CE 2.5 Contact Hours

# Translating the Human Genome to Manage Pediatric Postoperative Pain

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**Abstract:** Postoperative pain management is complex especially in the pediatric population where limited research exists to guide clinical practice. We currently cannot predict which children are at the greatest risk for pain, persistent postoperative pain, adverse analgesic effects, or opioid addiction. Instead, pain medications are prescribed based on perceived seriousness of the patient's illness/procedure, with little regard for individual genetic suitability. For the pediatric patient, personalized medicine has the potential to improve pain management and reduce risks of adverse analgesic effects, including opioid addiction. The purpose of this review article is to inform pediatric surgical nurses about the current status of genetic research related to pain sensitivity, genetic variants that affect analgesic metabolism, and the genetics of addiction. Application of this information in clinical practice remains merely a possibility; yet, vendors have begun to market genetic testing without clear guidelines for clinical interpretation. Genetic research efforts are progressing at a rapid pace, and the pediatric surgical specialist must be aware of both the potential implications for postoperative pain management as well as the current limitations given the level of research that is available to guide practice.

**KEY WORDS:** genetic suitability, pain sensitivity, pediatric, personalized pain management, postoperative pain

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## INTRODUCTION

More than 6 million children have surgery in the United States each year, and over 80% report moderate-to-severe pain after surgery (Sieberg et al., 2013). Postoperative pain management is complex. Yet, the challenge of postoperative pain treatment remains uniquely individual (National Institutes of Health, 2013). For example, we currently cannot predict which patients are at the greatest risk for pain or persistent postsurgical pain, which patients are at greatest risk for adverse analgesic effects, or which patients are at greatest risk for opioid addiction. Instead, pain medications are prescribed based on patient weight, perceived seriousness of illness, and invasiveness of surgical procedure, with little regard for individual patient genetic suitability (Diatchenko et al., 2006; Filligim et al., 2009; Karamessinis, Cooper, & Manworren, 2013; Kim et al., 2004; Logan & Rose, 2005; Manworren, Karamessinis, & Cooper, 2013; Mogil, 2004; Pinto, McIntyre, Ferrero, Almeida, & Araujo-Soares, 2013; Rakvag et al., 2005).

Our current system of prescribing analgesia is based on limited scientific knowledge. Analgesic selection, dose decisions, and medication administration frequencies are made based on empirical evidence, knowledge, and the experience and fears of prescribers, nurses, and children's parents (Logan & Rose, 2005; Manworren, 2000, 2010; Mogil, 2004; Pop, Manworren, Guzzetta, & Hynan, 2007). This trial-and-error approach places children at increased risk for poorly controlled postoperative pain and adverse analgesic effects (Federal Drug Administration, FDA Drug Safety Communication, 2012; Food and Drug Administration [FDA], 2013).

Physiogenomic analysis may allow translation of human genetics into clinical practice. This approach for identifying risk of acute postsurgical pain would acknowledge patients' individuality and diversity by applying and

testing our emerging knowledge of human pain genetics and pharmacogenomics into clinical practice. For example, we may find that pediatric patients with alleles associated with high pain sensitivity at pain relevant genes in experimental models and genetic alterations in pharmacodynamic and pharmacokinetic genes report more severe pain, require more opioid analgesics, and experience more analgesic adverse effects. We may find that pediatric patients with a genetic predisposition for addiction experience long-term consequences from our altruistic efforts to relieve their acute postsurgical pain. However, more clinical research is needed to identify and characterize these relationships and their relevance in pediatric patients.

The purpose of this review article is to inform pediatric surgical nurses of the current status of genetic research related to pain sensitivity, genetic alterations in pharmacodynamic and pharmacokinetic genes that affect analgesic metabolism, and the genetics of addiction. This article provides a primer of physiogenomic and epigenetic concepts to assure a foundational knowledge of human genetics and essential genetic and genomic nursing competency for pediatric surgical nurses. (see Glossary; American Nurses Association Consensus Panel on Genetic/Genomic Nursing Competencies, 2009; Greco, Tinley, & Seibert, 2012). We then focus on the current status of knowledge of pain sensitivity genes, genetic variation in responses to pain medications, and the genetics of opioid addiction. We conclude by outlining the gaps in the literature with questions for further research and by summarizing clinical implications for personalized healthcare.

## OVERVIEW OF PHYSIOGENOMICS

In the most general sense, a biological organism can be understood as a system that receives external stimuli (e.g., lifestyle, pathogens, drugs) and produces responses (e.g., medical outcomes, physiological responses). The function that connects input to output is complex and contains a large number of fixed parameters (genes) that determine the innate characteristics of the organism. Humans have approximately 20,000 genes, but it is estimated that individuals' human genomes vary by only 1.5% (www.genome.gov).

