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Pharmacoeconomics of genotyping-based treatment decisions in patients with chronic pain

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Abstract

Introduction: Genotyping-based treatment decisions may optimize treatment response and minimize adverse drug events (ADEs) in patients with chronic pain.

Objectives: To estimate the financial impact of genotyping-based treatment decisions in patients with moderate to severe chronic pain in a managed care setting.

Methods: A budget impact model was built with a 1-year time horizon to estimate costs of genotyping-based treatment decisions in a 1000-patient cohort. The model includes drug costs, type and cost of ADEs, distribution of treatments used, and genotyping costs. Event rates and health care costs were derived from primary literature. Three patient cohorts were assessed with and without genotyping-based treatment decisions: no genetic testing; 50% genetic testing; and 100% genetic testing. Sensitivity analysis was performed varying costs, adherence, and the percentage of patients treated according to genotyping results.

Results: Medical and ADE costs varied by patient severity and genotyping rates. Without genotyping, drug and ADE costs ranged from $1,544,377 to $24,313,844. With genotyping-based treatment, total costs ranged from $1,780,922 to $18,868,032. Sensitivity analysis, varying costs, adherence, and genotyping rates suggested genotyping improves outcomes and is cost saving in patients with chronic pain.

Conclusion: Genotyping-based treatment costs are offset by reduced medication utilization and adverse event costs. Genotyping should be considered for patients with chronic pain in clinical practice and within clinical trials.

Keywords: Genotyping, Chronic pain

1. Introduction

Chronic noncancer pain is associated with a wide range of injury and disease and is a leading cause of health care utilization in the United States.[1,19,23] Conservatively, chronic pain affects nearly 40 percent more people than diabetes, heart disease, and cancer combined.[1,6,23] Chronic pain is the most common cause of long-term disability and associated with impaired physical and physiological well-being with significant use of health services.[6,27,28,36] In a managed care setting, patients with chronic pain have been estimated to incur nearly $32,000 in direct total costs per year.[25]

Several large studies have demonstrated an increasing trend in opioid use among noncancer patients with opioids becoming one of the most prescribed classes of medication for chronic noncancer pain in the United States.[6,15,30] Increased opioid use brings potential therapeutic benefit and a higher rate of adverse drug events (ADEs). Association between genetic polymorphisms and the analgesic efficacy and clinical outcome of opioid analgesics for noncancer pain provide the potential for personalized treatment approaches leading to lower ADEs and better pain management.[19]

Greater than half of the variance in pain response to morphine is hypothesized to be related to genetic variation.[30] Although there is a strong rationale for expecting benefits from gene-based therapy, the actual impact has not been well-studied.[26] The objective of this study was to estimate the potential financial impact of genotyping-based treatment decisions in patients with moderate to severe chronic noncancer pain in a managed care setting.

2. Methods

A budget impact analysis was conducted over a 1-year time horizon using overall and average cost per patient modeling based on a theoretical 1000-patient cohort. This model assumed that all patients suffered chronic noncancer pain. Three 1000-patient cohorts were assessed under varying genotyping-based

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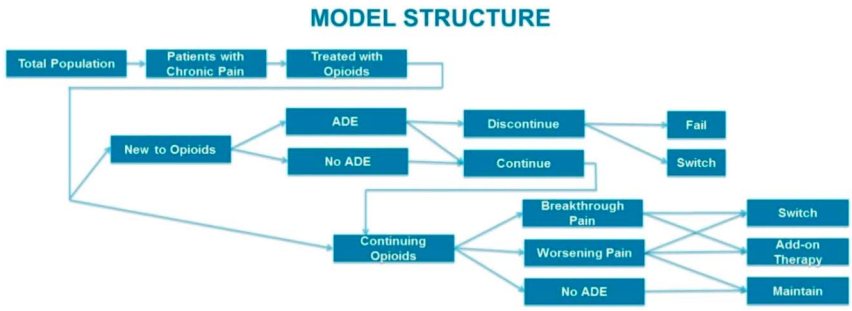

Figure 1. Model structure. ADE, adverse drug event.

testing scenarios. Patient cohorts were 100% mild cases; 50% mild and 50% severe cases; and 100% severe cases. The genotyping-based treatment decisions scenarios assessed were no genetic testing (standard of care), 50% genetic testing, and 100% genetic testing. The total annual costs assessed included medical, pharmacy, and genetic testing costs. Sensitivity analysis was performed to assess the robustness of outcomes by varying the model input parameters. The base case value for each parameter was varied from the default value ±50%.

An established model structure reflecting current clinical practice in the treatment of chronic noncancer pain was used.[4,11,12,14,16,21,22] The model was built in Microsoft Excel (Microsoft Corporation, Redmond, Washington) with a 1-year time horizon and included direct health care costs. The model was modified (**Fig. 1**) to include ADE rates, ADE costs, and the potential impact of genetic testing. Event rates, health care costs, and genetic testing impacts were derived from primary literature.[5,13,18,21] All costs were reported in 2016 US dollars.

