}.$$

The updating process involves sampling parameters from the prior distribution and calculating the expected response based on the model, then comparing the difference between the model expectation and the observed data. This difference is referred to as the objective function. The parameters are then adjusted based on the objective function and the new parameters are tested. This process runs iteratively until the objective function is as low as possible (referred to as "minimizing the objective function") suggesting that the parameters are the best to describe the current data. The result of Bayesian updating is a set of parameters conditional to the observed data balanced by the application of the principles of Bayes' theorem.

Bayesian model averaging (Hoeting et al. 1999) offers a systematic method for checking the robustness of one's results to alternative models. The standard practice of selecting a single model from some class of models, and then making inferences based on this model ignores model uncertainty, can impair predictive performance and overestimate the strength of evidence for predicting dose–exposure relationships. Bayesian model averaging allows model uncertainty to be incorporated into inference. The basic idea behind Bayesian model averaging is to make inferences based on a weighted average over model space which includes several models. This approach accounts for model uncertainty in both predictions and parameter estimates. The resulting estimates incorporate model uncertainty and thus may better reflect the true uncertainty in the estimates.

Table 2.2 Overview of selected dashboard systems

Software	Bayesian updating	Bayesian forecasting	Bayesian averaging	Dose	Drugs	Website
Abbottbase (Wong et al. 2013)	Yes	Yes	No	Yes, to an AUC	Aminoglycosides	NA
Drugcalc (García et al. 1994)	Yes	No	No	Yes to an AUC	Aminoglycosides	http://www.testandcalc.com/drugcalc/index.asp
Dosecalc (Mohan et al. 2004)	No	No	No	Yes to an AUC		NA
MW/Pharm (Usman et al. 2013)	Yes	Yes	No	Yes	180 drugs	http://www.mwpharm.nl/main.htm
CHOP Pediatric Knowledgebase Dashboard (Barrett et al. 2008)	Yes	Yes	No	Yes through forecast	Pediatric oncology (methotrexate)	http://pkb.chop.edu/index.php
NZ FirstDose Dashboard (Holford et al.)	No	Yes	No	Yes	Amikacin and vancomycin	http://www.firstdose.org/
TCIworks (Wong et al. 2013)	Yes	No	No	No	Gentamycin and enoxaparin	http://www.tciworks.info/
Warfarin dosing	No	No	No	Yes based on covariates	Warfarin	http://www.warfarindosing.org/Source/Home.aspx
Baysient dose evaluation system (Mould et al. 2013)	Yes	Yes	Yes	Yes, multiple	Any	http://www.baysient.com

NA not applicable

Bayesian forecasting (Elliott et al. 2006) then involves using the updated individual parameters to forecast the likely exposure and response that a given patient will exhibit with varying dose regimens based on the individual parameter estimates obtained via Bayesian model averaging and Bayesian updating. However, when the software does not have the capacity to do Bayesian updating, then the forecasting is generally based on the patient covariates which is generally less precise.

The majority of dashboard systems available are for use with aminoglycoside antibiotics and warfarin although there is one (Knowledgebase) that deals with dosing pediatric oncology. A list of several currently available systems is provided in Table 2.2. As can be seen, these systems utilize varying aspects of Bayesian methods to determine an individualized dose.