The nucleus of each of our individual cells contains deoxyribonucleic acid (DNA). DNA, our genetic blueprint, can be replicated for cell division or transcribed into messenger ribonucleic acid (mRNA), which is then translated into amino acid sequences during protein synthesis (Griffiths, Wessler, Carroll, & Doebley, 2012). These processes are the basis for life generation and also translating our genetic blueprint to each cell. Thus, differences among individuals are often attributable to the presence or absence of different genes. However, not all individual variations can be attributed to differences in DNA sequence and genotype. Many phenotypic differences are a result of changes that occur over time above the level of nucleotides and genes; these are called epigenetic changes (Griffiths et al., 2012; Gudsnuk & Champagne, 2011; see Epigenetics (below) for more details).

The health science that studies, analyzes, and diagnostically applies these genetic and epigenetic phenomena is called physiogenomics. Physiogenomics is a powerful systems biology method that utilizes genetic variation to link genes and physiological characteristics into pathways and to study the detailed interactions among them. In its simplest application, physiogenomic analysis effectively identifies genotype(s) related to a singular phenotype (i.e., an observable characteristic). A genotype is expressed when proteins and RNA molecules are made from information encoded in the gene's DNA. Genotype expression thereby contributes to an individual's phenotype, such as low pain sensitivity.

Physiogenomics is a medical application of sensitivity analysis, the study of the dependence of a system on changes in its components (Holford, Windemuth, & Ruaño, 2006; Ruaño, Windemuth, & Holford, 2006). In physiogenomics, single nucleotide polymorphisms (SNPs) provide the variable components of genes, and analysis of the relationship between that variation and the physiological response to external stimuli provides information about which genes play important roles in the physiological processes. SNPs in the human genome are being studied for correlation with drug responses and other phenotypes. The associated gene markers are combined into SNP ensembles harnessing their combined predictive power to estimate functional variability among individuals. Thus, physiogenomics may be a way for us to predict pain sensitivity and analgesic response.

### Physiological Genotypes

Physiological genotypes have several unique features. They are predictive models incorporating haplotypes from various genes and any covariates (e.g., baseline levels). Physiological genotypes are multigenetic in nature and also include clinical information routinely gathered in medical care. They harness the combined power of genotypes ("nature") and phenotypes ("nurture") to predict drug responses and the responses to other environmental challenges. Physiological genotypes provide answers to clinical management questions with high reliability and impact, and they can be used to address in a yes/no manner issues such as the risk of side effects

from a medication or whether a pain medication will be effective for managing a child's postoperative pain.

Various specific genetic features of physiological genotypes are attractive for studying environmental interactions in prevention and treatment of pain. The genotype component does not change. Some genotypes associated with a phenotype can become a surrogate marker for the actual measurement of the phenotype. This capability may be particularly useful when measurement of the phenotype is difficult, expensive, or confounded by environmental conditions, (e.g., postoperative pain and addiction). Most importantly, genotyping technologies are rapidly decreasing in cost and are becoming increasingly automated. To this end, multiple genotypes from different genes coding for proteins in interacting pathways allow sampling the genetic variability in entire physiological networks quite economically. The complete system-wide genotype can be determined from a small sample of peripheral blood or saliva, without the invasive biopsy often required for other biomarkers. This is especially important when gathering specimens in the pediatric population.

### Physiogenomic Models

The purpose of genetic association screening is to identify any of a large set of genetic markers (SNPs, haplotypes) and physiological characteristics that have an influence on the status of the patient (e.g., being able to test for high pain sensitivity and high risk of adverse analgesic effects). The objective is to find a set of physiogenomic factors that together provide a way of predicting the outcome of interest. The association of an individual factor with the outcome may not have sufficient discrimination ability to provide the necessary sensitivity and specificity, but by combining the effect of several such factors, this objective may be achieved. Genetic association studies have helped to identify potential genes that contribute to pain sensitivity, analgesic metabolism, and addiction.

## EPIGENETICS

Epigenetics, the study of cellular processes that determine the function of genes (Griffiths et al., 2012), may also play an important role in understanding the complexity of childhood pain, pain management, and addiction. Epigenetic changes occur at the molecular level, involving DNA or its supporting proteins. These functional changes lead to alterations in activation or transcription of ascribed genes, whereas the structure and sequence of DNA remain unchanged.

