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Research & Development
Improving Veterans' Lives — www.research.va.gov

Neuropathic and Phantom Pain

A clinical challenge for Veterans and for others

Stephen G. Waxman, MD, PhD

Pain: A common complication of nerve injury and traumatic limb amputation

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" I was wounded on July 1st 1862. Walking a mile I had my right arm amputated, never quite losing consciousness. I never think of my right arm with thoughts of using it.

The fingers remain in my mind, however, half-closed. As with everybody who has lost a limb, pain occurs often… "

From a letter to S. Weir Mitchell, MD
Written by a Veteran of the Civil War

Neuropathic Pain

Hyperexcitability of pain-signaling nerve cells

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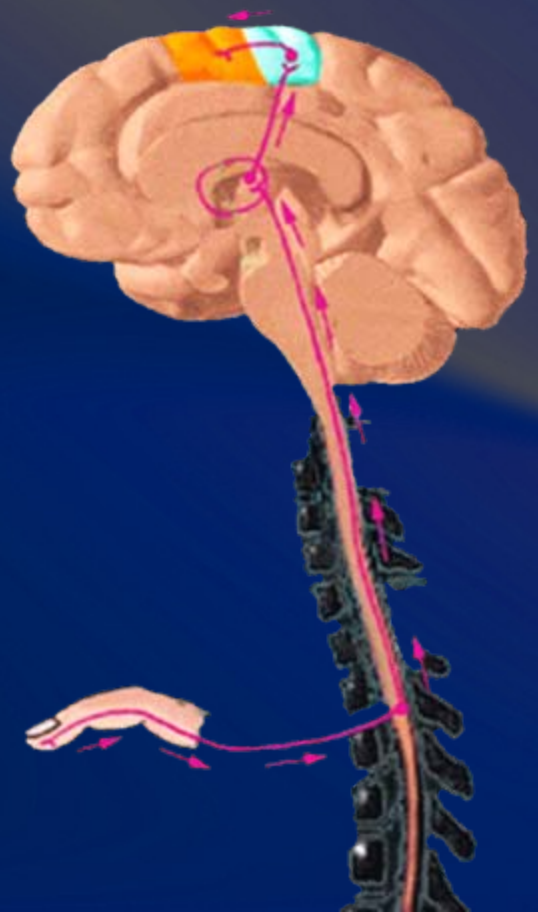
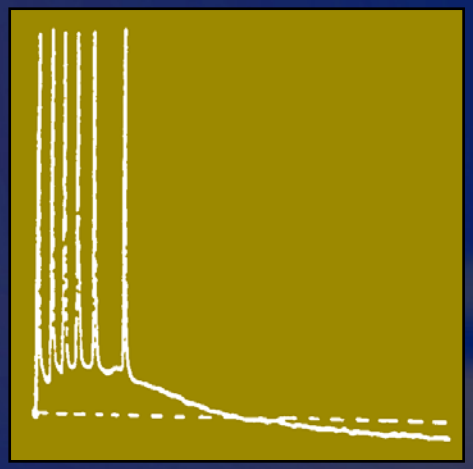
Peripheral nerve injury
Traumatic limb amputation
SCI



Diabetic neuropathy
Post-herpetic neuralgia
With cancer chemotherapy



Why search throughout the world to find a rare genetic disorder?

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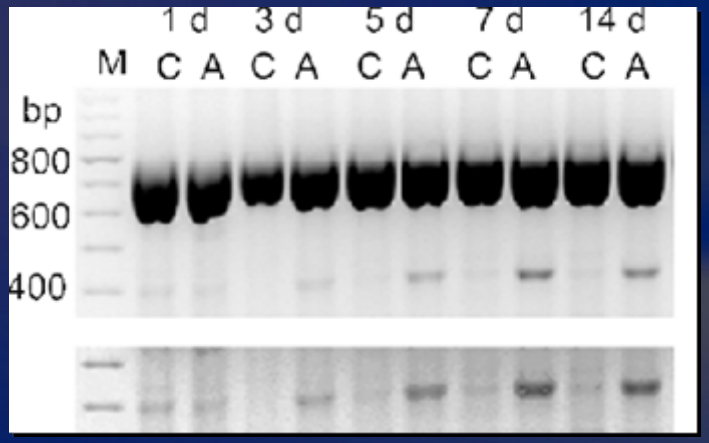
Rare genetic disorders are “experiments of nature” that can identify 1 gene out of 30,000 that functions abnormally to cause a human disorder.