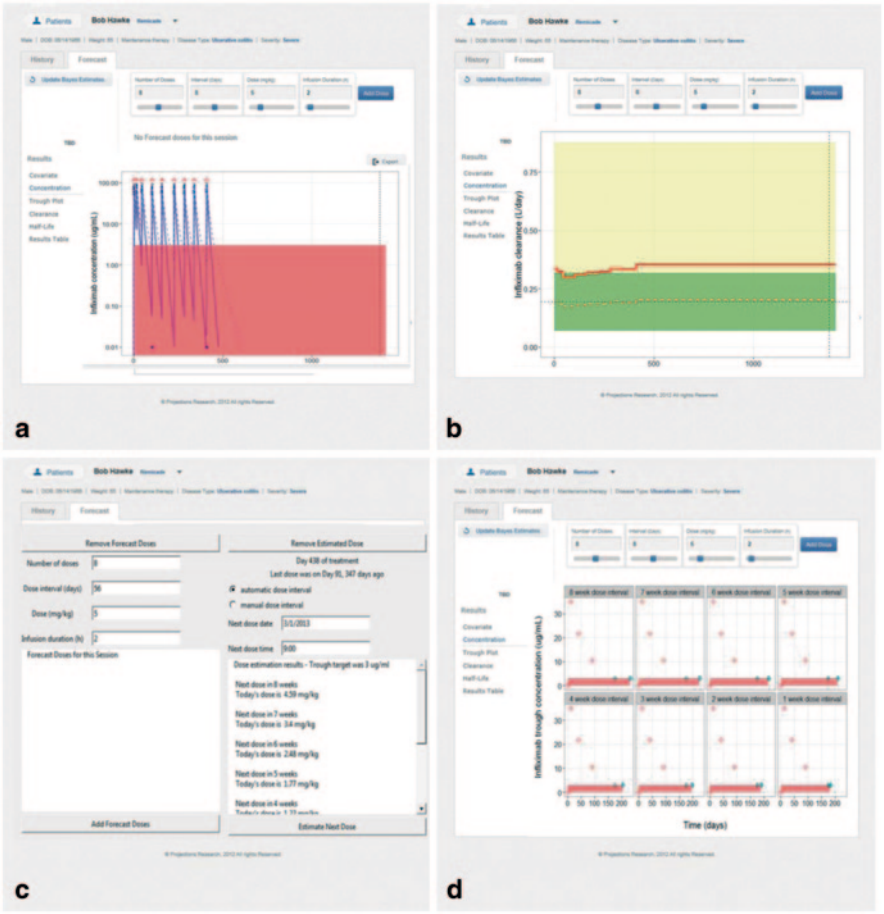

Fig. 2.3 Common dashboard screens. *Panel A* shows the agreement between the model with Bayesian updated parameters (*blue lines*) and the observed data (*blue dots*). Note that the concentrations are within the red shaded region suggesting that this patient is not at or above the target level. *Panel B* shows the patients individually estimated clearance over time. The *green region* is ±3 standard deviations of a typical patient with those covariates. The fact that this patient's clearance is in the *yellow shaded area* suggests that the doses and frequency needed to maintain this patient at the target level will probably exceed the labeled recommendations. *Panel C* shows the dose optimization screen where the clinician can determine either an appropriate regimen (e.g., dose and interval), or can enter the next patient visit to ensure the patient is adequately covered during the interval. *Panel D* shows the expected troughs from all of the recommended dose regimens to ensure they are high enough to achieve a desirable response (https://www.baysient.com)

2.3 Dashboard Systems

In general, dashboard systems have several components including: (1) patient data management, (2) updating/forecasting, and (3) dose recommendations. Figure 2.3 shows screen shots of the results from Bayesian updating and forecasting as well

as the dose recommendation screens. These screens can also be used as a basis for communicating with various health-care providers and patients as the results of delayed or missed doses can be readily shown, potentially improving compliance and an understanding of why medicine responses vary. The output from the Bayesian updating also can be a useful diagnostic for patients whose clearance is so high that maintaining an effective concentration will require very high doses and/or very short dose intervals.

2.3.1 A PK System: Infliximab

In clinical use, infliximab is administered in two "phases": an induction phase where doses are administered frequently (e.g., at weeks 0, 2, and 6) and a maintenance phase where doses are given every 8 weeks. More than one third of patients show no or little response to induction therapy (primary nonresponders) and in up to 50% of responders, tumor necrosis factor (TNF) antagonist therapy becomes ineffective over time (secondary nonresponders; Peyrin-Biroulet et al. 2008). Loss of response to infliximab, which is often due to development of neutralizing antidrug antibodies (ADAs) and subtherapuetic drug concentrations, is an ongoing challenge in managing of patients with chronic inflammatory disease.

