Picking the Most Effective Pain Medicine

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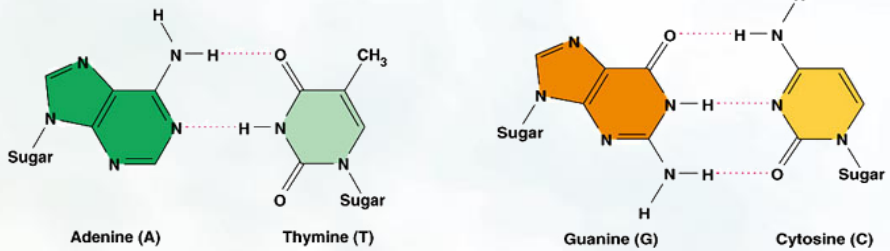
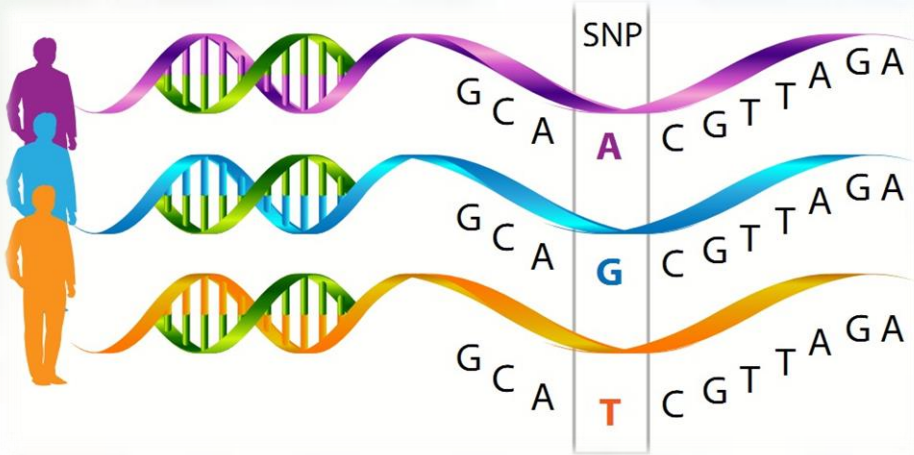
Variations in DNA

- Humans share 99.9% of their DNA
- The remaining 0.1% is what sets us apart from one another
  - ✓ Physical appearance
  - ✓ Susceptibility to disease
  - ✓ Response to medications
- We can detect the sequence of DNA and identify changes that may make one patient more susceptible to a disease, or respond differently to a medication, than another patient.
  - ✓ Reduce trial-and-error
  - ✓ Avoid ADEs

SNPs : Single Nucleotide Polymorphisms

- DNA is composed of nucleotides:
- SNPs are **p**olymorphisms at the **s**ingle **n**ucleotide level
  - ✓ Not the same as a mutation! A SNP has to be present in at least 1% of population
- Our DNA has ~10 million SNPs.
  - ✓ One gene may have 1000s of SNPs
  - ✓ Sometimes it is necessary to look at a combination of SNPs together

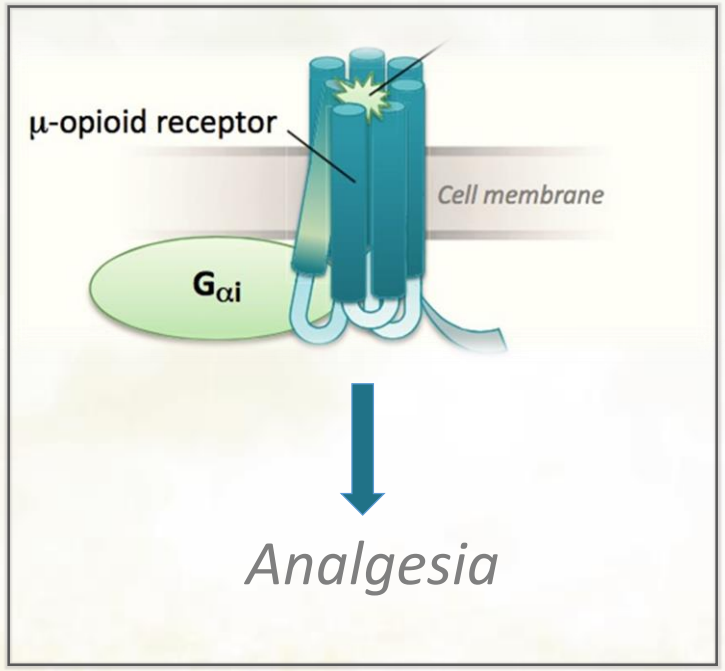




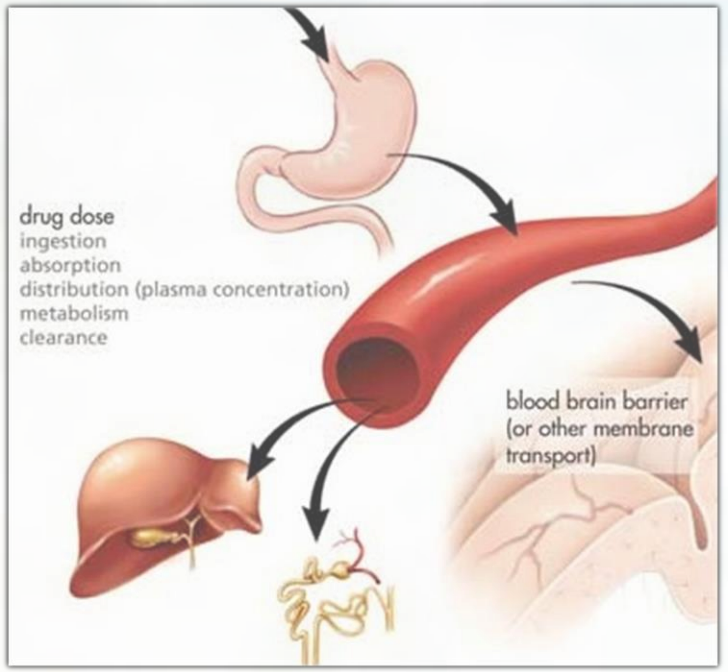
https://neuroendoimmune.wordpress.com/2014/03/27/dna-rna-snp-alphabet-soup-or-an-introduction-to-genetics/

Which SNPs are clinically-relevant?

<u>Pharmacodynamics</u>: Site of action –
“What the drug does to the body”



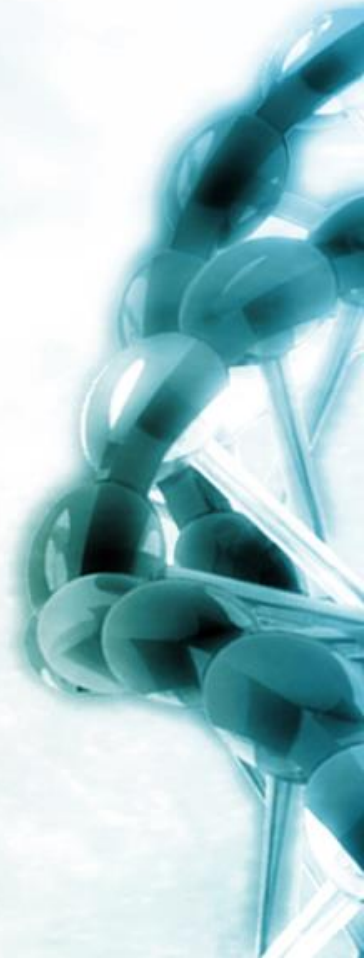
Violin JD et al. 2014. Trends in Pharmacological Sciences. 35(7)



<u>Pharmacokinetics</u>: Metabolism –
“What the body does to the drug”

