Pharmacogenomics at Boston Children's Hospital

Catherine Brownstein, MPH, PhD
Boston Children's Hospital

Statistics

- 395 bed (soon to be 430+ beds) quaternary care, Magnet hospital
- All transplants – first pediatric hand transplant center. Only thing we don't do is burns (and we try to stay away from pesky adults!)
- >65,000 ED visits, >25,000 admissions and >550,000 clinic visits per year
- Awarded most NIH pediatric research dollars in the US
- Cerner CPOE since 2005
- First pediatric institution to receive HIMSS7 designation

Gene Partnership Vision

POLICYFORUM

MEDICINE

Reestablishing the Researcher-Patient Compact

Well-intentioned regulations protecting privacy are denying important information to patient subjects. Advances in information technology mean that a better approach to clinical research is possible.

Isaac S. Kohane,[1,2,3]* Kenneth D. Mandl,[1,2,3] Patrick L. Taylor,[2,4] Ingrid A. Holm,[2,5] Daniel J. Nigrin,[1,2,3] Louis M. Kunkel[2,5,6]

In the name of privacy and protection of study subjects, the research community has, albeit with good intentions, broken the historical doctor-patient compact, distorting an ideal of information exchange that might inform subjects of health risks or benefits (1, 2). To minimize privacy risks in genomic research, investigators and institutional review boards (IRBs) construe that federal regulations require anonymized data. This disallows communicating pertinent results back to subjects. Such results could help the subjects and would justify the beneficence of that research (3). When large cohorts are enrolled for genomic and clinical characterization (4–6), both sides agree not to reconnect findings from the aggregated data or to infer meaning or insight for a specific patient, or to make that knowledge available to the patient. The scientific motivation behind this mutual commitment never to communicate or identify has origins in the evolution of modern study design (7). It has coincided with the growth of grass-roots privacy concerns, the enactment of Health Insurance Portability and Accountability Act (HIPAA) (8), the Office of Human Research

common as more genetic signatures are linked with pertinent phenotypes. Further, this highlights only one of several opportunities (15) missed because of an understandable but overreaching paternalism.

The advent of genome-scale measurements and health information technologies allows us to reconnect patient subjects and researchers in a manner respectful of regulations and privacy concerns and to maximize potential benefit to the public and the individual in the course of research. A solution must anonymize information while making discoveries available to participants who "tune in." Although seemingly paradoxical, it is comparable to UHF/VHF television. To "participate," an individual buys a television and privately decides when and what he watches. In the research analogy, a subject's "programming" is a product of her own information and the aggregated study results. Her reception of research results depends on whether she "tunes in" to the broadcast.