There is a strong relationship between serum drug concentrations and response. Studies conducted in both rheumatoid arthritis (RA) and inflammatory bowel disease (IBD), have shown that patients with higher trough drug concentrations achieve superior outcomes without added safety risks (Seow et al. 2010; Maser et al. 2006; Radstake et al. 2009). These findings suggest that therapeutic drug monitoring may be used to direct dose adjustment and support clinical decision making. Infliximab concentrations ≥ 12 μg/ml at 4 weeks after infusion and/or >1.4 μg/ml at dosing trough are considered to be predictive of therapeutic response (Baert et al. 2003). Following dosing, infliximab concentrations have been shown to be highly variable between individuals and differ over time even within an individual patient. The differences in the observed concentration–time profiles can be partially explained by patient covariates and disease characteristics (Nestorov 2005).

The formation of ADAs can profoundly affect drug clearance, resulting in low or nonmeasurable drug concentrations and subsequent loss of therapeutic response. In addition, other factors can affect infliximab PK including concomitant use of immunosuppressive agents, serum albumin concentration, body weight, the degree of systemic inflammation (e.g., serum albumin concentration and TNF burden), and disease pathophysiology (e.g., type of IBD, RA or psoriasis). The effect of weight on infliximab clearance is not linear (Xu et al. 2012) although clearance increases as weight increases. Thus, dosing based on weight (e.g., mg/kg) does not always provide efficacious drug exposure. Consequently, monitoring of serum drug concentrations is particularly important in patients with both low weight and high inflammatory burden. Gender has been shown to influence infliximab, with clearance being higher in males (Ternant et al. 2008; Fasanmade et al. 2009) although the fact that clearance is higher in males may also be related to weight as males

generally have a higher body weight than females. In addition, an inverse relationship exists between serum albumin concentration and infliximab clearance (Fasanmade et al. 2009). The impact of albumin translates to lower response rates (Fasanmade et al. 2010). Patients with a baseline serum albumin concentration below the normal range (a common finding associated with severe inflammation) have lower remission rates following treatment with infliximab.

Recently, a study of patients with rheumatoid arthritis treated with infliximab has shown that a high body mass index (BMI) negatively influences clinical response to anti-TNF agents (Klaasen et al. 2011). Research into the role of mesenteric fat in chronic inflammatory diseases has intersected with investigations into the importance of adipose tissue as a metabolically active source of inflammatory cytokines (e.g., TNF; Coppack 2001) in patients with insulin resistance. Therefore, obese patients would be expected to have higher circulating TNF than patients with normal weight, suggesting that obese patients may require higher drug doses than those currently recommended.

Given the complexity and number of patient factors affecting infliximab PK, together with the large remaining unexplained variability and the high rate of loss of response (Ordás et al. 2012), dashboard systems could provide needed clarity in making dosing decisions (Mould et al. 2013). A retrospective evaluation of a dashboard system (Mould et al. 2013) demonstrated that the dashboard system designed for infliximab was able to accurately predict dose regimens that would provide therapeutically appropriate exposure and that the time of identification of the regimen was substantially shorter than via clinical ("manual") adjustment of the dose (Fig. 2.4).

2.3.2 A PD System: Warfarin

Warfarin is one of the most frequently prescribed oral anticoagulants and is used to prevent thromboembolic events. Warfarin exerts its anticoagulant effect through inhibition of vitamin K epoxide reductase, interfering with the recycling of reduced vitamin K. The time course of warfarin's anticoagulant activity depends on the clearance of vitamin K-dependent clotting factors (e.g., factors II, VII, IX, and X). The earliest changes in the INR, a measure of the sum of the activity of the coagulation factors II, VII, and X, are typically noted at 1–2 days after the administered dose. Warfarin is a racemic mixture; S-warfarin is approximately three to five times more potent than R-warfarin (Breckenridge et al. 1974). S-warfarin is metabolized by CYP2C9, a polymorphic enzyme, which results in large BSV in Pk and subsequent drug exposure (Takahashi and Echizen 2003). Genetic variants in vitamin K epoxide reductase complex 1 (VKORC1) have also been identified (Rost et al. 2004), which further contributes to variability in PD response (INR) to warfarin and thus the dosing. Perlstein et al. (2012) proposed an adaptive dose strategy with starting doses determined on genotype. Hamberg et al. (2007) developed a

