Published in final edited form as:

Curr Pharmacol Rep. 2018 June ; 4(3): 276–283. doi:10.1007/s40495-018-0139-0.

Emerging roles for clinical pharmacometrics in cancer precision medicine

Sujit Nair¹ and Ah-Ng Tony Kong²

¹Amrita Cancer Discovery Biology Laboratory, Amrita Vishwa Vidyapeetham University, Amritapuri, Clappana P.O., Kollam – 690525, Kerala, India

²Center for Cancer Chemoprevention Research and Department of Pharmaceutics, Rutgers, The State University of New Jersey, 160 Frelinghuysen Road, Piscataway, NJ-08854, USA

Abstract

Purpose of review—Although significant progress has been made in cancer research, there exist unmet needs in patient care as reflected by the ‘Cancer Moonshot’ goals. This review appreciates the potential utility of quantitative pharmacology in cancer precision medicine.

Recent findings—Precision oncology has received federal funding largely due to ‘The Precision Medicine Initiative’. Precision medicine takes into account the inter-individual variability, and allows for tailoring the right medication or the right dose of drug to the best subpopulation of patients who will likely respond to the intervention, thus enhancing therapeutic success and reducing “financial toxicity” to patients, families and caregivers. The National Cancer Institute (NCI) committed US\$ 70 million from its fiscal year 2016 budget to advance precision oncology research. Through the ‘Critical Path Initiative’, pharmacometrics has gained an important role in drug development; however, it is yet to find widespread clinical applicability.

Summary—Stakeholders including clinicians and pharmacometricians need to work in concert to ensure that benefits of model-based approaches are harnessed to personalize cancer care to the individual needs of the patient *via* better dosing strategies, companion diagnostics, and predictive biomarkers. In medical oncology, where immediate patient care is the clinician’s primary concern, pharmacometric approaches can be tailored to build models that rely on patient data already digitally available in the Electronic Health Record (EHR) to facilitate quick collaboration and avoid additional funding needs. Taken together, we offer a roadmap for the future of precision oncology which is fraught with both challenges and opportunities for pharmacometricians and clinicians alike.

* Authors to both of whom correspondence should be addressed: Dr. Sujit Nair, MPharm, PhD, Professor of Pharmaceutical Sciences, Amrita Cancer Discovery Biology Lab, Amrita Vishwa Vidyapeetham University, Amritapuri, Clappana PO, Kollam – 690525, Kerala, India, sujit108@gmail.com. Dr. Ah-Ng Tony Kong, PhD, Distinguished Professor and Glaxo, Professor of Pharmaceutics, Director, Graduate Program in Pharmaceutical Science, Ernest Mario School of Pharmacy, Rutgers, The State University of NJ, 160, Frelinghuysen Road, Piscataway, NJ-08854, USA. kongt@pharmacy.rutgers.edu.

Conflict of interest:

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Keywords

Precision medicine; pharmacometrics; precision oncology; personalized medicine; cancer; quantitative models; quantitative pharmacology; electronic health record

1.0 Introduction

Precision Medicine as defined by the US Food and Drug Administration (FDA) is an *“innovative approach to tailoring disease prevention and treatment that takes into account differences in people’s genes, environments, and lifestyles”* [1] and has received tremendous encouragement, federal funding and public recognition from The Precision Medicine Initiative [2] announced by President Obama in the 2015 State of the Union Address in the United States. Indeed, precision medicine takes into account the individual variability between patients, hence it allows for tailoring the right medication or the right dose of drug to the best subpopulation of patients who will likely respond to the intervention, thus enhancing therapeutic success and reducing “financial toxicity” to patients, families and caregivers. The historical term ‘personalized medicine’, although often used interchangeably with ‘precision medicine’, refers more to an individualized treatment that caters more exclusively to the needs of a single patient, and is largely being replaced by the term ‘precision medicine’ in most current day scenarios. With advances in basic research, molecular biology, genomics and indeed bioinformatics, it is more possible today to apply precision medicine to clinical scenarios with the availability of large scale biologic databases (human genome sequence), patient characterization methods (proteomics, genomics, metabolomics) and computational (big data) analysis tools at our disposal [3]. Out of a total of US\$ 215 million from the Precision Medicine Initiative invested in the National Institute of Health (NIH)’s fiscal year 2016 budget, the National Cancer Institute (NCI) is using US \$ 70 million to advance the field of precision oncology (or cancer precision medicine) and has launched several precision medicine clinical trials such as Lung-MAP, ALCHEMIST, NCI-MPACT, NCI-MATCH, and NCI-COG Pediatric MATCH trials [4].