By locating these genes, we can identify molecules and therapeutic targets that are relevant to **common disorders.**



A Model Disease: Primary Erythromelalgia

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The "Man on Fire" Syndrome

- Severe burning pain, triggered by mild warmth
- Autosomal dominant, 100% penetrant
- < 50 families, scattered around the world
- Cause: Mutations in a single gene that encodes sodium channel Nav1.7

Sodium Channels:

Nerve cells have molecules that act as molecular batteries

Sodium channels produce nerve impulses

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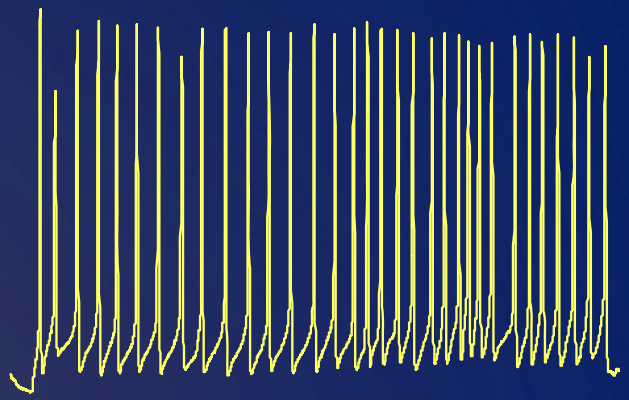
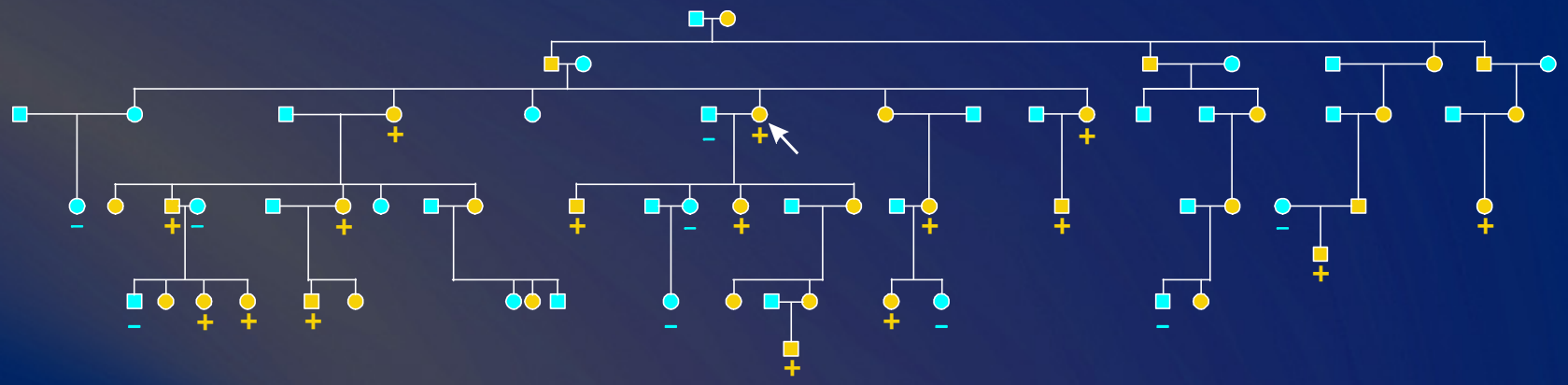
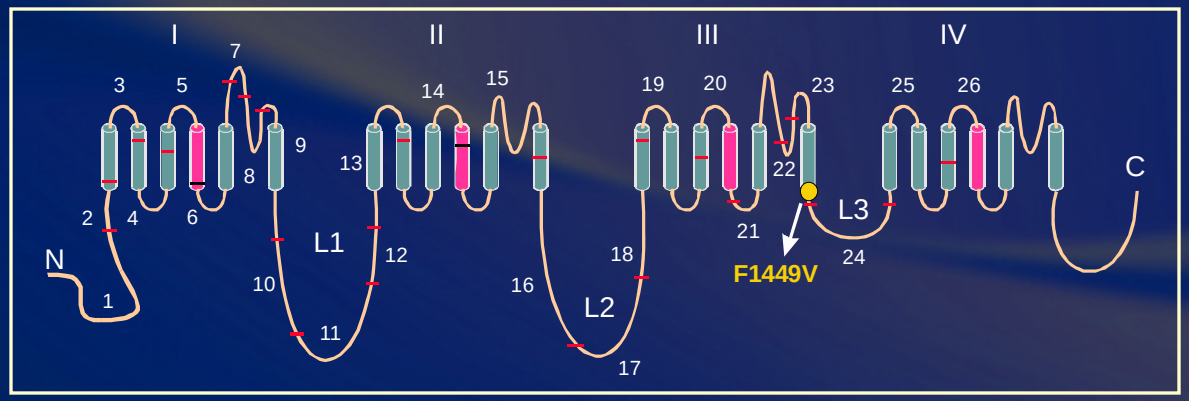