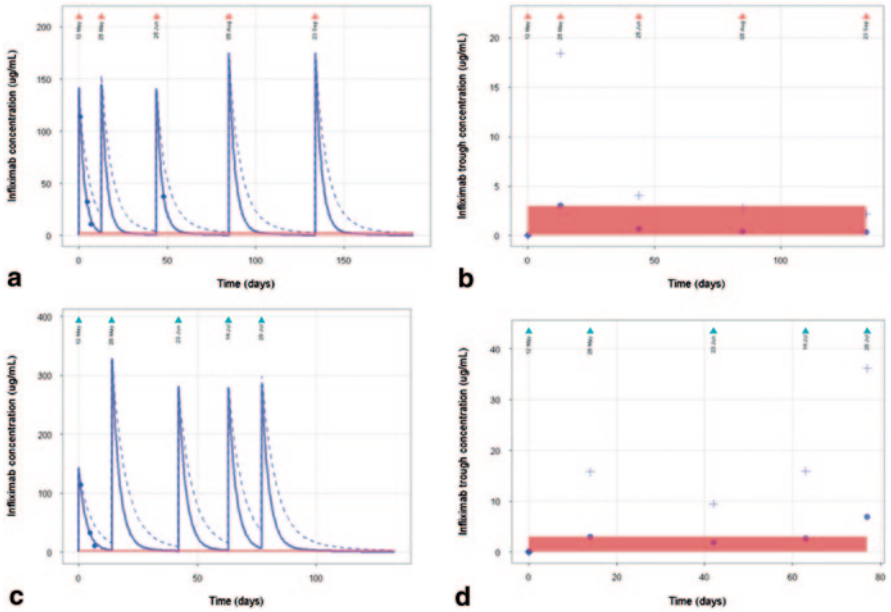

Fig. 2.4 Infliximab dashboard guided dosing. This figure compares conventional and dashboard guided dosing (Mould et al. 2013). The patient is an ulcerative colitis patient with severe disease, managed with infliximab, which is available as 100 mg increments, and dose is typically rounded up to use the entire vial. For conventional dosing: 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 became ADA positive. Plots show the predicted time course of infliximab concentrations (*panel* **a** *solid line, left*) and the concurrent infliximab trough concentrations (*panel* **b** *filled circles right*). For the 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 subjected to Bayesian updating and forecasting. The remaining information is forecast using the dashboard. A dose of 10 mg/kg (700 mg), administered every 4 weeks was found to be likely to maintain therapeutic exposure. The use of a dashboard shortened the time necessary to identify an appropriate dose regimen (2 weeks as compared to 20 weeks for conventional dose selection). Plots show the predicted time course of infliximab concentrations (*panel* **c** *solid line, left*) and the concurrent infliximab trough concentrations (*panel* **d** *filled circles right*)

PK and PD model that took into account patient age and genotype to relate doses, concentrations, and INR. This model was subsequently used to guide dosing in pediatric patients (Hamberg et al. 2013) with generally good success.

Investigating the models proposed by Hamberg et al. (2007) shows the large impact of both age and genotype on the PK and PD of warfarin (Figs. 2.5 and 2.6). Simulated results of model-guided dosing show that INR can be controlled well in a wide range of patients, regardless of age or genotype (Fig. 2.7),

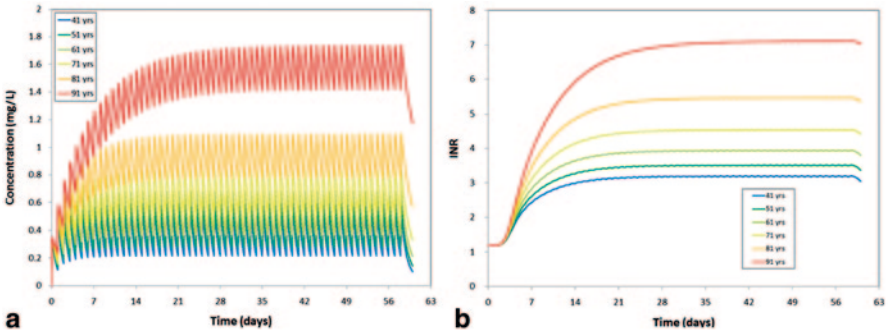

Fig. 2.5 PK and PD of warfarin: CYP2C9 1*1 VKORC1 GG 5 mg QD. *Panel A* shows the long time to steady state following administration of 5 mg daily administration. Patients with advanced age develop very high warfarin concentrations. *Panel B* shows the expected INR, and again the time to reach a stable response is several days. Owing to the very high concentrations in the elderly, the resulting INR is extremely high in this group

