Personalizing Pain Management and Opioid Therapy

Janet Robishaw, PhD
Senior Associate Dean for Research
Chair and Professor, Biomedical Science
Florida Atlantic University
Charles E. Schmidt College of Medicine

Disclosures and Conflicts

- I have no actual or potential conflict of interest in relation to this program/presentation.

- Research support:

Robishaw, MPI
R01 DA044015
Genetic Predictors of Opioid Addiction
2017-2022

Robishaw, MPI
R01 HL134015
Genetic Heterogeneity of Sleep Apnea
2016-2021

Robishaw, PI
R01 GM114665
Novel Aspects of G_{olf} Signaling
2015-2019

Robishaw, MPI
R01 GM111913
GPCR Variants in Complex Diseases
2015-2019

Learning Objectives

1. Review the scope and root cause of opioid use disorder

2. Discuss the effects of opioid medications on the brain and body

3. Stress the importance of clinical judgement and discovery to address the opioid crisis

4. Highlight the clinical implications between opioid use disorder and heroin abuse

Two Endemic Problems

Chronic Pain

Debilitating disorder

100 million Americans

Costs $630 billion dollars per year

#1 presenting complaint to doctors

#1 reason for lost productivity

#1 treatment –opioid medications

Opioid Use Disorder

Chronic, relapsing disorder

2 million Americans

Costs $80 billion per year

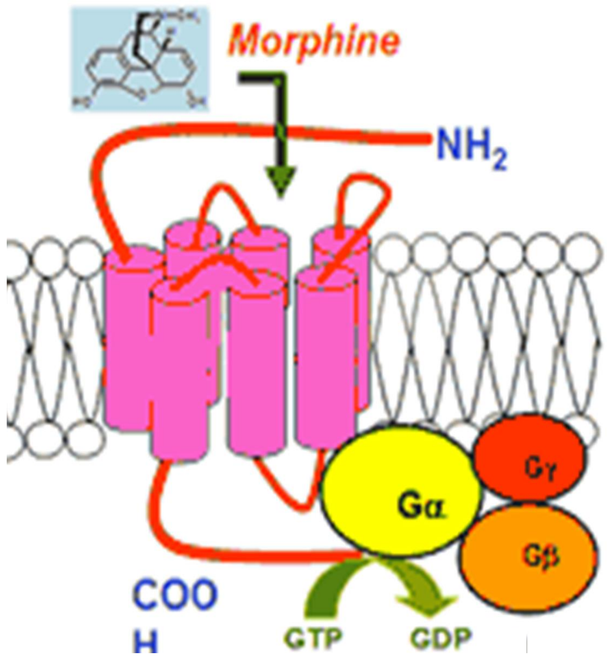
1 cause of accidental death

#1 driver of heroin epidemic

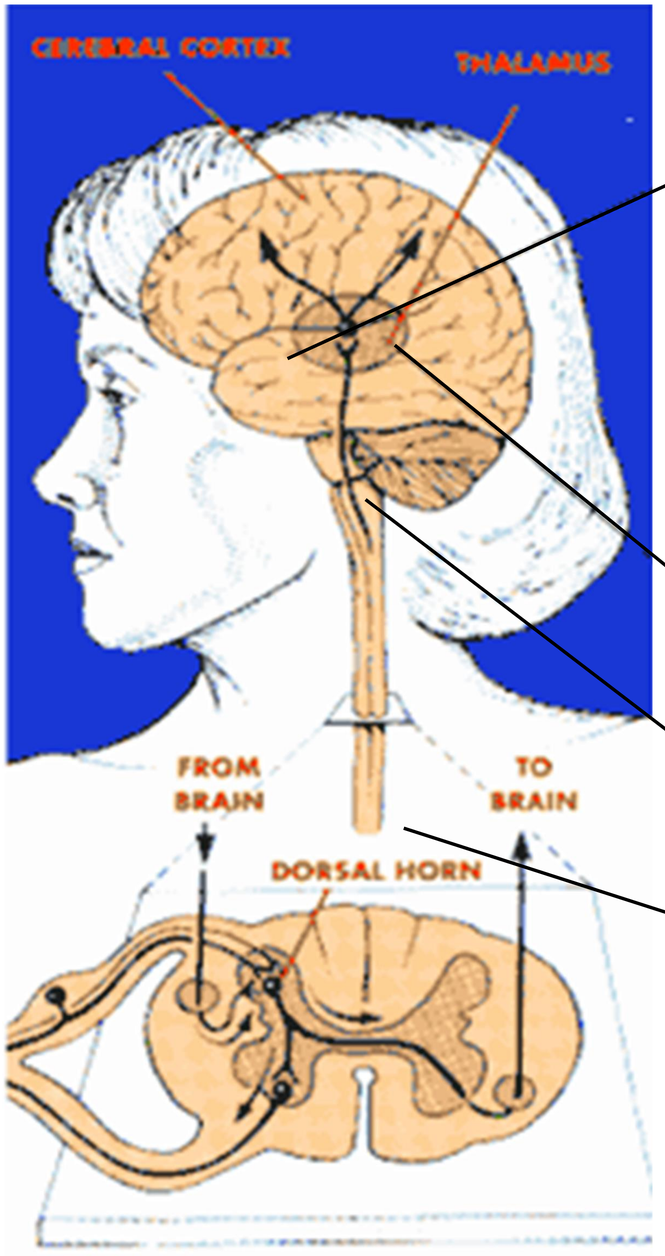
? treatment

Pain Relief and "Addiction" Share A Common Mechanism of Action

μ-Opioid Receptor



These receptors are dispersed throughout the body, thereby accounting for their differential effects on pain and reward paths.