Proove Genetic Testing

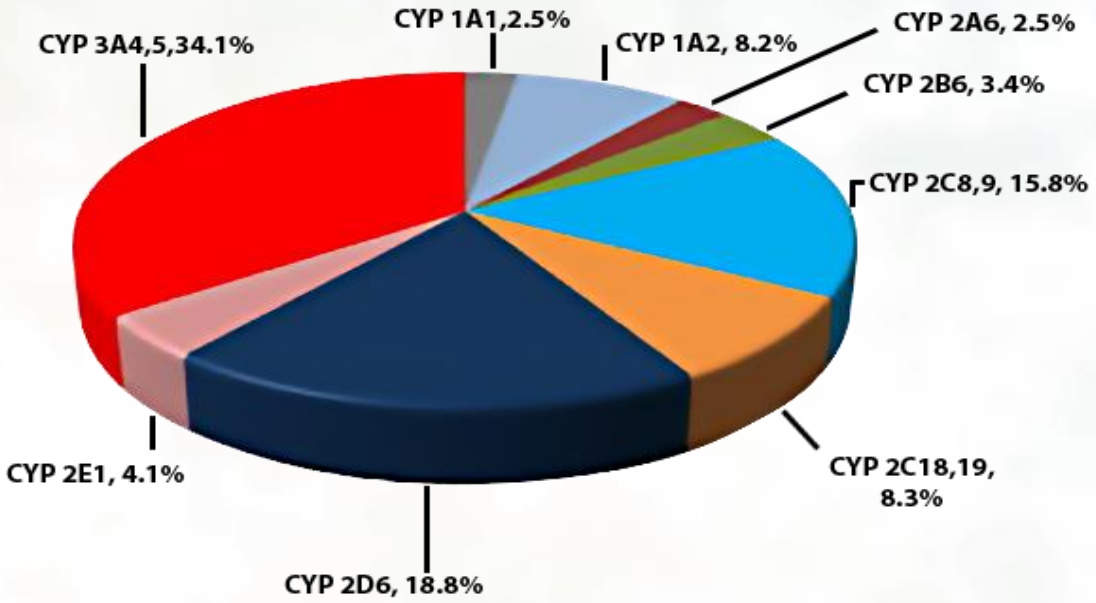
PROOVE DRUG METABOLISM	Patients on any medication
PROOVE OPIOID RESPONSE	Patients on or starting opioids
PROOVE NON OPIOID RESPONSE	Patients on or starting Ibuprofen, Acetaminophen, Gabapentin, or Alprazolam
PROOVE PAIN PERCEPTION	Patients experiencing pain
PROOVE OPIOID RISK	Patients on or starting opioids
PROOVE NSAID RISK	Patients on or starting NSAIDs



Drug Metabolism Genetic Profile

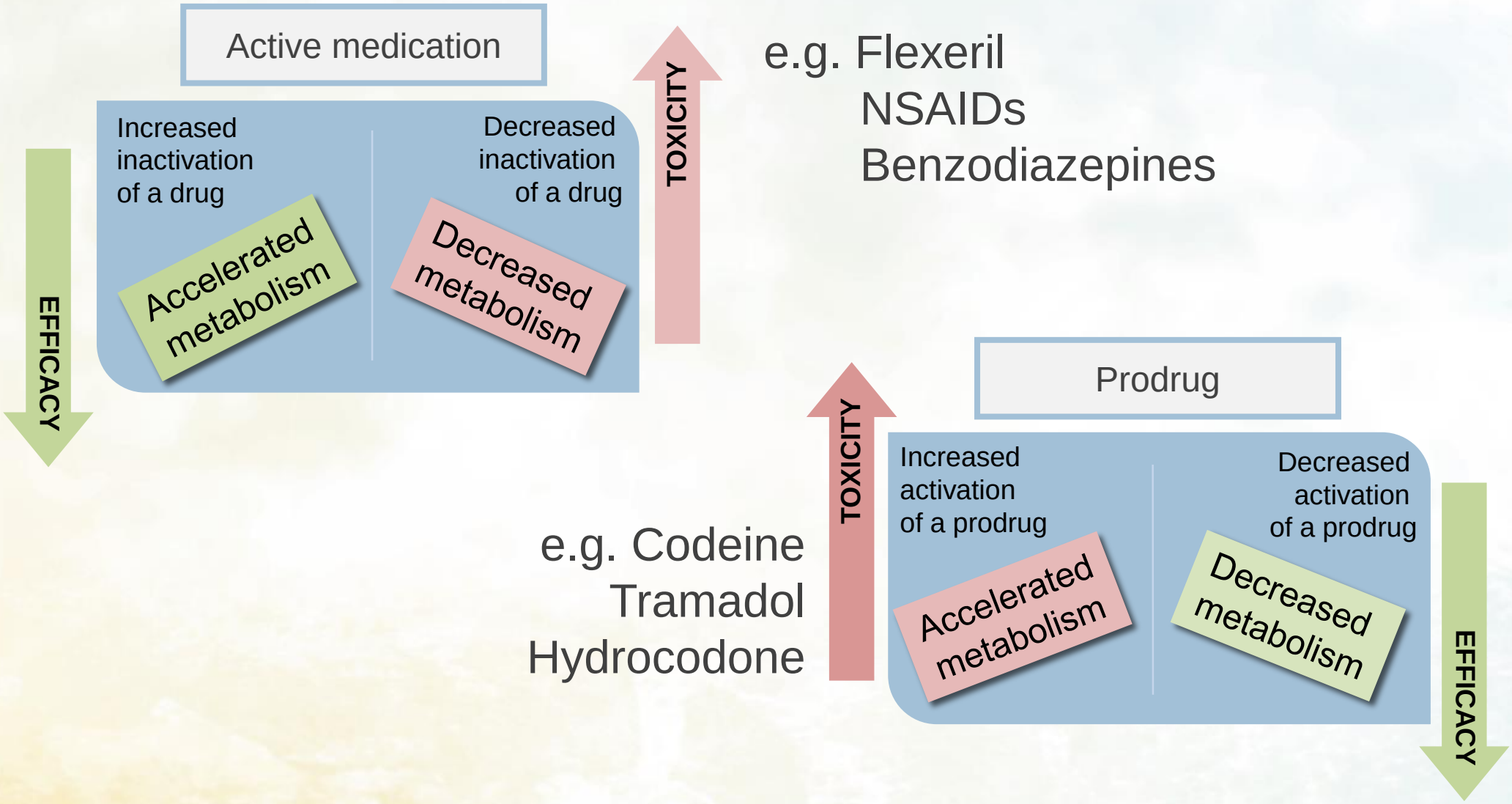
Clinical Validity

Correlation with Condition



Proportions of drugs metabolized by CYP450

Which SNPs are clinically-relevant?



PROOVE DRUG METABOLISM

Drug Metabolism

Intended Use:
Avoid ADEs, trial-and-error and effectively choose medications likely to work for patients

Pain Medications	Standard Precaution	Caution	Extreme Caution
Non-Opioids	Carbamazepine (Tegretol) Carisoprodol (Soma) Cyclobenzaprine (Flexeril) Gabapentin (Neurontin)		
Opioids	Buprenorphine (Butrans) Fentanyl (Duragesic) Hydromorphone (Dilaudid) Morphine (MS Contin, Avinza) Oxymorphone (Opana) Tapentadol (Nucynta)	Hydrocodone (Norco, Vicodin) Methadone (Dolophine)	Codeine Oxycodone (OxyContin, Percocet) Tramadol (Ultram)
NSAIDs	Tolmetin sodium (Tolectin)	Diclofenac (Voltaren) Etodolac (Lodine) Fenoprofen (Nalfon) Flurbiprofen (Ansaid) Ibuprofen (Advil, Motrin) Indomethacin (Indocin) Ketoprofen Ketorolac (Toradol) Meclofenamate (Meclomen) Mefenamic acid (Ponstel) Meloxicam (Mobic) Nabumetone (Relafen) Naproxen (Naprosyn, Aleve) Oxaprozin (Daypro) Piroxicam (Feldene)	Celecoxib (Celebrex)
Benzodiazepines	Alprazolam (Xanax) Bromazepam (Lexotanil) Clonazepam (Klonopin) Diazepam (Valium) Flurazepam (Dalmane) Midazolam (Versed) Temazepam (Restoril) Triazolam (Halcion)	Lorazepam (Ativan) Oxazepam (Serax)	

Cardiology	
Anti-Platelets	Clopi Prasu Ticag Vorap
Anti-Coagulants	Dabig Rivar Warfa
ACE Inhibitors	Enala Lisino Ramip
Angiotensin II Receptor Blockers	Olme
Alpha-2 Agonists	Guant
Sodium Channel Blockers	
Beta-Blockers	Ateno Bisopr Carvedil Labetalol (Sotalol (Betapace)
Calcium Channel Blockers	Amlodipine (Norvasc) Diltiazem (Cardizem) Felodipine (Plendil) Nifedipine (Adalat) Verapamil (Calan, Verelan)
Statins	Atorvastatin (Lipitor) Lovastatin (Mevacor) Pravastatin (Pravachol) Simvastatin (Zocor)

Psychotropics	
SSRIs	Sertra
SNRIs	Desve Levon
Tricyclic Antidepressants	
Atypical Antidepressants	Bupro Vilazo
Typical Antipsychotics	Thiot
Atypical Antipsychotics	Asenapine (Saphris) Lurasidone (Latuda) Paliperidone (Invega) Quetiapine (Seroquel) Ziprasidone (Geodon)

Fluvastatin (Lescol) Rosuvastatin (Crestor)		
	Olanzapine (Zyprexa)	Aripiprazole (Abilify) Iloperidone (Fanapt) Pimozide (Orap) Risperidone (Risperdal)