2.1. Model inputs

2.1.1. Target population

The analysis focused on patients with mild (treated up to 180 days) and severe (treated more than 120 days) chronic pain treated with opioids. Mild cases were added each quarter over the course of the year and treated for 180 days.[21] Mild cases from the previous quarter continued as prevalent patients for the duration of their treatment. Treatment for severe cases started after 120 days of therapy and continued for 1 year.[17]

2.1.2. Drug treatments

Six treatment options and their rate of use were identified (**Table 1**).[21] The formulary allocation percentages, unit costs, daily average consumption, and copays for each treatment were obtained from the IMS National Prescription Audit reported in Merchant et al,[21] adjusted to 2016 dollars. These values were based on a weighted average by using a blended rate for the available strengths for each drug.

Table 1
Treatment type and rates.

Drug name	%
Tapentadol ER	10.0
Oxycodone CR	22.0
Morphine sulfate ER	27.6
Hydromorphone ER	0.7
Oxymorphone ER	6.3
Fentanyl transdermal	33.4
Total	100

CR, controlled release; ER, extended release.

2.1.3. Treatment adverse drug events

The model accounted for the costs of ADEs associated with each treatment (**Table 2**).[21] The ADE cost was based on Medicare payments for physician office visits, emergency department visits, hospitalization, surgery, diagnostic tests, and other interventions associated with treating opioid-induced side effects (OISEs) and pain management.[5] As not all patients seek medical care for treating OISEs or for inadequate pain management (some patients may self-manage), these costs were only assigned to the proportion of patients who received treatment because of an OISE. The model assumed that all patients who switched to another treatment or failed treatment would have an office visit, and that a smaller percentage of patients who failed opioid therapy would undergo other tests and procedures.

2.1.4. Genetic testing

The cost of genetic testing was set at $600 per test. Although some literature indicates that genetic testing may improve outcomes by as much as 75%, our model conservatively assessed the possibility of only a 25% improvement expressed increased efficacy, a reduction in ADEs, and reduced resource utilization.[2,30,33] The overall budget impact of using genetic testing to optimize treatment was calculated over a 1-year period.

3. Results

In the hypothetical cohort of 1000 patients with mild chronic noncancer pain, the health system incurs $1,544,377 in health care costs per year. With genetic testing guiding treatment decisions, medical and pharmacy costs decrease for these patients by $34,407 and $351,688, respectively. However, total costs increase over $230,000, as the medical and pharmacy savings do not fully offset the cost of testing in this cohort of patients (**Table 3**).

In the cohort with patients with 50% mild and 50% severe chronic noncancer pain, the total cost to the health system is over $12 million. With genetic testing guiding treatment decisions, medical and pharmacy costs decrease by $2,364,771 million and $818,884, respectively. Total costs are reduced by over $2.5 million, as the medical and pharmacy savings are more than offset by the cost of testing in this cohort of patients (**Table 4**).

Table 2

Adverse drug treatments.

Drug name	Percentage of patients with each opioid-induced side effects (OISE)				
	Nausea or vomiting	Somnolence	Dizziness	Pruritus	Constipation
Tapentadol ER	19.6%	12.1%	12.1%	5.4%	14.5%
Oxycodone CR	40.8%	16.9%	16.9%	13.9%	35.2%
Morphine sulfate ER	29.7%	33.6%	33.6%	20.1%	43.2%
Hydromorphone ER	33.5%	50.4%	50.4%	20.8%	27.6%
Oxymorphone ER	38.8%	18.3%	18.3%	15.7%	26.9%
Fentanyl transdermal	44.0%	22.0%	12.0%	6.5%	10.0%

CR, controlled release; ER, extended release.

In the cohort with patients with 100% severe chronic noncancer pain, the total cost to the health system is over $24 million. With genetic testing guiding treatment decisions, medical and pharmacy costs decrease for these patients by $4,695,177 million and $1,379,039, respectively. Total costs are reduced by over $5 million, as the medical and pharmacy savings are more than offset by the cost of testing in this cohort of patients (**Table 5**).

Sensitivity analysis–varying benefits of genotype-guided treatment and efficacy assumptions by ±10% made little difference to any of the scenarios assessed model results.

4. Discussion

Both patients and physicians want efficient, effective pain relief without ADEs. Currently, management of chronic, noncancer pain often takes an empirical, step-wise approach, starting with nonopioid analgesics and progressing to opioids. In addition to their addiction potential, opioids are fraught with a myriad of other side effects including life-threatening ones. Thus, identification of patients who might not respond appropriately to usual doses of an opioid, or who may be at an increased risk of an adverse drug reaction, would be helpful to both the clinician and patient. Much of the variability in opioid pharmacokinetics and pharmacodynamics is due to variations in the genotypes of individuals, especially about variations in the cytochrome P4502D6 and P4503A, UDP-glucuronosyltransferase 2B7, opioid receptor mu–1 (OPRM1), opioid receptor kappa–1, opioid delta receptor–1, drug transporter, and catechol-O-methyltransferase genes.[3] Therefore, knowledge of a patient's pharmacogenetic profile should provide a more rational approach to opioid management. Indeed, the results of this analysis suggest that treatment decisions based on genotyping results in fewer ADEs and lower medical and pharmacy costs in patients with moderate or severe pain.

