Cincinnati Children's

2015 Research Annual Report

Anesthesiology

RESEARCH AND TRAINING DETAILS

Click to view members

Faculty	**60**
Joint Appointment Faculty	**2**
Research Fellows	**10**
Research Students	**5**
Support Personnel	**30**
Direct Annual Grant Support	**$936,373**
Direct Annual Industry Support	**$227,279**
Peer Reviewed Publications	**61**

CLINICAL ACTIVITIES AND TRAINING

Clinical Staff	**168**
Staff Physicians	**3**
Staff Psychiatrists	**2**
Clinical Fellows	**19**
Clinical Students	**145**
Other Students	**63**
Inpatient Encounters	**39,157**
Outpatient Encounters	**21,942**

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Research Highlights

Anesthesiology Emphasizes Research

Research in the Department of Anesthesiology ranges from basic science investigations of anesthetic neurotoxicity, to examination of psychosocial factors that contribute to surgery cancellation. The Department of Anesthesiology continues to place a major emphasis on supporting research by providing our faculty with both time and resources to find ways to better treat epilepsy, to relieve pain, and to more safely and effectively anesthetize children. A total of 36 of our 60 faculty have published during FY15.

Growth in Research on Pain Mechanisms

To foster research within the department, we have hired a new director of research, Robert C. Coghill, PhD, as well as a new translational researcher, Christopher D. King, PhD. This new team will amplify existing research into pain mechanisms by adding expertise in quantitative sensory testing and neuroimaging. Their addition into an already outstanding multi-disciplinary pain research environment solidifies Cincinnati Children's position as a leader in developing better ways to treat pain in children.

National and International Leadership in Research

Our faculty serve at both national and international levels where they help shape the future of research. They guide the selection of papers for publications in scientific journals: Andreas Loepke, MD, PhD, serves on the editorial boards of *Pediatric Anesthesia* and the *Journal of Perioperative Science*; Steve Danzer, PhD**,** serves as a contributing editor to *Epilepsy Currents*; and Robert Coghill, PhD, is section editor for the *International Association for the Studay of Pain (PAIN)*.

They lead their peers in advocacy for research and safety: Michael Jankowski, PhD, is co-chair of the Basic Science Shared Interest Group of the American Pain Society; and Dr. Danzer is chair of the Basic Science Committee of the American Epilepsy Society; John McAuliffe, MD, is president of The American Society of Neurophysiological Monitoring; and C. Dean Kurth, MD, is president of Wake Up Safe.

Finally, they help agencies decide how to fund research: Dr. Danzer serves as a standing member of the National Institutes of Health (NIH) Study Section for Clinical Neuroplasticity and Neurotransmitters; while Robert Coghill, PhD, serves as an ad hoc reviewer for several NIH study sections and on the Research Grants Committee of the American Pain Society.

Trainees Excel in Research

Anesthesiology faculty contribute to the future of research by mentoring the development of outstanding young scientists and clinical researchers. Our trainees have garnered many awards. Kathryn Green, a Summer Undergraduate Research Fellowship (SURF) student mentored by Dr. Michael Jankowski, received first place in the Capstone Poster session for all SURF programs; while Dr. Jankowski's graduate student, Jessica Ross, and post-doctoral fellow, Luis Queme, received Young Investigator awards to attend the American Pain Society meeting. Dr. Steve Danzer's graduate student, Shatrunjai Singh, was awarded a fellowship at The Data Incubator, in Washington, DC, while one of Dr. Danzer's other graduate students, Bethany Hosford, received a University Research Council (URC) Graduate Student Research Fellowship.

Significant Publications

LaSarge CL, Santos VR, **Danzer SC**. Pten Deletion from Adult-Generated Dentate Granule Cells Disrupts Granule Cell Mossy Fiber Axon Structure. *Neurobiol Dis. 2015* Mar;75:142-50.

Epilepsy is a major child health problem and can range from a life threatening event to a very subtle disorder. Even in

mild forms, epilepsy can have a deleterious effect on learning and intellectual development. One brain region, the hippocampus, is critically involved in learning and memory. A sub-region of the hippocampus, the dentate gyrus, is thought to serve as a gate that regulates the flow of information into the hippocampus. Breakdown of this gating mechanism might be an important factor in temporal lobe epilepsy. Work by post-doctoral fellow Candi LaSarge and colleagues in Steve Danzer's laboratory explored the role of the PTEN gene on connectivity of granule cells in a mouse model of temporal lobe epilepsy. They found that when the PTEN gene was knocked out, a complex set of morphologic changes occurred that would disrupt gating, such that information coming into the hippocampus would undergo less filtering. As such, these altered connections between neurons could play an important role in temporal lobe epilepsy.