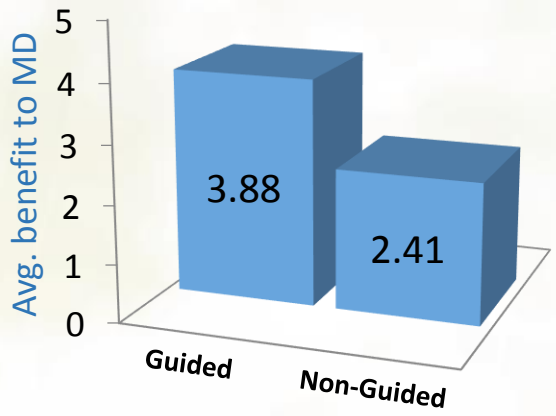
Drug Metabolism Genetic Profile

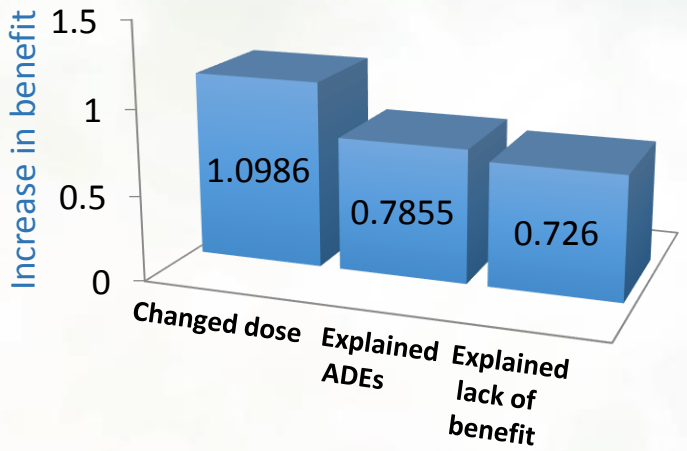
PROOVE DRUG METABOLISM

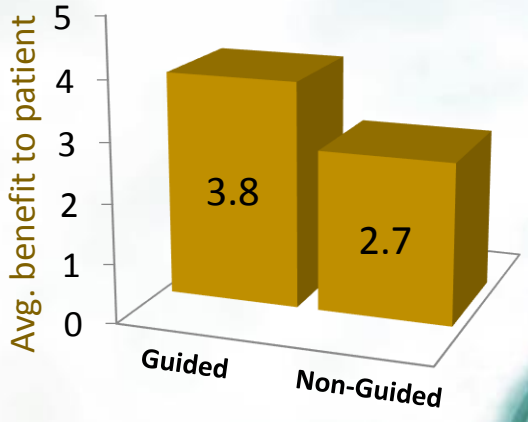
Clinical Actionability

Impact on Decision

In a prospective study of 122 patients, physicians who used the test rated its benefit on decision making as 3.88 on a 5-point scale (1.47 points higher than controls).







Clinical Utility

Correlation with Outcomes

Physicians who used the test rated its benefit on patient care as 3.80 on a 5-point scale (1.10 points higher than controls). Improvement within 60 days

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PROOVE OPIOID RESPONSE

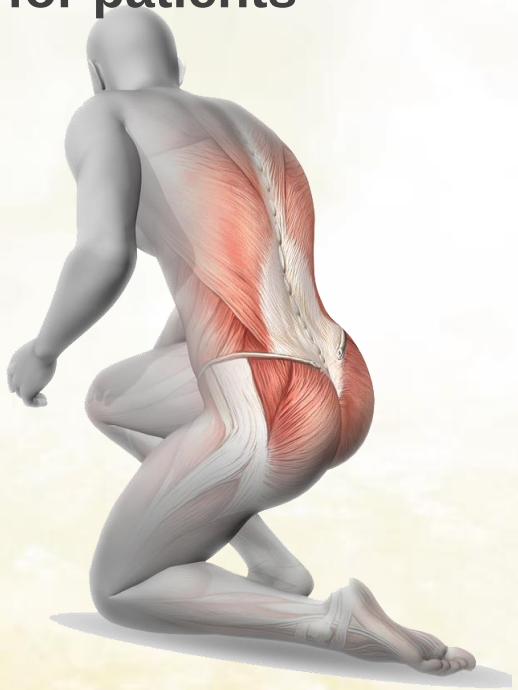
Opioid Response

Intended Use:
Avoid trial-and-error, ADEs, and effectively choose medications likely to work for patients

Therapy Selection	Dosing Recommendation
Likely Good Responder	
Oxycodone Roxicodone, Oxycontin, Oxecta, OxyIR, Endone, Oxynorm	This patient is predicted to be a normal metabolizer of Oxycodone. Prescribe at standard label recommendations. — Normal Dose
Hydrocodone Xodol, Vicodin, Norco, Lortab, Lorcet	This patient may experience insufficient pain relief with average doses of Hydrocodone. Monitor the patient's analgesic response and consider prescribing an increased dose if necessary. — Higher Dose
Likely Poor Responder	
Tramadol Ryzolt, Ultram, ConZip	This patient is at risk of experiencing an adverse drug event (ADE) with Tramadol. According to published guidelines, consider a 30% decreased dose and be alert for ADEs, or use an alternative to tramadol that is not oxycodone or codeine. — Lower Dose
Morphine Avinza, Duramorph, Kadian, DepoDur, Astramorph	This patient is not predicted to have abnormal metabolism of Morphine. Prescribe at standard label recommendations. — Normal Dose
Hydromorphone Exalgo, Dilaudid, Dilaudid-hp	This patient is not predicted to have abnormal metabolism of Hydromorphone. Prescribe at standard label recommendations. — Normal Dose

Non-Opioid Response

Intended Use:
Avoid trial-and-error, ADEs, and effectively choose medications likely to work for patients



Therapy Selection	Dosing Recommendation	
Likely Good Responder		
Duloxetine • Cymbalta	This patient may experience increased clearance of Duloxetine. Monitor the patient's analgesic response and consider prescribing an increased dose if necessary.	Normal Dose
Acetaminophen • Tylenol • Panadol	This patient is not predicted to have abnormal metabolism of Acetaminophen. Prescribe at standard label recommendations.	Normal Dose
Likely Poor Responder		
Ibuprofen • Advil • Brufen • Motrin • Nurofen	This patient is predicted to experience reduced clearance rates and increased risk of adverse drug events with ibuprofen. Consider lowering dose and/or reducing frequency of use.	Lower Dose
Gabapentin • Fanatrex • Gabarone • Gralise • Neurontin • Nupentin • Neogab	Gabapentin is not appreciably metabolized by the CYP450 family of enzymes; therefore, no dosage changes based on CYP450 genetics are recommended. However, if this patient requires concomitant treatment with opioids, (s)he may experience increases in gabapentin concentrations. In this case, carefully observe for signs of central nervous system (CNS) depression, such as somnolence, sedation and respiratory depression, and reduce the dose of gabapentin or opioids appropriately. Reduction of gabapentin dose may also be required in patients who have age-related compromised renal function.	Normal Dose
Alprazolam • Xanax	This patient may experience increased exposure to Alprazolam due to reduced clearance of the medication. Consider lowering dose.	Lower Dose

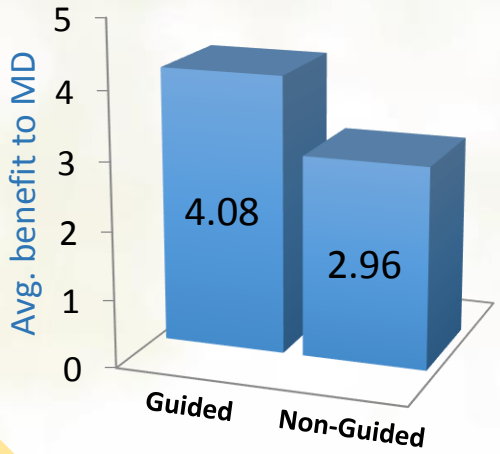
Non-Opioid Response Genetic Profile

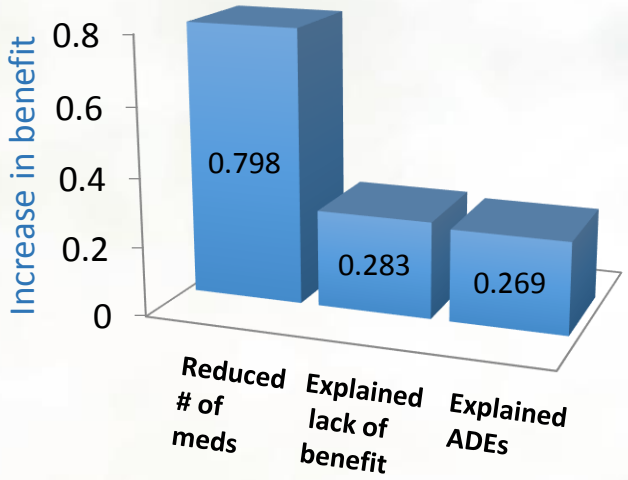
PROOVE NON OPIOID RESPONSE

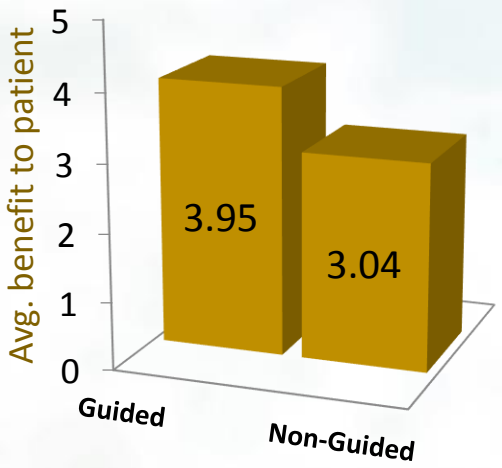
Clinical Actionability

Impact on Decision

In a prospective longitudinal study of 6,908 patients across 92 different research sites, physicians who used the test rated its benefit in decision making as a 4.08 on a 5-point scale (1.12 points higher than controls).