Brain Regions Involved in Pleasure and Reward
Increase dopamine release

Brain Regions Involved in Pain Perception

Brainstem Involved in Respiratory Control

Spinal Cord Involved in Pain Transmission
Prevent ascending transmission
Turn on descending inhibitory systems
Inhibit peripheral nocioceptors

Body
GI motility

Clinician-Patient Conundrum

Clinician: How to provide the most effective pain treatment for the majority of pain patients, and cause the least harm to the remaining minority at high risk for opioid use disorder.

Patient: How to maintain access to much needed pain relief without recrimination, or risk of opioid use disorder.

One Solution

Stop prescribing opioids for chronic pain

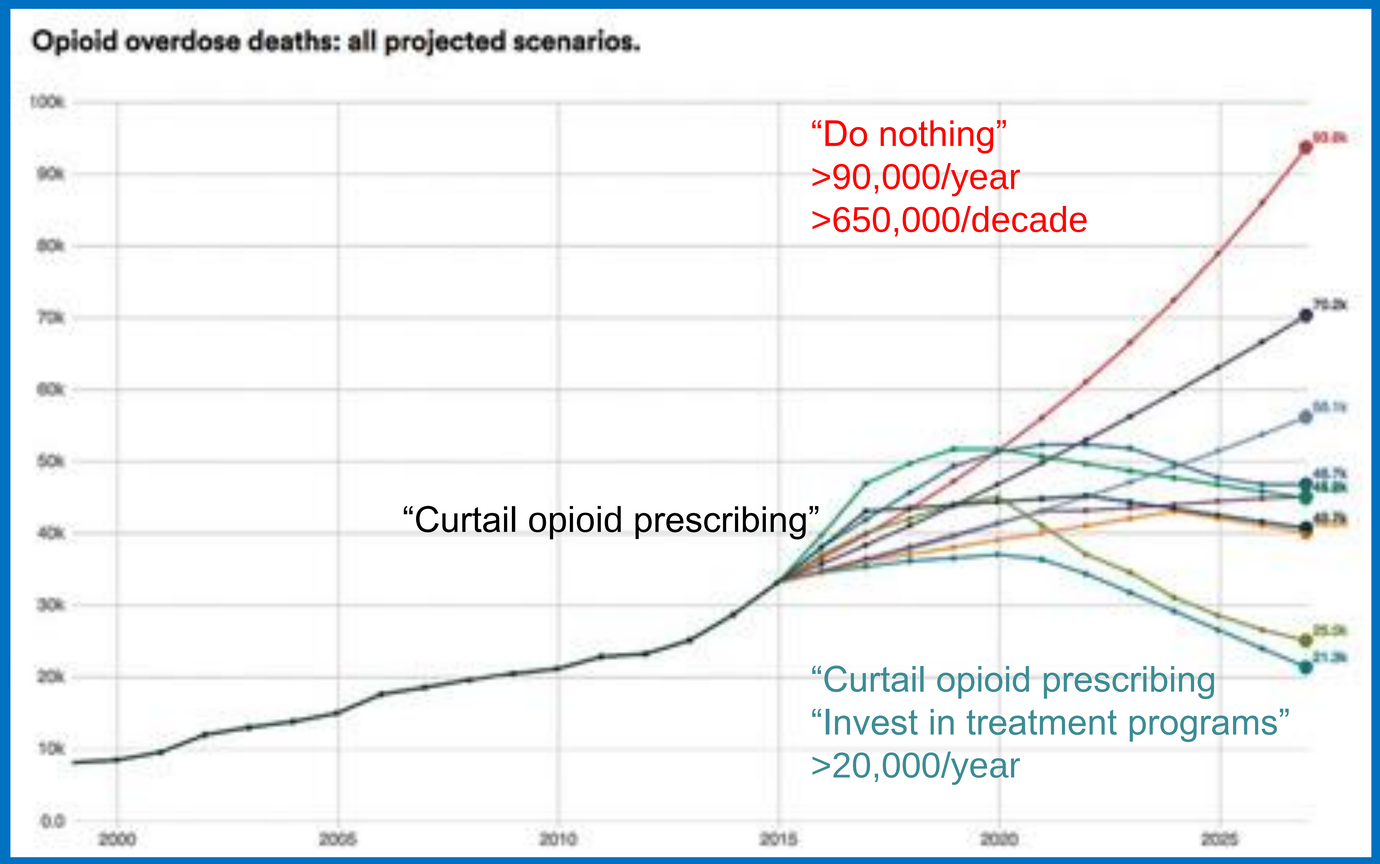
Media Storm

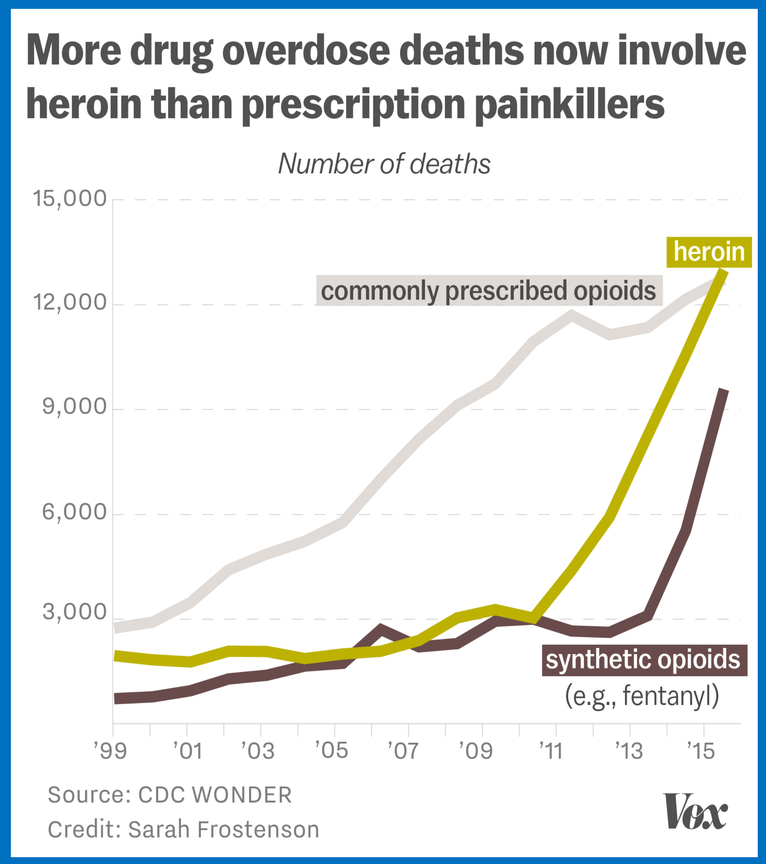
New CDC Guidelines

Surgeon General Weighs In

For every complex problem, there is a solution that is neat, simple, and *wrong*."

-H.L. Mencken