Ross JL, Queme LF, Shank AT, Hudgins RC, **Jankowski MP**. Sensitization of Group III and IV Muscle Afferents in the Mouse after Ischemia and Reperfusion Injury. *J Pain.* 2014 Dec;15(12):1257-70.

Chronic pain is far more prevalent in children than one would ever hope. In particular, some forms of chronic pain that strike children, such as pain during Ehlers–Danlos syndrome and fibromyalgia, are associated with a great deal of pain in the muscle. Other forms of pain, such as that arising from sickle cell anemia, are related to reduced blood flow to certain body regions. However, very little is known about how muscle damage is signaled and what types of changes occur in signaling when blood flow to the muscle is blocked. Work by graduate student Jessica Ross and colleagues in Michael Jankowski's laboratory found that, after blockade of blood flow to a muscle, more nociceptive primary afferents (peripheral nerve cells that respond to information about potential damage to the body) responded to the types of chemicals that are given off during muscle activity. During a brief blockade of blood flow, these primary afferents also became more sensitive to light pressure. However, when blood flow was blocked for longer periods of time, the neurons became more sensitive to heat. Thus, different neural mechanisms are engaged during different durations of reduced blood flow. These findings provide an explanation for how different types of injuries to muscles are associated with different types of pain and sensitization, and underscore the need to develop multiple drug therapies for muscle pain.

SadhasivamS, **Chidambaran V**, Zhang X, Meller J, Esslinger H, Zhang K, Martin LJ, **McAuliffeJ**. Opioid-Induced Respiratory Depression: Abcb1 Transporter Pharmacogenetics. *Pharmacogenomics J.* 2015 Apr;15(2):119-126.

Children undergo surgeries for many reasons, but nearly all of the surgeries are associated with some form of post-operative pain. Opioid drugs such as morphine are key tools for the treatment of post-operative pain.These drugs are effective at relieving pain, but can also slow or even stop breathing if too much is given. Different individuals respond to these drugs very differently, such that an individual whose body processes the drug in one way may get respiratory depression, while other individuals getting the same dose do not experience this dangerous side effect. Senthil Sadhasivam and colleagues examined the genetic make up of 263 children undergoing tonsillectomy to see if differences in a gene called ABCB1 were related to respiratory depression. This gene encodes a molecule called P-glycoprotein that helps transport opioid drugs like morphine out of the brain and into the blood. They found that children with certain types of the ABCB1 gene were at far greater risk of prolonged hospital stays from respiratory depression.These findings provide an important foundation for the individualization of treatment in that they can permit the identification of individuals at risk of respiratory depression before any opioids are given. This is an important step towards ensuring that every child can have safe and effective pain relief after surgery.

Pratap JN, **Varughese AM**, Mercurio P, Lynch T, Lonnemann T, Ellis A, Rugg J, Stone WR, Bedinghaus C. Reducing Cancelations on the Day of Scheduled Surgery at a Children's Hospital. *Pediatrics.* 2015 May;135(5):e1292-9.

Time in the operating room is a precious and expensive resource. The operating room is filled with highly specialized equipment and requires a large team of highly trained individuals to perform surgery. Many patients wait weeks, or even months, for surgeries. If appointments for surgery are cancelled at the last minute, this important resource is

wasted, and the expenses are passed on to everyone's health care costs. Reducing day of surgery cancellations is thus very important to ensure that children get the care that they require and to keep health care costs under control. Nick Pratap and colleagues developed and tested interventions to help parents keep their child's appointment for surgery. These interventions included providing clear and focused instructions in a colorful and personalized format, text message reminders, and changes in the check-in process to identify patient illness near the day of surgery. Implementation of these interventions reduced OR time lost to day of surgery cancellations by 17%. This means that more children received the care that they required in a timely fashion, while simultaneously keeping costs under control.