DNA methylation and histone changes are the most common epigenetic mechanisms. DNA methylation (addition of a methyl group to the DNA molecule), gene expression regulation (phenotype), and changes in the chromatin structure of the gene are examples of molecular changes that directly involve DNA. Changes to supporting proteins often involve histones and influence the packaging, ordering, and storage of DNA. Methylation or demethylation of histones can turn on, turn off, amplify, or silence gene expression. Gene expression involves the transcription of DNA to mRNA and the translation of mRNA into protein. Protein synthesis, a continuous process, is essential for enzymatic activity and metabolism. DNA methylation patterns are inherited during cell division, and epigenetic patterns determine the different types of cells in the body during cell differentiation. Any interruptions or alterations in the enzymes that regulate DNA methylation or histone modification can lead to epigenetic pattern changes. For example, epigenetics can explain why identical twins can exhibit dramatically different phenotypes later in life (Champagne, 2010; Gudsnuk & Champagne, 2011).

Pediatric nurses can appreciate how environmental factors contribute to epigenetic changes in neurons and neuronal networks and how those changes affect long-term outcomes. The effect of epigenetics on the development and function of neuronal networks begins at conception and continues into childhood (Champagne, 2010; Kaufman, Plotsky, Nemeroff, & Charney, 2000). Early experiences have the potential to alter the phenotype over time. Early pain experiences have been known to alter sensitivity and potentially chronicity of pain later in life (Gluckman, Hanson, Cooper, & Thornburg, 2008; Godfrey & Barker, 2001). Animal models have shown that sensory stimulation in the environment plays an important role in neuron function and influences neuron differentiation and neuronal pathway development through epigenetic modifications (Cutfield, Hofman, Mitchell, & Morison, 2007; Dubois et al., 2008; Dudink, Kerr, Paterson, & Counsell, 2008; Felitti et al., 1998; Markham & Greenough, 2004). This environmental programming is a function of three variables—genes, appropriately supportive environment, and nutrition—as well as how these three variables interact together (Fox, Levitt, & Nelson, 2010; Markham & Greenough, 2004). However, whether these effects are mediated through specific epigenetic changes is currently unknown.

Epigenetic research in humans is rapidly advancing and so is the realization that childhood pain experiences have significant effects on neuronal development and long-term outcomes. The long-term effects of pain and the mechanisms that mediate its influence on neuronal responsiveness and changes in neuronal cell biology in response to pain and stress remain unclear. Epigenetic research has the potential to lead to the identification of

biological markers, gene expression profiles, and profile changes that occur over time in response to early life experiences. Combined with knowledge gained through the use of advanced technologies, epigenetic studies have the promise to refine our understanding of how the brain matures and functions from multiple perspectives (Fox et al., 2010; Markham & Greenough, 2004; McGrath, Cone, & (Abou) Samra, 2011). Such understanding will pave the way for care practices that best support neurodevelopment and lead to the best possible outcomes. As scientists overcome biological, technical, and cost-related challenges, epigenetic research has a great potential for determining key environmental factors that affect the developing genome, allowing for targeted interventions to relieve and prevent long-term pain.

Focusing research activities on greater understanding of the basic biological mechanisms of the development of pain sensitivity will allow for increasingly targeted pharmacologic interventions and maximize the benefits gained from pain management and other supportive pediatric care practices. In the next sections, we focus on preliminary evidence of candidate genes as biological markers for pain sensitivity, analgesic metabolism, and addiction. Eventually, these or similar genetic markers may be used by the pediatric surgical clinician for determining genetic suitability for personalized postoperative pain management interventions.

## PAIN SENSITIVITY GENES

Well known to clinicians is the tremendous variability of patients' experiences of pain. For example, our clinical research provides evidence of this variability in subjective reports of pain intensity among adolescents experiencing postoperative pain (Figure 1; Karamessinis et al., 2013; Manworren et al., 2014, 2013; Manworren, Paulos, & Pop, 2004). However, knowledge of patient characteristics and variables that increase risk for more severe postoperative pain is limited.

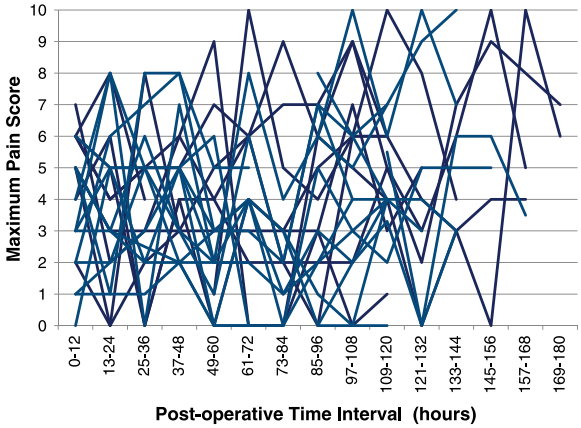


**FIGURE 1.** Variability of maximum pain scores over postoperative stay (hours) for 22 adolescents after pectus excavatum repair.

