

## Comprehensive Review

## A Review of the Role of Genetic Testing in Pain Medicine

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**Background:** Pain clinicians have always been challenged by the variability of response to pain treatment. Differences in the degree of pain stimulation and pain sensitivity, weight and age differences, prior opioid use and tolerance, as well as the differences in bioavailability of various opioid formulations have been cited as causes for the wide variability in analgesia seen with opioids. Genetics may explain the variability of responses and help to predict more effective (or less dangerous) medication choices and doses. Genetics may also help to predict the response to specific opioids and antidepressants.

**Objectives:** In this review article, we discuss the genetic influence of nociception, analgesia, and hyoanalgesia. The CYP450 enzymes involved in the metabolism and activity of opioids and adjuvant analgesics are genetically controlled, as are the opioid receptors and a variety of brain chemistries.

**Methods:** This article discusses the specific pain implications of genetic variations in CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A7, OPRM1, OPRK1, OPRD1, COMT, GABA, UGT, MC1R, GCH1, ABCB1, P-glycoprotein, 5HTR1A, 5HTR2A, MTHFR, CACNA2D2, and 5-HTTLPR.

**Results:** Recent research findings suggest the relationship between genetic predisposition and clinical behavior, including the risk of opioid misuse and addiction. While urine drug testing may hint at genetic issues regarding opioid metabolism, cheek swab DNA testing has become economically viable, and we review the current and future genetic pain issues that may influence the decisions that pain clinicians make every day.

**Conclusion:** Genetic testing may explain and predict many of the clinical responses seen with opioids and adjuvant medications, and may help the clinician identify those patients at genetic risk of opioid misuse and addiction.

**Key words:** Genetics, genetic testing, opioid metabolism, drug interactions, urine drug testing, opioid risk evaluation, opioid receptors

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*“If it were not for the great variability among individuals, medicine might as well be a science and not an art.” William Ostler (1892)*

Clinicians who treat pain have noted that the response to opioids varies widely among patients, with opioid dose requirements varying in the clinical setting by as much as 40-fold (1). Differences in the degree of pain stimulation (a

fractured femur compared to a splinter in the toe) and pain sensitivity, weight and age differences, prior opioid use and tolerance, as well as the differences in bioavailability of various opioid formulations have been cited as causes for the wide variability in

analgesia seen with opioids. However, even measuring blood levels of opioids does not predict analgesia (2). The minimum effective blood level of opioids can vary widely (3). Just as there are differences in hair and eye color, there are differences in response to pain and to analgesic medications. We are beginning to recognize that, as is seen in much of medicine in the twenty-first century, genetics may explain the variability of responses and help to predict more effective (or less dangerous) medication choices and doses.

By identifying the genetic risks and the most effective analgesic for an individual patient, the clinician (at least theoretically) could improve the efficacy of the pain medication and decrease the risk of iatrogenically-induced overdose, addiction, and death.

### **Nociception**

Based on animal studies (4), there are at least 5 genetically distinct types of nociception:

1. Thermal nociception
2. Spontaneous responses to noxious chemical stimuli
3. Thermal hypersensitivity
4. Mechanical hypersensitivity
5. Afferent input-independent hypersensitivity

However, surgical trauma releases hundreds of chemicals over the first 48 hours, and local gene expression likely contributes to the pain phenotype (5). There are also genetic influences on nociceptive-signaling pathways, CNS plasticity, mechanisms influencing mood, and gender-related mechanisms (6). Unfortunately, experimental pain, such as dental surgery, may not be extrapolated to major surgery. In addition, anxiety, depression, and suffering can influence pain responses, and are hard to control experimentally.

### **Genetic vs Environmental Factors**

In the classic "nature versus nurture" scenario, investigators use twin pairs, both identical and fraternal, reared together or apart, to evaluate the heritability of a feature or a condition. Several twin studies have looked at pain conditions, and concluded that migraines have a 39% – 58% genetic contribution (8-10), low back pain a 21% – 67% genetic contribution (11-13), and menstrual pain 55% (14). In general, significant familial effects account for 24% – 32% of the observed variance detected for heat and cold pressor pain thresholds and opioid-mediated elevation in cold pressor pain tolerance (15).

### **Genetics of Analgesia**

When we give an opioid for pain relief, there is a continuum of responses, from good analgesia and improvement in function, to poor analgesia, to tolerance, to physical dependence, and to addiction (16). There are several ways that genetics can influence analgesic response, including drug metabolism enzymes, drug transporters, opioid or other pain medication receptors, and structures involved in the perception and processing of pain. There are 2 specific genetic issues involving analgesia:

1. The genetic contribution of a variety of different pain types, because if a genetic basis underlies how pain is expressed, including the varying mechanisms of nociceptive, neuropathic, and visceral pain, then the potential exists for new analgesic targets.
2. The genetic influence on drug effectiveness and safety (17).

### **Genetic Hypoanalgesia**

There are several well-studied hereditary disorders of insensitivity to pain, including "hereditary insensitivity to pain with anhidrosis" (18), familial dysautonomia (Riley-Day syndrome) (19), Lesch-Nyhan syndrome (20,21), de Lange syndrome (22), and Tourette's syndrome (23). More than 200 candidate genes have been identified that may be involved in pain processing.

### **Drug Actions**

Drug pharmacokinetics describes a patient's metabolic status, or their ability to metabolize certain drugs. As an example, a patient with impaired metabolism may be unable to activate a prodrug such as codeine into the active morphine metabolite. Pharmacodynamics describes a patient's ability to respond to a drug at the level of the drug target or receptor. Here, an example would be a patient who has a nonfunctional receptor for a certain drug who will be unable to respond to that drug regardless of the dosage. Pharmacogenetics describes the genetic influence on both the pharmacokinetics and pharmacodynamics. Polymorphic genes that encode the drug-metabolizing enzymes, drug transporters, drug receptors, and other proteins can serve as valuable markers, predictive of the efficacy and adverse responses in human subjects. Pharmacogenomics is the science that examines the inherited variations in genes that dictate drug response, predicting whether a patient will have a good response to a drug, a bad response to a drug, or no response at all. So, pharma-

cogenetics refers to the study of inherited differences in drug metabolism and response, while pharmacogenomics refers to the general study of the many genes that determine drug behavior. The distinction between the 2 terms is considered arbitrary and they can be used interchangeably.

Today, many of the complexities of human drug response are sufficiently well understood to transform the field of pharmacogenetics from a descriptive to a predictive science, leading to safer and more effective prescribing and dosing (17). This kind of testing is being used more frequently in cancer treatment (e.g. BRCA1 in breast cancer) and internal medicine (VKORC1 for warfarin metabolism), but only very recently in pain medicine.

### **Pain Conditions**

Allele-based association studies are expected to shed light on the medical mystery of why pain persists in some patients but not others, despite seemingly identical traumas.

In other words, why do some diabetic patients develop only numbness as the manifestation of their peripheral neuropathy while others with the same blood sugar fluctuations develop a painful peripheral neuropathy? Why do only some shingles patients develop post herpetic neuralgia? Why don't all of the persons in a car accident develop the same whiplash pain?