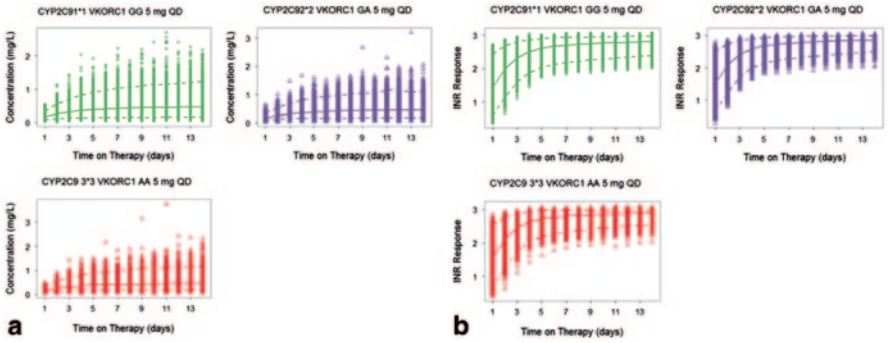

Fig. 2.6 The impact of genotype on warfarin PK and PD. *Panel A* is the range of expected concentrations following a 5 mg QD dose of warfarin in a 50-year-old individual. As can be seen here, there are distinct differences in the CYP2C9 status for concentrations but the remaining variability is high, resulting in substantial overlap between these subpopulations. *Panel B* shows the INR based on VKORC1 genotype. Partly owing to the substantial remaining variability in the INR model and the variability in exposure, the expected range of INR values is quite wide

suggesting that a dashboard approach to warfarin therapy could result in better INR control and fewer bleeding events. There is currently a web application available to improve the safety and efficacy of warfarin developed by Brian F. Gage (Table 2.2). While representing an improvement in safety and efficacy over current dose approaches for warfarin, this application makes use of only the patient factors (genotype and age), there is considerable BSV remaining even after accounting for these factors. Thus, Bayesian-based approaches could further improve safety and efficacy.

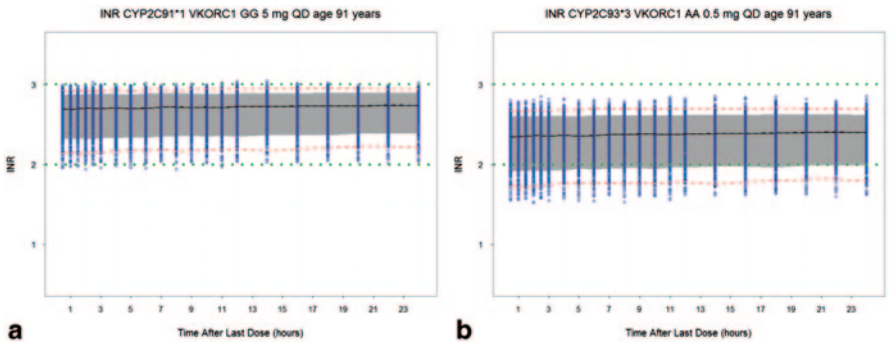

Fig. 2.7 The impact of individualized treatment on international normalized ratio (*INR*) levels. The panels below show the impact on the variability of INR in elderly patients with two different genotype combinations. *Panel A* shows the expected range of INR following individualized warfarin dosing for a 91-year-old subject with CYP2C91*1 and VKROC1 GG. *Panel B* shows the expected range of INR in a 91-year-old subject with CYP2C93*3 and VKORC1 AA. In both panels, the majority of patients are within the target range and the INR values do not exceed 3