Variability in pain sensitivity, pain tolerance, and responses to analgesics is only partially explained by the personal and sociocultural context in which the pain is experienced, interpreted, and expressed (Fillingim, King, Ribeiro-Dasilva, Rahim-Williams, & Riley, 2009; Logan & Rose, 2005; Manworren et al., 2013; Mogil, 2004; Pinto et al., 2013). When considering modifiable psychological characteristics associated with increased postoperative pain intensity and analgesic use, some researchers conclude that adolescents' postoperative pain may be interpreted as a self-fulfilling prophecy (Logan & Rose, 2005). Adolescents who predicted preoperatively that they would have more intense pain reported more severe pain intensity and required more opioid analgesics than those who predicted less postoperative pain (Logan & Rose, 2005). In fact, adolescents may be intuitively aware of their unique pain phenotype; but clinicians have failed to interrogate genetic markers to identify patients at greatest risk for pain.

Potential genetic markers for pain have been identified. Scientists have identified over 400 distinct genes that have a nociceptive phenotype (Lacroix-Fralish, Ledoux, & Mogil, 2007). A number of genes have been identified where variation (in the form of SNPs and/or a haplotype) is associated with individual variability in pain response. Experimental studies provide strong evidence of correlation of genetic variants with differential pain sensitivity. Many of these genes (*OPRM1*, *GCH1*, *SCN9A*, *KCNS1*, *5-HTTLPR*, and *TRPV1*) associated with variability in experimentally evoked pain response seem to affect pain susceptibility in clinical populations as well (Akbar et al., 2008; Costigan et al., 2010; McKemy, Neuhausser, & Julius, 2002; Reimann et al., 2010; Tegeder et al., 2006; see Table 1).

Perhaps, the most well-characterized "pain gene" is *COMT* (see Table 1). Variation within *COMT* is associated with experimental pain responses to heat, cold, pressure, and mechanical stimuli. In addition, *COMT* genotype is predictive of chronic pain in fibromyalgia, temporomandibular joint disorder, and postsurgical pain (Kim, Lee, Rowan, Brahim, & Dionne, 2006; Martinez-Jauand et al., 2013; Nackley et al., 2007). *COMT* variations resulting in increased enzymatic activity show a protective effect in clinical pain syndromes (Belfer & Segall, 2011; Oertel & Lotsch, 2008).

Regardless of an individual patient's pain susceptibility, postsurgical pain is treated with analgesics. Therefore, in addition to genetic associations with pain response, the pediatric surgical specialist must be aware of genetic

**Table 1: Select Genes Relevant to Pain, Analgesic Metabolism, and Addiction (Listed Alphabetically by Gene Symbol)**

| Symbol | Name | Role |
|---|---|---|
| *5-HTTLPR* | Serotonin transporter | Serotonin transporter |
| *ABCB1 (alias: MDR1)* | ATP binding cassette, subfam. B, member 1 | Critical to drug efflux at blood–brain barrier (bbb); variants may affect bbb transport of opioids |
| *COMT* | Catechol-O-methyltransferase | An enzyme involved in degradation of catecholamines and pain modulation |
| *CYP2C9* | Cytochrome p450 2C9 | Drug metabolism |
| *CYP2C19* | Cytochrome p450 2C19 | Drug metabolism |
| *CYP2D6* | Cytochrome p450 2D6 | Drug metabolism; catalyze norhydro-morphone formation |
| *CYP3A4* | Cytochrome p450 3A4 | Drug metabolism |
| *CYP3A5* | Cytochrome p450 3A5 | Drug metabolism |
| *GCH1* | GTP cyclohydrolase | Related to the generation of neuropathic pain |
| *DRD1* | Dopamine D1 receptor | G-protein coupled receptor, cell signaling |
| *GRIN2A* | 2A subunit of NMDA receptor | Ligand-gated receptor, cell signaling |
| *HTR2A* | 5-hydroxytryptamine (serotonin) 2A receptor gene | G-protein coupled receptor, cell signaling |
| *KCNS1* | Voltage-gated potassium channel S1 | Voltage-gated potassium channel S1 |
| *MC1R* | Melanocortin-1 receptor | G-protein coupled receptor, cell signaling, neuromodulator |
| *OPRD1* | δ-opioid receptor, type 1 | Variants explain significant variability in residual pain on morphine |
| *OPRM1* | Opioid μ-1 receptor, type 1 | 118A allele modifies opioid analgesic response and may be involved in substance use disorders |
| *SCN9A* | Voltage-gated sodium channels | Cell signaling |
| *TRPA1* | Transient receptor potential cation channel subfamily A, member 1 | Activation contributes to hyperalgesia and edema |
| *TRPV1AB* | Transient receptor potential cation channel subfamily V, member 1 | Vanilloid receptor activated by harmful heat, extracellular protons, capsaicin |