Part of the issue may be "piss poor protoplasm," a term that many young doctors learned as part of their medical training. In a study of Chinese volunteers, investigators found that an allele (COL9A2), which codes for a chain of collagen, was associated with a 4-fold increase in the risk of developing annular tears in people ages 30 to 39, and a 2.4-fold increase in the risk of developing degenerative disc disease and end-plate herniations in people ages 40 to 49 years old (24).

Another issue may be genetic predisposition of pain perception. COMT is an enzyme that inactivates biologically active catechols, including the neurotransmitters dopamine, noradrenaline, and adrenaline, which are involved in numerous physiological processes, including modulation of pain. Genetic variation in the COMT gene has been implicated in variable response to various experimental painful stimuli, variable susceptibility to develop common pain conditions, and the variable need for opioids in the medical management of pain (7).

### **Drug Interactions**

There are 3 major types of enzyme interactions. A substrate is any medication metabolized by that

enzyme. An inhibitor is a medication that slows the metabolism of another medication, which may result in excessively high blood levels, extended effect, and related toxicity; however, if this is a drug that has to be activated (a prodrug), there may be decreased effect. An inducer is a medication that boosts the metabolism of another medication, which may result in accelerated breakdown, increase clearance, shortened duration, subtherapeutic levels, or withdrawal; it may also cause increased activity in a prodrug.

### **Clinical Potential for Disaster**

There are potentially many drug interactions, and that risk increases with increased numbers of medications being used. Glintborg et al (25) looked at 200 patients discharged from the hospital; the average age was 75, and the median number of drugs used was 8 (with a range of 1 to 24). They calculated a potential of 476 drug interactions in 63% of the patients. In another study, patients who were taking 3 to 5 drugs had a 29% risk of interactions, while patients who were taking 11 or more drugs had a 96% risk of interaction. Only 1% of patients were aware of the potential for drug-drug interactions (26).

### **Cytochrome P450 Enzymes (CYP450)**

The CYP450 enzyme system is a heme-containing, microsomal drug-metabolism superfamily involved in biosynthesis and degradation of endogenous compounds, chemicals, toxins, and medications. There have been 57 enzymes identified in humans, and they are divided into families, subfamilies, isoenzymes, and allele variants (27). Metabolism of most currently used drugs occurs by about 8 clinically relevant enzymes: CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A7, all of which have different (but partially overlapping) catalytic activities. Many of the medicines commonly used are substrates (Table 1), inhibitors (Table 2), or inducers (Table 3) of medicines used in pain treatments. Table 4 reflects some of the recently identified CYP3A7 interactions (28).

There are also multiple potential interactions between herbs, supplements, or foods and prescription medications. For instance, intestinal CYP3A4 concentration can be decreased by 47% within 4 hours of grapefruit consumption, decreasing the absorption of many medicines, including methadone (29). St. John's wort, commonly taken for depression, induces CYP3A4 and CYP2C19 enzymes. The induction of CYP2C19 "enormously" decreased the blood levels

of omeprazole (30). St. John's wort can decrease verapamil, midazolam, statins, methadone (31), digoxin, and HIV medication levels (via CYP3A4 induction) (32), as well as potentially causing a serotonin syndrome with SSRIs.

Smoking is a potent inducer of CYP1A2, leading to decreased caffeine levels (which may be the cause of the increased agitation seen with smoking cessation, as caffeine levels increase when the induction stops). Since methadone is also metabolized by CYP1A2, a smoker stabilized on methadone can have dangerous increases in methadone levels with smoking cessation (33). In a study comparing smokers to nonsmokers, the smokers had higher pain scores, and took larger doses of hydrocodone, but had significantly lower serum levels of hydrocodone (34).

### Why Consider Genetic Testing?

There are several potential reasons to consider genetic testing, including (but not limited to) the ability to identify or predict likelihood of efficacy and toxicity. Specifically, genetic testing may provide instructive data to improve the selection, dosing, and evaluation of medical treatment. One of the most common uses of genetic testing in pain medicine is the evaluation of drug metabolism.

Drugs are metabolized slowly in individuals carrying a genetic polymorphism that causes absent or decreased enzyme activity, and these individuals are at an increased risk for adverse drug reactions or therapeutic failure. However, drug therapy could be ineffective if the drug is metabolized too quickly because of a genetic polymorphism. Knowledge of these polymorphisms be-

Table 1. Commonly used substrates.

1A2	2B6	2C19	2D6	3A4
Amitriptyline	Bupropion	Barbiturates	Codeine	Alprazolam
Nabumetone	Methadone	Topiramate	Tramadol	Midazolam
Desipramine	Ketamine	Diazepam	Meperidine	Cyclosporine
Tizanidine	Testosterone	Amitriptyline	Oxycodone	Sildenafil
Imipramine		Imipramine	Hydrocodone	Indinavir
Acetaminophen	2C9	Clomipramine	Dextromethorphan	Verapamil
Cyclobenzaprine	Valproic acid	Sertraline	Amitriptyline	Atorvastatin
Clozapine	Piroxicam	Citalopram	Nortriptyline	Lovastatin
Fluvoxamine	Celecoxib	Phenytoin	Doxepin	Digoxin
Theophylline	Ibuprofen	Carisoprodol	Tamoxifen	Amiodarone
Melatonin	Warfarin	Clopidogrel	Amphetamines	Methadone
Duloxetine			Duloxetine	Erythromycin
Caffeine			Metoclopramide	Trazodone
Lidocaine			Propranolol	Fentanyl
Warfarin			Venlafaxine	Buprenorphine
Methadone				

Table 2. Common inducers of CYP enzymes

1A2	2C9	2C19	2D6	3A4
Carbamazepine	Rifampin	Carbamazepine	Carbamazepine	Carbamazepine
Griseofulvin	Ritonavir	Rifampin	Phenobarbital	Phenytoin
Lansprazole	Barbiturates	Ginko	Phenytoin	Nevirapine
Omeprazole	St. John's Wort		Rifampin	Modafinil
Ritonavir			Dexamethasone	Topiramate
Tobacco				Butabotal
St. John's Wort				St. John's Wort

Modified from Indiana University web site{, #150} and Genelex web site,{Oesterheld, 2012 #151} among others].

Table 3. Common inhibitors of CYP enzymes.

1A2	2C9	2C19	2D6	3A4
Fluvoxamine	Fluvoxamine	Fluoxetine	Duloxetine	Ketoconazole
Ciprofloxacin	Paroxetine	Fluvoxamine	Cimetidine	Erythromycin
Mexiletine	Amiodarone	Paroxetine	Sertraline	Mifepristone
Verapamil	Modafinil	Topiramate	Fluoxetine	Nefazodone
Caffeine	Tamoxifen	Modafinil	Haloperidol	Grapefruit
Grapefruit juice		Birth control pill	Methadone	Indinavir
			Paroxetine	Ritonavir
			Quinidine	Verapamil
			Celecoxib	Diltiazem
			Bupropion	
			Ritonavir	
			Amiodarone	
			Metoclopramide	
			Chlorpromazine	
			Ropivacaine	

Modified from Indiana University web site{, #150} and Genelex web site,{Oesterheld, 2012 #151} among others.

fore beginning a drug therapy could help in choosing the right agent at a safe dosage, especially those drugs with a narrow therapeutic index and a high risk for the development of adverse drug reactions (ADRs) (35). In a literature review of ADRs from 1995 to 2000, more than one half of the drugs cited are metabolized by at least one enzyme with known poor functioning alleles (36).