Clinical Utility

Correlation with Outcomes

In a study of 6,908 patients, physicians who used the test rated the benefit in patient care as 3.95 on a 5-point scale (0.91 points higher than controls).

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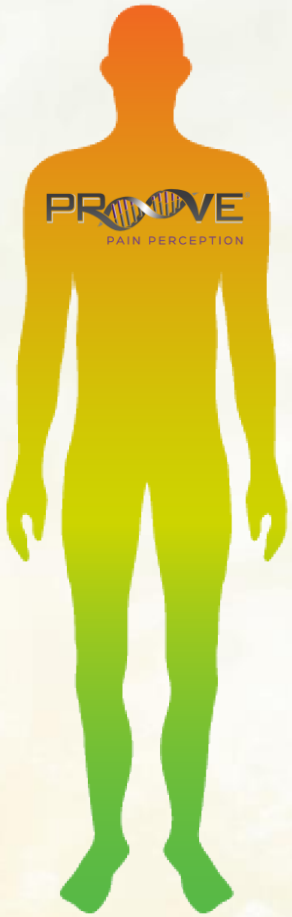
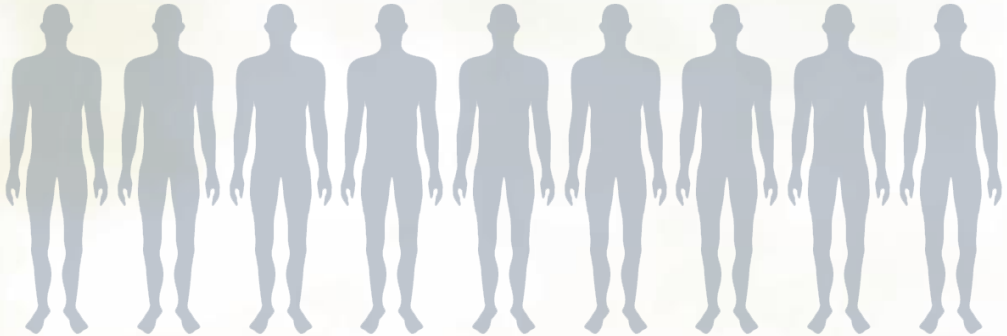
Objectively Assess Pain Perception



We All Feel Pain Differently.



Human Molecular Genetics

The test accounted for 96% of the population and correlated with sensitivity (p<0.0004) to experimental pain.

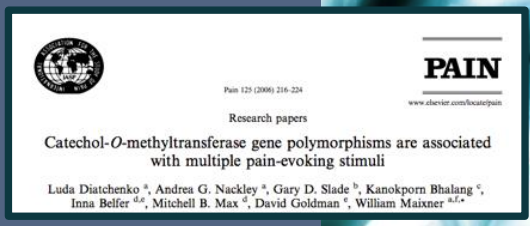

Human Molecular Genetics, 2005, Vol. 14, No. 1 135–143
doi:10.1093/hmg/ddi013
Advance Access published on November 10, 2004

Genetic basis for individual variations in pain perception and the development of a chronic pain condition

Luda Diatchenko[1,6,*], Gary D. Slade[2], Andrea G. Nackley[1], Konakporn Bhalang[3], Asgeir Sigurdsson[1], Inna Belfer[4,7], David Goldman[4], Ke Xu[4], Svetlana A. Shabalina[5], Dmitry Shagin[6], Mitchell B. Max[2], Sergei S. Makarov[6] and William Maixner[1]

Pain

The test was associated with multiple forms of pain stimuli.


PAIN

Pain 125 (2006) 216–224

www.elsevier.com/locate/pain

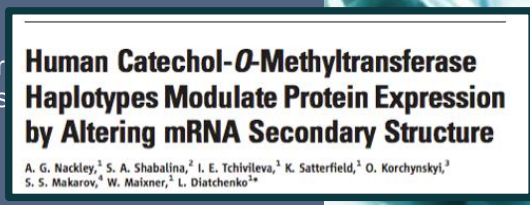
Research papers

Catechol-*O*-methyltransferase gene polymorphisms are associated with multiple pain-evoking stimuli

Luda Diatchenko [a], Andrea G. Nackley [a], Gary D. Slade [b], Kanokporn Bhalang [c], Inna Belfer [d,e], Mitchell B. Max [d], David Goldman [e], William Maixner [a,f,*]

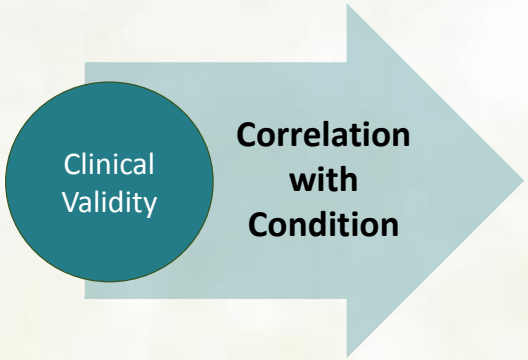
Science

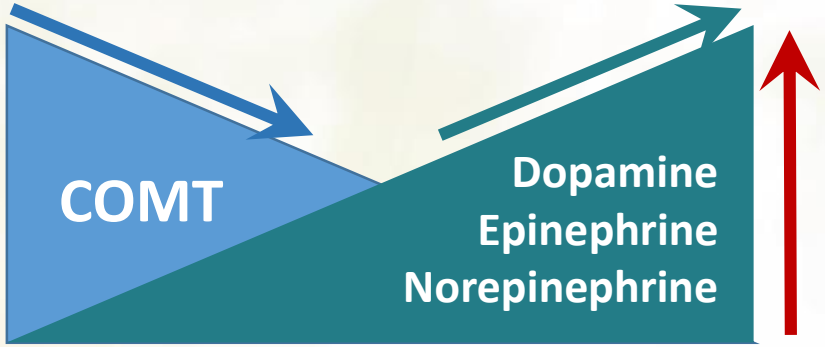
The test influenced messenger RNA local stem-loop structures directing downstream protein levels and enzymatic activity


Human Catechol-*O*-Methyltransferase Haplotypes Modulate Protein Expression by Altering mRNA Secondary Structure

A. G. Nackley,[1] S. A. Shabalina,[2] I. E. Tchivileva,[3] K. Satterfield,[3] O. Korchynskyi,[3] S. S. Makarov,[4] W. Maixner,[5] L. Diatchenko[1]*

Pain Perception Clinical Utility





COMT Activity	Pain Sensitivity	Clinical Implications
High	Low	Quicker recovery from surgical procedures; lower opioid requirements; under-reporting pain
Moderately High	Moderately Low	Quicker recovery from surgical procedures; lower opioid requirements
Average	Average	Quicker recovery from surgical procedures; lower opioid requirements
Moderately Low	Moderately High	Higher opioid requirements, may be magnifying pain
Low	High	Longer recovery from surgical procedures; higher opioid requirements; pain magnifying

Tammimäki, A. & Männistö, P. T. Catechol-O-methyltransferase gene polymorphism and chronic human pain: a systematic review and meta-analysis. *Pharmacogenet Genomics* **22**, 673-691, doi:10.1097/FPC.0b013e3283560c46 (2012)

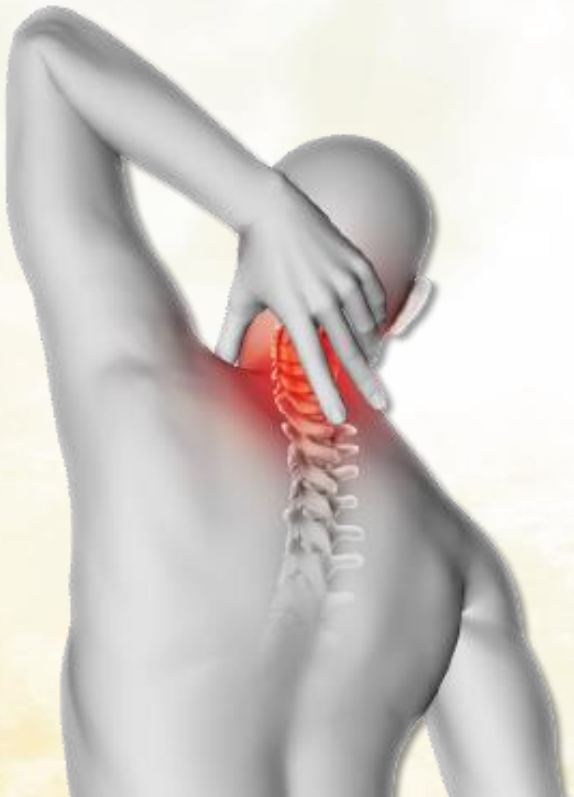
McLean, S. A. *et al.* Catechol O-methyltransferase haplotype predicts immediate musculoskeletal neck pain and psychological symptoms after motor vehicle collision. *J Pain* **12**, 101-107, doi:10.1016/j.jpain.2010.05.008 (2011).