Overactive sodium channels produce static

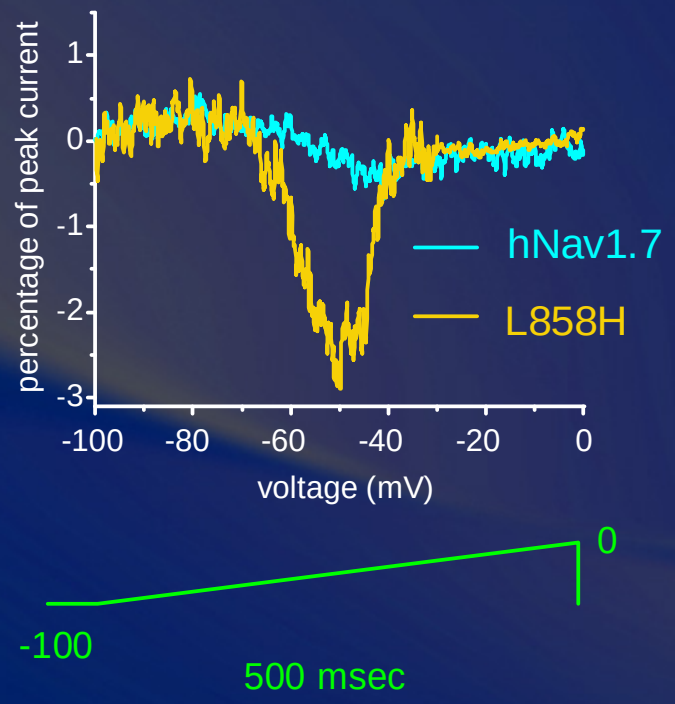
Mutations in Nav1.7 Produce Pain





Biophysical Analysis:

The “man on fire” mutations cause over-activity of Nav1.7



Nav1.7 gain-of-function makes pain-signaling neurons overactive

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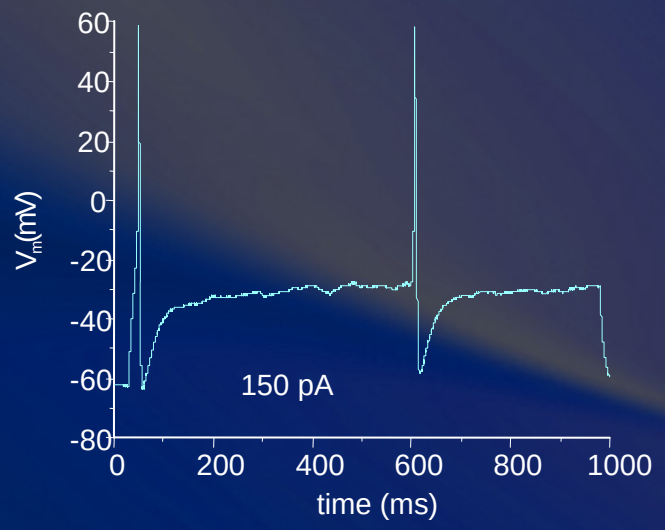
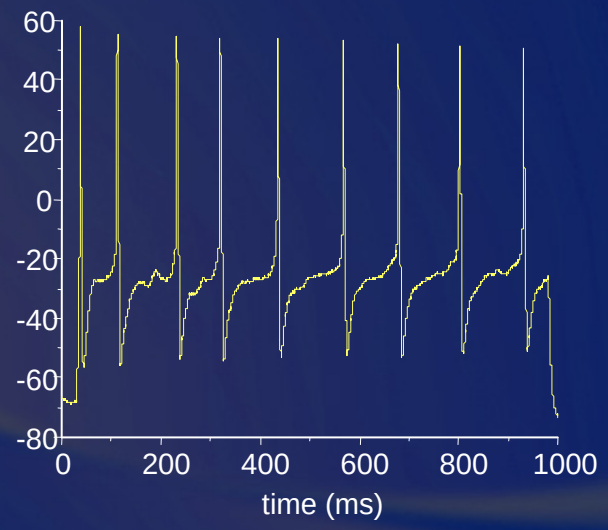
So pain-signaling nerve cells send inappropriate signals to the brain