Pharmacometrics is a broad umbrella term that encompasses and describes all of drug, disease and clinical trial information in a quantitative manner. Clinical pharmacometrics refers to pharmacometrics when applied specifically to clinical pharmacology for therapeutic use in patients. Pharmacometric approaches have found applicability in the drug development scenario in pharmaceutical industry; however, their application to clinical situations in oncology is only truly beginning and is limited by the need for a collaborative framework between clinicians and pharmacometricians in a hospital oncology care setting where immediate patient care is the prime concern. Translational pharmacometrics can include the entire gamut of pharmacometric approaches from bench-to-bedside. For example, Cook and Bies [5] have reviewed key concepts in disease progression modeling elsewhere. However, the real value of clinical pharmacometrics is in aiding the clinician in tailoring the treatment to suit the appropriate subpopulation of patients, or in deciding the right dose for therapeutic efficacy, or in identifying a companion diagnostic or predictive biomarkers for faster clinical intervention in the specific patient population to cite a few examples. In this review, we draw attention to some of the recent advances in clinical

pharmacometrics in precision oncology care and highlight the immense potential and benefits of such approaches going forward to enable better therapeutic success for the cancer patient and eventually lower the rising costs of cancer care through tailor-made precision medicine for appropriate subpopulations.

2.0 Clinical pharmacometrics for cancer precision medicine

Although significant progress has been made in cancer research, there still exist unmet needs in patient care as reflected by the Cancer Moonshot [6] initiative. Through the Critical Path Initiative, the US FDA has been promoting quantitative modeling in drug development since 2004 [7, 8]. Thus, pharmacometrics has gained a critical role in drug development settings (model-based drug development, MBDD) especially in big pharma industry; however, the use of pharmacometric approaches in the clinical setting (model-based patient care [9]) is currently nascent. Stakeholders such as clinicians and pharmacometricians need to work in concert to ensure that the benefits of model-based epistemology are harnessed to personalize cancer care to the individual needs of the patient via better dosing strategies, companion diagnostics, predictive biomarkers, etc. Recently, it has been advocated that routinely collected medical record data in hospitals may be used to generate population models in oncology clinical care settings by encouraging collaborations between clinicians and pharmacometricians without the financial burden of a formal study [10]. We review some of the examples in the literature under various variables that impact upon cancer precision medicine for the benefit of the reader as follows:

(a) Pharmacokinetic (PK)-guided dosing

Patel et al [11] administered the mFOLFOX6 regimen with 5-fluorouracil (5-FU) at a dose of 2400mg/m² over 46 hr every 2 weeks to 70 colorectal cancer patients. Interestingly, the continuous infusion dose for 5-FU was adjusted for cycles subsequent to the first cycle using a PK-guided algorithm in order to attain a predetermined target area under the AUC (area under the plasma concentration time curve). The novel PK-guided algorithm achieved the target AUC within four cycles of dosing and translated into less GI toxicity and fewer underdosed patients thus enabling personalized cancer therapy for these colorectal cancer patients. In another study on 84 colorectal cancer patients (stage 2–4) administered mFOLFOX6 or mFOLFIRI regimens, Kline et al [12] administered 46 patients with 5-FU doses based on body surface area and 38 patients with 5-FU doses that were adjusted based on PK monitoring. It was observed that personalized dosing by 5-FU PK monitoring improved disease-free survival and reduced adverse drug reactions (ADR) in stage 2–3 patients of colorectal cancer. Notably, Pauley et al [13] used between-course individualized dose adjustments of high-dose methotrexate in 485 patients with acute lymphoblastic leukemia (ALL). The doses were adjusted based on clearance values from previous course of high-dose methotrexate for each individual and resulted in fewer extreme steady-state plasma concentration (C_{ps}) values and faster excretion as compared to conventional dosing resulting in fewer grade 3–4 toxicities.

(b) Inter-individual variation in drug-metabolizing enzymes (DMEs)

Takashina et al [14] evaluated the influence of gene polymorphisms on fentanyl PK and central ADR in sixty Japanese cancer patients undergoing conversion to a fentanyl transdermal reservoir system. In this study, the CYP3A5*3/*3 allele group showed higher plasma concentrations as well as higher incidence of central ADR than the *1/*1 and the *1/*3 groups. Further, fewer patients carrying the ABCB1 1236TT allele required rescue medication as opposed to the 1236C allele. Thus, these gene polymorphisms clearly affected the PK of fentanyl and may be used as a personalized diagnostic to predict clinical response in patients being converted to the transdermal fentanyl delivery system. Interestingly, Cai et al [15] studied the association between IVS14+1 G>A genotype of the dihydropyrimidine dehydrogenase (DPD) with 5-FU plasma concentrations and ADR in 80 metastatic colorectal cancer patients. This study showed that the 5-FU dose for patients with heterozygous DPD IVS14+1 mutation should be reduced to mitigate ADR, while homozygous patients should avoid 5-FU administration.