Dai F et al. (2010) Association of catechol-O-methyltransferase genetic variants with outcome in patients undergoing surgical treatment for lumbar degenerative disc disease. The Spine Journal 10:949-957.

PROOVE PAIN PERCEPTION

Pain Perception

Intended Use:
Interpret patient's self-reported pain to guide appropriate use of Rx and non-Rx treatment



Pain Sensitivity Index

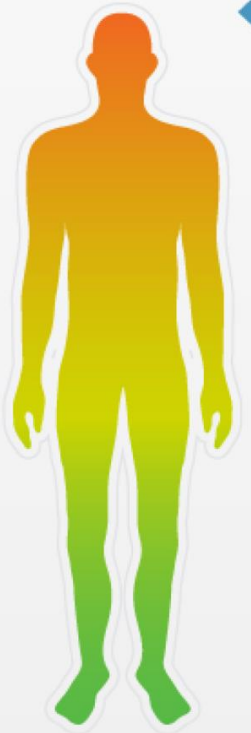
5 HPS/APS

- 1 - LPS/LPS = LOW- (lowest pain sensitivity)
- 2 - APS/LPS = MODERATELY LOW
- 3 - APS/APS = AVERAGE
- 4 - HPS/LPS = MODERATELY HIGH
- ✔ 5 - HPS/APS & HPS = HIGH- (highest pain sensitivity)

Jane Doe is genetically predisposed to high pain sensitivity and may be perceiving an exaggerated level of pain. Patient pain numeric rating scores may be inconsistent with medical evaluations. This patient may take longer to recover from surgical procedures or injuries and continue to experience pain with average doses of pain medication. Consideration of alternative therapies, including cognitive-behavioral therapy, that target altered neurochemistry may be warranted.

High Pain Sensitivity

HPS/APS

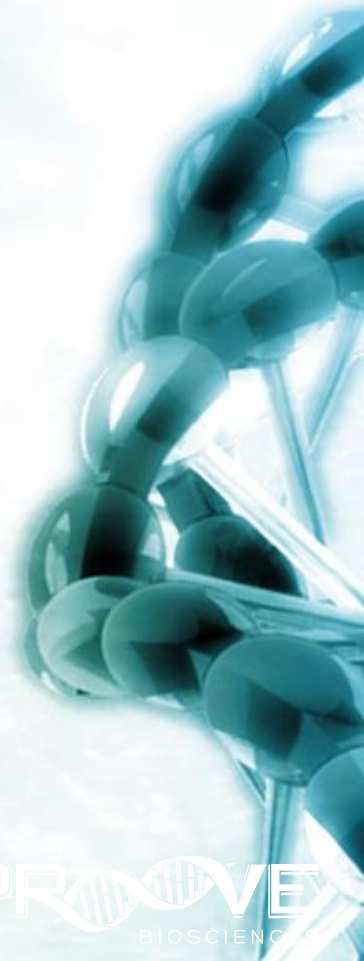


Genotype

Catechol-O-Methyltransferase (S-COMT promoter A/G) rs6269	A/A
Catechol-O-Methyltransferase (COMT his62his C/T) rs4633	C/C
Catechol-O-Methyltransferase (COMT leu136leu C/G) rs4818	C/C
Catechol-O-Methyltransferase (COMT val108/158met A/G) rs4680	G/G
Serotonin 2a Receptor (HTR2A) rs7997012	G/G
Dopamine Beta Hydroxylase (DBH) rs1611115	C/C
Serotonin Transporter (SLC6A4) rs140701	C/T
Methylenetetrahydrofolate Reductase (MTHFR) rs1801133	G/A
$GABA_A$ Receptor, gamma2 (GABRG2) rs211014	C/C
Opioid Receptor, Mu 1 (OPRM1) rs1799971	A/G

Additional Factors

(+) Gender (+) Age (-) Depression (-) Mental Health



PROOVE BIOSCIENCES

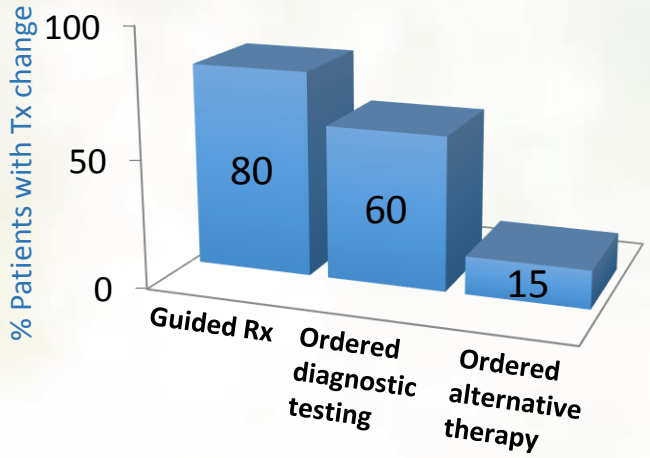
Pain Perception Genetic Profile

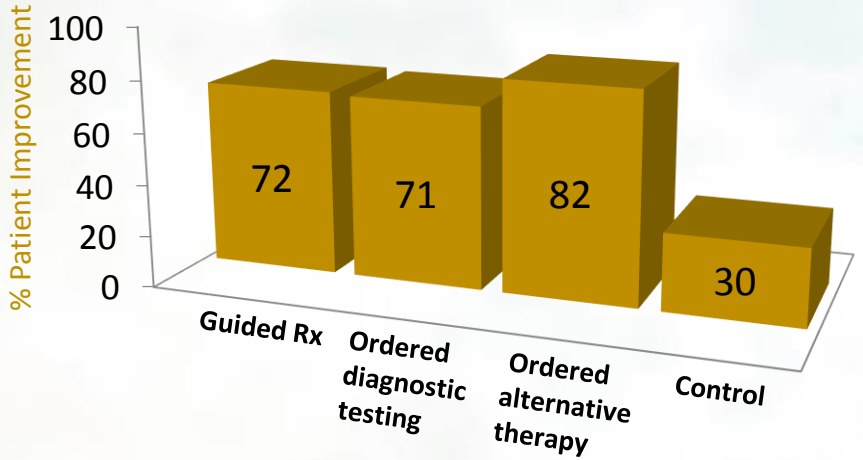
PROOVE PAIN PERCEPTION

Clinical Actionability

Impact on Decision

In a prospective longitudinal study of 134 patients, physicians made a treatment change in 40% of patients





Clinical Utility

Correlation with Outcomes

Comparing clinical outcomes of those who made treatment changes vs. those who did not, over 70% of patients improved in status after their physician made an action based on the genetic testing

