Saving Costs and Improving Quality of Care Using a Novel Pharmacogenomic (PGx) Clinical System

A Clinical Overview

Zeil Rosenberg, MD, MPH* and Xuemin Lu, Ph.D.*

Introduction

Pharmacogenomic (PGx) testing, an important element of Precision Medicine, has the potential to save lives, improve quality of care and save health care dollars in an increasingly value driven healthcare environment. The goal of PGx testing is to provide the right dose of medication patients at the right time, utilizing each patient's individual genetic make-up. The rise of advanced genomic technologies has allowed for a recent, rapid decline in the cost of genetic sequencing, making it affordable across the healthcare spectrum. At present, however, a large gap between the PGx testing promise and improved patient outcome reality persists. Current medical practice has not fully appreciated the potential of PGx data in improving patient care and cost savings. Barriers to pharmacogenomic testing uptake vary, as would be expected for any new technology. Many physicians are uncertain of their ability to make sense of PGx data. Other clinicians may not see the relationship between drug metabolism and medication compliance and/or treatment outcome. Some physicians only do PGx testing upon a patient's request or may limit testing to one or a few genes at a time thereby requiring multiple visits for re-testing when the patient is prescribed new drugs at later dates. Pharmacogenomics is widely underutilized in the medical environment. In total, these barriers lead to an unnecessarily high cost of care as well as delayed treatment optimization.

Admera health developed the molecular diagnostic test PGxOne™ Plus to address these gaps in care. It uses advanced genomic technologies to comprehensively and cost-effectively identify PGx-related genetic variants within the patient's genotype. This determines if the patient has ultra-rapid, poor, somewhat diminished, or normal metabolism for a large number (>220) of commonly used prescription drugs. With the rapid and dramatic drop in cost to sequence multiple genes at once, it is now also feasible for patient testing and analysis to be done simultaneously. As an example, it has been shown that testing patients in a managed health care environment using a small 5-gene panel was more cost-effective when testing occurs at the time the patient first presents for care, i.e. a "preemptive" strategy. Early testing provides more informed patient decisions in both the near and short term, because the information on future treatment regimens can be referenced as needed for a range of drugs. Testing for multiple gene variants at one times creates a lifetime pharmacogenomic medical record. As the patients genotype will not change over time, this record has been shown to reduce multiple testing or

"reactive" testing i.e. when the pharmacogenomic test is ordered in response to an adverse drug reaction or when starting a new drug covered by the test[1]. Such a lifetime record is accessible to the patient for future usage regardless of changes in medications or change in providers with no extra testing needed, thus saving time and cost.

Critical for early adoption of technology is providing the pharmacogenomic information in a clinician-friendly report format to facilitate immediate dosage adjustment or drug substitution and aid in the prevention of adverse drug events (ADEs). Testing 50 genes of known importance in pharmacogenomics, PGxOne™Plus is the most comprehensive test available today and incorporates drugs used in fourteen therapeutic areas including cardiology, psychiatry and oncology. Additionally, the PGxOne™Plus test provides drug-drug interaction (DDI) and food-drug interaction (FDI) information alongside pharmacogenomic testing results. All results can be imported directly into any enterprise-wide electronic health record system.

Economic and Clinical Benefits of Pharmacogenomics Testing

Inconsistent prescribing behaviors, poor patient monitoring, and an aging population has contributed to the U.S. healthcare system spending $300 billion on prescription medications in 2014, an amount expected to rise 6.3% every year for the next decade[2]. For every dollar expended on prescription drugs, an additional $0.50 is wasted on treating adverse drug reactions (ADRs), accumulating to an extraordinary $136 billion of preventable annual excess health care spending[3].

Pharmacogenomics testing offers patient centered precision to improve treatment efficacy and to alleviate many unnecessary healthcare costs. Pharmacogenomic information aids clinicians in tailoring drug selection and dosing to the individual's genetic make-up. Having this information leads in turn to optimized drug benefit, better and more cost-efficient treatment plans, reduced excess healthcare usage, prevention of adverse drug reactions, and strengthened patient adherence to their drug regimens. As more comprehensive gene panels covering more drugs become available in the market, further increases in patient care improvement and additional cost savings will continue to materialize.