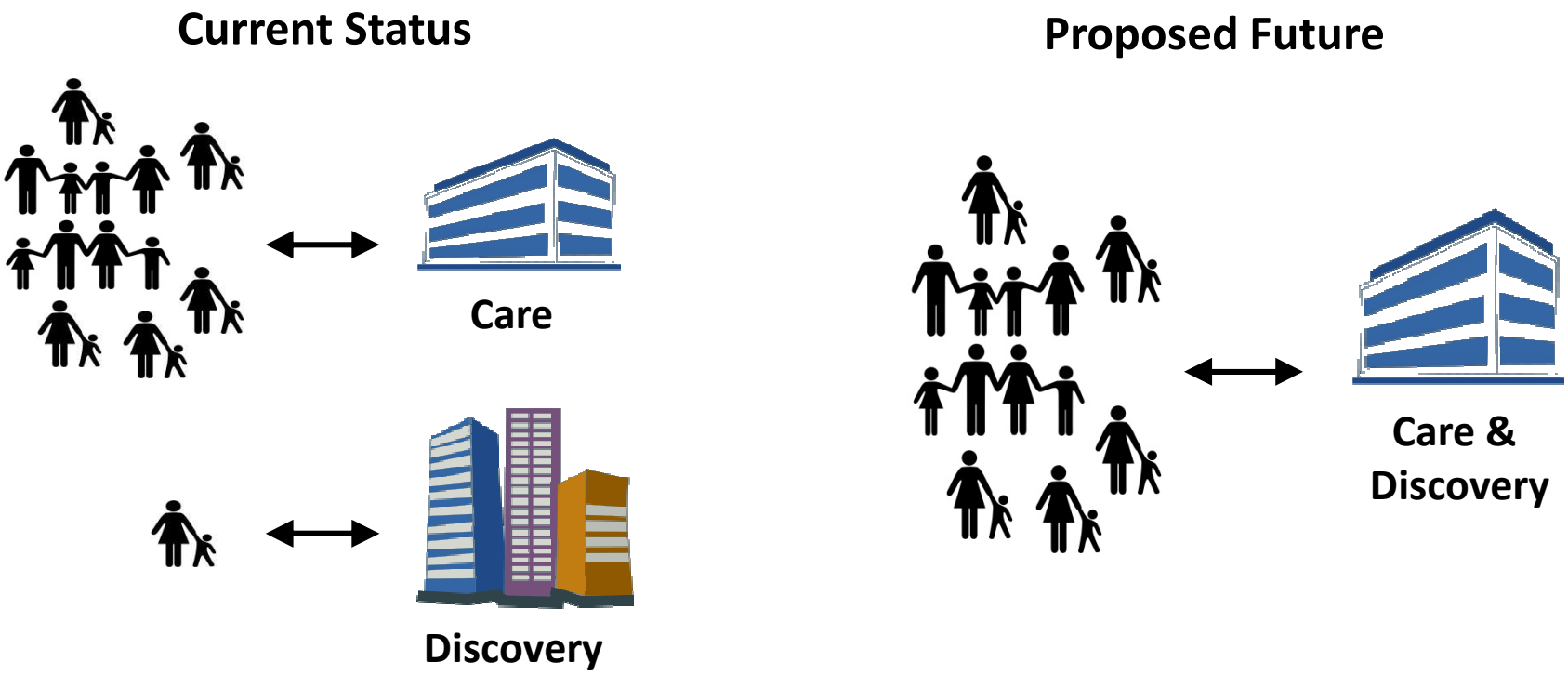
We propose a collaborative clinical research regime, the Informed Cohort (see Figure, page XXX). IC subjects are enrolled at their health-care institution through an extensive informed consent process. If they choose,

encrypted, preventing compelled third-party disclosures (19), for example, by subpoena. Only the patient can decide to whom personally identified information will be disclosed and under what circumstances (20–22). Thus, each patient owns an integrated copy of his or her traditional record data plus high-throughput genome-scale measurements made on his or her own biomaterials. For example, she may consent to share a part of her PCHR data, which is then anonymized and entered into a population database. Her data can be studied in an IRB- and HIPAA-compliant manner across topics including population genomics, public health, medication effects, and quality of care. Data can be shared with appropriate parties including biomedical researchers and public health authorities. Under no circumstances would there be an attempt to contact or to discover the identity of the patient. Anonymized data-gathering can be a dynamic process for longitudinal studies of individuals (23).

The IC design allows patients to be contacted as necessary and as desired by each patient. As shown in the figure, each PCHR has an "agent" the listener. The agent has a dedicated purpose: to intercept broadcasts over the Internet from the health-care system with

- Institutional genetic research repository
- Link to EMR
- Longitudinal participant engagement
- Facilitate large-scale research and discovery (multi-institution?)
- Investment into cutting edge research

A Significant Opportunity Exists for BCH



More explicitly integrate research and clinical care into the patient experience and in the eyes of the public