Using Genetics to Personalize Pain Management and Opioid Therapy

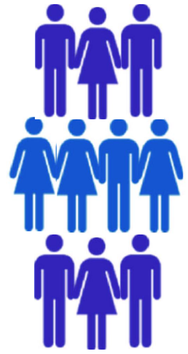
One-size fits-all medicine

Stratified medicine

Precision medicine

Stratification

Patients are grouped by:
Disease subtypes
Clinical Features
Genetic Factors



Personalisation

Individuals are treated by:
Disease subtypes
Clinical Features
Genetic Factors

Low Risk for Opioid Addiction

Use genetics to optimize pain management and opioid regimen

High Risk for Opioid Addiction

Avoid opioid therapy
Implement alternative treatment plans

Novel Drug Targets

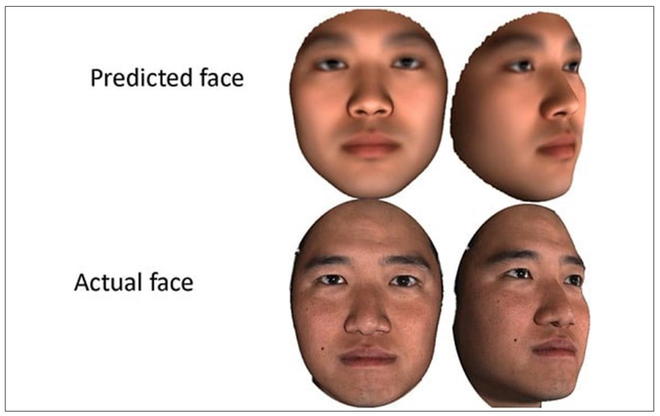
Precision medicine

Next Generation DNA Sequencing
Machine Learning

Information

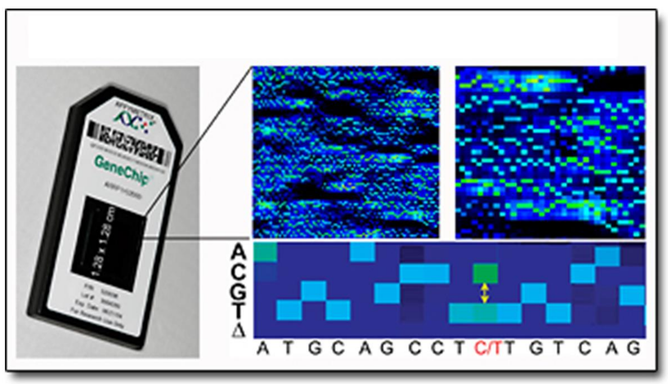
List of
Genetic Variants

Knowledge



A Genetic
Reconstruction of a Face

Power



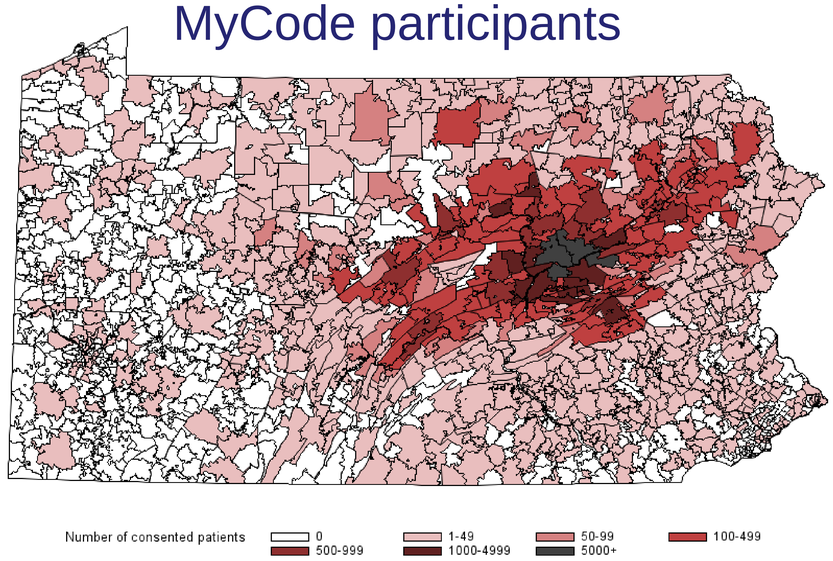
Genetic Test for
Opioid Addiction Risk

Geisinger: A “Learning Healthcare System”