Cost saving

The clinical value of pharmacogenomics is clear in several studies. For example, recently published data documented medication cost savings averaged $1860 over a three-year stay when PGx testing information was integrated elderly patients having polypharmacy regimens in a long term care facility[4]. In another study, comparing a group of pharmacogenomic tested versus untested patients > 65 years of age, hospitalization rates for the tested group was only 9.8% vs. 16.1% for the untested group. The emergency room visit rate was reduced to 4.4% compared to 15.4% for the untested group[5]. The cost-saving from using the Admera Health PGxOne™ Plus test has potential for even greater health cost reductions as our test covers significantly more drugs and include larger number of genes than used in the referenced studies.

Pharmacogenomic – based prescription approaches help physicians pinpoint the most effective polypharmacy treatment plan for an individual, further reducing excess healthcare expenditure.

In a study examining the impact of a 17-gene pharmacogenomic testing panel on polypharmacy patients, 50% of those on five or more medications were safely able to eliminate or refine at least one drug from their drug regimen after testing[4]. These pharmacogenomic-driven changes save $621 per patient annually. As 11% of all Americans are prescribed at least five medications[6, 7] the savings in medication costs has tremendous potential when used to modify complex polypharmacy use.

Of additional value to the clinician, treatment plans determined with active use of pharmacogenomic testing enables patient confidence in, and subsequent adherence to, their medical regimens. In one study, 95% of tested participants viewed having a pharmacogenomic-driven prescription system favorably and 46% followed pharmacogenomics-backed recommendations[5]. Not only do pharmacogenomics generate considerable cost savings, but also they inspire a culture of trust in their prescriptions, enhancing treatment compliance and clinical effectiveness. In a large study of pharmacogenomic testing, patient adherence to medication plans consistently improved in those provided with such tests as compared to those given the standard of care[8]. As a result, PGx tested patients experienced an average decrease in pharmacy costs of $1,035 per patient per year [9].

Reduction in Adverse Drug Reactions (ADRs)

Many of the cost reductions from pharmacogenomic testing can be attributed to diminished adverse drug reactions (ADRs). Adverse drug reactions, frequently seen in patients found to have either poor or ultra-rapid drug metabolism, may lead to extended hospital stays[10] and additional costs up to $6,000 per year[11] . With precision medicine, enabled by pharmacogenomic testing, it is possible to minimize these steep costs that accompany unanticipated adverse drug reactions from prescription medication [12, 13].

For example, numerous studies exploring the effects of pharmacogenomics-based prescribing for patients diagnosed with mental illnesses have found that testing prevents ADRs. This is caused directly by getting a patient onto their proper regimen more rapidly and indirectly by increasing patient medication adherence. For non-responders, drugs being administered may simply be ineffective. For ultra-responders, the risk of bleeding and other unwanted side effects from many common psychotropic drugs directly threatens a patient's health and quality of life. Poor and ultra-rapid metabolizers taking antidepressants experience increased medical care costs by 69%, medical visits by 67%, sick leave days by 300%, and disability claims by 400% [14]. Once pharmacogenomic testing was provided to screen for both poor or ultra-rapid metabolism, health care costs were reduced 28% for those with schizophrenia and other psychiatric illnesses [15]. Since a single antidepressant treatment failure costs $1,043, pharmacogenomic testing is especially advantageous in terms of reduced treatment failure and ADRs [13, 16].