*Note.* NMDA = N-methyl-D-aspartate receptor (glutamate) subfamily B.

associations with differences in analgesic metabolism and analgesic response. Individualized care for patients undergoing painful procedures can benefit from the growing understanding that pharmacological analgesia is also under genetic control.

## GENETIC VARIATION IN RESPONSES TO PAIN MEDICATIONS

In our studies of analgesic needs to treat postoperative pain, we found tremendous variation in pediatric patients' analgesic requirements to achieve optimal pain relief (Karamessinis et al., 2013; Manworren et al., 2014, 2013; Pop et al., 2007). Deficiencies in current knowledge of analgesic efficacy in pediatrics have been identified (Berde et al., 2012; Gregoire & Finley, 2007). Given that opiate analgesics are commonly used to treat postoperative pain in clinical settings, it should come as no surprise that genes whose products affect opioid receptor function also affect analgesic response.

Variants in pharmacodynamic and pharmacokinetic genes (*CYP2D6, CYP2C9, CYP2C19, CYP3A4, CYP3A5, ABCB1*). These gene variants may be useful for identifying patients at greatest risk for postoperative pain and life-threatening adverse analgesic effects (see Table 1). For example, the response to codeine administration (another μ-opioid receptor agonist) is heavily influenced by functionality of cytochrome P450 2D6, a metabolic enzyme encoded by *CYP2D6*.

In 2011, over 1.5 million pediatric patients were prescribed codeine, but in August 2012, the FDA warned against prescribing codeine for postoperative tonsillectomy pain after three children died from overdoses attributed to a genetic variant of *CYP2D6* (Federal Drug Administration, FDA Drug Safety Communication, 2012; IMS Health, 2013). Individuals with *CYP2D6* duplication genotype are categorized as ultra-rapid metabolizers (Berde et al., 2012). This genetic variant causes ultra-rapid metabolism of codeine resulting in toxic levels of morphine.

In contrast, those with low *CYP2D6* function have a relatively weak analgesic response to codeine and therefore experience no pain relief from this analgesic.

The FDA advised prescribers to weigh the benefits and risks, to consider an alternate analgesic for children, and to caution parents to monitor their children for potential adverse effects from codeine (FDA, 2013). Then in 2014, clinical guidelines emphasized that a potential benefit of *CYP2D6* testing is identification of higher risk of ineffective analgesia or adverse events (Crews et al., 2014). The guidelines also provided recommendations clinicians can use for prescribing codeine based on *CYP2D6* genotype.

Like codeine, genetic alterations in pharmacodynamic and pharmacokinetic genes can alter the effectiveness and increase the danger of using other analgesics to treat postoperative pain. We currently consider pharmacogenomic testing only after children fail several trials of analgesic therapy or experience adverse effects. For example, 16 of 19 children (84%) referred for genetic testing because of analgesic ineffectiveness or adverse effects eventually had significant *CYP2D6* genetic variants identified; four were ultra-rapid metabolizers, eight were deficient, three were poor metabolizers, and one was a null metabolizer. Of the three patients with functional *CYP2D6* status, two were *CYP2C19* null metabolizers (Manworren, Jeffries, Ruaño, Seip, & Zempsky, in press).

It stands to reason that the interaction of genetic variation in pain sensitivity and alterations in analgesic metabolism may critically influence and explain individual pain variability. For example, *COMT* contributes to variability in morphine-induced analgesia both independently and in a gene–gene interaction with *OPRM1* such that patients heterozygous (i.e., gene pair dissimilarity) for the *OPRM1 A11G* and *COMT G1947A* require less morphine after surgery compared with all other genotype groups (Kolesnikov, Gabovits, Levin, Voiko, & Veske, 2011). Of these high-priority pain candidate genes, only a small number have been evaluated for a relationship with postoperative pain, and this lack of knowledge poses a serious barrier to the integration of pharmacogenetics/genomics into personalized postsurgical care.