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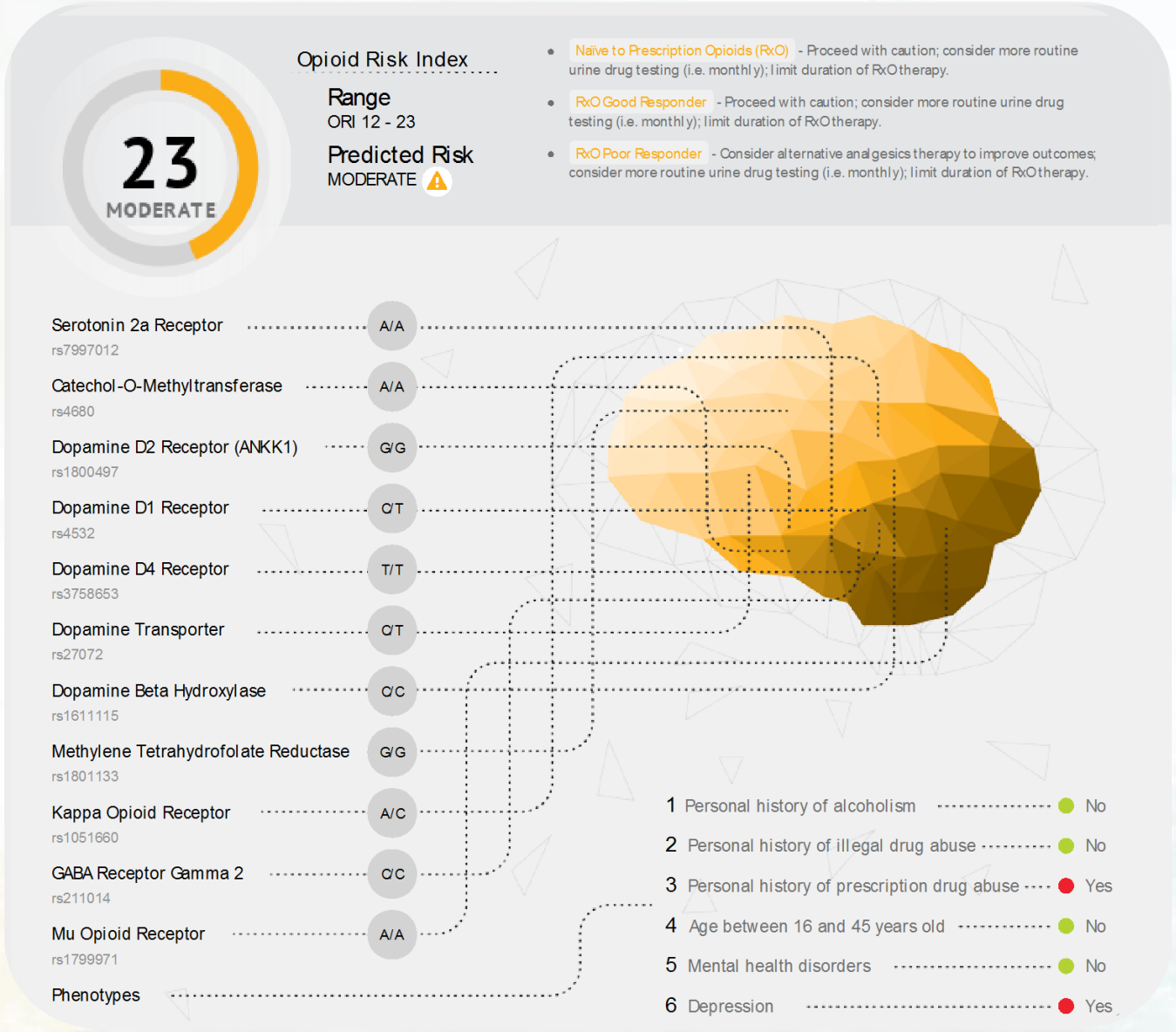
PROOVE OPIOID RISK

Opioid Risk

Intended Use:

Stratify risk to cost, effectively use opioids in low risk, monitor/rotate in moderate risk, avoid/limit in high risk



Opioid Risk Genetic Profile

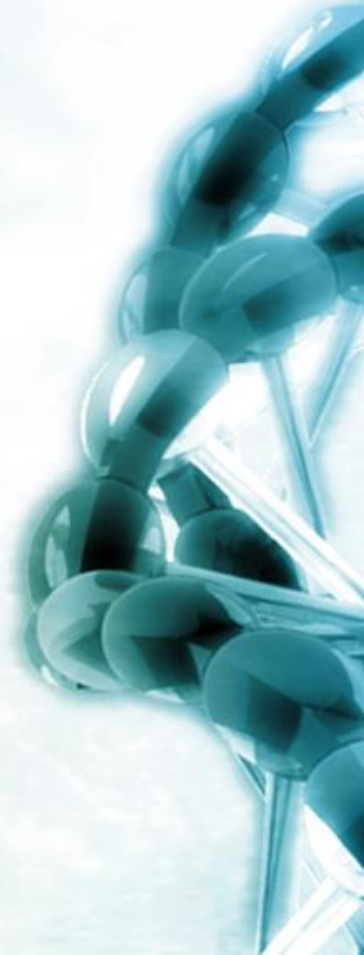
PROOVE OPIOID RISK

Clinical Validity

Correlation with Condition

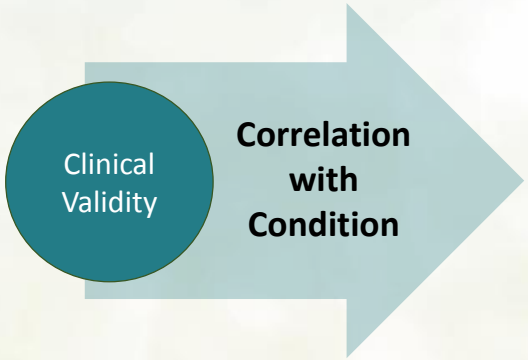
Individual genes have been independently found to correlate with abuse-related disorders

- Genetic variants are located within four important neurochemical pathways associated with the brain reward pathways
  - Serotonergic
  - Endorphinergic
  - GABAergic
  - Dopaminergic circuits



Opioid Risk Genetic Profile

PROOVE OPIOID RISK



Gene	Disorder
Serotonin 2A Receptor	• Alcohol abuse[6] • Anxiety[7] • Depression[8] • Drug Abuse[9]
Serotonin Transporter	• Alcohol abuse[10] • Substance abuse[11]
Catechol-O-Methyltransferase	• Alcohol abuse[12] • Methamphetamine abuse[13]
Dopamine D2 Receptor	• Alcohol, cocaine, nicotine dependence[14]
Dopamine D1 Receptor	• Heroin addiction[15,16]
Dopamine D4 Receptor	• Drug abuse[17]
Dopamine Transporter	• Cocaine addiction[18] • Methamphetamine addiction[19]
Dopamine Beta Hydroxylase	• Alcohol abuse[20] • Cocaine addiction[20,21] • Smoking addiction[22]
Methylene Tetrahydrofolate Reductase	• Bipolar disorder, depression, schizophrenia[23]
Human Kappa Opioid Receptor	• Alcohol abuse[24]
Gamma-Aminobutyric Acid	• Alcohol abuse[25] • Methamphetamine dependence[26]
Human Mu Opioid Receptor	• Complex regional pain syndrome[27] • Heroin dependence[28]

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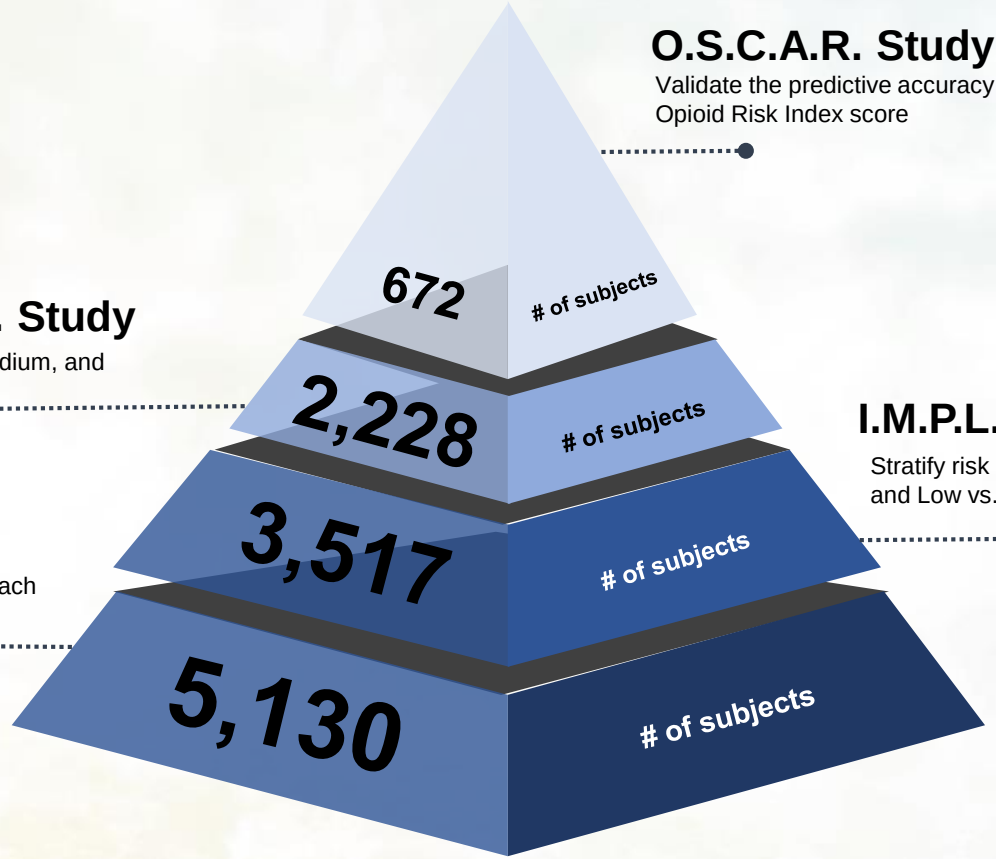
Opioid Risk Genetic Profile