### Types of Metabolizers

Patients can be classified by how effectively they metabolize a medication, which is based on how many copies of normal or abnormal alleles they inherited (Table 5). An extensive metabolizer (EM) has 2 normal or "wild type" alleles and is considered "normal." An intermediate metabolizer (IM) has one normal and one reduced allele or 2 partially deficient alleles. A poor metabolizer (PM) has 2 mutant alleles leading to a very limited or complete loss of activity, while the ultra rapid metabolizer (UM) has multiple copies of functional alleles leading to excess activity.

There is also an ethnic distribution of this polymorphism. Approximately 7% – 10% of Caucasians are CYP2D6 deficient (PM), but only 1% – 2% of Asians and 2% – 4% of African-Americans are poor metabolizers. However, approximately 30% of Asians and African-Americans have intermediate metabolism of CYP2D6. On the other hand, approximately 29% of Ethiopians, 10% of Southern Europeans, and 1% – 2% of Northern Europeans are ultra metabolizers (37). In psychiatry, 52% of the

Table 4. CYP3A7 interactions.

Compound	Action
Amiodarone	Inhibitor
Buprenorphine	Substrate
Caffeine	Substrate
Carbamazepine	Substrate
Cimetidine	Inhibitor
Ciprofloxacin	Inhibitor
Clotrimazole	Inducer
Codeine	Substrate
Dextromethorphan	Substrate
Erythromycin	Inhibitor
Fluconazole	Inhibitor
Fluvoxamine	Inhibitor
Gestodene	Inhibitor
Imipramine	Substrate
Ketoconazole	Inhibitor
Nefazadone	Inhibitor
Oxazepam	Substrate
Oxycodone	Substrate
Phenobarbital	Inducer
Phenytoin	Inducer
Propranolol	Substrate
Testosterone	Substrate
Verapamil	Inhibitor
Vincristine	Substrate

Modified from [www.genecards.org/cgi-bin/carddisp.pl?gene=CYP3A7&drugbank=115#drugbank](http://www.genecards.org/cgi-bin/carddisp.pl?gene=CYP3A7&drugbank=115#drugbank).

psychiatric and 62% antidepressant or antipsychotic drugs are metabolized by CYP2D6 (38). A prospective one-year clinical study of 100 psychiatric inpatients suggested a trend toward longer hospital stays and higher treatment costs for UMs and PMs of CYP2D6 (39). Tamoxifen must be metabolized via CYP2D6 to endoxifen to be effective; a PM might therefore be at risk for failure of breast cancer treatment (40). And, as we will see shortly, CYP2D6 activity can have substantial influence on the opioids that are commonly used in pain management.

These alternate genes, known as SNPs (single nucleotide polymorphisms), are identified by letters or numbers. For example, normal functional activity alleles of the CYP2D6 gene are designated CYP2D6\*1 and CYP2D6\*2. The 4 most common mutant alleles are CYP2D6\*3, CYP2D6\*4, CYP2D6\*5, and CYP2D6\*6 and account for 93% – 97% of the PM phenotypes in the Caucasian population.

#### **OPRM1**

The gene encoding the mu-opioid receptor is OPRM1. The analgesic efficacy of mu-acting drugs has been linked to the 118 SNP of OPRM1, the gene encoding the mu-1 receptor. The frequency of the variant G allele varies from 10% to 48% depending on the population studied. Liu and Wang (41) reported a prevalence of 31.3% of the AA (wild type) genotype, 58.3% of the AG genotype, and 10.4% of the GG genotype. Studies show that patients carrying the GG (homozygous variant) genotype require much higher opioid doses to achieve pain relief (42,43). OPRM1 AA patients required an average dose of 112 mg morphine/24 hrs, AG patients required 132 mg morphine/24 hrs, and GG patients required 216 mg morphine/24 hrs (44).

OPRM1 genetic variants may also explain differences in response to intrathecal opioid analgesia. Two hundred pregnant women were prospectively recruited and genotyped for the 304 A/G polymorphism. Those requesting neuraxial labor analgesia were given intrathecal fentanyl; the investigators found that women with the G variant were more responsive to intrathecal fentanyl (45), suggesting that different opioids have different responses to different polymorphisms. OPRM1 mutations have also

been associated with heavy alcohol use (Asp40 allele) (46), heroin dependence (47), nicotine abuse (48), and chemotherapy-induced neuropathic pain (41).

#### **OPRK1**

The gene OPRK1 encodes the kappa-opioid receptor; the binding of dynorphins to the kappa-opioid receptor has been shown to produce aversive states, which may prevent the development of opioid use reinforcement. Variations in the genes encoding the kappa-opioid receptor are associated with the risk for alcohol dependence (49), opioid addiction (50,51), and schizophrenia (52). The 36G>T alleles are also associated with postoperative and chronic pain (53).

#### **OPRD1**

The delta-opioid receptor gene is called OPRD1. Mutations in this gene have been associated with cocaine and opioid addiction (54). A study of more than 1,400 heroin addicts found that the delta opioid gene (OPRD1) alleles rs2236857 and rs58111 had a high association with heroin abuse (55).

#### **COMT**

As previously mentioned, COMT metabolizes catecholamines and is important for dopaminergic and adrenergic/noradrenergic/serotonin neurotransmission. It has been estimated that approximately 10% of the variability in pain sensitivity is related to COMT SNPs (44). Polymorphism at amino acid position 158 (Val158Met) has been shown to impact human pain response. Individuals with a homozygous 158Met genotype showed diminished regional mu-opioid response to pain when compared with heterozygotes (56), and has been associated with decreased morphine requirements for analgesia (57). Pain catastrophizing and low COMT activity was associated with higher postoperative pain score after shoulder surgery (58). COMT is also associated with depression and the response to antidepressant medications; several alleles are being studied, including Val158Met, to predict response to specific antidepressant medications (59).

#### **GABA**

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the human brain, which plays a role in regulating neuronal excitability. The 1519T>C GABA (A) alpha 6 gene is associated with alcohol dependence (60) and methamphetamine dependence (61).

Table 5. Population distribution of isoenzymes.

Gene	PM	IM	EM	UM
CYP2C9	2-4%	>35%	60%	NA
CYP2C19	2-20%	24-36%	14-44%	30%
CYP2D6	10%	35%	48%	7%

**UGT**

Uridine diphosphate glucuronosyltransferase is involved in the metabolism of many drugs (such as morphine and acetaminophen) as well as the biotransformation of important endogenous substrates (e.g. bilirubin, ethinylestradiol) (62). UGT2B7 metabolizes morphine into 2 different compounds – morphine-6-glucuronide (M6G), which is analgesic, and morphine-3-glucuronide (M3G), which actually causes pain and may account for some of the opioid-induced-hyperalgesia (OIH) seen with high levels of morphine (63). UGT2B7 inhibition can influence the levels of M3G compared to M6G. A study of 20 patients with sickle cell disease showed that the presence of UGT2B7 -840G allele was associated with significantly reduced glucuronidation of morphine, contributing to the variability of hepatic clearance of morphine (64). Tamoxifen, diclofenac, naloxone, carbamazepine, TCAs, and benzodiazepines are all inhibitors of UGT2B7 (65), potentially leading to opioid hyperalgesia (another reason not to use benzodiazepines).