(c) Gender and Geriatric

Pfreundschuh et al [16] investigated higher rituximab doses for elderly male patients with diffuse large B-cell lymphoma (DLBCL) as the male sex in these patients are associated with unfavorable PK and prognosis. 268 patients (120 female, 148 male) in the age group of 61–80 years received 6 cycles of CHOP and 8 cycles rituximab (males 500 mg/m², females 375 mg/m²). At this dose level, the exposure in males was slightly better than in females. In a planned subgroup analysis for elderly males, the 500 mg/m² dose was not more toxic than the 375 mg/m² dose and improved progression free survival (PFS) overall survival. Indeed, the sex-specific PK study enabled safe and personalized administration of higher rituximab dose in elderly males and negated the adverse prognosis of male sex devoid of any increase in toxicity.

(d) Pediatric

Zhou et al [17] reported the first population PK study of vancomycin in the pediatric age group with malignant hematological disease so as to define the appropriate dosing regimen for these children. 70 children in the age group of 0.3 to 17.7 years were administered 40 to 60 mg/kg/day of vancomycin and a patient-tailored dosing regimen was optimized. Traditional pediatric dose (mg/kg basis) simulations as well as patient-tailored dose simulations were performed. It was shown that the patient-tailored approach decreased variability in vancomycin AUC and steady state trough concentrations (C_{ss}/min) as opposed to the mg/kg basis dose and that a greater number of patients (60%) in the patient-tailored arm reached the target C_{ss}/min than with the mg/kg basis dose (49%).

(e) Predictive biomarkers

Buil-Bruna et al [18] used mechanism-based PK/PD (pharmacokinetic/pharmacodynamic) modeling to identify predictive biomarkers for early prediction of disease progression in small cell lung cancer (SCLC) thus enabling personalized medicine with efficient therapeutic intervention for at risk patients. 22 treatment-naïve SCLC patients were administered first-line chemotherapy (etoposide plus either carboplatin or cisplatin).

Biomarker samples for serum lactate dehydrogenase (LDH) and neuron-specific enolase (NSE) were obtained during the treatment period and a biomarker model was developed and validated externally. An encouraging result of this study was that biomarker data that was gathered only during the treatment period was sufficient to reliably predict 75% of follow-up tumor assessment results.

A semi-mechanistic model including K/PD compartments and a cell lifespan model has been used to describe the kinetics of circulating tumor cell (CTC) count and prostate specific antigen (PSA) concentration to predict treatment efficacy or for therapeutic adjustment in metastatic castration-resistant prostate cancer [25]. CTC is a surrogate marker that may potentially replace the largely popular PSA. The model used data from 223 patients treated by chemotherapy and/or hormone therapy and quantified the dynamic relationships between the longitudinal kinetics of both these markers during treatment.

(f) Tumor dimensions and FDG-PET response

Schindler et al [19] performed pharmacometric modeling of diameter, density and volume of liver metastases to guide early beneficial interventions in imatinib-treated patients with gastrointestinal stromal tumors (GIST). In another study [20], PK/PD modeling was used on individual lesion FDG-PET response to serve as a predictor for overall survival in patients with sunitinib-treated GIST.

(g) Systems pharmacology

To assess the potential for optimal preloading with anti-CD20 antibody radioimmunotherapy, Kletting et al [21] developed a PBPK model to describe the biodistribution of this antibody. Simulations were conducted using MATLAB Simulink for varying tumor permeabilities, spleen sizes and tumor burdens, and the optimal amount of unlabeled antibody was identified. It was found that individual parameters, most notably the tumor uptake index, greatly influenced the optimal preload. The study concluded that personalized dosing for anti-CD20 antibody radioimmunotherapy is imperative to account for interpatient variability and, in general, a reduction of antibody is advocated. Interestingly, Gallo and Birtwistle [22] have described enhanced PD (ePD) models based on systems pharmacology and incorporating genetic data that would be useful along with PK/ePD models for customizing precision medicine in cancer care.

In addition, Majid et al [23] constructed a population PK model of eribulin combining data from seven phase 1 studies, one phase 2 study, and one phase 3 study, as well as a PK/PD model of efficacy and tumor response, to describe eribulin exposure-response relationships and better inform clinicians treating patients with metastatic breast cancer. In this study, inter-individual variability was found to be 52% for both clearance and exposure. Further, liver function markers such as albumin, bilirubin and alkaline phosphatase contributed 7.3% of inter-individual variability in clearance of eribulin thus significantly impacting eribulin PK.