Increase in medication adherence

While pharmacogenomics may obviate the direct costs of ADR treatment, increased confidence in and adherence to drug therapy can also lead directly to reductions in healthcare costs. The lack of adherence to prescriptions decreases drug regimen efficacy and is a vicious cycle; genetic differences account for variation in drug effects and may result in greater medication

discontinuation rates further hindering regimen effectiveness [17, 18] and increased medical costs. Genomic testing has been found to positively correlate with improved medication adherence [19], and data suggests that pharmacogenomic-driven prescription modifications can lower costs from noncompliance. In particular, one study found that patients demonstrated a 6.3% increase in regimen adherence after being provided pharmacogenomic testing, saving $562 in outpatient costs per person in four months [19]. Although the study was brief, these findings demonstrate the clinical utility and cost efficacy of pharmacogenomic testing.

Gene variants affecting common drugs are highly prevalent. According to the Vanderbilt University Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment (PREDICT) program, preemptive pharmacogenetic testing for 5 targeted genes identified at least one actionable variant in 91% of genotyped patients (*1*). Considering the lifetime permanence of genetic information and pharmacogenomic testing results having ongoing relevance, the potential cost savings generated by current studies are conservative estimates.

Selected Applications for Pharmacogenomic Testing in Specialty Areas

After decades of discovery research, inherited variations have been identified in 50 genes that affect in excess of 220 commonly prescribed medications and that are actionable in the clinic. This pharmacogenomic variability in the clinic setting is driving implementation of an evidence-based strategy for improving the appropriate use and safety of medications, providing a rational cornerstone for precision medicine. Pharmacogenomic testing already can provide benefit in multiple therapeutic areas, including cardiology, psychiatry, pain management and oncology. Several examples are detailed below.

Cardiology

A recent major meta-review systematically assessed the quality and quantity of the pharmacogenomics knowledgebase to determine its clinical utility for cardiac drugs. Investigators identified 51cardiovascular drugs with positive published pharmacogenomic evidence including 23 higher-evidence drugs warranting clinical summaries i.e. worthy of consideration for clinical implementation. This data impacts 7 of the 9 most commonly prescribed cardiovascular agents in the United States (*20*) including simvastatin, metoprolol, clopidogrel and warfarin.

Statins

Statins remain a core pharmaceutical in the U.S. healthcare system with simvastatin being the third most prescribed drug. One aspect of statin therapy that remains difficult for prescribers is the ability to predict individual patient response to therapy. These include both efficacy and genetic predisposition to possible adverse effects. Adverse effects commonly experienced by patients include myopathy (a well-recognized cause for therapy non-compliance) or, in extreme cases, rhabdomyolysis which can be fatal. Plasma concentrations of statins can vary greatly amongst patients. For example, a recent study observed as much as a 45-fold variability in plasma atorvastatin and rosuvastatin concentration in patients receiving the same dose (*21*). The

gene supported by the most evidence as a pharmacogenomic determinant of statin pharmacokinetics is SLCO1B1. The evidence for a link between the effects of the gene variants on statin-induced myopathy is particularly strong for simvastatin and this body of evidence has led to the creation of gene-based dosing recommendations for this particular statin (*22*). The CIPC (Clinical Pharmacogenomics Implementation Consortium) has recommended that patients with specific genetic variants be prescribed an alternative statin or that simvastatin dose be restricted to 20 mg/day. Besides these dose recommendations, a study of 647 PGx tested cardiology patients documented that clinical care supported with genetic test results and having risk information provided to patients modified patient behavior and improved patient adherence to statin therapy (*23*, *24*).

Clopidogrel

Clopidogrel blocks a receptor (P2Y12 ADP) on platelets and has been shown to reduce cardiovascular events in patients presenting with an acute coronary syndrome (ACS), particularly in those undergoing percutaneous coronary intervention (PCI). However, there is a large degree of inter-individual variability in the pharmacodynamic response to clopidogrel (*25*). One source of this variability is the metabolism of clopidogrel, which is a prodrug requiring biotransformation in the liver to generate its active metabolite. Cytochrome P-450 (CYP) isoenzymes, specifically CYP2C19, play a key role in clopidogrel metabolism and carriers of reduced-function genetic variants in CYP2C19 have lower active clopidogrel metabolite levels and diminished platelet inhibition. A recent meta-analysis of the association of CYP2C19 genotype and clinical outcomes in 9,685 patients indicated that carriage of even one reduced function CYP2C19 allele appears to be associated with a significantly increased risk of major adverse cardiovascular events, particularly stent thrombosis (*26*) . In line with these findings, the FDA has issued a Black Box Warning alerting physicians to the risks of diminished effectiveness on poor metabolizers.