**MC1R**

The Melanocortin-1 receptor (MC1R) gene variants show evidence of potential for targeted analgesia based on sex. There is evidence that women, more than men, respond to kappa-induced analgesia, which is mediated by the MC1R (66). Inactive MC1R variants have been associated with increased opioid analgesia from morphine-6-glucuronide and, in women only, of kappa-opioid agonists (57). Women carrying 2 nonfunctional alleles displayed greater pentazocine (kappa agonist) analgesic response. Interestingly, 75% of individuals with red hair and pale skin phenotypes carry 2 or more inactivate variants of the MC1R (66,67).

**GCH1**

Guanosine triphosphate cyclohydrolase 1 (also known as dopa-responsive dystonia gene) codes for a pathway that synthesizes tetrahydrobiopterin (BH4), a cofactor essential in neurotransmitter synthesis, which is up-regulated in neuropathic and inflammatory pain (68). It is associated with pain sensitivity susceptibility to chronic widespread pain (CWP) (69).

**ABCB1**

Mutations of the ATP-binding cassette sub-family B gene (ABCB1) (SNP 1236C>T) have been associated with higher methadone doses (>150mg/d) in methadone-maintained heroin addicts (70). There may be differ-

ences between male and female patients at this gene as well; men with the TT allele had higher beta-endorphin levels than men who had the more common CC allele, while the opposite was true in women (71), and women had a higher risk of postoperative c-section pain 3 months after surgery with the TT allele (72). There has been noted to be an association between the ABCB1/MDR1 and the OPRM1 gene polymorphisms related to morphine pain relief; combining evaluation of the 2 genes allowed detection of 3 response groups, resulting in a sensitivity close to 100% and specificity of more than 70% in predicting morphine relief (73).

**P-glycoprotein**

The P-glycoprotein gene (permeability glycoprotein, abbreviated as P-gp or Pgp), also known as multidrug resistance protein 1(MDR1), is another glycoprotein that in humans is encoded by the ABCB1 gene. ABCB1/MDR1 codes for a transport protein in the liver, kidney, and GI tract, as well as outward transport at the blood-brain barrier (74). Mutations such as 3435C>T, that confers decreased transporter function, have been associated with increased respiratory depressive effects of fentanyl, presumably because of decreased excretion (57). The ABCB1 / MDR1 gene is also a major determinant of morphine bioavailability and the OPRM1 gene encodes for the opioid receptor, the primary site of the action of morphine. Mutations in either of these 2 genes affect the efficacy of morphine. Campa et al (73) genotyped 145 patients for the SNP C3435T of the ABCB1/MDR1 gene and the A80G SNP of the OPRM1 gene; they observed 3 pain groups: strong responders, intermediate responders and nonresponders with close to 100% sensitivity and 70% specificity ( $P < 0.00001$ ).

**5HTR1A and 5HTR2A**

The serotonergic (5HT) system is involved in modulating depression and physical function. A recent study of 224 patients 6 months after lumbar disc surgery found that female patients carrying at least one A allele of the 5HTR2A 1438A/G SNP had significantly higher depression scores when they had significant postoperative pain. In addition, patients homozygous for the 5HTR1A 1019G allele had higher Beck Depression Inventory scores, and women who were homozygous for either the 5HTR1A G allele or the 5HTR2A A allele had lower levels of postoperative functioning than did the other genotypes, suggesting that 5HTR1A and 5HTR2A genes have gender-dependent effects on depression and physical function in patient with pain (75).

### **MTHFR**

Methylene tetrahydrofolate reductase (MTHFR C677T) is a gene that codes for the enzyme involved in the conversion of homocysteine to methionine involved in cell replication and DNA methylation. The C677T variant has been associated with early heart disease and strokes, as well as depression (76), schizophrenia (77), autism (78), migraines (79), fibromyalgia (80), bipolar disorders (81), and Alzheimer's syndrome (82).

### **CACNA2D2**

The calcium channel fragment gene CACNA2D2 encodes one of the alpha2/delta subunits of the voltage dependent calcium channel complex (83). This calcium channel interacts with the G-protein of the mu opioid receptor, with potential effects on opioids, as well as being the effective site for gabapentin and pregabalin (84). Patients with a high response to opioids (specifically to remifentanil) had a much higher incidence of the GG CACNA2D2 allele (71).

### **5-HTTLPR**

Serotonin-transporter-linked polymorphic region (5-HTTLPR) is the gene that codes for the serotonin transporter molecule. There are at least 14 allelic variants, many of which appear to be related to post traumatic stress disorder (PTSD) (85,86), suicidal behavior (87), migraines (88), postpartum depression (89), and irritable bowel syndrome (90), but not fibromyalgia (as had been previously reported) (91). Remifentanil had a significantly better response in patients with SA/SA and SA/LG genotypes compared to LA/LA genotypes.

### **Personality and Genetics**

A recent study published by Kuhnen et al (92) suggested that different human behavior is associated with the presence of the 5-HTTLPR short allele (SL/SS). The study compared the 5-HTTLPR LL (long allele homozygous), SL (long/short allele heterozygous), and the SS (short allele homozygous). Aside from decreased financial risk taking, the SL and SS subjects had an increase in neurotic behavior. This correlated with increased likelihood of being anxious, worrying, feeling vulnerable, having self-doubt, and more importantly, they were also prone to feeling negative emotions (92). The inability to correctly cope with negative emotions can cause an exacerbation of pain (93). Patients that fit in this category also have a tendency to focus on and magnify pain sensations, which is called pain catastrophizing. This brings on the possibility of depression.

5-HTTLPR may also be related to excess craving disorder behaviors such as alcoholism (94), heroin addiction (95), and smoking. In alcoholic detoxification, the LL genotype was significantly associated with higher relapse rate (96). Because increasing evidence shows that chronic pain is tied into genetic variation (93), understanding the genetic makeup of individuals can further pain medicine in a relatively new way.

Many studies have been published relating certain genetic variations with aberrant behaviors and risk-related co-morbidities. Those genes include the dopamine D2 receptor A1 allele (97,98), the dopamine D4 receptor (99), and others related to neurotransmitters in the mesolimbic pathways.

### **Genotype-based Dose Adjustments (Gene-dose)**

Standard dose adjustments look at the differences in pharmacokinetic parameters, such as clearance and area under the curve (AUC). Genotype-based dose adjustments would suggest a standard dose (say, 2 tablets of medication X) for an EM; however, a PM might need only one tablet, an IM might need 1.5 tablets, and an UM might need 3 or more tablets of the same medication to get the same effect (100). In a study of antidepressant drugs, it was calculated that, for a CYP2D6 PM patient taking nortriptyline, the therapeutic dose would be 50mg, while an UM patient would need a dose of 500mg to reach the same blood levels (100).