Exploration for such interactions in pediatric surgical patients is ideal because many of these healthy patients have no previous surgical pain or analgesic experiences (see Figure 2). This lack of experiences with opioid analgesics also hampers our ability to identify which pediatric patients are at the greatest risk for subsequent opioid misuse and addiction, but perhaps, unlocking the genetic code of addiction is also the key to personalizing our opioid misuse and addiction prevention strategies.

## GENES OF ADDICTION

Severe postoperative pain is treated with opioids. An unfortunate consequence of opioid analgesic treatment for postsurgical pain can be opioid addiction. This adverse analgesic effect may also be under genetic control.

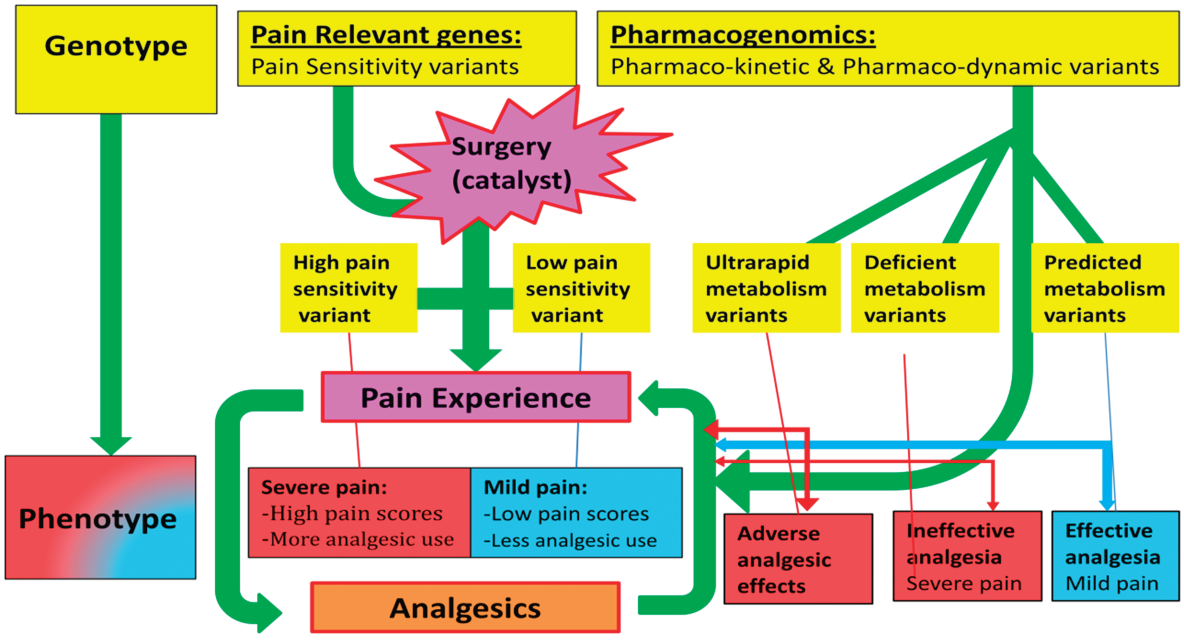


**FIGURE 2.** Model of physiogenomic analysis of pain-relevant genes and pharmacogenomics.

The current standard of practice is to reassure patients and families that less than 1% of individuals treated for acute pain become addicted to opioids. This conclusion and belief has been supported by two classic studies. Marks and Sachar (1973) found that less than 1% of hospitalized patients receiving 100 mg of meperidine by intramuscular injection every 4 hours became addicted. Then, Porter and Jick (1980) found that, of 12,000 hospitalized medical inpatients who received at least one dose of an opioid analgesic, only four were diagnosed as addicts, and all four had a previous history of substance abuse.

However, more recent estimates suggest that 6%–15% of Americans are addicted to drugs (Centers for Disease Control and Prevention [CDC], 2011; U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, 2013). What has changed since the 1970s and 1980s is the availability of opioids. The CDC reports that enough hydrocodone products are prescribed annually for every American adult to receive a 5-mg dose every 4 hours for a month (Paulozzi, Jones, Mack, & Rudd, 2011). As opioid use for the treatment of pain has become more common, prescription opioid addiction and misuse have, too.