WT Nav1.7



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Nav1.7 also drives *acquired* pain

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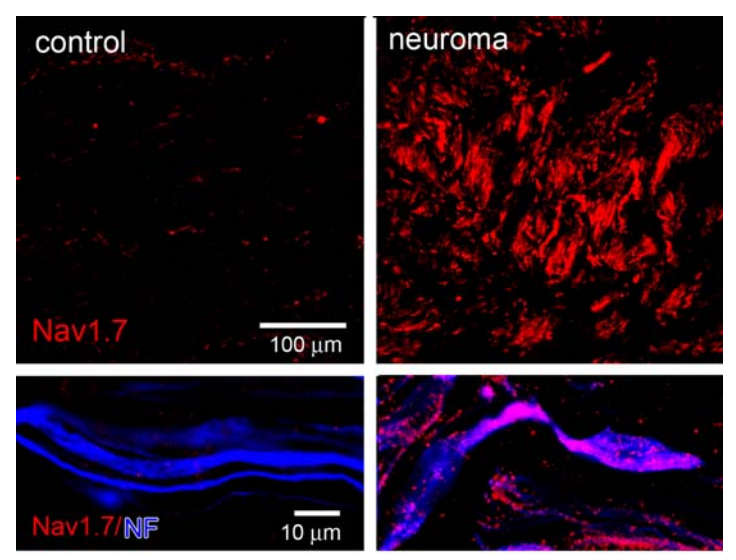
Nav1.7 is over-produced in injured nerve fibers after nerve injury and traumatic limb amputation



Black et al, Annals of Neurology, 2008

Sodium Channel Nav1.7: A Molecular Driver of Pain

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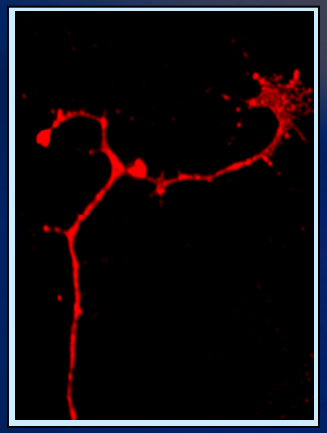
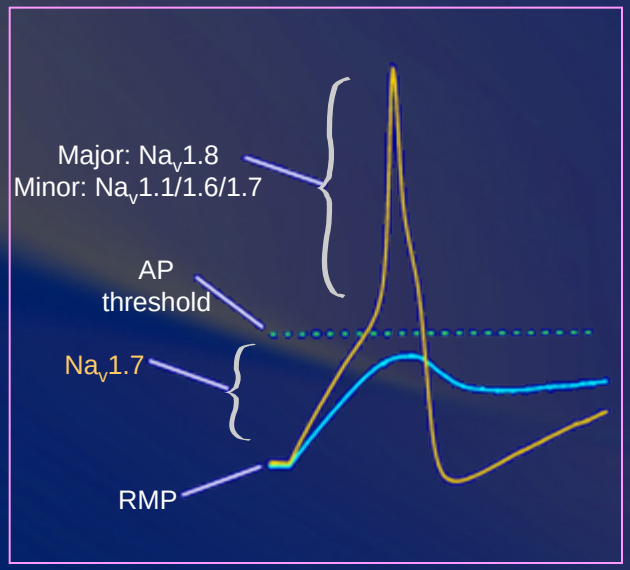
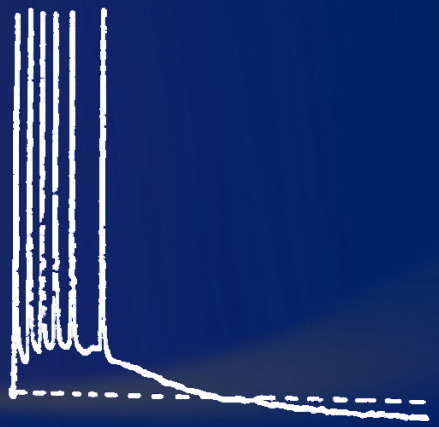
Over-activity of Nav1.7: Produces Hyper-excitability in Pain-Signaling Nerve Cells