### **CYP2D6 Influence on Opioids**

Codeine is an inactive compound (a prodrug), metabolized by CYP2D6 into its active form, morphine. It has only a weak affinity for the mu receptor, 300 times less than morphine (101). Therefore, CYP2D6 PM patients and patients taking CYP2D6 inhibitors (see Table 3) who are given Tylenol#3 are really being given only Tylenol, while UM patients may have dangerously high levels of morphine after standard doses (102). Tramadol is metabolized by CYP2D6 to its M1 metabolite, which is at least 6 times more potent than the parent compound (103). Hydrocodone displays weak binding capacity for the mu receptor, but the CYP2D6 enzyme demethylates it into hydromorphone, which has much stronger mu binding than hydrocodone (104). Otton et al (105) found that subjects identified as EM reported more "good opiate effects" and fewer "bad opiate effects" than PM or EM patients pretreated with quinidine (a potent CYP2D6 inhibitor). They concluded that activity of CYP2D6 may limit the abuse liability of



hydrocodone. A study looking at 25,200 urine samples from patients taking only hydrocodone showed a 60-fold variability in hydrocodone/hydromorphone ratios. They identified 0.6% UM and 4% PM, with a 134-fold between-subject variability (106). Oxycodone is metabolized by glucuronidation to noroxycodone (which has less than 1% of the analgesia potency of oxycodone), and by CYP2D6 to oxymorphone. Oxycodone is an analgesic, not a prodrug; however, oxymorphone is an active metabolite of oxycodone, and may have significant impact on analgesia. Because oxycodone is dependent on the 2D6 pathway for clearance, it is possible that toxicity and overdose can occur with 2D6 inhibitors (107).

Yang et al (108) showed that 71% of a group of postoperative patients with acute severe pain were PM for CYP2D6, compared to other metabolizers. They also found that PMs of CYP2D6 who were smokers had more pain than the nonsmokers. UM of CYP2D6 required less morphine in the postoperative period than did any other CYP metabolizer group (109).

Drugs of abuse are also metabolized by CYP2D6. Methamphetamine acts as both a substrate and a competitive inhibitor of CYP2D6, while MDMA acts as a high affinity substrate and potent inhibitor of the enzyme, so that methamphetamine and MDMA users, regardless of their genotype, act as poor metabolizers of CYP2D6 (110).

### CYP3A4 Influence on Opioids

CYP3A4 is also involved in opioid metabolism. Fentanyl and buprenorphine are excreted via CYP3A4, and blood levels would be expected to rise in PM patients or those receiving CYP3A4 inhibitors (111). Methadone has been widely reported to be metabolized by CYP3A4 (112,113), though some evidence suggests that is primarily metabolized by CYP2B6 (114), and patients who are homozygous for the variant CYP3B6\*6 gene required lower doses of methadone than the heterozygotes or noncarriers (115).

### Other Influences on Analgesics

As another example, amitriptyline is metabolized by CYP2C19 to nortriptyline, which is then metabolized and excreted by CYP2D6. Genetic testing of CYP2D6 and CYP2C19 can identify patients at low or high risk for side effects of amitriptyline therapy. Carriers of 2 functional CYP2D6 alleles had a significantly lower risk of side effects than carriers of only one functional allele, with the lowest risk seen for carriers of 2 functional CYP2D6

alleles combined with only one functional CYP2C19 allele. (116). The authors noted that two-thirds (65%) of patients (normal CYP2D6 and normal to poor CYP2C19) could receive standard doses of amitriptyline (which is very inexpensive) with little or no side effects, but those patients with normal CYP2C19 and poor CYP2D6 were at very high risk for anticholinergic and mental side effects, and ought to be treated with newer (and more expensive) medications.

### Psychoactive Drugs

A wide variety of treatment options are available in the realm of psychoactive medication. These options can become a complex issue based on genetic factors. Furthermore, around the world, billions of dollars are spent on antidepressants (117). When physicians begin psychoactive medication treatment, their ability to predict an outcome is generally limited to how the patient will respond, assuming previous medication success or failures have not been accounted for. It is normal to use the method of trial and error to predict which psychoactive drugs will help in treatment of depression (117). Hence, there is currently no standard of care that can reliably and continuously predict the efficacy of psychoactive medication. With these uncertainties, genetic testing can be a key component in treatment.

### The Potential for Drug Interactions

Globally, chronic pain is associated with chronic non-communicable diseases such as diabetes, arthritis, depression, and asthma (118). This leads to the use of multiple medications that can interact with each other. For example, paroxetine has a positive correlation with CYP2D6 inhibition, but its strength as an inhibitor depends on the individual subject (119). This becomes a 2-tier issue, because an individual with increased amounts of CYP2D6 alleles can be a UM, offsetting any inhibition by paroxetine, even though paroxetine is a good inhibitor (119). As another example, duloxetine is known to be effective in major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathic pain, and, in Europe, postoperative stress urinary incontinence (120,121). Though it is cleared by CYP1A2, and the metabolites are inactive, duloxetine has the ability to inhibit CYP2D6 (121). Additionally, patients that have hepatic insufficiency have trouble with duloxetine metabolism and elimination; with a cirrhotic liver, the half-life of duloxetine is 3 times longer (120). Consequently, understanding the individual's genetic layout can minimize unwanted interactions with medication.

### Urine Drug Testing

Many urine drug testing (UDT), especially office point of service testing (POST) dipsticks, give a simple positive or negative result (Fig. 1). But some quantitative urine screens report opioid metabolites (Table 6), which can give clues as to the genetic make-up of a patient. In this example, there is poor conversion of hydrocodone to hydromorphone, as well as poor conversion of oxycodone to oxymorphone, suggesting a CYP2D6 deficiency or inhibition. Table 7 shows a complete lack of CYP2D6 conversion of hydrocodone to hydromor-

phone. If this patient had complaints of poor analgesia, changing to hydromorphone or oxymorphone would be expected to bypass the CYP2D6 enzyme and provide better pain relief. On the other hand, a UM of CYP2D6 might be unexpectedly sensitive to an opioid, such as in this example of increased conversion of oxycodone (Table 8).

Most normetabolites (such as norhydrocodone and noroxycodone) have longer elimination half-lives than the parent drugs, so that urine samples that test



Fig. 1. Urine point of service testing (image courtesy of Andrea Trescot, MD).

Table 6 Urine drug screen showing poor conversion of hydrocodone to hydromorphone and oxycodone to oxymorphone.

Test	Test Method	Test Outcome	Measured Results*	Creatinine Normalized **	Cutoff*
<b>Natural and Semi-Synthetic Opioids</b>					
Codeine	LC-MS/MS	Neg		-	50.00
Morphine	LC-MS/MS	Neg		-	50.00
Hydrocodone	LC-MS/MS	POS	530	640	50.00
Norhydrocodone	LC-MS/MS	POS	494	595	50.00
Hydromorphone	LC-MS/MS	POS	78	95	50.00
Oxycodone	LC-MS/MS	POS	8,388	10,119	50.00
Noroxycodone	LC-MS/MS	POS	2,358	2,845	50.00
Oxymorphone	LC-MS/MS	POS	899	1,085	50.00

Table 7. Complete lack of hydrocodone conversion to hydromorphone.

<b>Natural and Semi-Synthetic Opioids</b>					
Codeine	CONFIRMATION	Negative			50ng/mL
Morphine	CONFIRMATION	Negative			50ng/mL
Hydrocodone	CONFIRMATION	POSITIVE	1372	990	50ng/mL
Norhydrocodone	CONFIRMATION	POSITIVE	4422	3,192	50ng/mL
Hydromorphone	CONFIRMATION	Negative			50ng/mL

negative for the parent compound can be still positive for the normetabolite (Table 9) (122). Checking for metabolites in the urine can also uncover adulterations such as in this example (Table 10), where the dipstick was positive for hydrocodone and methadone, as was prescribed, but the urine drug screening showed a complete lack of metabolites, consistent with scraping the pills into the urine (which this patient admitted to when confronted by the results).