Prescription opiate misuse results in significant morbidity and mortality often because of unintentional overdose. In 2011, 34.2 million Americans aged ≥12 years had used an opiate for nonmedical use some time in their lives, and approximately 13% of high school seniors reported using prescription opioids such as oxycodone and hydrocodone (McCabe, West, Teter, & Boyd, 2012; U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, 2012). Since 2004, emergency room visits related to opiate pain relievers increased to 153%, by over 220,000 visits (U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, 2013). The deaths from prescription opiate misuse now outnumber deaths from motor vehicle collisions (Paulozzi et al., 2011). Data suggest that, for every one opioid-related death, there are 10 treatment admissions for prescription opiate misuse, 32 emergency department visits for misuse, 130 people who misuse, and 825 nonmedical users (CDC, 2011; Kochanek, Xu, Murphy, Miniño, & Kung, 2011; Warner, Chen, Makuc, Anderson, & Minimo, 2011).

The concern in healthcare today is the transition of patients from taking thoughtfully prescribed opioids for the treatment of pain to using drugs compulsively. Clinicians may see a "flip of the switch" to opioid misuse patterns. However, there is a more gradual process from initial exposure, to intermittent use, to regular use, to dependence, and to misuse and then a cycle of cessation, withdrawal, and relapse with drug abuse (Ballantyne & LaForge, 2007). This change in behavior is thought to be because of alterations in neuroplasticity and reduced ability to inhibit drug-associated cues (Kauer & Malenka, 2007). Furthermore, the healthcare provider and the patient find themselves ill prepared for the transition to problematic opioid misuse (St. Marie, 2014).

A precursor to addiction is exposure. Although opioid analgesics are indicated for treatment of moderate-to-severe pain after surgery, this first exposure may act as a catalyst to begin the cycle of opioid addiction. Addiction is defined as a primary chronic neurobiologic disease of reward, motivation, and memory, characterized by compulsive use, use despite harm, impaired control, and craving (American Society of Addiction Medicine, 2012). Family history of substance use disorders is associated with a higher risk for opioid addiction (Edwards et al., 2011). Family history suggests a genetic link, and genetic vulnerability for opioid use disorder has been found in polymorphism of the μ-opioid receptor gene or *OPRM1*, *GRIN2A*, *HTR2A*, and *DRD1* (Cao et al., 2014; Kreek et al., 2012; Zhao et al., 2013; Zhu et al., 2013).

When there is repeat exposure to opiate substances, long-term adaptations occur in the mesolimbic system that become very established and may account for the long-term behaviors associated with substance use disorder (Nestler, 2014). The epigenetic mechanisms of drug-related changes include structural, synaptic, and behavioral plasticity expressed through a gene network. However, these mechanisms also interact with environmental factors such as modeling behavior of drug taking and access to substances that enhance the reward system of the brain, the mesolimbic dopaminergic pathway.

Eventually, the pediatric surgical specialist may be able to predetermine addiction risk for patients before opioids are prescribed for pain. Using knowledge gained through genetic polymorphisms, pediatric surgical providers can begin now to adapt their pain management treatment to optimize early assessment and intervention of problematic use of opioids. Further research may increase sensitivity and specificity of assessments and interventions.

## FUTURE RESEARCH

Genetic variants encoding pain receptors and neuromodulators (*COMT*, *GCH1*, *OPRM1*, *OPRD1*, *MDR1*, *TRPA1*, *TRPV1*) and pharmacodynamic and pharmacokinetic genes (*CYP2D6*, *CYP2C9*, *CYP2C19*, *CYP3A4*, *CYP3A5*, *ABCB1*) may be used to identify patients at risk for postoperative pain and to aid treatment decisions tailored to each

individual. This critical approach to managing acute postsurgical pain acknowledges patients' individuality and diversity. Further exploration of the role of these genetic variants in postoperative pain is needed.

Longitudinal studies with children requiring repeated surgical interventions will also build our knowledge of individual variability of acute pain and pain epigenetics, thus exploring individual pain changes and responses with repeated surgical insults and potentially providing insight into mechanisms and variables involved in the development of persistent surgical pain and chronic pain. Here, we outline several research gaps that require further exploration.

### Research Gaps

1. Current knowledge of pain sensitivity genes is limited to adults in experimental pain conditions and limited acute and chronic pain conditions. Do these results translate to postoperative pain? Are they applicable to pediatric patients?
2. Genetic variants in *CYP2D6* have been implicated in children's deaths after surgery (e.g., from codeine administration). Do other genetic variants influence postoperative analgesic metabolism and effectiveness?
3. Tremendous variability exists in pediatric patients' reports of postoperative pain severity. Are there genetic markers to preoperatively identify patients at greatest risk for postoperative pain and/or altered analgesic metabolism and adverse analgesic effects, including addiction?
4. Can these findings be translated into clinical practice? Can we identify patients at greater risk for postoperative pain and/or analgesic adverse effects, including addiction? Can we make treatment decisions tailored to the individual before painful surgical experiences?
5. Some children require repeated surgical procedures. Do repeated insults alter the postoperative pain outcomes associated with genetic markers? Would longitudinal studies provide insight into variables and mechanisms involved in persistent surgical pain, chronic pain, and development of substance abuse and addiction?