PROOVE OPIOID RISK

Clinical Validity

Correlation with Condition



O.S.C.A.R. Study
Validate the predictive accuracy of the Opioid Risk Index score

I.M.P.L.O.R.E. Study
Stratify risk into High, Medium, and Low vs. the SOAPP-R

I.M.P.L.O.R.E. Study
Stratify risk into High, Medium, and Low vs. the ORT

P.I.L.L. Study
Validate the significance of each individual gene in the panel

 |

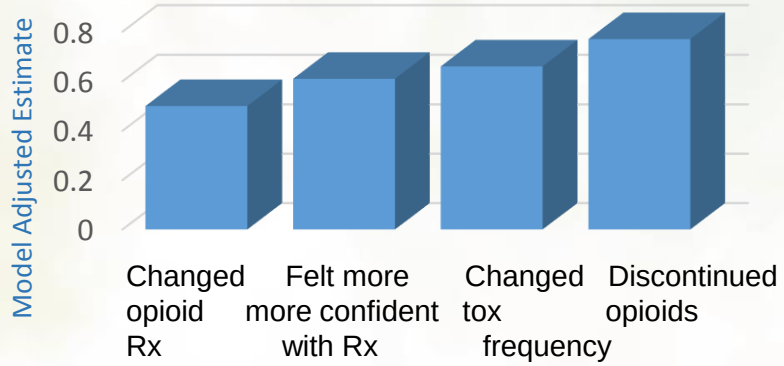
Opioid Risk Genetic Profile

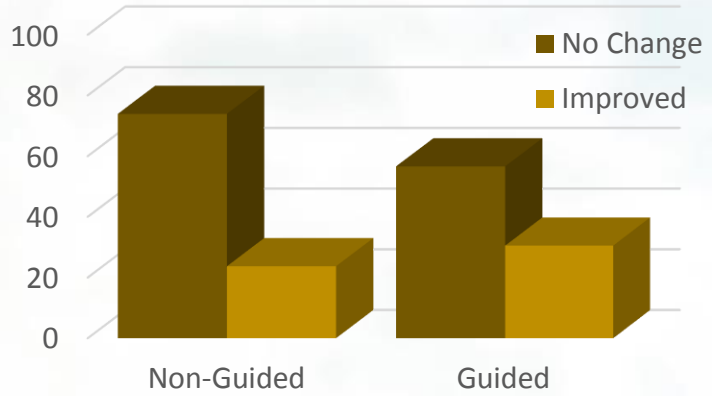
PROOVE OPIOID RISK

Clinical Actionability

Impact on Decision

In a prospective longitudinal study of 473 Orthopedic Surgery patients, physicians rated the benefit of the test on decision making and patient care a 4.10/5



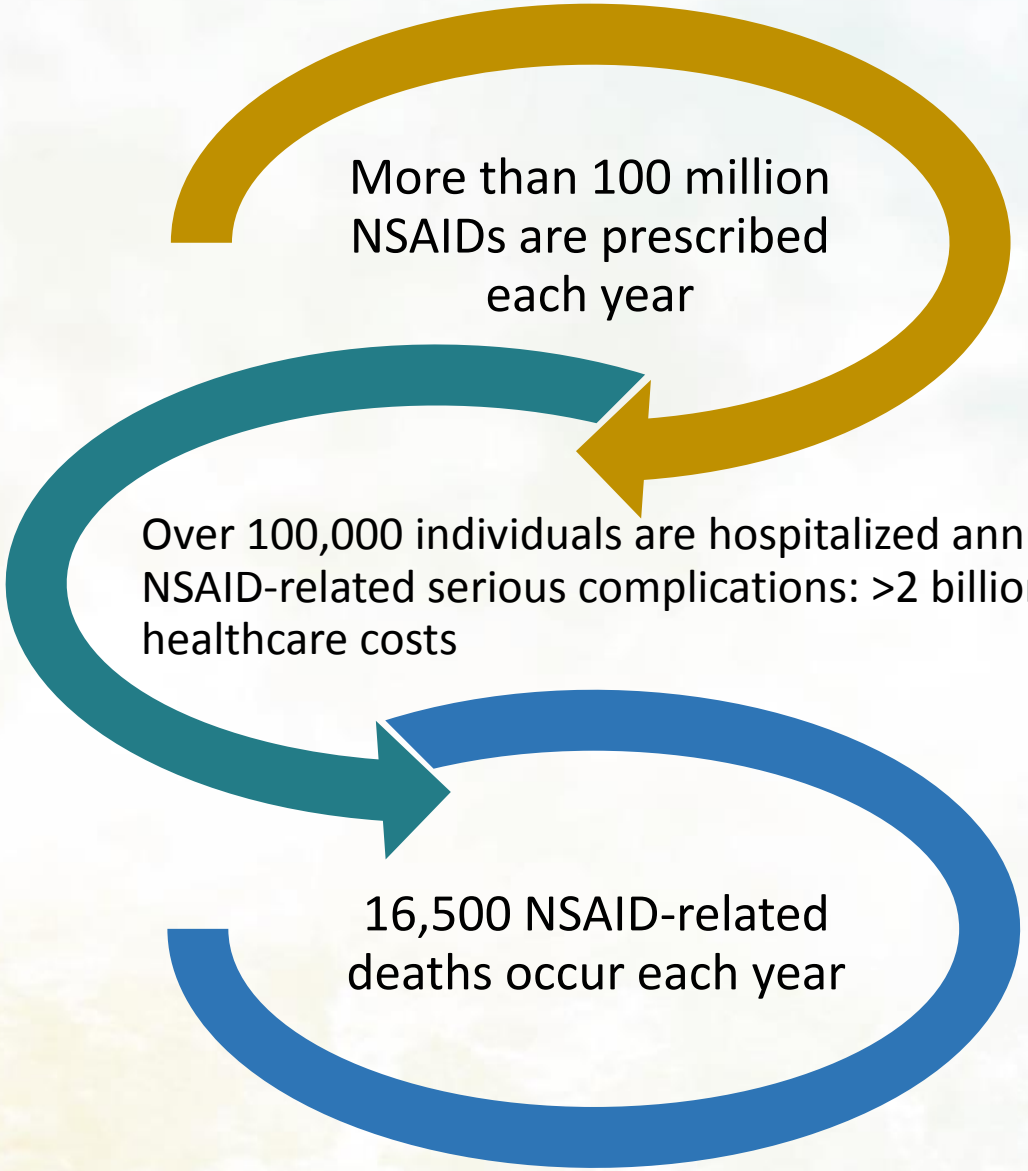


Clinical Utility

Correlation with Outcomes

In a study of 1,781 patients across 76 research sites, physicians who used the test rated it 0.71 points higher on a 5-point scale. Improvement within 60 days