### Considerations and Limitations for Urine Drug Testing

UDT can have some drawbacks when testing certain patient populations. Results should be viewed with caution, since smoking, food, and other medication can

interfere with metabolite outcomes from a urine drug test (123). Additionally, qualitative results can lead to false-positives; when the false-positive comes up continuously, the patient may be discharged inappropriately (124). Other variables, aside from genetic make-up, can influence the length of time the substance would likely be in the urine, such as time of last ingestion and short-term versus long-term use of a drug (123).

Metabolites can be completely missed in a urine drug test because of adulteration, subversion, poor handling, false-negatives due to enzyme-mediated immunoassay (EIA) poor specificity, and cutoff selections (125). Moreover, some patients can be UMs and the metabolite of concern can clear before the urine test is done. On the other end of the spectrum, some patients will be PMs, and

Table 8. *Increased conversion of oxycodone to oxymorphone.*

Oxycodone	LC-MS/MS	POS	647	387	50.00
Moroxycodone	LC-MS/MS	POS	1,683	1,006	50.00
Oxymorphone	LC-MS/MS	POS	5,212	3,117	50.00

Table 9. *Normetabolite remaining in urine.*

Test	Test Method	Test Outcome	Measured Results*	Creatinine Normalized **	Cutoff*
<b>Natural and Semi-Synthetic Opioids</b>					
Codeine	LC-MS/MS	Neg		-	50.00
Morphine	LC-MS/MS	Neg		-	50.00
Hydrocodone	LC-MS/MS	Neg			50.00
Norhydrocodone	LC-MS/MS	POS	77	71	50.00
Hydromorphone	LC-MS/MS	Neg		9	50.00

Table 10 *Lack of urine metabolites, consistent with adulteration.*

Test	Test Method	Test Outcome	Measured Results*	Creatinine Normalized **	Cutoff*
<b>Natural and Semi-Synthetic Opioids</b>					
Codeine	LC-MS/MS	Neg		-	50.00
Morphine	LC-MS/MS	Neg		-	50.00
<b>Hydrocodone</b>	<b>LC-MS/MS</b>	<b>POS</b>	<b>16,077</b>	<b>29,718</b>	<b>50.00</b>
Norhydrocodone	LC-MS/MS	Neg		-	50.00
Hydromorphone	LC-MS/MS	Neg		-	50.00
Oxycodone	LC-MS/MS	Neg		-	50.00
Noroxycodone	LC-MS/MS	Neg		-	50.00
Oxymorphone	LC-MS/MS	Neg		-	50.00
<b>Synthetic Opioids</b>					
Fentanyl	LC-MS/MS	Neg		-	2.00
Norfentanyl	LC-MS/MS	Neg		-	8.00
<b>Methadone</b>	<b>LC-MS/MS</b>	<b>POS</b>	<b>16,502</b>	<b>30,503</b>	<b>100.00</b>
EDDP (Methadone metabolite)	LC-MS/MS	Neg		-	100.00

<b>Patient Name:</b>	Date of Birth:	Genelex Laboratory# :
Referrer: Dr. Andrea Trescot	Client Account:	Sample Type: Buccal Swab
Date Collected:	Date Received:	Date Reported:
<b>Cytochrome P450 Test Result(s):</b>	▲ CYP2D6 Intermediate Metabolizer (*41 / *41) ☒ CYP2C19 Ultra Rapid Metabolizer (*17/*17) ✓ CYP2C9 Normal Metabolizer (*1/*1) ✓ VKORC1 Low sensitivity to warfarin (G/G)	
<b>Gene Phenotype(Genotype)</b>		

Fig. 2. Genetic testing result from Genelex (image courtesy of Andrea Trescot, MD).

TEST RESULTS			
Drug Class Ordered / Drugs Included	Genes Analyzed	Predicted Phenotype <sup>2</sup>	Haplotype <sup>3</sup>
<b>OPIOIDS</b>			
CODEINE, HYDROCODONE, OXYCODONE, TRAMADOL	CYP2D6	Extensive Metabolizer (EM)	*1/*2
<b>TRICYCLIC ANTIDEPRESSANTS</b>			
AMITRIPTYLINE, DESIPRAMINE, IMIPRAMINE, NORTRIPTYLINE	CYP2D6	Extensive Metabolizer (EM)	*1/*2
<b>BENZODIAZEPINES</b>			
DIAZEPAM, LORAZEPAM, OXAZEPAM	CYP2C19	Ultrarapid Metabolizer (UM)	*1/*17
	UGT2B15	Extensive Metabolizer (EM)	*1/*1
<b>SSRIs / SNRIs</b>			
CITALOPRAM, PAROXETINE, VENLAFAXINE	CYP2C19	Ultrarapid Metabolizer (UM)	*1/*17
	CYP2D6	Extensive Metabolizer (EM)	*1/*2
<b>METHADONE</b>			
METHADONE	CYP2B6	Intermediate Metabolizer (IM)	*1/*6

Fig. 3. Genetic testing result from Millennium (image courtesy of Andrea Trescot, MD).

therefore have no metabolite seen on the UDT as it has not been converted within the assumed time frame. In both cases, examples of 2 extremities, point of service testing or quantitative testing may miss the substance metabolite because of the genetic make-up. This issue is important enough to make sure further history taking and data gathering is done.

### DNA Testing

The use of oral samples or buccal swabs for specific genetic testing has recently been clinically validated and economically feasible, as the price has decreased dramatically (126). Several SNPs are readily available, providing information on CYP enzymes 2D6, 2C9, 2C19 as well as VKORC1 (reflecting the metabolism of warfarin) (Fig. 2). Additional testing for CYP2B6 and CYP2B15 (Fig. 3) as well as CYP3A4 and CYP3A5 (Fig. 4) is also available.

### How Do We Use Genetic Testing?

We can use genetic testing to explain and confirm ineffective or high opioid use. For example, patients

with CYP2D6 deficiencies would be expected to have poor (or relatively poor) relief from tramadol, codeine, hydrocodone, and oxycodone, while patients with CYP2D6 UM might be at risk for unexpectedly high levels of morphine from codeine (127). Switching to an opioid not metabolized by that enzyme (such as fentanyl or morphine) might be much more effective or less risky. For instance, patients with poor opioid efficacy from an inactive OPRM1 allele might benefit from an opioid with kappa agonist activity such as oxycodone instead of a pure mu agonist such as morphine.

### Opioid Risk

There is less evidence of (but a great deal of interest in) the predictive value of genetic testing. Can it predict the patients more likely to develop PTSD after a motor vehicle collision or more likely to fail antidepressants? Can it be used to predict those patients who are likely to participate in risky behaviors or those patients more likely to abuse opioids?