Geisinger Clinical Enterprise

- ✓>10 hospitals
- ✓>60 community practice sites
- ✓4 research sites
- ✓>2 million patients

MyCode participants



Geisinger Research Powered Cohort

- ✓Genetically homogeneous population
- ✓Standardized diagnostics & testing
- ✓Engaged patients
- ✓Longitudinal EHR
- ✓Genetic data

MyCode Research Cohort

MyCodeDemo > Report Manager 10/2/17, 2:59 PM

Home > MyCodeSummary > MyCodeDemo Home | My Subscriptions | Help

Find | Next

Geisinger mycode 100,000+ PARTICIPANTS

MyCode Demographics

Demographic	Type/Category	MyCode	All GHS
Total Population	N	156768	1729638
Sex	Female	95602 (61.0%)	906559 (52.4%)
Age	Average	51	52
Age	Median	54	55
Patient Status	Deceased	6265 (4.0%)	148785 (8.6%)
BMI	Average	30.9	31.1
Smoking Status	Ever Smoked	79362 (50.6%)	558328 (32.3%)
Number of Years	Median	12.8	2.7
Number of Encounters	Median	43	6
Number of Lab Results	Median	403	90
Number of Vital Measurements	Median	576	66
Ethnicity	Hispanic	3271 (2.1%)	73593 (4.3%)
Race	American Indian Or Alaska Native	171 (0.1%)	2128 (0.1%)
Race	Asian	652 (0.4%)	17665 (1.0%)
Race	Black Or African American	3271 (2.1%)	77886 (4.5%)
Race	Native Hawaiian Or Other Pacific Islander	287 (0.2%)	5418 (0.4%)
Race	Other	7 (0.0%)	8751 (0.5%)
Race	Unknown	1129 (0.7%)	31998 (1.8%)
Race	White	151251 (96.5%)	1584792 (91.6%)
Age	0-19	6941 (4.4%)	435113 (25.2%)
Age	20-29	16878 (10.8%)	241126 (13.9%)
Age	30-39	20342 (13.0%)	192743 (11.1%)
Age	40-49	22564 (14.4%)	193067 (11.2%)
Age	50-59	29366 (18.7%)	211951 (12.3%)
Age	60-69	29951 (19.1%)	187647 (10.8%)
Age	70-79	19802 (12.6%)	136187 (7.9%)
Age	80-89	9345 (6.0%)	99020 (5.7%)
Age	90+	1579 (1.0%)	32744 (1.9%)
BMI Categories	0-18.49	2377 (1.5%)	53092 (3.1%)
BMI Categories	18.5-24.99	32336 (20.6%)	382410 (22.1%)
BMI Categories	25-29.99	43679 (27.9%)	367085 (21.2%)
BMI Categories	30+	72990 (46.6%)	466757 (27.0%)
BMI Categories	Unknown	5386 (3.4%)	460294 (26.6%)

MyCode Demographics

Demographic	Type/Category	MyCode	All GHS
Total Population	N	219677	1729638
Sex	Female	95602 (61.0%)	906559 (52.4%)
Age	Average	51	52
Age	Median	54	55
Patient Status	Deceased	6265 (4.0%)	148785 (8.6%)
BMI	Average	30.9	31.1
Smoking Status	Ever Smoked	79362 (50.6%)	558328 (32.3%)
Number of Years	Median	12.8	2.7
Number of Encounters	Median	43	6
Number of Lab Results	Median	403	90
Number of Vital Measurements	Median	576	66

Using a Learning Healthcare System to Answer Real World Questions

1. Are opioids effective for chronic pain?

2. What is the prevalence of OUD in the chronic pain patient population?

3. Does genetic information improve the choice and dose of drugs for optimal pain relief?

4. Is it possible to identify a genetic signature to predict the risk of developing OUD that might be useful in preventing it?

Study Design

- ❑ > 300,000 patients receiving prescription opioids
- ❑ > 25,000 patients with diagnosis of chronic pain (non-cancer) and taking prescription opioids for > 3 mo
- ❑ Access to clinical data warehouse to allow rapid lookup of de-identified EHR information, medication orders, insurance billing information
- ❑ Linkable genetic data warehouse to identify molecular underpinnings of clinical parameters

Stories from Learning Healthcare System

Acute Pain Management

Patient

- A former fireman (R.C.) with recent surgery for a work-related injury.
- His surgeon prescribed **oxycodone** along with **morphine** for break-through pain.
- Despite this, he complained of pain scores of 9/10.
- After discharge, he was referred to his primary care doctor and enrolled on a MUA.

Doctor

- Thorough examination to rule out structural basis for pain
- Differential Diagnoses:
  - 1. Hyperalgesia
  - 2. Diversion
  - 3. Drug Seeking
- Urine Test positive for opioids and oxycodone
- No change to prescription order

Genetic Results

- As part of this research study, we return clinically actionable genetic variants to the provider.
- This patient was found to have a homozygous mutation in *CYPD26* gene, which encodes a liver enzyme that converts oxycodone to the more potent oxymorphone. Consistent with CPIC guidelines, providers are encouraged to consider alternative medications to provide better pain relief.
- The provider transitioned the patient to hydromorphone.
- At a follow up visit, the patient reported good pain relief.

FAU
Charles E. Schmidt College of Medicine
Florida Atlantic University

Pharmacogenetics Testing:

Importance of knowing genetic profile and selecting the right drug

- Many opioids are metabolized by CYP3A4/5 and CYP2D6, including the commonly prescribed oxycodone.
  -PGT guidance is available.