Re-envisioning GP:
rebranded as Research Connection

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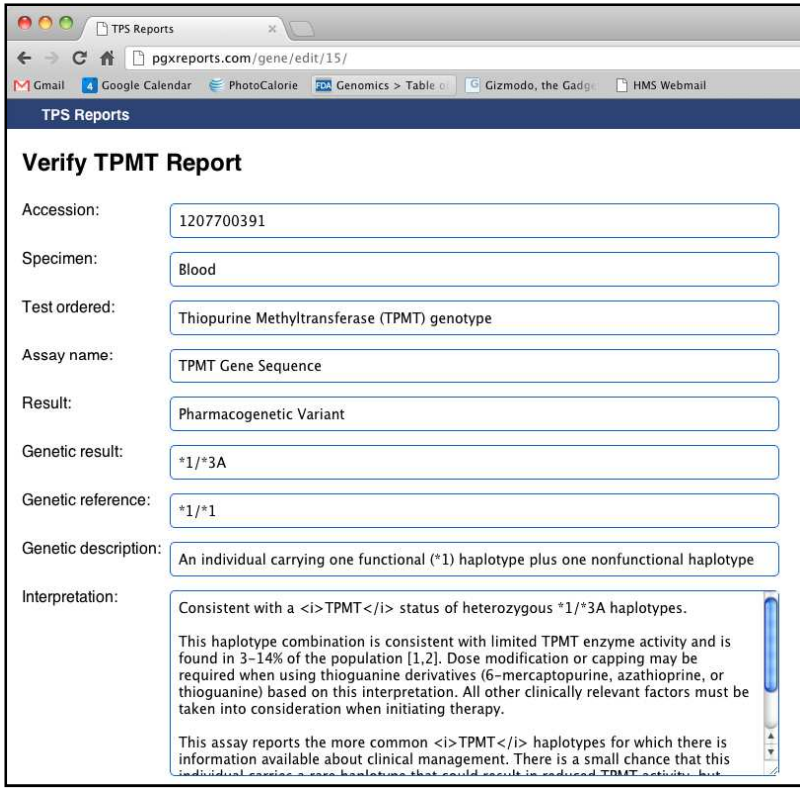
Pilot Projects

- **Pharmacogenomics**
  - **Clinical Pharmacogenomics Service**
  - **High throughput drug screening research**
- BCH Sequencing
- Cancer Genomics
- Neurodegeneration and Developmental disease

Pharmacogenomics at BCH

- April 1, 2012
  - Clinical Pharmacogenomic Oversight committee established, meeting monthly
- August 1, 2012
  - PGx result return (TPMT) to the EMR
    - PGx Specialty View
    - High-risk genotypes manually added into Problem and Diagnosis List
  - Interpretation report engine
  - Decision support PGx rules for prescribers and pharmacists
  - Formal consult process for the CPS in the EMR
  - Presented initial PGx training to the pharmacy staff, prescribers