The American College of Occupational and Environmental Medicine (ACOEM) Guidelines for the Use

Proove Drug Metabolism Report Card		GPA	Medication Metabolism Metric (M3)
2C9/VKORC1 – For NSAIDs (celecoxib, ibuprofen, diclofenac), phenytoin, warfarin, and other medication		<b>B</b>	<b>3</b>
2C19 - For diazepam, cytalopram, sertraline, and other medication		<b>C</b>	<b>2</b>
2D6 - For opioids, tapentadol, amphetamines (Adderall), tramadol, duloxetine, fluoxetine, paroxetine, venlafaxine, cyclobenzaprine, bupropion, and other medication		<b>C</b>	<b>2</b>
3A4, 5 - For buprenorphine, methadone, buprenorphine and naloxone, meperidine, fentanyl, and other medications.		<b>D</b>	<b>1</b>
<b>Overall Drug Metabolism G.P.A. (Genetic Predisposition Analysis)</b>		<b>C</b>	<b>2</b>
G.P.A. Reference Guide			
<b>Grade A - Accelerated</b>	Accelerated is defined as three or more active genes producing the drug metabolizing enzyme resulting in increased drug metabolism. Grade A metabolizers may require an increased dosage due to higher than normal rates of drug metabolism for the majority of medications and pro-drugs will require lower doses. Prescribing concomitant medications that inhibit metabolism to counterbalance this genetic predisposition may prove to be effective.		
<b>Grade B – Broad/Normal</b>	Broad/Normal is defined as two active forms of the gene producing the drug metabolizing enzyme, resulting in normal drug metabolism. Grade B metabolizers may respond in expected ways and may respond to substrates of the enzyme following standard dosing practices.		
<b>Grade C - Compromised</b>	Compromised is defined as one active form of the gene producing the drug metabolizing enzyme and therefore reduced drug metabolism. Grade C metabolizers may require lower than average drug dosages for optimal therapeutic response for the majority of medications and pro-drugs in higher doses. In addition, poly-pharmacy therapy should be monitored closely.		
<b>Grade D - Deficient</b>	Deficient is defined as having no active genes producing the metabolizing enzyme for the drug. Grade D metabolizers are at increased risk of drug-induced side effects due to diminished drug elimination or lack of therapeutic effect resulting from failure to generate the active form of the drug.		

Fig. 4. Drug metabolism report from Proove (image courtesy of Andrea Trescot, MD).

of Chronic Opioids (128) notes the “significant risk of substance abuse, addiction, and diversion related to genetic factors” (129). Studies of polymorphisms in the mu opioid receptor gene (OPRM1), which encodes the receptor target of heroin, morphine, and synthetic opioids, have contributed substantially to knowledge of genetic influences on opiate and cocaine addiction (130).

There is some emerging clinical research around the use of genetics and opioid risk evaluation. Intriguing information regarding potential risk of addiction and misuse may be available through genetic testing of opioid receptors, serotonin, GABA, and other brain chemistries that may predispose about half of all opioid risk (131) (Fig. 5). A recent pilot study suggests that genetic variations in the mesolimbic reward system of the brain may predict opioid risk (132). Another recent study evaluated patients over 2 years following narcotic

detoxification and found that genetic predisposition may predict successful outcomes of opioid abstinence (133).

#### Urine and Genetic Testing limitations

Due to lucrative financial incentives, UDT has been misused and abused by over-ordering (125). These abuses have resulted in a backlash by insurers, with proposed strict limitation on testing, which will likely decrease the quality and quantity of legitimate oral and urine testing. Christo and colleagues (125) developed an algorithmic approach to urine drug testing (Fig. 6).

Genetic testing is likely to suffer from the same inappropriate fiscally based prescribing. This can possibly affect the consumer considering genetic testing, since costs are variable, and can range from a few hundred to a thousand dollars or more (134). Clinical utility and cost-effectiveness are still being debated (135), since

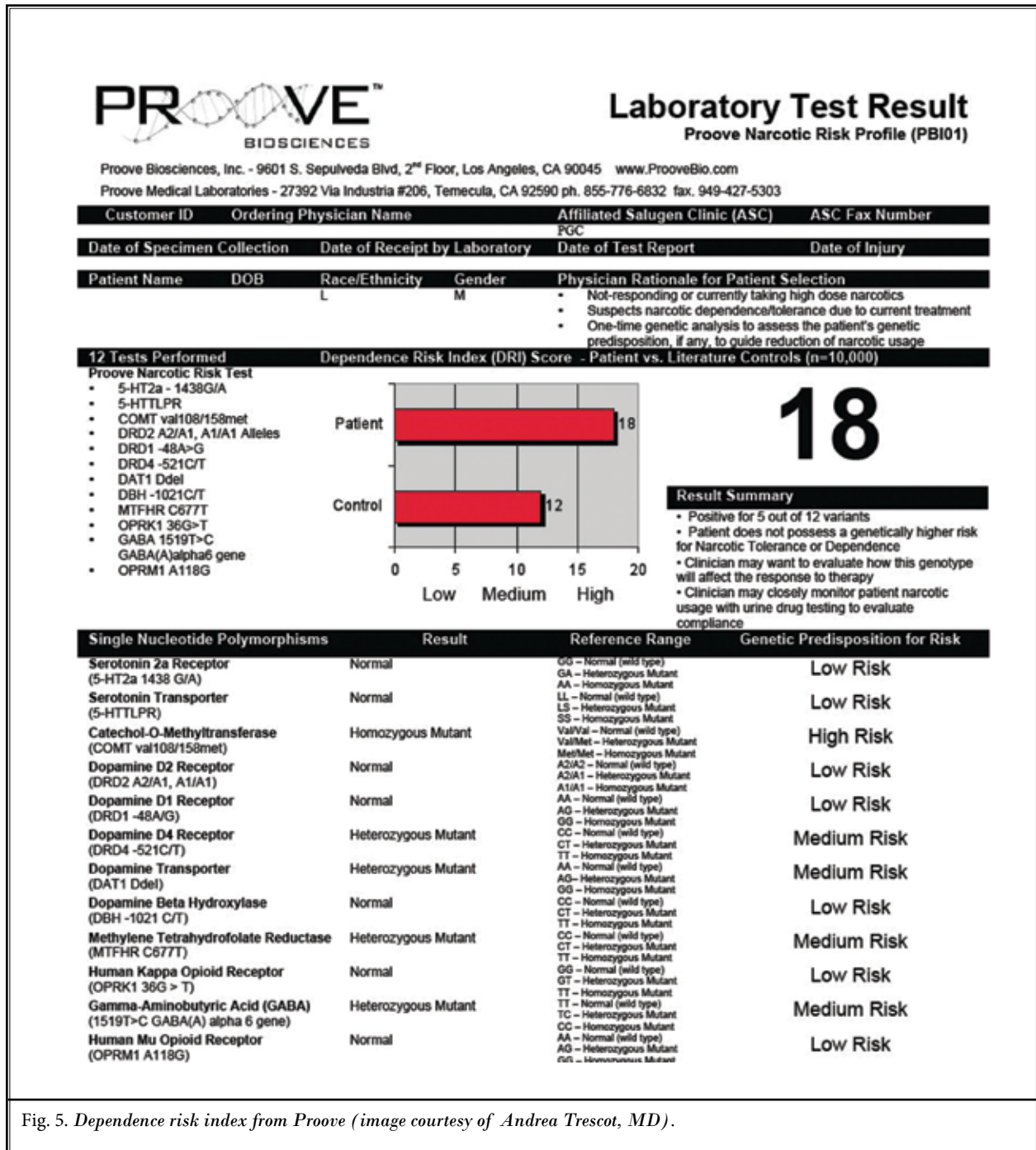


Fig. 5. Dependence risk index from Proove (image courtesy of Andrea Trescot, MD).

personalized medicine is in the younger stages of regulation. Lastly, pharmacogenetic results might require a consultation from a specialist, such as a geneticist, to interpret the data or a genetic counselor to discuss the outcome with the patient (136), which can further increase the overall cost.