- In our chronic pain population, the frequency of the poor metabolizer haplotype is ~10%, meaning that nearly 2,500 patients may not be receiving the optimal drug for pain relief.

- Despite its commercial availability and low cost point, pharmacogenetic testing is not routinely performed.

- Pharmacogenetic testing to optimize drug choice and dosage should be routinely considered and implemented.

1. Relling MV, Klein TE. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. Clin Pharmacol Ther. 2011 Mar;89(3):464-7.
2. Swen JJ, Nijenhuis M, de Boer A, et al. Pharmacogenetics: from bench to byte--an update of guidelines. Clin Pharmacol Ther. 2011 May;89(5):662-73.
3. Gharani N, Keller MA, Stack CB, et al. The Coriell personalized medicine collaborative pharmacogenomics appraisal, evidence scoring and interpretation system. Genome Med. 2013 Oct 18;5(10):93.

Stories from Learning Healthcare System

Chronic Pain Setting

Patient

- A year later, R.C. reported severe pain that was negatively impacting his quality of life.
- He requested a higher opioid dosage.

Doctor

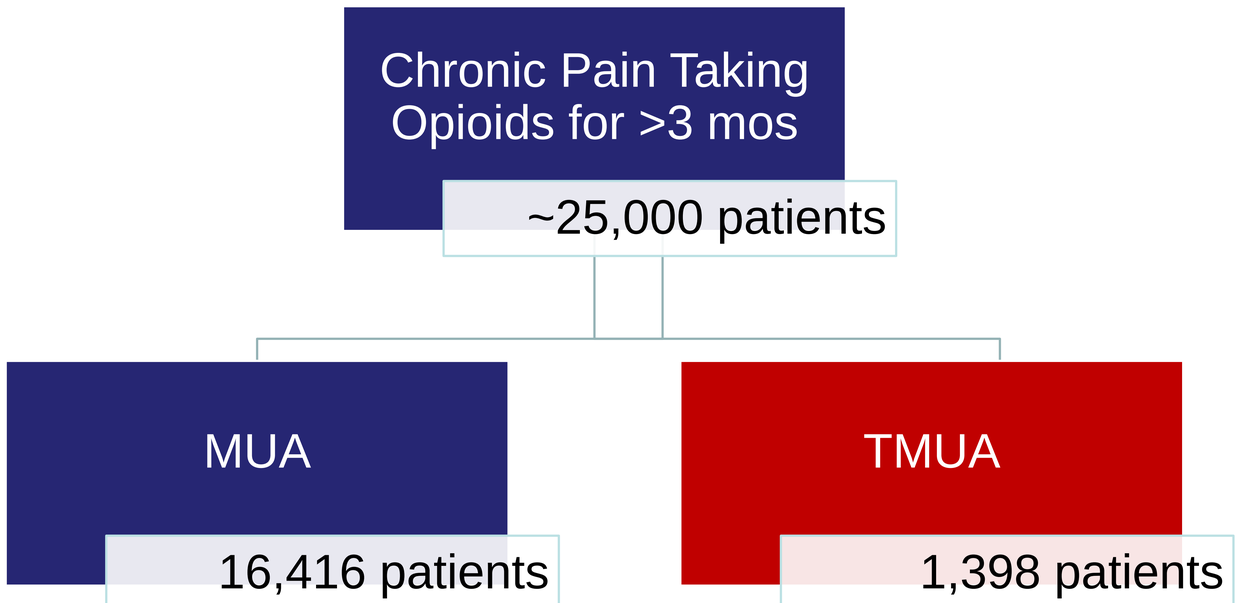
- EHR review revealed ED visits and pharmacy notes requesting early refills for opioid meds.
- Differential Diagnoses:
  - Drug Seeking
- Provider terminated MUA and made referral to addiction specialist.

Genetic Results

- Patient had no *known* genetic risk factors for addiction, but this was not conclusive since known genetic variants account for <5% of heritable risk.

Diagnosis of OUD:

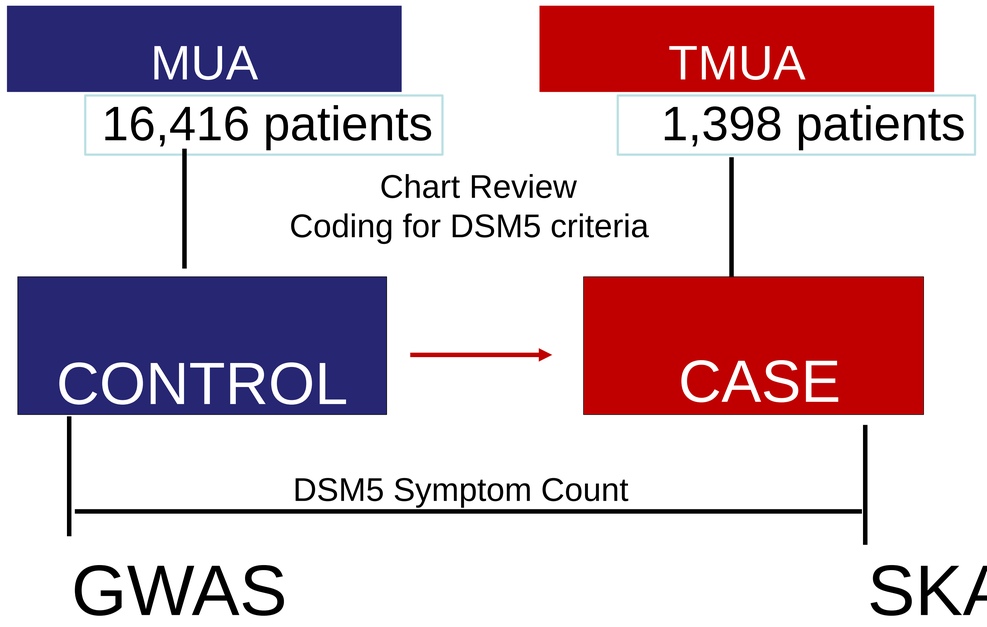
Importance of knowing whom and how to treat