2.4 Conclusions

Decision makers in many different fields are increasingly confronted with greater and greater amounts of information from diverse sources, which renders difficult choices when it comes to making the best decisions. Individualizing drug selection and dose choices by health-care providers is no exception. However, dashboard systems for personalized medicine, while still in their infancy, are evolving rapidly and are appealing as evidenced by the first-generation examples discussed in this chapter. Personalized medicine in the future will be characterized by the necessity to have decision support systems to aggregate and clinically interpret next-generation sequencing data, premarketing clinical trial data, and postmarketing clinical research findings in order to tailor medicines to individual patients. Dashboard-based data analytic platforms designed for individual selection of drugs and doses are clearly needed for faster and more informed decision making in therapeutics. The ability to add new patient data to the dashboard, visualize dose-PK/PD-outcome relationships, and drill down into the data to identify patient covariates and explore "what if" scenarios will be critical attributes of effective dashboard systems.

In the future, new drug development programs should consider data collection during the clinical phases that would facilitate development of dashboard software (Mould et al. 2013). This approach would facilitate the use of model-based drug development (MBDD) in the pharmaceutical industry with important benefits. The use of dashboard systems would be analogous to the gathering of information to support the codevelopment of molecular diagnostics and targeted medicines, but it would take the concept of personalized medicine one step further by equipping practitioners with not only the diagnostic–drug pair but also a qualified support

system to deliver individualized treatment for each patient at the point of care. One remaining issue is to what extent the FDA would regulate dashboards as devices, as standalones, or as an accessory for usage with a specific medicine, as a clinical decision support tool.

2.5 Summary

In summary, the following issues have been discussed:

- A description of personalized medicine.
- An outline of current dosing paradigms.
- A brief history of the use of decision support tools in health care.
- A description of the dashboard concept and overview of how they work.
- Potential benefits of using dashboards in clinical care.
- Two example systems (infliximab and warfarin) have been presented.
- Other possible uses of such systems (e.g., drug development).

Acknowledgments The authors are grateful to the many readers of draft versions for their valuable contributions to the manuscript.

Conflict of Interest/Disclosure Dr. Mould is Founder and President of Projections Research Inc., a consulting company working with the pharmaceutical industry; she is also founder of Baysient LLC, a company developing dashboard systems.

Author Contributions The authors contributed equally to the manuscript.

References

Anderson BJ, Holford NH (2013) Understanding dosing: children are small adults, neonates are immature children. Arch Dis Child 98(9):737–744

Baert F, Noman M, Vermeire S, Van Assche G, D'Haens G, Carbonez A, Rutgeerts P (2003) Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med 348(7):601–608

Barrett JS, Mondick JT, Narayan M, Vijayakumar K, Vijayakumar S (2008) Integration of modeling and simulation into hospital-based decision support systems guiding pediatric pharmacotherapy. BMC Med Inform Decis Mak 8:6

Breckenridge A, Orme M, Wesseling H, Lewis RJ, Gibbons R (1974) Pharmacokinetics and pharmacodynamics of the enantiomers of warfarin in man. Clin Pharmacol Ther 15:424–430

Conti R, Veenstra DL, Armstrong K, Lesko LJ, Grosse SD (2010) Personalized medicine and genomics: challenges and opportunities in assessing effectiveness, cost-effectiveness, and future research priorities. Med Decis Making 30(3):328–340

Coppack SW (2001) Pro-inflammatory cytokines and adipose tissue. Proc Nutr Soc 60(3):349–356

Dashboard development and data visualization tools for effective BI (2014) http://searchcio.techtarget.com/definition/dashboard. Accessed 22 Aug 2014

Domínguez Hernández KR, Aguilar Lasserre AA, Posada Gómez R, Palet Guzmán JA, González Sánchez BE (2013) Development of an expert system as a diagnostic support of cervical cancer in atypical glandular cells, based on fuzzy logics and image interpretation. Comput Math Methods Med 2013:796–387

Egorin MJ (2003) Horseshoes, hand grenades, and body-surface area-based dosing: aiming for a target. J Clin Oncol 21(2):182–183

Elliott G, Granger CWJ, Timmermann AG (2006) Handbook of economic forecasting, vol 1, Chap. 1. Elsevier, Netherlands