Sodium Channel Nav1.7: A Molecular Driver of Pain

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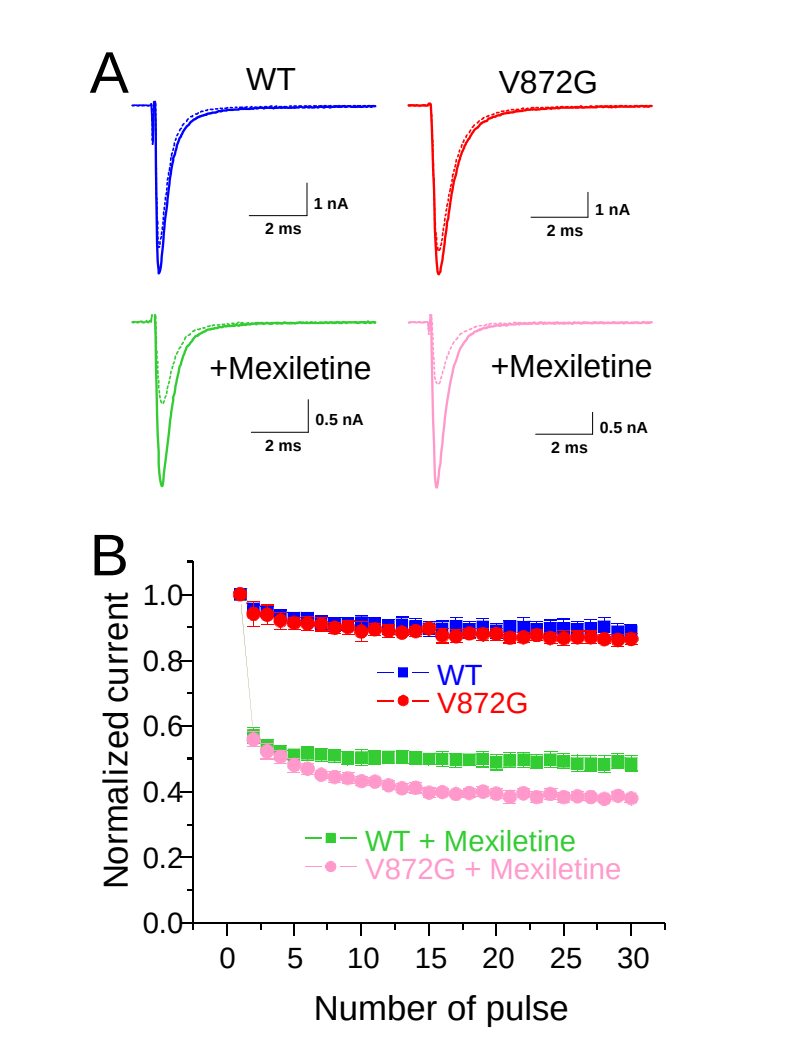
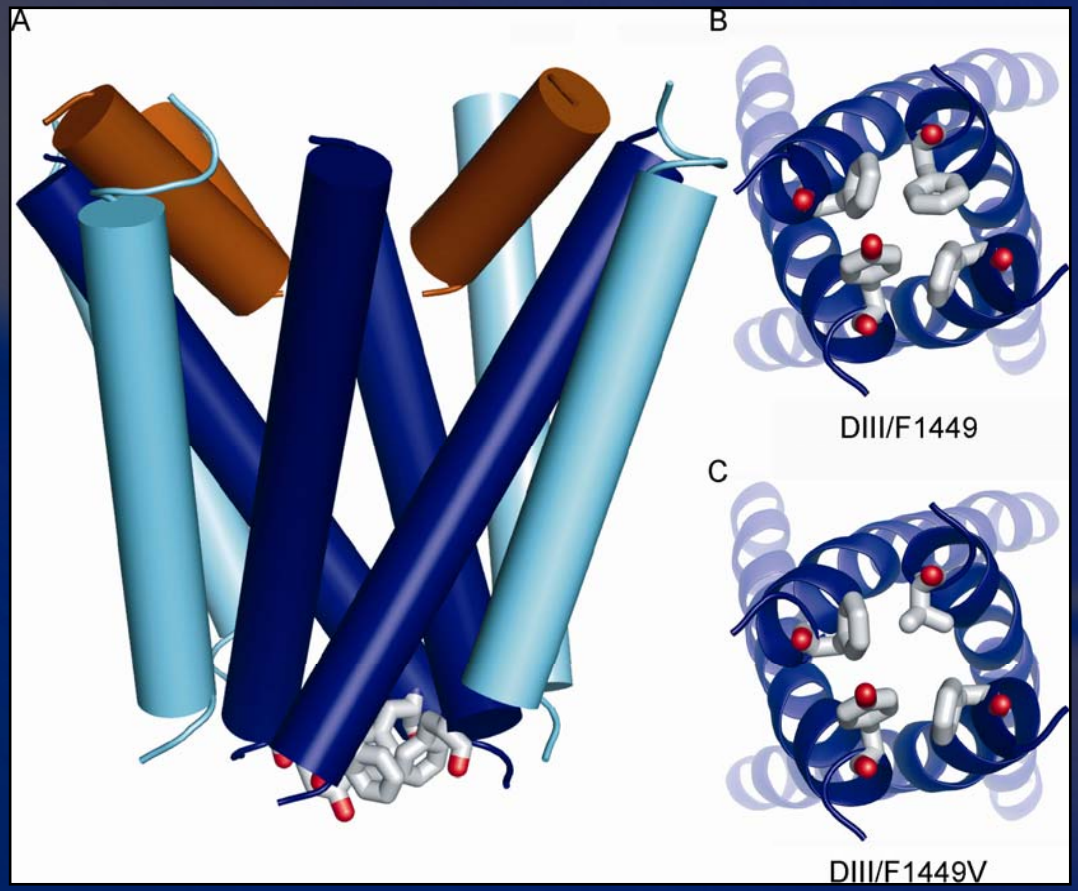
Subtle changes in the Nav1.7 gene make some people more sensitive to pain medications.