Warfarin

Bleeding abnormalities can cause alarm for the cardiologist. The genes CYP2C9 and VKORC1 affect warfarin dose requirements, leading to potentially life threatening bleeding. Conversely with improper dosing, coagulation effects can lead to strokes and other embolic events. Warfarin, along with its S-enantiomer, accounts for the majority of the anticoagulation effect. CYP2C9 genetically controls the clearance of the S- enantiomer, accounting for about 40% of the anticoagulation effect, while 40% of patients have poor activity of the CYP2C9 gene. These effects lead to delays in achieving steady state and inaccurate international normalized ratio (INR) measurements. Genetic testing of CYP2C9 and VKORC1 can guide the selection of a target warfarin plasma level while combining these two genetic tests can potentially further improve anticoagulation control. A variety of algorithms have been published to accurately take advantage of this fact (*27*).

Psychiatry

Use of pharmacogenomics in psychiatry to help patients get better more quickly has been rapidly increasing, particularly in the treatment of major depressive disorder (MDD).

Up to 42% of patient variance in antidepressant response is associated with common genetic variations, and there are over 10 psychotropic medications for which the US Food and Drug Administration has approved black box drug labelling (*28*). Selective Serotonin Reuptake Inhibitors (SSRIs) are a first-line treatment option for major depressive and anxiety disorders. Inter-individual differences in pharmacokinetic parameter values and treatment outcomes with SSRIs are associated with CYP2D6 or CYP2C19 genetic polymorphisms.

Common adverse drug reactions induced by this drug class include central nervous system effects (e.g. insomnia, headache), gastrointestinal dysfunction, and sexual dysfunction. Serious adverse events such as arrhythmias caused by QT prolongation have been associated with SSRIs, particularly for individuals prescribed citalopram who are CYP2C19 poor metabolizers (*29*). Patients may be predisposed to poor therapeutic outcomes due to CYP2D6 or CYP2C19 genetic polymorphisms that alter SSRI bio-transformation. Paroxetine and fluvoxamine are extensively metabolized by CYP2D6 to compounds with little pharmacological activity towards serotonin reuptake inhibition (*30, 31*). Thus variations in CYP2D6 activity may result in lower or greater exposure to these drugs. Existing *CYP2D6* and/or *CYP2C19* genotype results may provide the potential benefit of identifying patients who are at increased risk of experiencing adverse drug reactions or therapeutic failure (*32*). Reducing the trial and error approach currently taking place in psychiatry with many of these common drugs serves to improve quality of care, getting patients feeling better more quickly and improving adherence to a successful regimen.

Pain Management

On August 25, 2016 the US Surgeon General issued a letter to all physicians nationwide about the urgent need to address the opioid overdose epidemic in the U.S. (*33*). His letter stated that since 1997 opioid deaths have quadrupled and currently nearly 2 million people in the US have an opioid use disorder. Evidence- based prescribing is one of three solutions that were advocated. Chronic pain management is an area where precision medicine can have a great impact on patient quality of life, considering the enormous variation in efficacy demonstrated to pain medications. One prominent finding from multiple studies is that the gene CYP2D6 is involved in the metabolism of almost all commonly prescribed opioid medications that could have an impact on the patients' therapeutic outcome (*34*). The monetary cost of managing chronic pain is estimated at over $600 billion in in US annually (*35*).

Oxycodone

In a randomized crossover double-blind placebo controlled study in healthy individuals those who were phenotyped as CYP2D6 ultra-metabolizers (UM) showed a 1.5- 6 fold increase in analgesic effect than normal metabolizers. Poor metabolizers (PM) had a 2-20 fold reduction of effects compared to normal metabolizers (*36*).