Exposure-response analyses were performed on guadecitabine, a hypomethylating agent, along with modeling and simulation incorporating DNA demethylation and absolute neutrophil count (ANC) from 79 and 369 patients in two phase 1/2 studies to predict the

optimal dosing regimen for phase 3 in myeloid malignancies [24]. Herein, an indirect response model described the long interspersed nucleotide element (LINE-1) methylation time course whereas a K/PD model linked the dosing rate with decrease in ANC.

(h) Metronomic chemotherapy

A metronomic regimen of cancer chemotherapy is an alternative dosing schedule which involves repeated and regular administration of low-dose cancer chemotherapeutics [26]. Metronomic chemotherapy has several advantages including lower treatment costs, lower toxicity and commendable efficacy that is superior to that of maximum-tolerated-dose (MTD) therapy [27]. Indeed, metronomic regimens tend to be highly empirical in nature with difficulties in standardizing an optimal dose or treatment schedule [28], and, hence, there is an unmet need to generate PK data of critical oncology drugs administered in metronomic regimens. Thus, theoretical model-based strategies [26] are imperative to refine dose and treatment schedules for the success of precision medicine in oncology. For example, Ciccolini et al [29] reported a PK/PD model to identify the most effective administration schedule for metronomic chemotherapy with gemcitabine.

(i) Hematopoietic cell transplant

McCune et al [30] developed a population PK model for initial and Bayesian dose personalization after intravenous administration of busulfan to 1,610 hematopoietic cell transplant recipients. In this study, the target C_{ss} of 770 ng/mL was achieved over a wide age spectrum from infants to adults, with a greater proportion of initial doses achieving the therapeutic window with this model (72%) as opposed to dosing recommended by the FDA (57%) or the European Medicines Agency (EMA, 70%). To minimize the ADR such as oral mucositis, GI and liver toxicity with intravenous melphalan in hematopoietic stem cell transplantation, Mizuno et al [31] developed a population PK model to individualize exposure using 15 adult patients administered 140 or 200 mg/m² of melphalan by intravenous infusion. An optimal sampling strategy was developed for model-based precision dosing of melphalan in these patients. Further, Sanghavi et al [32] developed a PK model to personalize fludarabine dosing in patients undergoing hematopoietic stem cell transplant with reduced intensity conditioning (RIC). The PK model from 87 adults predicted population clearance of F-ara-A, the active component of fludarabine, accounting for kidney function and body weight. This personalized dosing model would also be useful in obese and impaired kidney function patients.

(j) Pharmacogenomics of monoclonal antibodies

We have previously described [33] in detail key pharmacometric variables in the anticancer efficacy of anti-PD-1 immune checkpoint inhibitor nivolumab including target engagement, metabolism, systems pharmacology, and clearance. We have also summarized [34] ongoing and completed Phase 1, 2 and 3 clinical trials investigating the safety and anticancer efficacy of anti-PDGFR alpha mAb olaratumab which recently received accelerated approval, orphan drug status, fast track and breakthrough therapy designation from the US FDA for metastatic soft tissue sarcoma. Since PD-L1, a ligand for PD-1, is a weak biomarker for nivolumab therapy in clinical practice [33], model predictions for the best responders in a stratified patient population when coupled with immunopharmacogenomic studies would enable

greater therapeutic success through tailoring the precise treatment to the right patients and also serve to lower the “financial toxicity” to patients and families. Similarly, since soft tissue sarcomas are heterogeneous with 50 different histologic subtypes, pharmacometric model-based approaches can help understand and investigate (i) whether subsets of patients with higher PDGFR alpha expression might have potentially longer progression free survival or overall survival benefit on treatment with olaratumab, or (ii) whether any subset of PDGFR alpha-expressing patients may not respond to olaratumab but may benefit from combination therapy with olaratumab and doxorubicin, the current standard of care [34].

(k) Chronic Kidney Disease (CKD)

Khosravan et al [35] conducted a phase 1, single-dose study to study the PK of sunitinib at a dose of 50 mg and found that exposure of receptor tyrosine kinase inhibitor sunitinib was decreased in subjects that had end-stage renal disease potentially leading to lower efficacy. Janus and Launay-Vacher [36] have excellently reviewed elsewhere why clinicians need to be aware of the need to individualize treatment in hemodialysis patients who are increasingly being prescribed anticancer drugs.