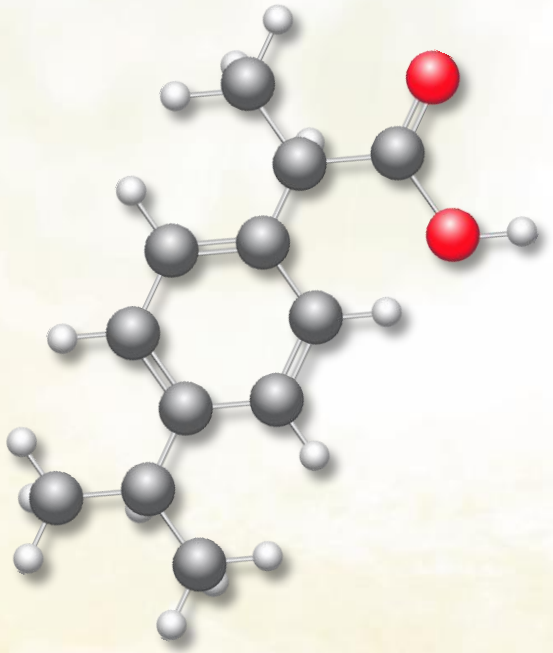
NSAID Risk Genetic Profile



PROOVE
NSAID RISK

NSAID Risk

Intended Use:
Avoid ADEs associated with NSAID use



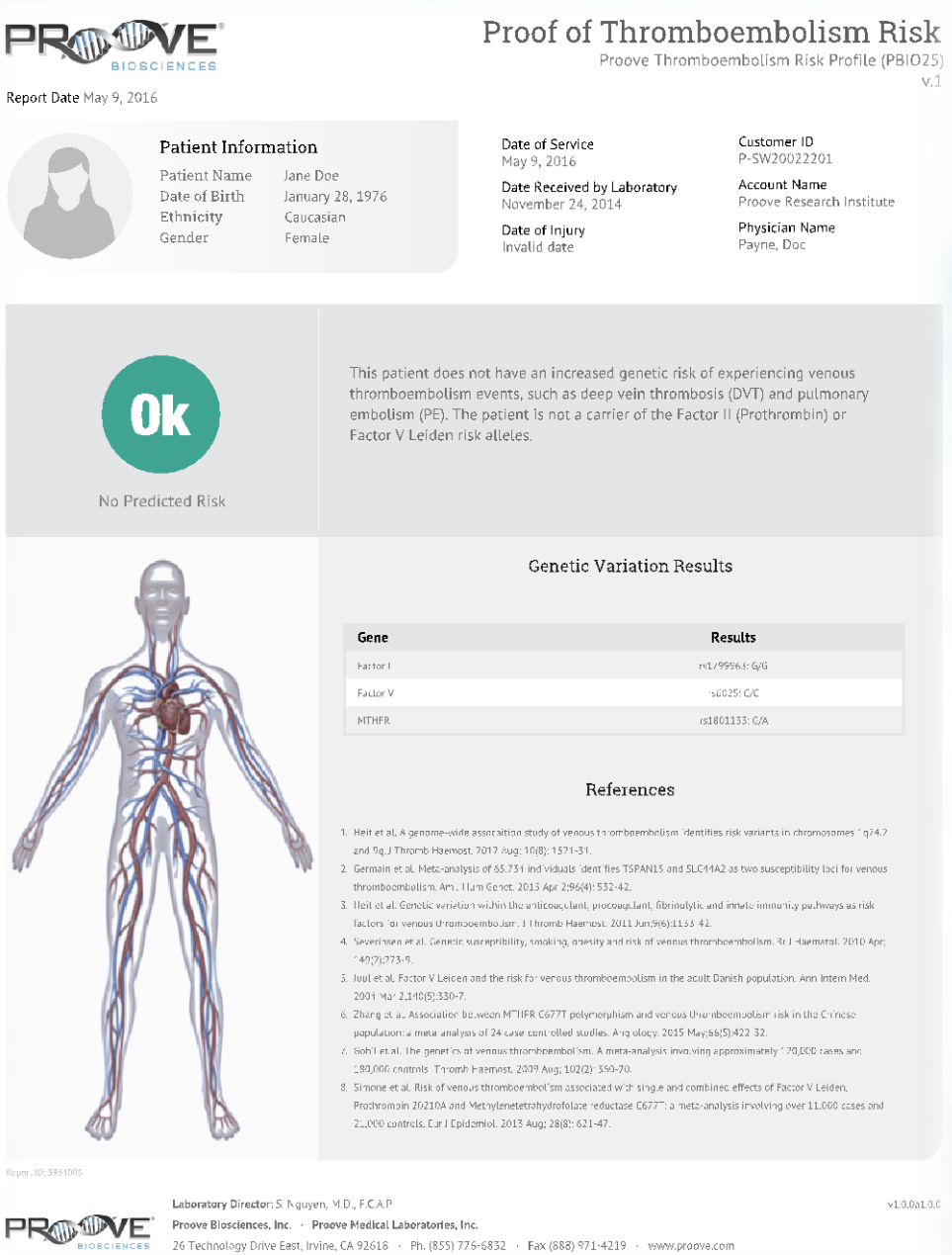
Bleeding / Ulcer		
	This patient is predicted to be at elevated risk of developing an NSAID-induced ulcer disease and gastro-intestinal bleeding due to COX-1 and NSAID metabolizing enzyme polymorphisms. Consider treatment to reduce risk of gastric ulcers, such as Proton Pump Inhibitors (PPIs) or Histamine H2-receptor antagonists. Evaluating CYP2C19 and CYP2D6 genetics, respectively, for these treatments with the Proove Drug Metabolism profile can help to make the appropriate selection.	Predicted Risk
Cardiovascular		
	This patient has a COX-1 genetic variant that is predicted to be ineffectively regulated with aspirin treatment. If taking aspirin, this patient is at increased risk of experiencing an adverse cardiovascular event due to aspirin resistance. Consider alternatives to aspirin for heart disease and stroke prevention. In general, this patient carries a COMT genotype that confers a higher risk of Coronary Artery Disease and cardiovascular disease (CVD). However, treatment with aspirin and Vitamin E has been shown to prevent incident CVD in patients with this genotype.	Some Predicted Risk
Aspirin Resistance		
	This patient is predicted to be at increased risk of aspirin resistance. Consider an alternative to aspirin for prevention of heart disease and stroke. Aspirin inhibits platelet activation and aggregation via multifactoral mechanisms - including those determined by heritable factors, such as variants in multi-drug resistance efflux pumps and COX1 genes. Aspirin resistance refers to an absence of an expected pharmacological effect and/or poor clinical outcomes, such as recurrent vascular events.	Some Predicted Risk
H.Pylori Gastropathies		
	This patient is not predicted to be at increased risk of developing gastropathies with concomitant NSAID use.	Ok No Predicted Risk

Thromboembolism Risk

Q2

Intended Use:

Proactive diligence with venous thromboembolism



PROOVE BIOSCIENCES

Proof of Thromboembolism Risk

Proove Thromboembolism Risk Profile (PBIO25) v.1

Report Date May 9, 2016

Patient Information

Patient Name	Jane Doe
Date of Birth	January 28, 1976
Ethnicity	Caucasian
Gender	Female

Date of Service: May 9, 2016
Date Received by Laboratory: November 24, 2014
Date of Injury: Invalid date
Customer ID: P-SW20022201
Account Name: Proove Research Institute
Physician Name: Payne, Doc

Ok

No Predicted Risk

This patient does not have an increased genetic risk of experiencing venous thromboembolism events, such as deep vein thrombosis (DVT) and pulmonary embolism (PE). The patient is not a carrier of the Factor II (Prothrombin) or Factor V Leiden risk alleles.

Genetic Variation Results

Gene	Results
Factor I	rs1799963: G/G
Factor V	rs6025: C/C
MTHFR	rs1801133: G/A

References

1. Heit et al. A genome-wide association study of venous thromboembolism identifies risk variants in chromosomes 1q24.2 and 9q. J Thromb Haemost. 2017 Aug; 10(8): 1571-31.
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7. Gohil et al. The genetics of venous thromboembolism. A meta-analysis involving approximately 120,000 cases and 180,000 controls. Thromb Haemost. 2009 Aug; 102(2): 360-70.
8. Simone et al. Risk of venous thromboembolism associated with single and combined effects of Factor V Leiden, Prothrombin 20210A and Methylenetetrahydrofolate reductase C677T: a meta-analysis involving over 11,000 cases and 21,000 controls. Eur J Epidemiol. 2013 Aug; 28(8): 621-47.

Report ID: 3991005

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Future Directions

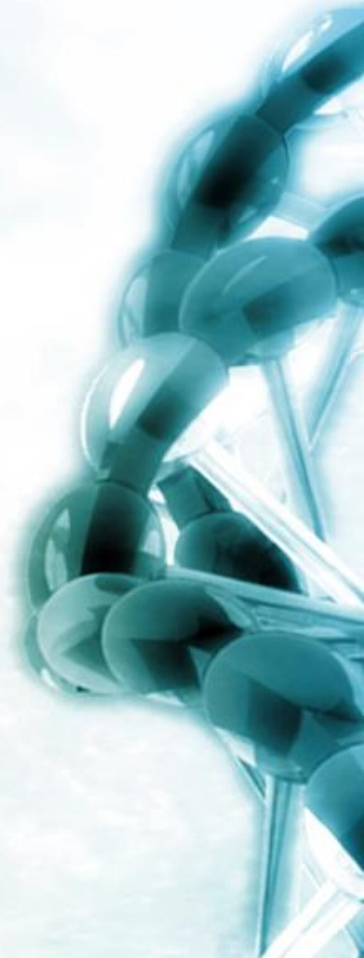
- Can genetic information predict/improve outcomes in Orthopedics?

Pain Outcome Measures
- Post-op meds
- Pain Scores (NRS/VAS/SPID)

Safety Outcome Measures
- Complications
  - Post-Op
  - Surgical
- VTE
  Infections
  Anesthesia-related
- Readmission
  Re-operation

Functional Outcome Measures
- Time to full function
  - Independent mobilization
  - Full weight bearing
  - Duration of OccT or PT
- Range of motion
  Stiffness
- Quality of Life

Other
- Nutritional data points
- Cost of care processes
- Cognitive functioning



Thank you!

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