Tramodol

A meta-review of 56 studies by Lassen noted that the CYP2D6 polymorphism was the identified gene involved on the metabolism of tramadol and its effect on pain relief. The poor metabolism (PM) phenotype was associated with a 75 % reduction in the clearance of the active metabolite in one key study of 298 persons. (*37*)

Cancer pain

Cancer related pain is estimated to affect 49-57% of patients with curable cancer and up to 75% of patients with advanced disease (*38*). Studies suggest that pain is an independent factor for cancer survival (*39-42*). Opioids remain the cornerstone of clinical pain management. Currently genetic factors may be responsible for 12-60% of response variability in opioid therapy (*43*). Using pharmacogenomics has the potential to provide evidence-based treatment guidance. One key element of using pharmacogenomics for the treatment of cancer pain is employing a preemptive testing strategy in cancer patients so that the results will be available at the point of care when needed.

Conclusion

Pharmacogenomics (PGx) represents a dynamic component of Precision Medicine that is immediately available to and actionable by physicians in order to both reduce costs and improve patient care quality. Admera Health's approach to genetic testing and the test we offer differs significantly from others available in the market. The PGxOne™ Plus pharmacogenomic testing panel provides both physicians and patients a portable and lifetime record whereby any treating physician, not just the initial prescribing physician, can obtain pharmacogenomic results in a very easy to interpret format. The reports can be generated as a hard copy or fully integrated into an electronic medical record system. The patient can obtain a hard copy for their own records to bring with them should they change providers. Such portability, along with the market leading 50 gene scope of the panel covering over 220 drugs represents a paradigm shifting approach leveraging advancements in Precision Medicine, to promote comprehensive lifetime care. This novel, pharmacogenomic test-driven clinical approach addresses quality of care for each individual patient, based on their own genetic make-up, recognizing that patients' medications, health conditions and providers change, while at the same time promoting cost savings and quality enhancement in a value driven health environment.

**ZR is Vice President, Medical Affairs and XL is Clinical Scientist, Medical Affairs at Admera Health, 126 Corporate Drive, So. Plainfield, N.J. 07080 Tel (908)222-0533.*

References:

1. S. L. Van Driest *et al.*, Clinically actionable genotypes among 10,000 patients with preemptive pharmacogenomic testing. *Clin Pharmacol Ther* **95**, 423-431 (2014).
2. Centers for Medicare and Medicaid Services. Available from: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/Downloads/proj2014.pdf. CMS; 2013. Accessed November 27, 2015.
3. US Food and Drug Administration [homepage on the Internet. Costs associated with ADRs. Available from: http://www.fda.gov/NewsEvents/Testimony/ucm114949.htm. Accessed November 27, 2015.
4. J. S. Saldivar *et al.*, Initial assessment of the benefits of implementing pharmacogenetics into the medical management of patients in a long-term care facility. *Pharmacogenomics and personalized medicine* **9**, 1-6 (2016).
5. D. Brixner *et al.*, The effect of pharmacogenetic profiling with a clinical decision support tool on healthcare resource utilization and estimated costs in the elderly exposed to polypharmacy. *Journal of medical economics* **19**, 213-228 (2016).
6. J. H. Gurwitz, Polypharmacy: a new paradigm for quality drug therapy in the elderly? *Archives of internal medicine* **164**, 1957-1959 (2004).
7. Centers for Disease Control and Prevention and National Center for Health Statistics. Prescription Drug Use Continues to Increase: US Prescription Drug Data for 2007–2008. CDC; 2010. Available from: http://www.cdc.gov/nchs/data/databriefs/db42.pdf. Accessed November 27, 2015.
8. J. Benitez, M. R. Jablonski, J. D. Allen, J. G. Winner, The clinical validity and utility of combinatorial pharmacogenomics: Enhancing patient outcomes. *Applied & translational genomics* **5**, 47-49 (2015).
9. J. M. C. J.D. Allen, J.G. Winner, A.G. Marshak, B.M. Dechairo. (Colorado Springs, CO, 2014).
10. G. Ruano *et al.*, Length of psychiatric hospitalization is correlated with CYP2D6 functional status in inpatients with major depressive disorder. *Biomark Med* **7**, 429-439 (2013).
11. W. H. Chou *et al.*, Extension of a pilot study: impact from the cytochrome P450 2D6 polymorphism on outcome and costs associated with severe mental illness. *Journal of clinical psychopharmacology* **20**, 246-251 (2000).
12. T. Dervieux, B. Meshkin, B. Neri, Pharmacogenetic testing: proofs of principle and pharmacoeconomic implications. *Mutation research* **573**, 180-194 (2005).
13. K. R. Gardner, F. X. Brennan, R. Scott, J. Lombard, The potential utility of pharmacogenetic testing in psychiatry. *Psychiatry journal* **2014**, 730956 (2014).
14. J. Winner, J. D. Allen, C. A. Altar, A. Spahic-Mihajlovic, Psychiatric pharmacogenomics predicts health resource utilization of outpatients with anxiety and depression. *Translational psychiatry* **3**, e242 (2013).
15. L. Herbild, S. E. Andersen, T. Werge, H. B. Rasmussen, G. Jurgens, Does pharmacogenetic testing for CYP450 2D6 and 2C19 among patients with diagnoses within the schizophrenic spectrum reduce treatment costs? *Basic & clinical pharmacology & toxicology* **113**, 266-272 (2013).
16. J. S. McCombs *et al.*, The cost of antidepressant drug therapy failure: a study of antidepressant use patterns in a Medicaid population. *The Journal of clinical psychiatry* **51 Suppl**, 60-69; discussion 70-61 (1990).
17. C. J. Kobylecki *et al.*, CYP2D6 genotype predicts antipsychotic side effects in schizophrenia inpatients: a retrospective matched case-control study. *Neuropsychobiology* **59**, 222-226 (2009).
18. G. M. Murphy, Jr., S. B. Hollander, H. E. Rodrigues, C. Kremer, A. F. Schatzberg, Effects of the serotonin transporter gene promoter polymorphism on mirtazapine and paroxetine efficacy and