3.0 Population Pharmacogenomics and Pharmacometrics

In discovery research in the pharmaceutical industry, population pharmacogenetics could be employed to optimize clinical trial design by appropriate stratification of patient populations, in identifying at-risk patients for serious adverse events (SAE), and in optimization of drug dosage [37]. It is now possible to facilitate a more efficient clinical trial design by stratification of the target population into hyper-responders, responders, and non-responders, by using appropriate inclusion/exclusion criteria for relevant subpopulations. Indeed, this, in turn, will enhance safety and improve efficacy for the appropriate subpopulation where precision oncology care will entail maximum benefit and minimum risk of SAEs [38]. Several examples have now begun to be reported in the literature which make a case for the role of population pharmacogenomics in various cancer phenotypes, which are thus amenable to better management with precision oncology-guided diagnostics, therapeutics, or theragnostics. As a diagnostic example, Myszka et al [39] reported using targeted massively parallel sequencing that Ukrainian and Polish women exhibit two frameshift deletions (172_175del and 509_510del) in PALB2 which should be included in genetic testing for predisposition to breast as well as ovarian cancers in these populations. To cite a therapeutic example, Das et al analyzed gastric tumors from a Phase 3 Japanese study using NanoString technology and reported that suppression of Wnt5A is a predictor of improved progression free survival (PFS) with anticancer drug S-1 but not with the combination regimen of irinotecan plus S-1, which knowledge will help in improving therapeutic efficacy of gastric cancer management.

Such examples may be found across a diverse variety of cancers where pharmacogenomics knowledge may be harnessed in achieving precision oncology-based improvement in care. When coupled with model-building strategies under the pharmacometrics umbrella where pharmacogenomic data is incorporated in the model along with safety and efficacy data, it will prove to be a more potent tool in the hands of the pharmacometrician or clinician to

benefit the cancer patient. We have previously delineated [40] interactions between long non-coding RNA (lncRNA) and microRNA (miRNA) in cancer translational medicine. We have also previously enumerated [41] the regulatory architecture of signature miRNA networks that may play bifunctional role(s) of chemoresistance to, and chemoprevention against, various common cancers, which may be explained, at least in part, by stress constraints in the cancer milieu, and by temporal and/or spatial differences in the tumor microenvironment. Further, we have described [42] the pharmacometrics of nutraceutical sulforaphane in prostate cancer prevention. Taken together, it follows that a pharmacodynamic/pharmacogenomics (PD/PG) model incorporating both signature miRNAs and lncRNAs in chemoresistance as well as corresponding signal transduction pathways would help in improving the success of cancer chemotherapy as has been demonstrated by Jusko's group [43] by the PD/PG model of insulin resistance genes in skeletal muscle of adrenalectomized rats dosed with methyl prednisolone. It would further be desirable to develop a first generation PK/PD/PG model that combines information from PK, PD, and PG data including information on drug, cancer type, clinical trial, dose, tissue and circulating biomarkers, and potential companion diagnostics from the early or intermediate discovery stage through Phase 0 or microdosing studies and right through Phase 4 post-marketing surveillance to build a robust and reliable model that will be useful to the clinician and improve patient care [38].

4.0 The Road to the Future: Perspectives on Challenges and Opportunities in Precision Oncology

The roadmap for the future of precision oncology is fraught with both challenges and opportunities for both pharmacometricians and clinicians alike who need to work together in concert to truly enable the benefits of cancer precision medicine to reach the appropriate patient subpopulation. We summarize in Table 1 some of the key challenges and opportunities that are in need of being addressed effectively using pharmacometric approaches.

Acknowledgments

This work is supported in part by NIH R01 CA200129 to Prof. Ah-Ng Tony Kong from the National Cancer Institute (NCI), National Institutes of Health (NIH) and in part by institutional funds from Rutgers, The State University of New Jersey, USA.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. US Food and Drug Administration. The Precision Medicine Initiative. <https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/PrecisionMedicine-MedicalDevices/default.htm>
2. Obama White House Archives. The Precision Medicine Initiative. <https://obamawhitehouse.archives.gov/node/333101>

3. Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med*. 2015; 372(9):793–795. [PubMed: 25635347]
4. National Cancer Institute. NCI and the Precision Medicine Initiative. 2017. <https://www.cancer.gov/research/areas/treatment/pmi-oncology>
5. Cook SF, Bies RR. Disease Progression Modeling: Key Concepts and Recent Developments. *Curr Pharmacol Rep*. 2016; 2(5):221–230. [PubMed: 28936389]
6. National Cancer Institute. Cancer Moonshot. <https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative>
7. US Food and Drug Administration. Innovation or stagnation: challenge and opportunity on the critical path to new medical products. 2004. <https://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/default.htm>
8. Ribba B, Holford NH, Magni P, Troconiz I, Gueorguieva I, Girard P, et al. A review of mixed-effects models of tumor growth and effects of anticancer drug treatment used in population analysis. *CPT Pharmacometrics Syst Pharmacol*. 2014; 3:e113. [PubMed: 24806032]
9. Kloft C. Pharmacometrics and systems biology in oncology: is there an intersection? *Int J Clin Pharmacol Ther*. 2013; 51(1):89–90. [PubMed: 23260011]
10. Buil-Bruna N, Lopez-Picazo JM, Martin-Algarra S, Troconiz IF. Bringing Model-Based Prediction to Oncology Clinical Practice: A Review of Pharmacometrics Principles and Applications. *Oncologist*. 2016; 21(2):220–232. [PubMed: 26668254]
11. Patel JN, O’Neil BH, Deal AM, Ibrahim JG, Sherrill GB, Olajide OA, et al. A community-based multicenter trial of pharmacokinetically guided 5-fluorouracil dosing for personalized colorectal cancer therapy. *Oncologist*. 2014; 19(9):959–965. [PubMed: 25117066]
12. Kline CL, Schiccitano A, Zhu J, Beachler C, Sheikh H, Harvey HA, et al. Personalized dosing via pharmacokinetic monitoring of 5-fluorouracil might reduce toxicity in early- or late-stage colorectal cancer patients treated with infusional 5-fluorouracil-based chemotherapy regimens. *Clin Colorectal Cancer*. 2014; 13(2):119–126. [PubMed: 24461492]
13. Pauley JL, Panetta JC, Crews KR, Pei D, Cheng C, McCormick J, et al. Between-course targeting of methotrexate exposure using pharmacokinetically guided dosage adjustments. *Cancer Chemother Pharmacol*. 2013; 72(2):369–378. [PubMed: 23760811]
14. Takashina Y, Naito T, Mino Y, Yagi T, Ohnishi K, Kawakami J. Impact of CYP3A5 and ABCB1 gene polymorphisms on fentanyl pharmacokinetics and clinical responses in cancer patients undergoing conversion to a transdermal system. *Drug Metab Pharmacokinet*. 2012; 27(4):414–421. [PubMed: 22277678]
15. Cai X, Fang JM, Xue P, Song WF, Hu J, Gu HL, et al. The role of IVS14+1 G > A genotype detection in the dihydropyrimidine dehydrogenase gene and pharmacokinetic monitoring of 5-fluorouracil in the individualized adjustment of 5-fluorouracil for patients with local advanced and metastatic colorectal cancer: a preliminary report. *Eur Rev Med Pharmacol Sci*. 2014; 18(8):1247–1258. [PubMed: 24817302]
16. Pfreundschuh M, Murawski N, Zeynalova S, Ziepert M, Loeffler M, Hanel M, et al. Optimization of rituximab for the treatment of DLBCL: increasing the dose for elderly male patients. *Br J Haematol*. 2017; 179(3):410–420. [PubMed: 28990173]
17. Zhao W, Zhang D, Fakhoury M, Fahd M, Duquesne F, Storme T, et al. Population pharmacokinetics and dosing optimization of vancomycin in children with malignant hematological disease. *Antimicrob Agents Chemother*. 2014; 58(6):3191–3199. [PubMed: 24663023]
18. Buil-Bruna N, Sahota T, Lopez-Picazo JM, Moreno-Jimenez M, Martin-Algarra S, Ribba B, et al. Early Prediction of Disease Progression in Small Cell Lung Cancer: Toward Model-Based Personalized Medicine in Oncology. *Cancer Res*. 2015; 75(12):2416–2425. [PubMed: 25939602]
19. Schindler E, Krishnan SM, Mathijssen R, Ruggiero A, Schiavon G, Friberg LE. Pharmacometric Modeling of Liver Metastases’ Diameter, Volume, and Density and Their Relation to Clinical Outcome in Imatinib-Treated Patients With Gastrointestinal Stromal Tumors. *CPT Pharmacometrics Syst Pharmacol*. 2017; 6(7):449–457. [PubMed: 28379635]