Fasanmade AA, Adedokun OJ, Ford J, Hernandez D, Johanns J, Hu C, Davis HM, Zhou H (2009) Population pharmacokinetic analysis of infliximab in patients with ulcerative colitis. Eur J Clin Pharmacol 65(12):1211–1228

Fasanmade AA, Adedokun OJ, Olson A, Strauss R, Davis HM (2010) Serum albumin concentration: a predictive factor of infliximab pharmacokinetics and clinical response in patients with ulcerative colitis. Int J Clin Pharmacol Ther 48(5):297–308

Fasanmade AA, Adedokun OJ, Blank M, Zhou H, Davis HM (2011) Pharmacokinetic properties of infliximab in children and adults with Crohn's disease: a retrospective analysis of data from 2 phase III clinical trials. Clin Ther 33(7):946–964

García MJ, Gavira R, Santos Buelga D, Dominguez-Gil A (1994) Predictive performance of two phenytoin pharmacokinetic dosing programs from nonsteady state data. Ther Drug Monit 16:380–387

Gill J (2008) Bayesian methods: a social and behavioral sciences approach, 2nd edn. Chapman and Hall Boca Raton, Florida, pp. 56–60

Guidance for industry estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078932.pdf. Accessed 3 Sept 2014

Hamberg AK, Dahl ML, Barban M, Scordo MG, Wadelius M, Pengo V, Padrini R, Jonsson EN (2007) A PK-PD model for predicting the impact of age, CYP2C9, and VKORC1 genotype on individualization of warfarin therapy. Clin Pharmacol Ther 81(4):529–538

Hamberg AK, Friberg LE, Hanséus K, Ekman-Joelsson BM, Sunnegårdh J, Jonzon A, Lundell B, Jonsson EN, Wadelius M (2013) Warfarin dose prediction in children using pharmacometric bridging–comparison with published pharmacogenetic dosing algorithms. Eur J Clin Pharmacol 69(6):1275–1283

Ho WR, Germain MJ, Garb J, Picard S, Mackie MK, Bartlett C, Will EJ (2010) Use of 12x/month haemoglobin monitoring with a computer algorithm reduces haemoglobin variability. Nephrol Dial Transplant 25(8):2710–2714

Hoeting JA, Madigan D, Raftery AE, Volinsky CT (1999) Bayesian model averaging: a tutorial. Stat Sci 14(4):382–417

Holford SD, Holford NHG, Anderson BJ Online dose calculation tool for determining dosing regimens in the very young. http://www.paganz.org/sites/default/files/slides/Admin/Online%20dose%20calculation%20tool%20for%20determining%20dosing%20regimens%20in%20the%20very%20young.pdf. Accessed 23 Aug 2014

Klaasen R, Wijbrandts CA, Gerlag DM, Tak PP (2011) Body mass index and clinical response to infliximab in rheumatoid arthritis. Arthritis Rheum 63(2):359–364

Lesko LJ, Schmidt S (2012) Individualization of drug therapy: history, present state, and opportunities for the future. Clin Pharmacol Ther 92(4):458–466

Maser EA, Villela R, Silverberg MS, Greenberg GR (2006) Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. Clin Gastroenterol Hepatol 4(10):1248–1254

Miskulin DC, Weiner DE, Tighiouart H, Ladik V, Servilla K, Zager PG, Martin A, Johnson HK, Meyer KB (2009) Medical directors of dialysis clinic Inc. Computerized decision support for EPO dosing in hemodialysis patients. Am J Kidney Dis 54(6):1081–1088

Mohan M, Batty KT, Cooper JA, Wojnar-Horton RE, Ilett KF (2004) Comparison of gentamicin dose estimates derived from manual calculations, the Australian 'Therapeutic guidelines: antibiotic' nomogram and the SeBA-GEN and DoseCalc software programs. Br J Clin Pharmacol 58:521–527

Mould DR, Green B (2010) Pharmacokinetics and pharmacodynamics of monoclonal antibodies: concepts and lessons for drug development. Bio Drugs 24(1):23–39

Mould DR, Upton RN (2012) Basic concepts in population modeling, simulation and model based drug development. CPT: Pharmacometrics Syst Pharmacol 1:e6