## CLINICAL IMPLICATIONS: PERSONALIZED MEDICINE

Personalized medicine advances a new model of treating children's pain from trial and error to a targeted approach based on individual genetic findings. The application of personalized medicine to pediatric clinical practice is of high medical impact. By identifying children and adolescents at genetic risk for severe postoperative pain, adverse analgesic effects, and addiction, we expect to improve our current system for managing children's postoperative pain. By preoperatively screening pediatric patients' allelic status at pain-relevant genes and genes that regulate analgesic metabolism, we can formulate individualized treatment strategies for better pain control and reduced analgesic adverse effects. Gene-guided analgesic prescription will enable individualized management of children and adolescent acute postsurgical pain. However, more research is needed before this model of care can be realized. Current evidence is not sufficiently robust to recommend routine use of these potential genetic predictors of postoperative pain, and results of these tests have not been translated into clinical guidance for predicting analgesic response or more effective pain treatment strategies.

Ultimately, our long-term goal is to advance personalized pain management strategies by identifying variables that affect pediatric postoperative pain management outcomes and test interventions to optimize pain relief while reducing the occurrence of analgesic adverse effects, including addiction. Personalized pain management strategies can then be prospectively studied for correlates of genotypic variants in pain sensitivity, pharmacodynamic and pharmacokinetic genes, with postoperative outcomes. Improving knowledge of the genomic mechanisms and risk factors associated with pain will lead to the design of personalized interventions instead of routinely using standardized treatment protocols, enhancing clinicians' capability for patient-oriented interventions.

## CONCLUSION

Personalized medicine focuses on the needs of each individual to deliver the best treatment available to that person, taking into account personal and clinical characteristics.

Genomics has revolutionized biomedical science, and characterizing an individual's genotype offers the possibility of learning considerable details regarding each patient's physiology and response to surgery and postoperative care before surgery. However, the efficacy of a personalized health surgical program is not solely coded in genes but also in other aspects of nature and environment. All of these features come together in a physiogenomic model that can help to identify the individual's risk of surgical intervention and response to surgical care.

Genetic research efforts are rapidly progressing; and vendors have begun to market genetic testing without clear guidelines for clinical interpretation. The pediatric surgical specialist must be aware of both the potential genetic implications for postoperative pain management as well as the current limitations for genetic knowledge translation to guide clinical practice.

Children are particularly vulnerable to the long-term consequences of unrelieved pain and adverse analgesic effects, including addiction (Huth, Broome, Mussatto, & Morgan, 2003; Institute of Medicine, 2011; Jain et al., 2014; Polkki, Pietila, & Vehvilainen-Julkunen, 2003). There is a need to advance personalized medicine in pediatric pain management by identifying patients at greater risk

for postoperative pain and making treatment decisions tailored to the individual. Additional research will be needed to advance personalized medicine in the care of pediatric surgical patients, but this innovative approach to managing postsurgical pain may advance a new paradigm for treating acute pain.

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## Glossary (www.genome.gov/glossary)

| Term | Definition |
|---|---|
| Epigenetics | Study of heritable changes caused by activation and deactivation of genes without changes in the underlying DNA sequence of an organism |
| Genetic variation | The differences between individual genomes |
| Genetics | Study of a single gene |
| Genomics | Study of an entire individual's genome |
| Genotype | An individual's collection of genes. The term can also be used in referring to the two alleles inherited for a specific gene. |
| Haplotype | A set of SNPs or combination of alleles found on the same chromosome or a set of DNA variations (polymorphisms) that tend to be inherited together |
| Pharmacogenetic | Study of correlation of variation in single genes with drug responses |
| Pharmacogenomic | Study of correlation of genomic variation associated with drug responses |
| Phenotype | An observable trait, such as red hair or low pain sensitivity |
| Physiological genotypes | Diagnostic models derived from physiogenomic diagnostics |
| Polymorphisms | One of two or more variants of a particular DNA sequence |
| Single nucleotide polymorphisms (SNPs) | Variations of a single base pair of a DNA sequence. This is the most common type of polymorphism. |

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