VA investigators are locating the parts of Nav1.7 that make it sensitive to medications



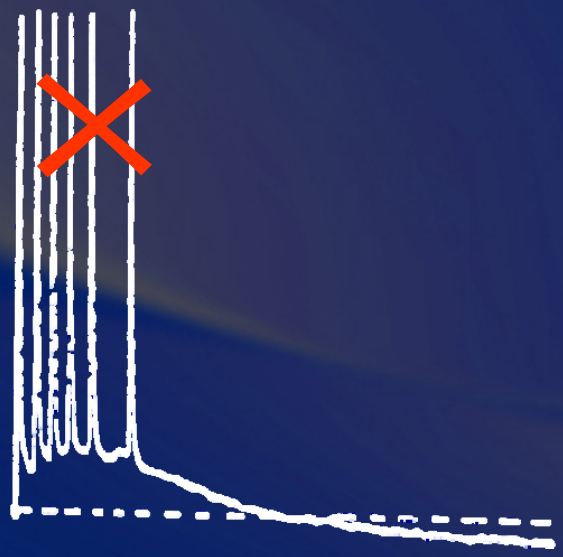
Molecular modeling and genomics

VA researchers are using this information to develop “personalized” therapies for pain



Molecule by molecule…

We are identifying and understanding the drivers of neuropathic pain. Now we are in a position to shut them off.



Turning Hope into Reality
… for Veterans and for others

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<xx.xxx@xx.xx>
To: Stephen.Waxman@yale.edu

I am 25 years old, tetraplegic (C5) and with constant pain after a ski accident. My doctors call it "neuropathic pain". On the internet I read about research. I'd like to know if I can keep my dream of taking a few steps and living without pain some day.

Yours truly

E…..

VA Research: Improving Veterans' Lives

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VA researchers are working tirelessly to find cures for chronic pain.