20. Schindler E, Amantea MA, Karlsson MO, Friberg LE. PK-PD modeling of individual lesion FDG-PET response to predict overall survival in patients with sunitinib-treated gastrointestinal stromal tumor. *CPT Pharmacometrics Syst Pharmacol*. 2016; 5(4):173–181. [PubMed: 27299707]
21. Kletting P, Meyer C, Reske SN, Glatting G. Potential of optimal preloading in anti-CD20 antibody radioimmunotherapy: an investigation based on pharmacokinetic modeling. *Cancer Biother Radiopharm*. 2010; 25(3):279–287. [PubMed: 20578833]
22. Gallo JM, Birtwistle MR. Network pharmacodynamic models for customized cancer therapy. *Wiley Interdiscip Rev Syst Biol Med*. 2015; 7(4):243–251. [PubMed: 25914386]
- 23**. Majid O, Gupta A, Reyderman L, Olivo M, Hussein Z. Population pharmacometric analyses of eribulin in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes. *J Clin Pharmacol*. 2014; 54(10):1134–1143. This manuscript is a very good study combining systems pharmacology and pharmacometric analyses of eribulin. [PubMed: 24771603]
24. Xu C, Goggin TK, Su XY, Taverna P, Oganessian A, Lowder JN, et al. Simultaneous Modeling of Biomarker and Toxicity Response Predicted Optimal Regimen of Guadecitabine (SGI-110) in Myeloid Malignancies. *CPT Pharmacometrics Syst Pharmacol*. 2017
25. Wilbaux M, Tod M, De Bono J, Lorente D, Mateo J, Freyer G, et al. A Joint Model for the Kinetics of CTC Count and PSA Concentration During Treatment in Metastatic Castration-Resistant Prostate Cancer. *CPT Pharmacometrics Syst Pharmacol*. 2015; 4(5):277–285. [PubMed: 26225253]
26. Benzekry S, Pasquier E, Barbolosi D, Lacarelle B, Barlesi F, Andre N, et al. Metronomic reloaded: Theoretical models bringing chemotherapy into the era of precision medicine. *Semin Cancer Biol*. 2015; 35:53–61. [PubMed: 26361213]
27. Hutchinson L. Metronomics - an alternative P4 medicine. *Nat Rev Clin Oncol*. 2016; 13(8):461. [PubMed: 27435266]
28. Bocci G, Kerbel RS. Pharmacokinetics of metronomic chemotherapy: a neglected but crucial aspect. *Nat Rev Clin Oncol*. 2016; 13(11):659–673. [PubMed: 27184418]
29. Ciccolini J, Barbolosi D, Meille C, Lombard A, Serdjebi C, Giacometti S, et al. Pharmacokinetics and Pharmacodynamics-Based Mathematical Modeling Identifies an Optimal Protocol for Metronomic Chemotherapy. *Cancer Res*. 2017; 77(17):4723–4733. [PubMed: 28655786]
30. McCune JS, Bemer MJ, Barrett JS, Scott Baker K, Gamis AS, Holford NH. Busulfan in infant to adult hematopoietic cell transplant recipients: a population pharmacokinetic model for initial and Bayesian dose personalization. *Clin Cancer Res*. 2014; 20(3):754–763. [PubMed: 24218510]
31. Mizuno K, Dong M, Fukuda T, Chandra S, Mehta PA, McConnell S, et al. Population Pharmacokinetics and Optimal Sampling Strategy for Model-Based Precision Dosing of Melphalan in Patients Undergoing Hematopoietic Stem Cell Transplantation. *Clin Pharmacokinet*. 2017
32. Sanghavi K, Wiseman A, Kirstein MN, Cao Q, Brundage R, Jensen K, et al. Personalized fludarabine dosing to reduce nonrelapse mortality in hematopoietic stem-cell transplant recipients receiving reduced intensity conditioning. *Transl Res*. 2016; 175:103–115.e104. [PubMed: 27094990]
- 33**. Nair S. Pharmacometrics and systems pharmacology of immune checkpoint inhibitor nivolumab in cancer translational medicine. *Advances in Modern Oncology Research*. 2016; 2(1):18–31. The manuscript gives a detailed account of pharmacometric and systems pharmacology variables in nivolumab immunotherapy.
34. Nair S, Iyer A, Vijay V, Bandlamudi S, Llerena A. Pharmacokinetics and systems pharmacology of monoclonal antibody olaratumab for inoperable soft tissue sarcoma. *Advances in Modern Oncology Research*. 2017; 3(3):114–125.
35. Khosravan R, Toh M, Garrett M, La Fargue J, Ni G, Marbury TC, et al. Pharmacokinetics and safety of sunitinib malate in subjects with impaired renal function. *J Clin Pharmacol*. 2010; 50(4):472–481. [PubMed: 19779038]
36. Janus N, Launay-Vacher V. Pharmacokinetic/pharmacodynamic considerations for cancer patients undergoing hemodialysis. *Expert Opin Drug Metab Toxicol*. 2017; 13(6):617–623. [PubMed: 28537215]