adverse events in geriatric major depression. *Archives of general psychiatry* **61**, 1163-1169 (2004).
19. J. Fagerness *et al.*, Pharmacogenetic-guided psychiatric intervention associated with increased adherence and cost savings. *The American journal of managed care* **20**, e146-156 (2014).
20. A. L. Kaufman *et al.*, Evidence for Clinical Implementation of Pharmacogenomics in Cardiac Drugs. *Mayo Clin Proc* **90**, 716-729 (2015).
21. M. K. DeGorter *et al.*, Clinical and pharmacogenetic predictors of circulating atorvastatin and rosuvastatin concentrations in routine clinical care. *Circulation. Cardiovascular genetics* **6**, 400-408 (2013).
22. J. A. Talameh, J. P. Kitzmiller, Pharmacogenetics of Statin-Induced Myopathy: A Focused Review of the Clinical Translation of Pharmacokinetic Genetic Variants. *Journal of pharmacogenomics & pharmacoproteomics* **5**, (2014).
23. S. L. Charland *et al.*, Providing patients with pharmacogenetic test results affects adherence to statin therapy: results of the Additional KIF6 Risk Offers Better Adherence to Statins (AKROBATS) trial. *The pharmacogenomics journal* **14**, 272-280 (2014).
24. J. P. Kitzmiller, D. K. Groen, M. A. Phelps, W. Sadee, Pharmacogenomic testing: relevance in medical practice: why drugs work in some patients but not in others. *Cleveland Clinic journal of medicine* **78**, 243-257 (2011).
25. D. J. Angiolillo *et al.*, Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. *Journal of the American College of Cardiology* **49**, 1505-1516 (2007).
26. J. L. Mega *et al.*, Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *Jama* **304**, 1821-1830 (2010).
27. P. Shahabi *et al.*, An expanded pharmacogenomics warfarin dosing table with utility in generalised dosing guidance. *Thrombosis and haemostasis* **116**, 337-348 (2016).
28. R. H. Perlis, Pharmacogenomic testing and personalized treatment of depression. *Clinical chemistry* **60**, 53-59 (2014).
29. K. A. Funk, J. R. Bostwick, A comparison of the risk of QT prolongation among SSRIs. *The Annals of pharmacotherapy* **47**, 1330-1341 (2013).
30. R. Mandrioli, L. Mercolini, M. A. Saracino, M. A. Raggi, Selective serotonin reuptake inhibitors (SSRIs): therapeutic drug monitoring and pharmacological interactions. *Curr Med Chem* **19**, 1846-1863 (2012).
31. S. W. Tang, D. Helmeste, Paroxetine. *Expert Opin Pharmacother* **9**, 787-794 (2008).
32. J. K. Hicks *et al.*, Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. *Clin Pharmacol Ther* **98**, 127-134 (2015).
33. http://i2.cdn.turner.com/cnn/2016/images/08/25/sg.opioid.letter.pdf.
34. T. Tverdohleb, B. Dinc, I. Knezevic, K. D. Candido, N. N. Knezevic, The role of cytochrome P450 pharmacogenomics in chronic non-cancer pain patients. *Expert opinion on drug metabolism & toxicology*, 1-9 (2016).
35. IOM (Institute of Medicine). 2011. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington, DC: The National Academies Press.
36. C. F. Samer *et al.*, The effects of CYP2D6 and CYP3A activities on the pharmacokinetics of immediate release oxycodone. *British journal of pharmacology* **160**, 907-918 (2010).
37. D. Lassen, P. Damkier, K. Brosen, The Pharmacogenetics of Tramadol. *Clinical pharmacokinetics* **54**, 825-836 (2015).
38. S. C. Teunissen *et al.*, Symptom prevalence in patients with incurable cancer: a systematic review. *Journal of pain and symptom management* **34**, 94-104 (2007).
39. S. Halabi *et al.*, Pain predicts overall survival in men with metastatic castration-refractory prostate cancer. *J Clin Oncol* **26**, 2544-2549 (2008).

40. C. Quinten *et al.*, Baseline quality of life as a prognostic indicator of survival: a meta-analysis of individual patient data from EORTC clinical trials. *Lancet Oncol* **10**, 865-871 (2009).
41. T. J. Smith *et al.*, Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival. *J Clin Oncol* **20**, 4040-4049 (2002).
42. J. E. Herndon, 2nd *et al.*, Is quality of life predictive of the survival of patients with advanced nonsmall cell lung carcinoma? *Cancer* **85**, 333-340 (1999).
43. A. Hajj, L. Khabbaz, J. L. Laplanche, K. Peoc'h, Pharmacogenetics of opiates in clinical practice: the visible tip of the iceberg. *Pharmacogenomics* **14**, 575-585 (2013).
44. Y. Zhang, S. D. Somtakoune, C. Cheung, M. Listiawan, X. Feng, Therapeutic Application of Pharmacogenomics in Oncology. *The AAPS journal* **18**, 819-829 (2016).
45. H. L. McLeod, E. Y. Krynetski, M. V. Relling, W. E. Evans, Genetic polymorphism of thiopurine methyltransferase and its clinical relevance for childhood acute lymphoblastic leukemia. *Leukemia* **14**, 567-572 (2000).
46. X. Feng, D. Pearson, M. Listiawan, C. Cheung, Pharmacogenomic Biomarkers for Toxicities Associated With Chemotherapy. *US Pharmacist* **37**, 2-7 (2012).
47. X. Feng, D. Vyas, B. Guan, Novel immune and target therapy for skin cancer. *US Pharmacist* **37**, 7-11 (2012).