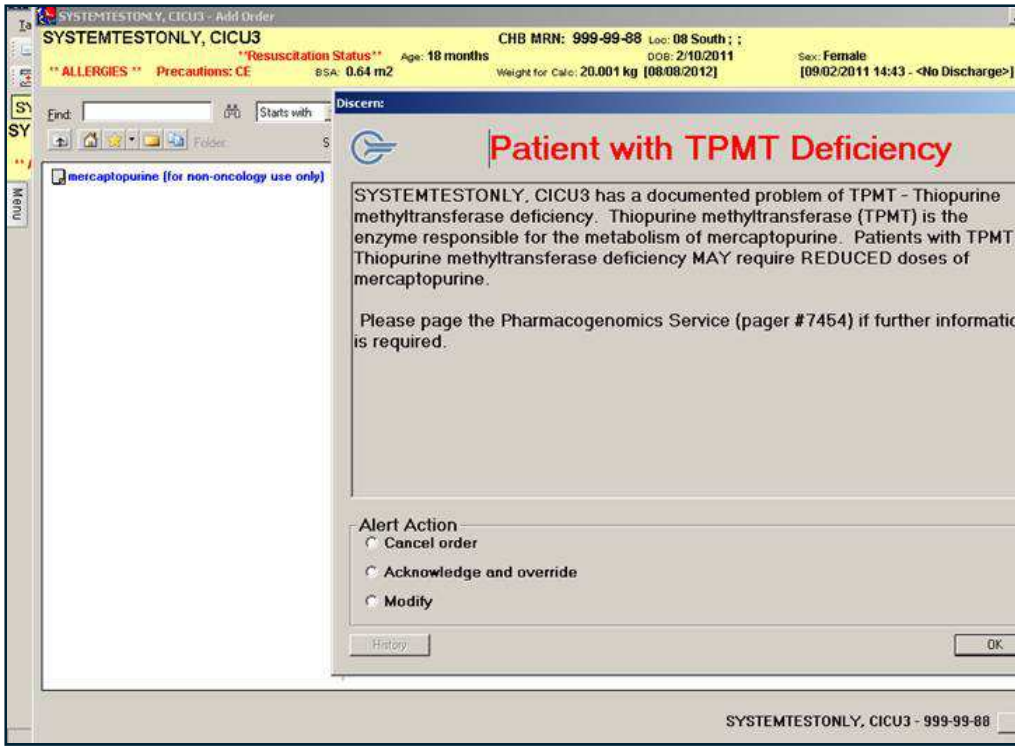


Pharmacogenomics at BCH

- **Oct 31, 2013:**
  - 246 TPMT samples run in house (GI, Oncology, and Transplant)
  - All results returned to the EMR
  - 89.7% wild type homozygous (consistent with literature)
  - 33% reduction in TPMT for non-wild type (on average, different for indication, genotype)

- **Clinical Decision Support Alerts**
  - 54.1% physician, remainder evenly split between NPs and pharmacists
  - 2.6 alerts per practitioner
  - 3.8 alerts per patient
  - ONLY patients with a variant status fire an alert

- **Sept. 2013**
  - Research into the clinical use and utility of PGx data



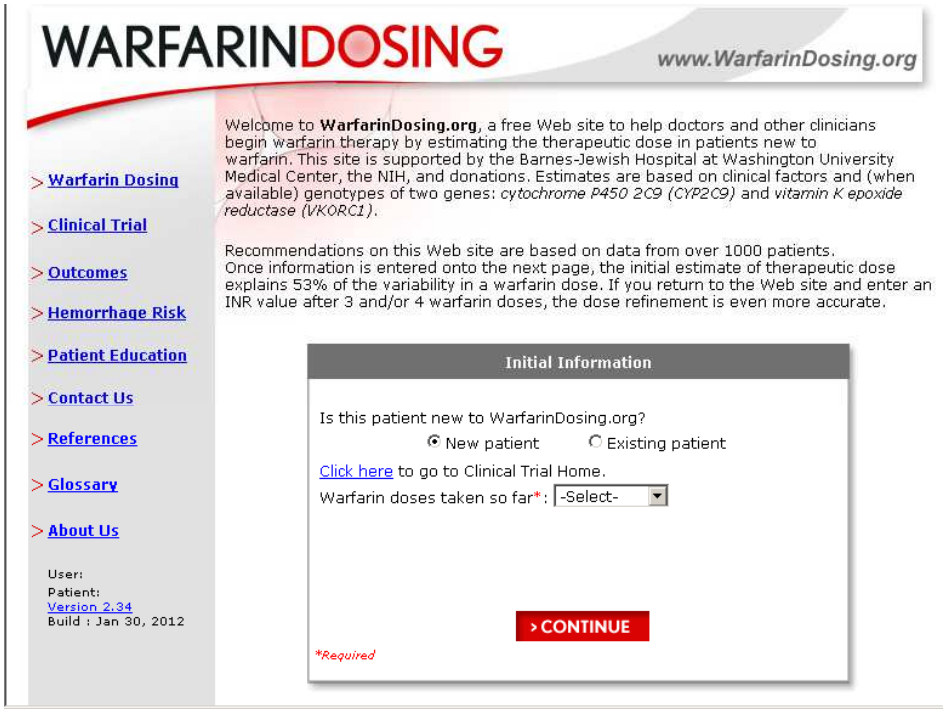
Clinically Actionable PGx tests (example)

- **Warfarin**
  - CYP 2C9
  - VKORC1
  - CYP 4F2

- There are multiple clinical variables, including age, race, body weight, sex, smoking status, liver disease and other concomitant medications.

- VKORC1 is responsible for approximately 25% of the warfarin dosing variation, so it is the most heavily weighted. This is followed by the clinical variables ~20% and by CYP2C9 at ~10%.

- www.warfarindosing.org



Warfarin testing at BCH

- Sending to ARUP (first pediatric institution)
- Basic genotyping with no dosing (not appropriate for under 18)
- Work together with anti-coagulation clinic for best use of information
- Validating most recent PD guidelines
- Retrospective data
- Submitting an IRB proposal to provide data as part of eMERGE consortium

When are PGx tests worth it?

- What is the number needed to treat?
- What is the ethnic variation?
- How much does the test cost to run? To interpret?
- Will it be reimbursed?
- What are the cost savings gained by implementing pre-emptive testing?