### Future Therapies

Knowledge of genetic issues is allowing more effective screening of drugs for inflammatory and neuropathic pain treatment (137). Currently, each patient is given a trial and error analgesic trial. However, in the near future, pharmacogenetic approaches may

## Genetic Testing in Pain

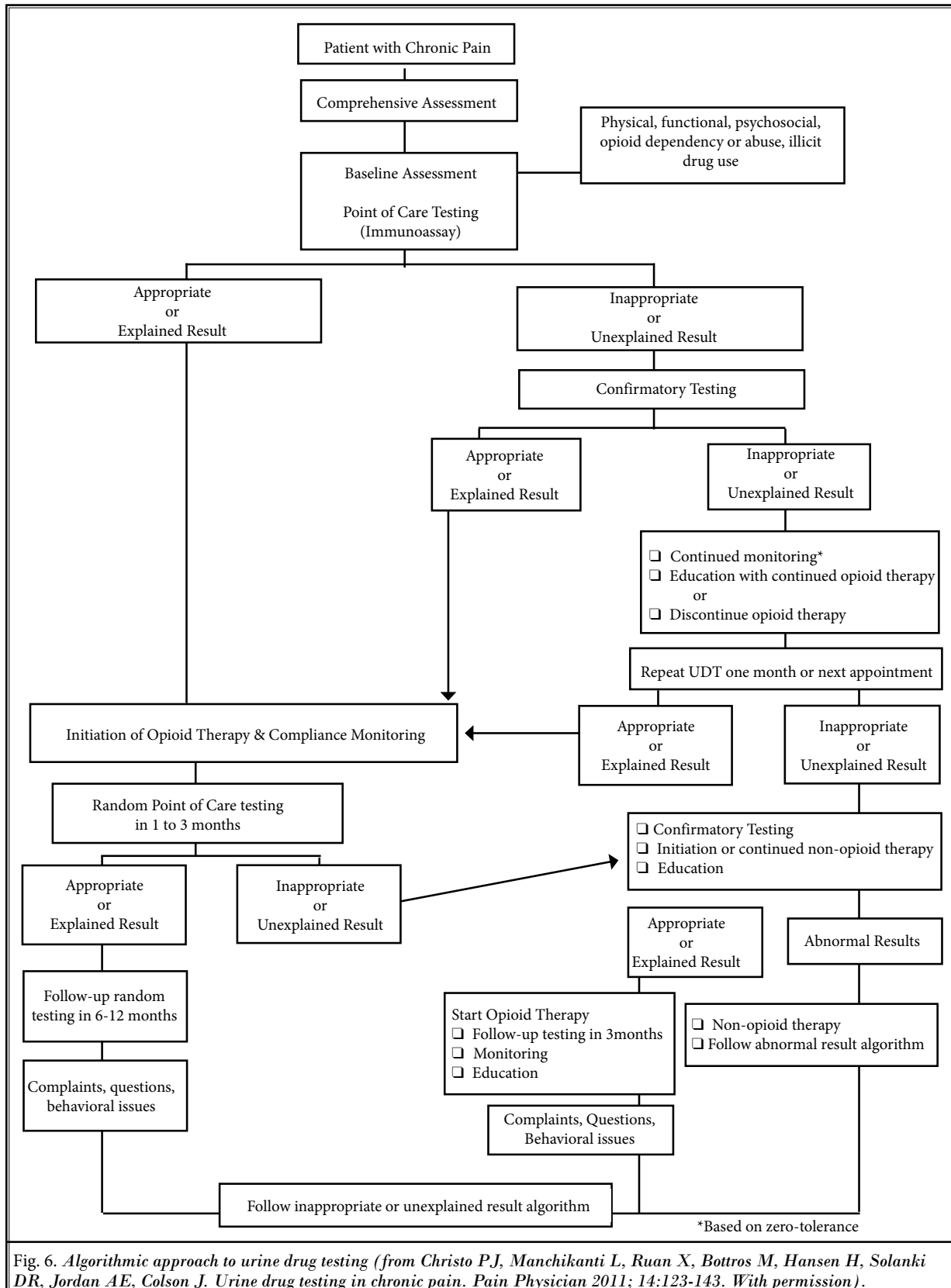


Fig. 6. Algorithmic approach to urine drug testing (from Christo PJ, Manchikanti L, Ruan X, Bottros M, Hansen H, Solanki DR, Jordan AE, Colson J. Urine drug testing in chronic pain. *Pain Physician* 2011; 14:123-143. With permission).

be implemented to best predict which medicine from the outset may be most appropriate for an individual, providing the therapy with the most sustained efficacy and the best side effect profile (138). "Integration of genetic analysis in clinical studies with carefully defined outcome measures will increase the likelihood of identifying clinical and genetic factors which can be used to predict opioid response" (139).

#### **What Should the Clinician Do?**

- Take a medication history of prior adverse effects or inadequate effects ("What has worked well for you in the past?" "What hasn't helped?" "Are you sensitive to medications or do you need larger than normal doses of medications?").
- Check for common potential interactions with opioids, especially CYP2D6 inhibitors.
- When starting new medications, check the metabolic pathway for activation or excretion issues.
- Be aware of potential drug-drug interactions when adding new medications.
- Use UDT quantitative metabolite results to evaluate potential drug interactions.
- Consider formal genetic testing to evaluate appropriate opioid choices and potentially to predict opioid risks.

#### **CONCLUSION**

Patient care may be improved by genotyping and following drug concentration levels (140). Pharmacogenetics and therapeutic drug monitoring can potentially minimize adverse events, while maximizing efficacy (141). Integration of genetic analysis in clinical studies

will increase the likelihood of identifying clinical and genetic factors that can be used to predict opioid responses (139). With knowledge of a patient's potential for beneficial response to a given opioid, a physician is armed with critical information that can guide therapeutic decisions. Incorporation of such biomarkers are emerging on the forefront of personalized medicine, and have the potential to dramatically improve the utility and efficacy of both current and future pain management strategies.

#### **Resources:**

An extensive, laminated list of P450 inhibitors can be ordered at <http://medicine.iupui.edu/flockhart/table.htm>

Pinnacle ([www.pinnaclelabservices.com](http://www.pinnaclelabservices.com)) genetic testing

#### **Drug testing**

Millennium ([millenniumlabs.com](http://millenniumlabs.com)) oral and urine  
Aegis ([www.aegislabs.com](http://www.aegislabs.com))  
Ameritox ([www.ameritox.com](http://www.ameritox.com))  
Pinnacle ([www.pinnaclelabservices.com](http://www.pinnaclelabservices.com)) oral and urine  
Genetic testing  
Millennium  
Genelex  
Proove  
Pinnacle ([www.pinnaclelabservices.com](http://www.pinnaclelabservices.com))  
Millennium ([millenniumlabs.com](http://millenniumlabs.com))  
Genelex ([genelex.com](http://genelex.com))  
Proove ([www.proovebio.com](http://www.proovebio.com))



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