We will win this battle!

Thank You

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Clinical & Research Genomics

Washington DC VA Medical Center

Jack H. Lichy, M.D., Ph.D.

What is Genomic Medicine?

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- **DNA & RNA Testing**:
  - *Personalized Medicine*
- **An Accepted Standard of Care**
- **Applications**
  - Sensitivity to Adverse Drug Reactions
  - Inherited Diseases & Syndromes
  - Cancer Diagnosis
  - Infectious Disease

Clinical & Research Genomics Core

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The Concept

The same technologies used for clinically required DNA testing in the *clinical* laboratory are made available to support *research* in a single core laboratory facility.

Clinical & Research Genomics Core

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Organization

- Clinical Laboratory directly meeting requirements of Veterans Healthcare
- CLIA Certified Laboratory for Research
- Collaborative
- Translational

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Support

- Start-up Grant from Office of Research and Development
- Clinical testing supported by clinical funds
- Research supported by grant funds

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Technologies

- FISH: Fluorescent *in situ* Hybridization
- PCR, DNA Sequencing
- Genotyping by Microarray Hybridization

Current Testing Capabilities

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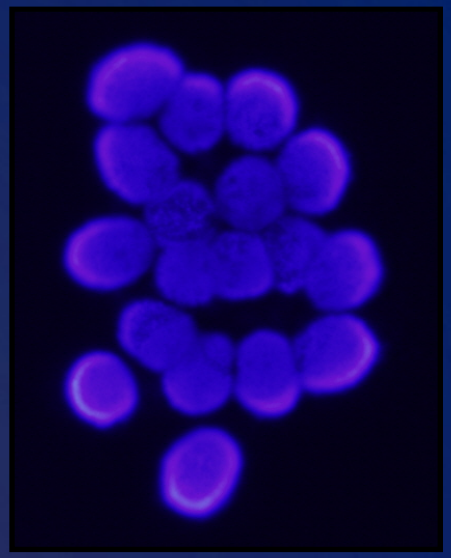
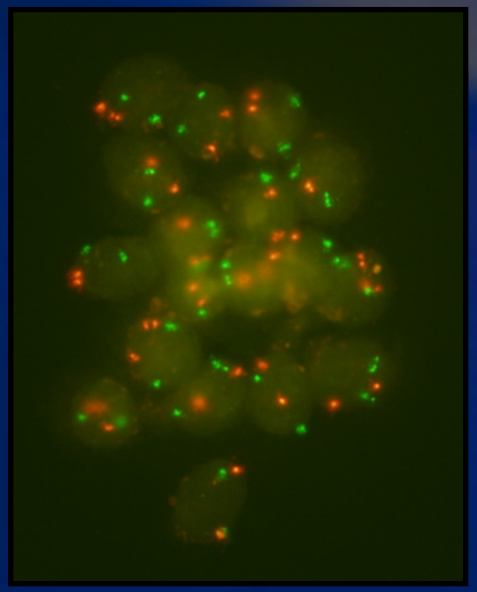
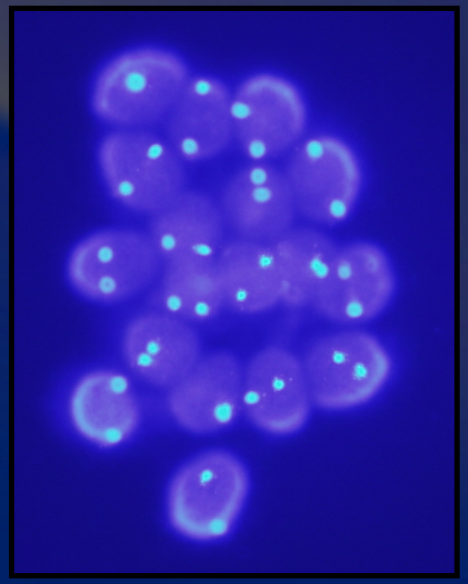
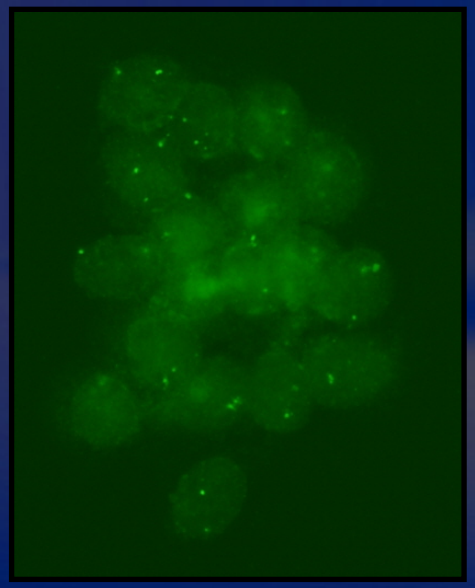
Urovysion:

A sensitive method for diagnosis of bladder cancer and early detection of recurrences.