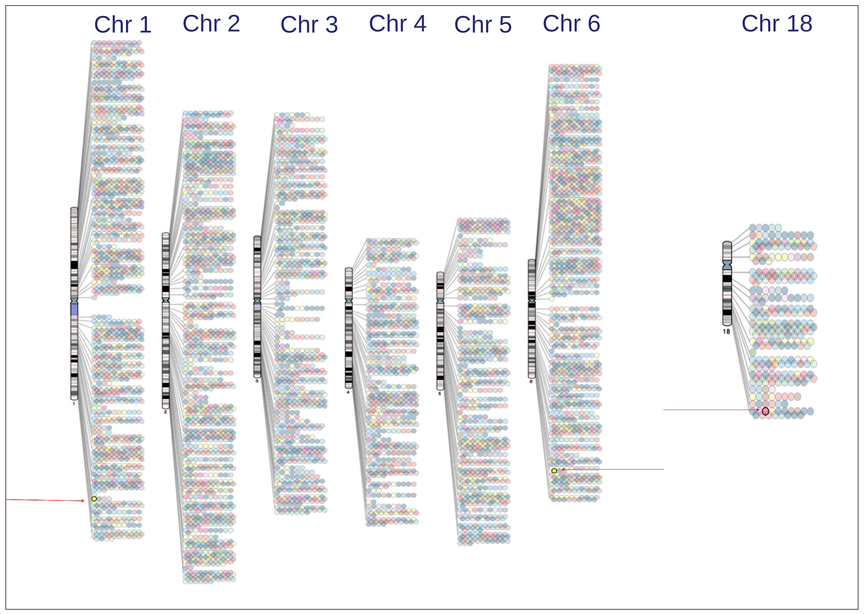
Pain in the Lower Back/Lumbar region ($p=10^{-13}$)
Alcohol Use Disorder ($p=10^{-21}$)
Nicotine Use Disorder ($p=10^{-67}$)
Other Substance Use Disorder ($p=10^{-78}$)
Depression ($p=10^{-13}$)
Anxiety ($p=10^{-18}$)

Genetic Signature of OUD:

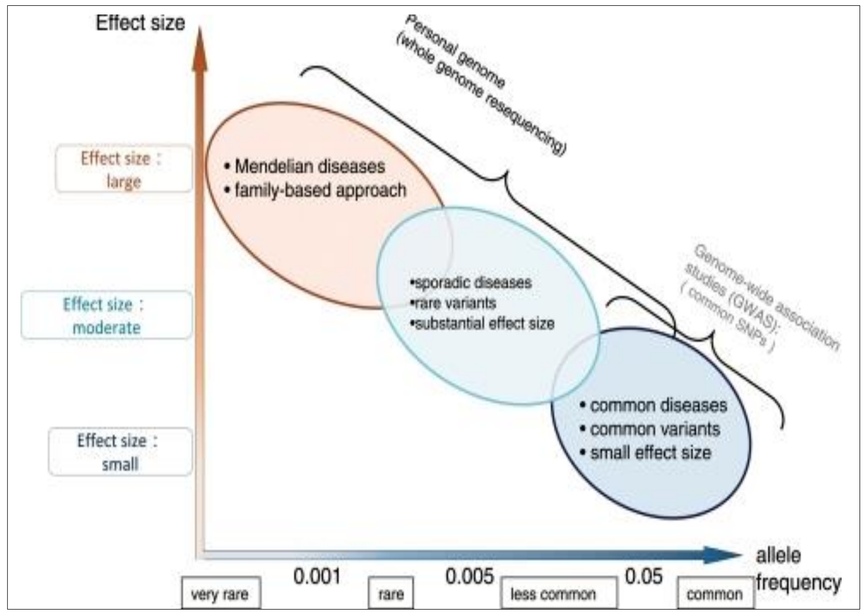
Development of predictive risk tool



Common SNPs account for <<5% of the total heritable risk



Rare variants may account for remainder of heritable risk



Schork, NJ, Murray SS, Frazer KA, Topol EJ. (2013) Common vs Rare Allele Hypotheses for Complex Diseases. Curr. Opin. Genet Dev 19(1): 212-219.