Clinically Actionable PGx tests (example)

- **Codeine**
  - **CYP 2D6**
- **Pseudogenes, indels and copy number variation (CNV)**
- **Assay is proving extremely difficult to design**
- **Most PGx researchers agree that CYP2D6 is NOT ready for mainstream use**

FDA Drug Safety Communication: Safety review update of codeine use in children; new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy

This update is in follow-up to the FDA Drug Safety Communication: Codeine use in certain children after tonsillectomy and/or adenoidectomy may lead to rare, but life-threatening adverse events or death issued on 8/15/2012.

View and print full DSC - DSC Update on Codeine 02-2013 [PDF -116KB]

En Español

Safety Announcement | Drug Facts | Additional Info for Patients | Additional Info for Healthcare Professionals | Data Summary | References

Safety Announcement

[2-20-2013] The U.S. Food and Drug Administration (FDA) is updating the public about new actions being taken to address a known safety concern with codeine use in certain children after tonsillectomy and/or adenoidectomy (surgery to remove the tonsils and/or adenoids). Deaths have occurred post-operatively in children with obstructive sleep apnea who received codeine for pain relief following a tonsillectomy and/or adenoidectomy. Codeine is converted to morphine by the liver. These children had evidence of being ultra-rapid metabolizers of codeine, which is an inherited (genetic) ability that causes the liver to convert codeine into life-threatening or fatal amounts of morphine in the body.

A new *Boxed Warning*, FDA's strongest warning, will be added to the drug label of codeine-containing products about the risk of codeine in post-operative pain management in children following tonsillectomy and/or adenoidectomy. A *Contraindication*, which is a formal means for FDA to make a strong recommendation against use of a drug in certain patients, will be added to restrict codeine from being used in this setting. The *Warnings/Precautions*, *Pediatric Use*, and *Patient Counseling Information* sections of the drug label will also be updated.

In August 2012, FDA announced it was reviewing the safety of codeine due to cases of deaths and serious adverse events in children who took the drug after a tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine. FDA conducted a comprehensive safety review to identify additional cases of overdose or death in children taking codeine and to determine if

Clinical Pharmacogenomics Consultation Service

- Official and “curb-side” consults by CPS pharmacists
- Inpatient and outpatient, hospital wide
- Referrals via genetics clinic, will send pre-screening questionnaire (it is short!)
- Reimbursement
  - currently in process of finding out!
  - For the consult and clinic visits – utilizing CDTM (collaborative therapy drug management) law, currently in credentialing hell

“Don’t want to be normal”

- Complex patients
- Multiple adverse reactions
- Adult referrals seen in clinic (no other CPS around, so referred to BCH)

“I know I have CYP2D6 sensitivity” (DTC results in the clinic)

- One of first cases
- Family insists child has a 2D6 variant, 2 non functioning alleles. No documentation anywhere but says *4/*5. Avoided every drug known to man. Very determined to avoid, living in fear.
- Testing done 17 years ago
- Part of identity.
- Retesting done
- “Can s/he get this drug?”