Division Publications

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2. Biesiada J, Chidambaran V, Wagner M, Zhang X, Martin LJ, Meller J, Sadhasivam S. **Genetic risk signatures of opioid-induced respiratory depression following pediatric tonsillectomy**. *Pharmacogenomics*. 2014; 15:1749-1762.
3. Buck D, Kreeger R, Spaeth J. **Case discussion and root cause analysis: bupivacaine overdose in an infant leading to ventricular tachycardia**. *Anesth Analg*. 2014; 119:137-40.
4. Chatterjee D, Friedman N, Shott S, Mahmoud M. **Anesthetic dilemmas for dynamic evaluation of the pediatric upper airway**. *Semin Cardiothorac Vasc Anesth*. 2014; 18:371-8.
5. Chidambaran V, Mavi J, Esslinger H, Pilipenko V, Martin LJ, Zhang K, Sadhasivam S. **Association of OPRM1 A118G variant with risk of morphine-induced respiratory depression following spine fusion in adolescents**. *Pharmacogenomics J*. 2015; 15:255-62.
6. Chidambaran V, Olbrecht V, Hossain M, Sadhasivam S, Rose J, Meyer MJ. **Risk predictors of opioid-induced critical respiratory events in children: naloxone use as a quality measure of opioid safety**. *Pain Med*. 2014; 15:2139-49.
7. Clay S, Morillo-Delerme J. **Pharmacology: Local Anesthetics**. In: DA Young, OA Olutoye, eds. *Handbook of Critical Incidents and Essential Topics in Pediatric Anesthesiology*. Cambridge, UK: Cambridge University Press; 2015:203-206.
8. Clay S, Morillo-Delerme J. **Plastic Surgery: Cleft Lip and Palate Surgery**. In: DA Young, OA Olutoye, eds. *Handbook of Critical Incidents and Essential Topics in Pediatric Anesthesiology*. Cambridge, UK: Cambridge University Press; 2015:463-465.
9. Clay S, Sadhasivam S. **Local Anesthetic Toxicity**. In: DA Young, OA Olutoye, eds. *Handbook of Critical Incidents and Essential Topics in Pediatric Anesthesiology*. Cambridge, UK: Cambridge University Press; 2015:59.
10. Coghill RC. **Central Nervous System Mechanisms Supporting the Construction of an experience of Pain Intensity**. In: AV Apkarian, ed. *The Brain Adapting with Pain : Contribution of Neuroimaging Technology to Pain Mechanisms*. Philadelphia: Wolters Kluwer Health; 2015.
11. Coghill RC. **Functional Imaging of Pain: Insights and Implications**. In: K Burchiel, ed. *Surgical Management of Pain*. New York: Thieme; 2015:919-932.

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Faculty, Staff, and Trainees

Faculty Members

C. Dean Kurth, MD, Professor
Leadership Anesthesiologist-in-Chief and Chair, Department of Anesthesiology

Elena Adler, MD, Associate Professor
Leadership Medical Director, Anesthesia Supply Chain, Department of Anesthesiology

Lori Aronson, MD, Associate Professor

Anne Boat, MD, Associate Professor
Leadership Director, Fetal Surgery Team, Department of Anesthesiology, Patient Family Experience Officer

David Buck, MD, Assistant Professor

Veronica Busso, MD, Assistant Professor
Leadership Clinical Director, Department of Anesthesiology

Vidya Chidambaran, MD, Associate Professor

Smokey Clay, MD, Assistant Professor
Leadership Co-Director, Core Fellowship Program; Department of Anesthesiology

Robert Coghill, PhD, Associate Professor
Leadership Director of Research, Department of Anesthesiology

Andrew Costandi, MD, Assistant Professor

Steve Danzer, PhD, Associate Professor

Bobby Das, MD, Assistant Professor

Hilary Flint, DO, Assistant Professor

Lisa Francis, DO, Assistant Professor

Kenneth Goldschneider, MD, Associate Professor
Leadership Director, Medical Pain Service and Chronic Pain Clinic, Division of Pain Management

Diane Gordon, MD, Assistant Professor

Joel Gunter, MD, Professor

Nancy Hagerman, MD, Assistant Professor
Leadership Co-Medical Director, Same Day Surgery and Pre-Anesthesia Consultation Clinic, Department of Anesthesiology