FAU
CHARLES E. SCHMIDT
COLLEGE OF MEDICINE
Florida Atlantic University

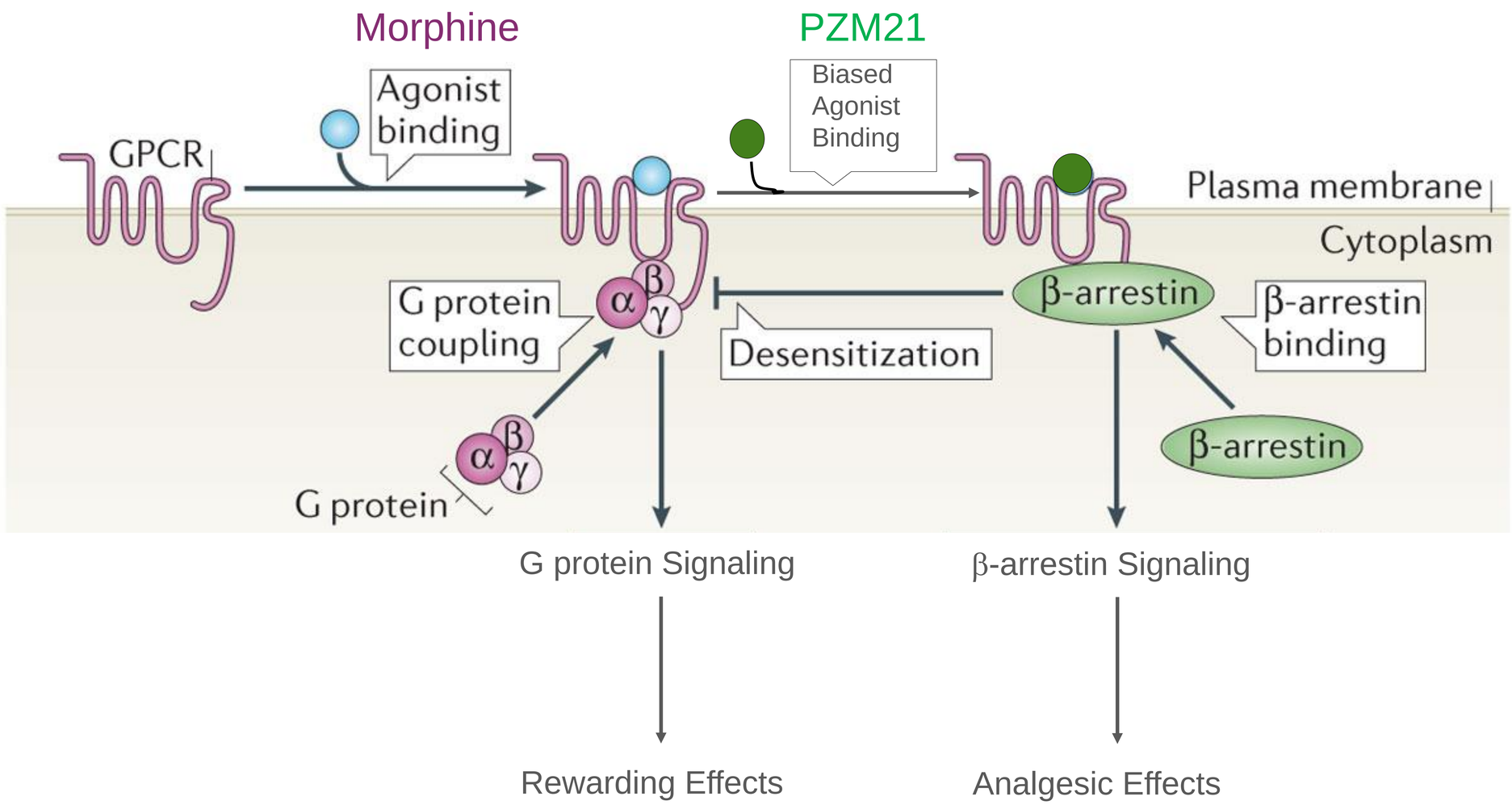
OUD Predictive Risk Tool:

Importance of knowing genetic susceptibility

- Genetics accounts for 50-70% risk of developing OUD
- Applies to population
- Identifying a “genetic signature” predictive of OUD in individuals is likely in the near future
- Combining a clinical assessment with the “genetic signature” will be useful in developing a predictive algorithm that can be applied prior to prescribing opioids

Stories from Learning Healthcare System

Importance of divergent mu-opioid receptor signaling as a novel drug target



Conclusions

- Opioids have been the mainstay of pain relief for decades but are variably effective for chronic pain and may incur risk of opioid use disorder.

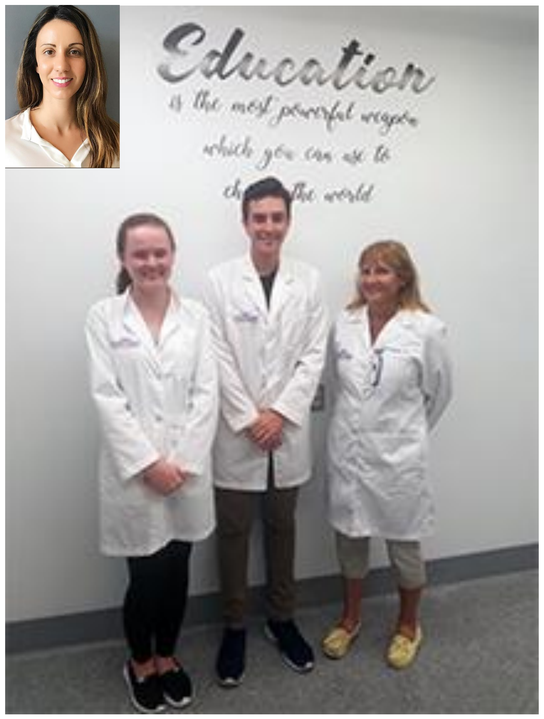
- Current attempts to prevent opioid use disorder focus on reining in prescribing, potentially increasing pain while reducing functionality and quality of life.

- It may be possible to address both problems without adversely affecting either by doing additional research and identifying genetic factors that increase the risk of “addiction”, which then become targets for new drug development.