Mould DR, Moyer B, Amur S, Mukherjee A (2013) The impact of new technologies on the science of clinical care and drug development. AAPS Magazine, December

Mould DR, Upton R, Wojciechowski J (2014) Dashboard Systems: Implementing Pharmacometrics from Bench to Bedside. AAPS J ePub June 2014

Nestorov I (2005) Clinical pharmacokinetics of tumor necrosis factor antagonists. J Rheumatol Suppl 74:13–18

Ordás I, Mould DR, Feagan BG, Sandborn WJ (2012) Monoclonal antibodies in inflammatory bowel disease: pharmacokinetic based dosing paradigms. Clin Pharmacol Ther 91(4):635–646

Papier A (2012) Decision support in dermatology and medicine: history and recent developments. Semin Cutan Med Surg 31(3):153–159

Perlstein TS, Goldhaber SZ, Nelson K, Joshi V, Morgan TV, Lesko LJ, Lee JY, Gobburu J, Schoenfeld D, Kucherlapati R, Freeman MW, Creager MA (2012) The creating an optimal warfarin nomogram (CROWN) study. Thromb Haemost 107(1):59–68

Peyrin-Biroulet L, Deltenre P, de Suray N, Branche J, Sandborn WJ, Colombel JF (2008) Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: meta-analysis of placebo-controlled trials. Clin Gastroenterol Hepatol 6(6):644–653

Radstake TR, Svenson M, Eijsbouts AM, van den Hoogen FH, Enevold C, van Riel PL et al (2009) Formation of antibodies against infliximab and adalimumab strongly correlates with functional drug levels and clinical responses in rheumatoid arthritis. Ann Rheum Dis 68(11):1739–1745

Rost S, Fregin A, Ivaskevicius V, Conzelmann E, Hörtnagel K, Pelz HJ, Lappegard K, Seifried E, Scharrer I, Tuddenham EG, Müller CR, Strom TM, Oldenburg J (2004) Mutations in VKORC1 cause warfarin resistance and multiple coagulation factor deficiency type 2. Nature 427:537–541

Seow CH, Newman A, Irwin SP, Steinhart AH, Silverberg MS, Greenberg GR (2010) Trough serum infliximab: a predictive factor of clinical outcome for infliximab treatment in acute ulcerative colitis. Gut 59(1):49–54

Sivyer A (1959) A dose-rate calculator. Br J Radiol 32(375):208–209

Takahashi H, Echizen H (2003) Pharmacogenetics of CYP2C9 and interindividual variability in anticoagulant response to warfarin. Pharmacogenomics J 3:202–214

Ternant D, Aubourg A, Magdelaine-Beuzelin C, Degenne D, Watier H, Picon L, Paintaud G (2008) Infliximab pharmacokinetics in inflammatory bowel disease patients. Ther Drug Monit 30(4):523–529

Tobler A, Mühlebach S (2013) Intravenous phenytoin: a retrospective analysis of Bayesian forecasting versus conventional dosing in patients [published online ahead of print 29 June 2013]. Int J Clin Pharm. doi:10.1007/s11096-013-9809-5

Usman M, Ashraf M, Khokhar MI et al (2013) Comparative pharmacokinetics of levofloxacin in healthy volunteers and in patients suffering from typhoid Fever. Iran J Pharm Res 12:147–154

Wong C, Kumar SS, Graham GG, Begg EJ, Chin PK, Brett J, Ray JE, Marriott DJ, Williams KM, Day RO (2013) Comparing dose prediction software used to manage gentamicin dosing. Intern Med J 43:519–525

Xu Z, Mould DR, Hu C, Ford J, Keen M, Davis HM, Zhou H (2012) A population-based pharmacokinetic pooled analysis of infliximab in pediatrics. ACCP national meeting, San Diego CA

Xu Z, Davis HM, Zhou H (2013) Rational development and utilization of antibody-based therapeutic proteins in pediatrics. Pharmacol Ther 137(2):225–247

Zineh I, Huang S-M (2011) Biomarkers in drug development and regulation: a paradigm for clinical implementation of personalized medicine. Biomark Med 5(6):705–713