Elizabeth Hein, MD, Associate Professor

Michael Jankowski, PhD, Assistant Professor

Thomas Kabalin, MD, Associate Professor

Michael "Jack" Kibelbek, MD, Associate Professor

Christopher King, PhD, Assistant Professor

Rachael Koll, MD, Assistant Professor

Renee Kreeger, MD, Assistant Professor

Jennifer Lam, DO, Assistant Professor

Christopher Lee, MD, Assistant Professor

Erica Lin, MD, Assistant Professor

Andreas Loepke, MD, PhD, Associate Professor

Mohamed Mahmoud, MD, Associate Professor
Leadership Director, Division Anesthesia Imaging

Jagroop Mavi, MD, Assistant Professor

John McAuliffe, MD, MBA, Professor
Leadership Clinical Director, Interim Research Director, Division of Neurobiology

Marc Mecoli, MD, Assistant Professor

Mark Meyer, MD, Associate Professor
Leadership Director, Procedure Management, Division of Pain Management

Jeffrey Miller, MD, Associate Professor

David Moore, MD, Associate Professor
Leadership Clinical Coordinator, Anesthesia Fellow Pain Management Education, Division of Pain Management

Jacquelyn Morillo-Delerme, MD, Associate Professor
Leadership Co-Director of Anesthesia - Liberty Campus, Department of Anesthesiology

Pornswan Ngamprasertwong, MD, Assistant Professor
Leadership Clinical Director, Co-Director of Anesthesia - Liberty Campus, Department of Anesthesiology

Vanessa Olbrecht, MD, Assistant Professor

Mario Patino, MD, Assistant Professor

Jayant "Nick" Pratap, MD, Assistant Professor

Joseph Previte, MD, FAAP, Associate Professor
Leadership Director, Information Technology Services, Department of Anesthesiology; Clinical Director, Division of Anesthesiology

David Richards, PhD, Associate Professor

John Rose, MD, Professor

Joanna Rosing, MD, Assistant Professor

Senthilkumar Sadhasivam, MD, MPH, Associate Professor
Leadership Director, Perioperative Pain Management, Division of Pain Management

Nancy Samol, MD, Assistant Professor
Leadership Director of Anesthesia - Liberty Campus, Department of Anesthesiology

Paul Samuels, MD, Associate Professor
Leadership Director, Education, Department of Anesthesiology

Michael Sikora, MD, Assistant Professor

Matthew Sjoblom, MD, Assistant Professor
Leadership Co-Director of Anesthesia - Liberty Campus, Department of Anesthesiology

Ximena Soler, MD, Assistant Professor
Leadership Director, Liver Transplant Surgery Team, Department of Anesthesiology

James Spaeth, MD, Associate Professor
Leadership Associate Director, Department of Anesthesiology; Director, Cardiac Anesthesia Team, Department of Anesthesiology

Theodore Striker, MD, Professor

Rajeev Subramanyam, MD, Assistant Professor

Alexandra Szabova, MD, Associate Professor

Rachel Thienprayoon, MD, Assistant Professor

Anna Varughese, MD, MPH, Associate Professor
Leadership Associate Director, Department of Anesthesiology; Director, Quality, Department of Anesthesiology; Co-Medical Director, Same Day Surgery and Pre-Anesthesia Consultation Clinic; Department of Anesthesiology; Associate Director, Perioperative Services

Norbert Weidner, MD, Associate Professor
Leadership Director, Palliative Care and Comfort Team, Division of Pain Management

Eric Wittkugel, MD, Associate Professor

Junzheng Wu, MD, Associate Professor

Joint Appointment Faculty Members

Susmita Kashikar-Zuck, PhD, Associate Professor (Behavioral Medicine & Clinical Psychology)

Anne Lynch-Jordan, PhD, Assistant Professor (Behavioral Medicine & Clinical Psychology)

Clinical Staff Members

- **Nancy Andersen, MD**, Staff Anesthesiologist
- **Clifford Hoffmann, MD**, Staff Anesthesiologist
- **Normidaris Jimenez, MD**, Staff Anesthesiologist
- **William Worden, MD**, Staff Anesthesiologist