Acknowledgements

Florida Atlantic University
Schmidt College of Medicine

Janet Robishaw (MPI)
Sarah Palumbo
Anna Stauffer
Gloria Brunori
Alex Gitin



Geisinger Health System

Vanessa Troiani (MPI)
Kayleigh Adamson
Raghu Metpally
Sarah Pendergrass
Sarath Krishnamurthy
Christopher Lam

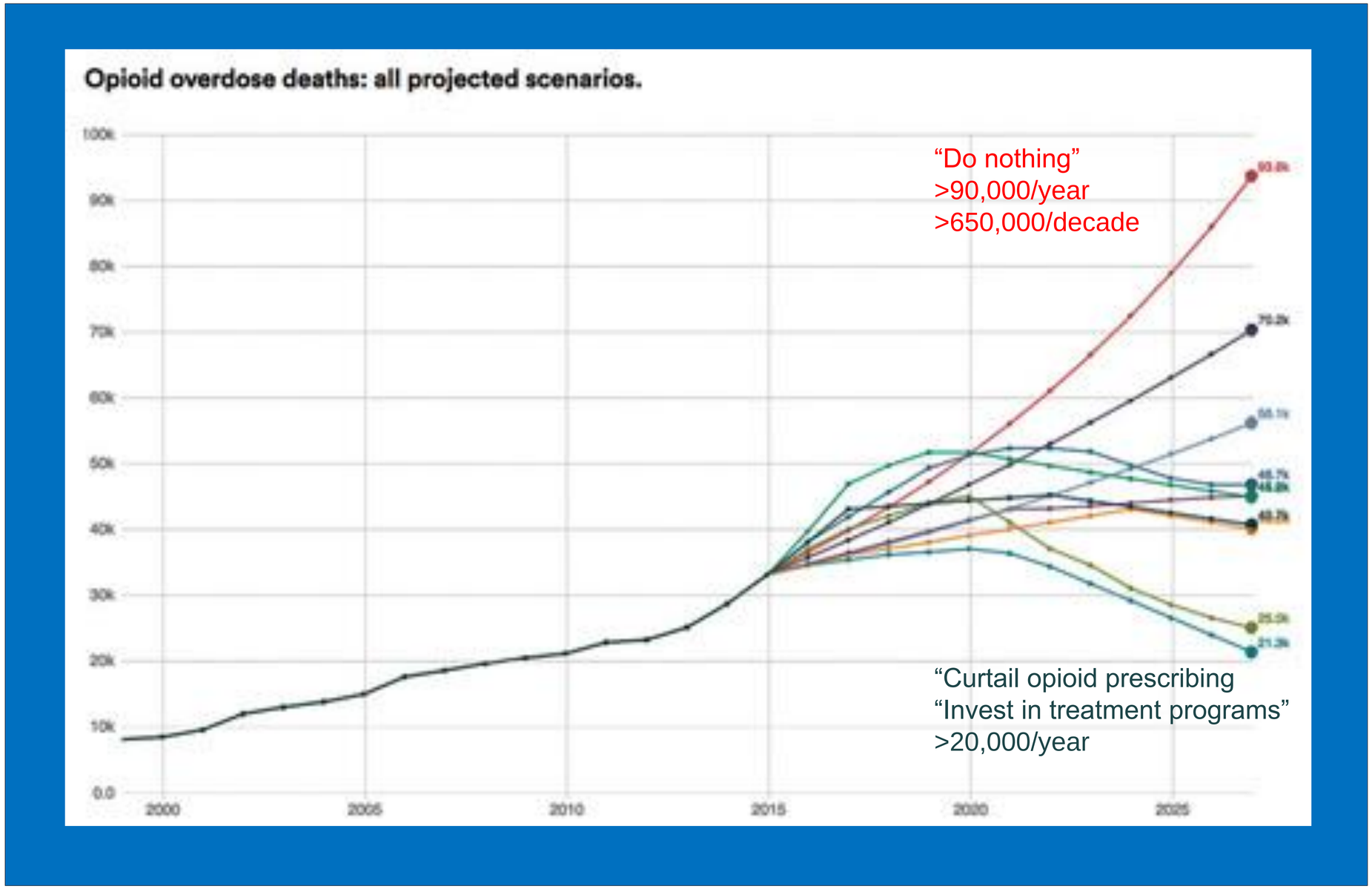
University of Pennsylvania
Perelman School of Medicine

Wade Berrettini (MPI)
Glenn Doyle
Rick Crist
Mingyao Li

Rowan University
Cooper Medical School

Tom Ferraro

Future Projections of Opioid Crisis



Research Driven Solutions

Start addressing the root cause by making better pain treatments available through research

Treatment of Chronic Pain

Short-Term Strategies	Intermediate Strategies	Long-Term Strategies

- Developing evidence based guidelines for pain management
- Implementing non-opioid alternatives
- Using genetics to optimize opioid therapy and reduce risk of OUD
- Designing opioids with abuse deterrent properties
- Identifying pain biomarkers

Stories from Learning Healthcare System

Chronic Pain Setting

Patient

- A.M. is a 45-year old female with fibromyalgia diagnosis. Despite a prescription for hydrocodone, she reports “unrelenting widespread pain that won’t stay in one spot”.
- Pain is negatively impacting every aspect of her life (eating, sleeping, job, marriage).
- She requests a higher opioid dosage.

Doctor

- EHR review revealed ED visits and pharmacy notes requesting early refills for opioid meds.
- Differential Diagnoses:
  - Urine test is positive for non-prescribed opioids
  - Suspected drug seeking
- Provider terminated MUA and made referral to addiction specialist.

Genetic Results

- Patient had no *known* genetic risk factors for addiction, but this was not conclusive since known genetic variants account for <5% of heritable risk.