Current Testing Capabilities

- **Predicting Optimum Drug Dosage**
  - Cytochrome P450's:
    - CYP 2C9, 2D6, 2C19, 3A4, 3A5
  - Others:
    - VKORC1, UGT1A1

"Here's my sequence . . ."

Current Testing Capabilities

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- **Prediction of Tumor Response to Therapy**
  - K-*ras* Mutation Detection
  - Microsatellite Instability
- **Diagnosis of leukemia and lymphoma**
  - Gene Rearrangement Assays
- **Risk factors for coagulation disorders**
  - Factor V Leiden
  - Prothrombin G20210A

The Research Core

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- Collaborative efforts to support a wide variety of research projects.
- **Examples:**
  - Evaluating Clinical Utility of Genetic Testing in Warfarin Dosing
  - Pharmacogenomic assay validation
  - Neurotransmitter expression in PTSD model
  - Testing genomic markers of risk for mental health disorders

Example: Warfarin Dosing

- Too Little → Thrombosis
- Too Much → Bleeding
- Complications cause 43,000 ED visits/year in USA.
- Wide variation in dose requirements

Warfarin Dosing: Clinical and Research Challenges

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Clinical:

- Implement genetic testing data into Warfarin dosing decisions.

Research:

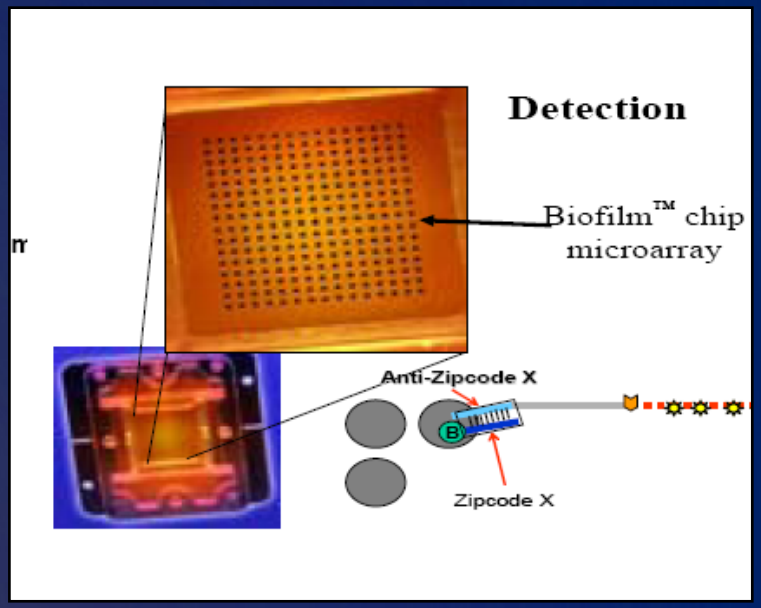
- Does genetic testing reduce the incidence of adverse reactions?
- Are there genetic markers of adverse reactions specific for minority populations?

Warfarin: Collaborations

- Clinical Staff
- Pharmacy
- ACOS Research
- ACOS Informatics
- Anticoagulation Research Lab

Warfarin: Accomplishments

- **Assay Development**
  - 3 well established markers
  - 11 markers seen in minority groups



- **Educational Activities**
- **Software evaluations**
  - Incorporating genetic data into dosing
  - Interface with Electronic Medical Record
- **Research Collaboration**

Benefits to Veterans

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- Tests already in use to support cancer diagnostics, clotting risk, Warfarin sensitivity
- Reduced costs for clinical tests
- Fewer days in the hospital
- Fewer serious adverse drug reactions
- More effective cancer treatments
- Disease Prevention: Knowing the risk