Trainees

- **Niekoo Abbasian, MD**, PGY-V, University of Illinois
- **Donna Maria Cortezzo, MD**, PGY-X, University of Conneticut
- **Ajay D'Mello, MD**, PGY-V, Cleveland Clinic
- **Natalie Hadaway, MD**, PGY-V, Saint Barnabas Medical Center
- **Ali Kandil, MD**, PGY-V, Saint Barnabas Medical Center
- **Megah Kanjia, MD**, PGY-X, University of Arkansas
- **Christina Kettelle, MD**, PGY-V, University of Arizona
- **Eugene Kim, MD**, PGY-X, Stony Brook Medicine
- **Elizabeth Leweling, MD**, PGY-V, Michigan State
- **Eapen Mathew, MD**, PGY-X, University of Connecticut
- **Sarah Norris, MD** , PGY-X, Medical College of Georgia
- **Suzanne Numan, MD**, PGY-V, University of New Mexico
- **Neil Patel, MD**, PGY-V, Thomas Jefferson University
- **Deepika Rao, MD**, PGY-V, University of Pennsylvania
- **Deborah Romeo, MD**, PGY-X, Virginia Commonwealth University
- **Diane Ruehlmann, MD**, PGY-V, University of Illinois
- **Ashley Smith, MD**, PGY-V, Beth Israel Deaconess Medical Center
- **Anurag Tewari, MD**, PGY-X, Dayanand Medical College & Hospital
- **Charlotte Walters, MD**, PGY-V, Texas Tech University

Grants, Contracts, and Industry Agreements

Grant and Contract Awards **Annual Direct**

Chidambaran, V

Morphine Pharmacogenomics to Predict Risk of Respiratory Depression in Children

National Institutes of Health

K23 HD082782	9/1/2014-6/30/2019	$121,375

Danzer, S

Contributions of Aberrant Granule Cells Integration to the Development of Epilepsy

National Institutes of Health

R01 NS062806	4/15/2015-3/31/2020	$259,148

Identification and Reversal of Primary and Secondary Epileptogenic Changes

National Institutes of Health

R01 NS065020	5/1/2014-4/30/2019	$218,750

Jankowski, M

Molecular Mechanisms Of Musculoskeletal Pain After Ischemic Tissue Injury

American Pain Society

	9/1/2012-8/31/2015	$50,000

Mechanisms of Muscle Afferent Sensitization after Ischemia

National Institutes of Health

R01 AR064551	9/17/2013-8/31/2018	$212,500

Mechanisms of Postnatal Cutaneous Afferent Development during Inflammation

National Institutes of Health

R03 HD077483	8/1/2013-7/31/2015	$48,600

Singh, S

Ontogenetic Silencing of Dentate Granule Cells as an Approach to Block Seizure Progression

American Heart Association

	7/1/2013-6/30/2015	$26,000

	Current Year Direct	**$936,373**

Industry Contracts

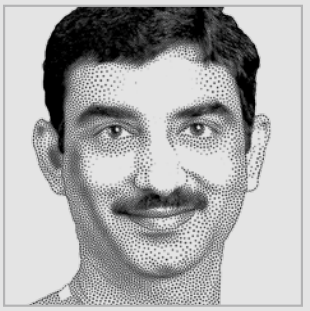
Patino, M

Masimo Corporation	$20,987

Sadhasivam, S

VistaPharma, Inc.	$206,292
Current Year Direct Receipts	**$227,279**
Total	**$1,163,652**

Genetic Variant Might Hold Key to Predicting Respiratory Depression and Personalizing Morphine Dosage



Senthilkumar Sadhasivam, MD, MPH

Vidya Chidambaran, MD

RESEARCH AND TRAINING DETAILS

Faculty	60
Joint Appointment Faculty	2
Research Fellows	10
Research Students	5
Support Personnel	30
Direct Annual Grant Support	$936,373
Direct Annual Industry Support	$227,279
Peer Reviewed Publications	61

Chidambaran V, Mavi J, Esslinger H, Pilipenko V, Martin LJ, Zhang K, Sadhasivam S. Association of OPRM1 A118G variant with risk of morphine-induced respiratory depression following spine fusion in adolescents. *Pharmacogenomics J.* 2015;15(3):255-262..

PUBLISHED ONLINE SEPT. 30, 2014
The Pharmacogenomics Journal

Better genetic-based predictors of morphine-induced respiratory depression could lead to more personalized pain-relief dosage for children recovering from surgery.

The key was found in μ1 opioid receptor genetic variant A118G, which decreases the binding potential of the μ-receptor in the brain, and therefore increases morphine requirement.

Postoperative respiratory depression is the most serious adverse effect of opioids. Researchers believe genetics account for up to 30 percent of the variability in respiratory depression.