37. Llerena A. Population pharmacogenetics and global health. *Drug Metab Pers Ther.* 2015; 30(2): 73–74. [PubMed: 25996490]
- 38*. Nair S, Llerena A. Editorial: New vistas in personalized medicine for ethnicity in cancer: Population pharmacogenomics and pharmacometrics. *Drug Metab Pers Ther.* 2018; 33(2) In Press June issue. The editorial provides perspectives on inter-individual variability and model-based approaches to cancer precision medicine.
39. Myszka A, Nguyen-Dumont T, Karpinski P, Sasiadek MM, Akopyan H, Hammet F, et al. Targeted massively parallel sequencing characterises the mutation spectrum of PALB2 in breast and ovarian cancer cases from Poland and Ukraine. *Fam Cancer.* 2017
40. Nair S. Current insights into the molecular systems pharmacology of lncRNA-miRNA regulatory interactions and implications in cancer translational medicine. *AIMS Molecular Science.* 2016; 3(2):104–124.
41. Nair S, Kong A. Architecture of signature miRNA regulatory networks in cancer chemoprevention. *Curr Pharmacol Rep.* 2015; 1(2):89–101.
- 42*. Nair S, Kong A. Pharmacometrics of nutraceutical sulforaphane and its implications in prostate cancer prevention. *Journal of Chinese Pharmaceutical Sciences.* 2016; 25(1):12–22. The manuscript describes the pharmacokinetics guiding the anticancer activity of nutraceutical sulforaphane from broccoli and other cruciferous vegetables.
43. Yao Z, Hoffman EP, Ghimbovski S, DuBois DC, Almon RR, Jusko WJ. Pharmacodynamic/ pharmacogenomic modeling of insulin resistance genes in rat muscle after methylprednisolone treatment: exploring regulatory signaling cascades. *Gene Regul Syst Bio.* 2008; 2:141–161.

Table 1**The Road to the Future: Challenges and Opportunities in Precision Oncology**

Challenges in Precision Oncology	Opportunities in Precision Oncology
Lack of validated disease signatures to assist the medical oncologist.	Pharmacometric models can help identify a panel of tissue and blood biomarkers or companion diagnostics as onco-signatures that can be validated rapidly in the laboratory.
Low predictive power of oncobiomarkers that dampens the enthusiasm of the clinician.	Pharmacometric approaches can help assess a large pool of oncobiomarkers to identify those with higher predictive power based on efficient modeling and simulation strategies.
Need for rapid identification of disease-causing variants in the target population.	Pharmacometric modeling and simulation in a stratified target population including next generation sequencing and high-powered bioinformatic data analysis can help in rapid delineation of variability in the population.
Need for close collaboration between clinicians and pharmacometricians in an oncology care hospital setting.	Pharmacometric approaches can be tailored to build models that rely on patient data already digitally available to the clinician in the Electronic Health Record (EHR) to facilitate quick collaboration and avoid additional funding needs.
Genetic heterogeneity in global population due to ethnicity and race leading to inter-population variability which skews precision interventions.	Pharmacometric models can be developed to account for differences in ethnicity and race in order to make the best estimate of genetic variability without repeating expensive clinical trials in different populations.
“Financial Toxicity” (Rising costs) of cancer drug development and cancer clinical trials from Phase 0 through 4 and corresponding rising costs of cancer care.	Pharmacometric strategies have already been shown to reduce the cost of drug development; similarly, pharmacometric clinical trial simulations will help to reduce the cost of clinical trials thus reducing the “financial toxicity” of cancer care for patients, families and caregivers.
Approval of many oncology therapies occurs without adequate investigation of individual variability between patients in clinical trials thus leading to a fixed dosing regimen being recommended for the general population under the approved indication. Thus, for a precision medicine-guided intervention, there is no adequate prior efficacy or safety data at the required dose level for the subpopulation, or it may not be feasible to administer such a dose due to limitation in dosing strength (such as limited tablet strength for oral drugs).	Incorporation of a pharmacogenomics arm in the clinical trial design to assess inter-individual variability in the population at the very outset in oncology trials will facilitate rapid generation of safety and efficacy data at the required dose level for precision-guided intervention in oncology care. The NCI precision oncology clinical trials may be used as a valuable reference tool. With dosing levels elucidated in appropriate subpopulations, formulation groups in big pharma will be able to provide the best oral, or other, dosage form in the necessary drug strength for precision oncology. For the many cancer drugs already approved, it may be possible to harness available literature and clinically test for polymorphisms or inter-individual variability with known drugs first, and then to design stratified trials using pharmacometric models to generate safety and efficacy data to delineate appropriate doses for the subpopulation.