For many drugs, the major groups of enzymes that metabolize them belong to the cytochrome P450 family, which are encoded by about 57 genes in humans. This family has been divided into 2 classes: class I composed of CYP1A1, CYP1A2, CYP2E1, and CYP3A4, which do not have important functional polymorphisms and are active in metabolizing procarcinogens and drugs; and class II composed of CYP2A6, CYP2B6, CYP2C9, CYP2C19, and CYP2D6, which are highly polymorphic and are important for the metabolism of many drugs.[29] Based on genetic analysis, patients may be broadly classified into poor metabolizers (PMs) if they carry 2 defective alleles resulting in an inactive enzyme, intermediate metabolizers with either 1 or 2 defective alleles leading to an enzyme with reduced activity, extensive metabolizers with 2 functional alleles and normal enzyme activity, and ultrarapid metabolizers (UMs) with more than 2 active gene copies and increased enzyme activity. With a drug such as codeine that is a prodrug and must be metabolized to morphine for full analgesic effect, a PM will have decreased efficacy because of low biotransformation to morphine, whereas an UM may develop a morphine overdose due to excessive biotransformation. Indeed, 2 case reports illustrate this issue: a 73-year-old man who had a UM developed life-threatening respiratory depression after 3 days of treatment with codeine; and an infant died of morphine overdose after breast feeding from a mother who was a CYP2D6 UM and was taking codeine.[10,20] CYP2D6 variants are also major determinants of the metabolism of hydrocodone, oxycodone, and tramadol, with PM demonstrating decreased efficacy and UM increased toxicity.[7,9,24,31,32,34] Methadone is primarily metabolized by CYP2B6 and UM that are at increased risk for cardiotoxicity.[8,35] Although fentanyl is metabolized by CYP34A, it is the opioid receptor's polymorphisms that affect efficacy. Some patients who are homozygous for the G allele of the OPRM1 rs1799971 marker have decreased efficacy relative to patients homozygous for the A allele.[37]

Ideally, for pharmacogenomic information to have its optimal effect, the testing should be performed on all adults before they require a drug that is susceptible to metabolic variation due to genetic polymorphisms. The results should be available in the electronic medical record in the order entry section, so when a physician orders a medication that, based on the patient's pharmacogenomic profile, may be toxic or nonefficacious at usual doses, an alert would appear with suggestions for alternative medications, much as drug–drug and drug–allergy alerts appear in today's electronic medical records. This "just-in-time" information

Table 3

Scenario A (mild cases).

	No genetic testing	Genetic testing	Difference
Medical costs	$137,626	$103,059	$34,407
Pharmacy costs	$1,406,751	$1,055,063	$351,688
Testing cost	$0	$622,800	$622,800
Total costs	$1,544,377	$1,780,922	$236,545

Table 4

Scenario B (mild and severe cases).

	No genetic testing	Genetic testing	Difference
Medical costs	$9,459,080	$7,094,311	($2,364,771)
Pharmacy costs	$3,275,539	$2,456,654	($818,884)
Testing cost	$0	$622,800	($622,800)
Total costs/savings	$12,734,620	$10,173,765	($2,560,855)

Table 5

Scenario C (severe cases).

	No genetic testing	Genetic testing	Difference
Medical costs	$18,780,578	$14,085,401	($4,695,177)
Pharmacy costs	$5,533,267	$4,154,228	($1,379,039)
Testing cost	$0	$622,800	($622,800)
Total costs/savings	$24,313,844	$18,868,032	($5,447,268)

is most likely to result in more appropriate drug prescribing, enhanced patient safety, and health care cost savings.

4.1. Limitations

Despite using a 25% improvement from genetic testing, the lack of published point estimates makes it difficult to estimate the full benefits of genotype-based treatment (eg, clinical improvement, reduction in ADEs, and total reduction in costs). Another limitation is that the model underestimates the full benefits of genotyping, as it does not take into account societal costs such as quality of life, work productivity, suicide, and caregiver burden nor the indirect costs associated with the clinical interpretation of the tests. The model assessed a limited set of therapy options; a future study that identifies potential drug–gene interactions and drug–drug–gene interactions may lead to a more comprehensive and effective method for predicting which patients are most likely to experience adverse drug reactions. Although no specific genetic tests or testing companies are recommended in this study, research identifying the benefits of genetic testing may benefit companies like Pathway Genomics, the sponsor of this study. Finally, the model is based on the established literature and may underestimate or overestimate the cost and outcomes if practice patterns have changed since the underlying model was developed.

5. Conclusion

The results of this budget impact model suggest genotyping-based treatment reduces medical and pharmacy costs for chronic pain sufferers. For mild pain sufferers, the reduction in medical and pharmacy costs do not fully offset the cost of testing. In populations with 50% or 100% patients with severe noncancer chronic pain, genetic testing costs are more than offset by reduced medical and pharmacy costs resulting in a net savings to the health system.

Disclosures

The authors have no conflict of interest to declare.

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