The study, published online Sept. 30, 2014, in *The Pharmacogenomics Journal*, was led by Senthilkumar Sadhasivam, MD, MPH, and Vidya Chidambaran, MD, both of the Division of Anesthesia, and also involved researchers from the Division of Human Genetics. It was the first clinical study to show significant association of a functionally relevant polymorphism — A118G — of the opioid receptor gene in predicting MIRD susceptibility.

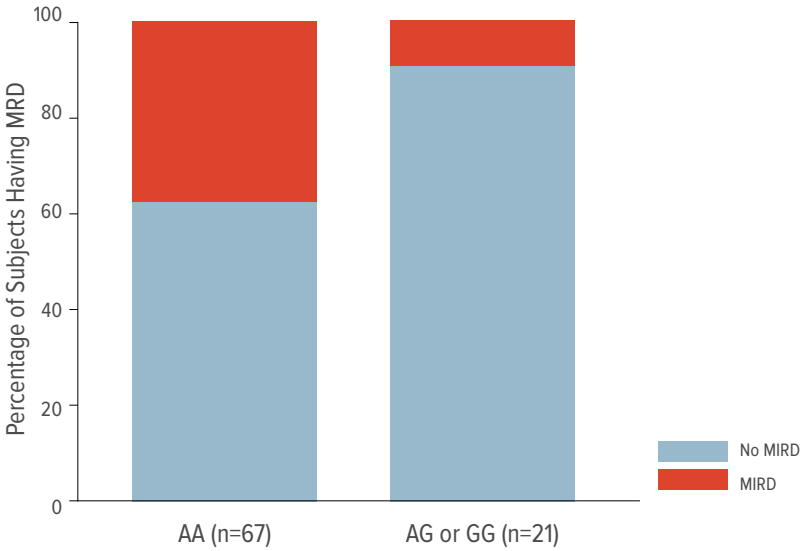
The team analyzed 88 cases of adolescents who had undergone spine fusion for scoliosis, and found that in the first 48 hours after surgery, MIRD in patients with AA genotype was significantly higher. The findings could have wide implications because the variant is present in an estimated 11-17 percent of the Caucasian population.

"This translates to immediate clinical relevance for a large part of the population," Chidambaran says, "as identifying genotype predicted risk of MIRD will facilitate safer individualized opioid dosing."

The team also has recently reported additional associations of respiratory depression in children with novel variants of the gene FAAH, published in January 2015, and with ABCB1, published in April 2015.

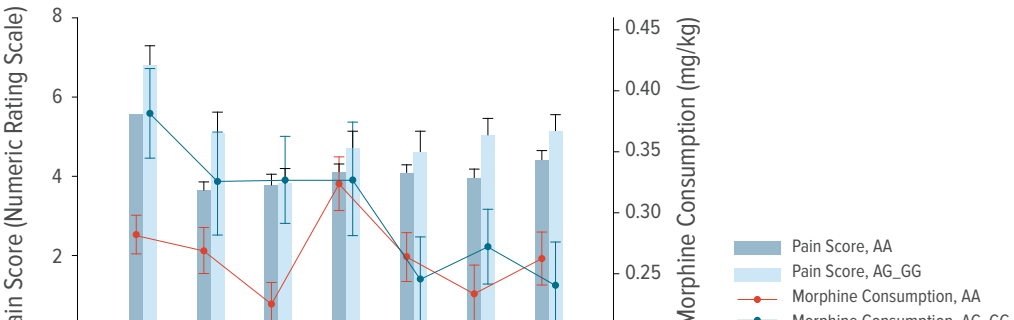
"These findings show that multiple genes play a role in opioids' clinical responses," Sadhasivam says. "As we identify more of these associations, the future of preoperative genetic risk signature stratification and personalizing postoperative pain management in children is promising."

MIRD IN PATIENTS WITH DIFFERENT GENOTYPES



This chart compares morphine-induced respiratory depression (MIRD) in the two genotype groups (AA and AG+GG) for the A118G polymorphism of the OPRM1 gene. Incidence was significantly higher in the AA subgroup (25/67 or 37 percent) compared with AG or GG subgroup (2/21 or 9 percent).

PAIN SCORES, MORPHINE CONSUMPTION POST-SURGERY



When looking across time, pain was highest two hours after surgery, and was consistently higher in individuals carrying a G allele (white bars). Differences in morphine consumption by genotype (blue and red lines) were greatest between two and 16 hours after surgery.