DTC problems

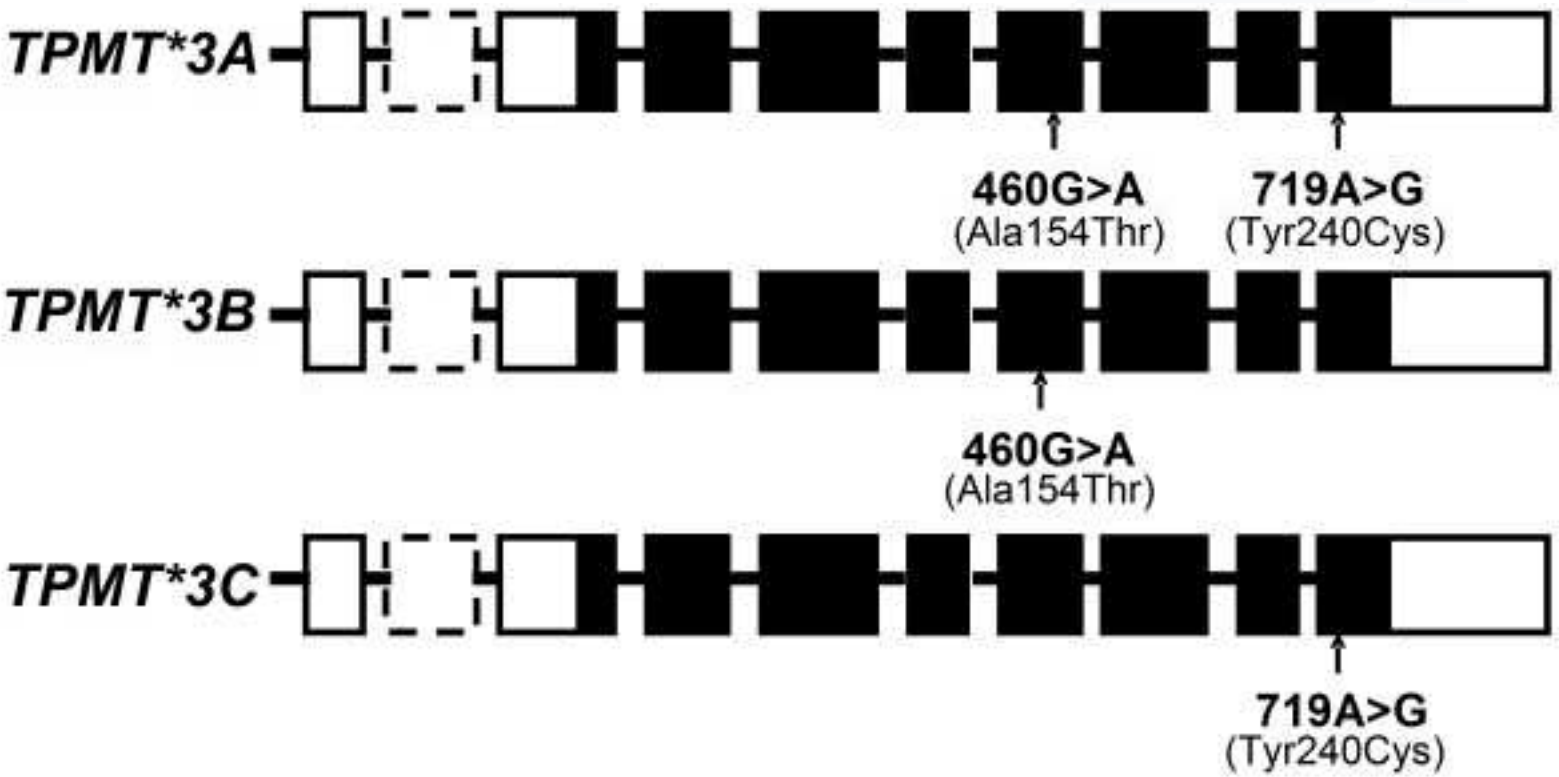


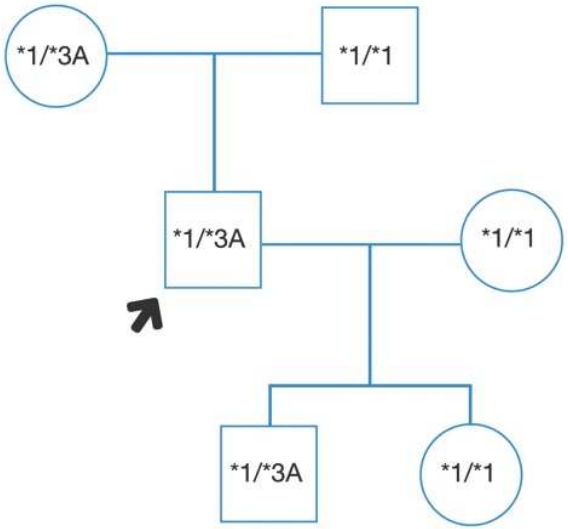
Image from: Recent Advances in Pharmacogenomic Technology for Personalized Medicine. Toshihisa Ishikawa and Yoshihide Hayashizaki

DTC problems

A

Has one *3B mutation and one *3C mutation. A person with these mutations typically has reduced TPMT function and increased risk of toxicity when treated with thiopurine drugs. See the technical report for more details. May have other mutations in the TPMT gene (not reported here).

B



C

Typical Risk

NAME	CONFIDENCE	YOUR RISK	AVG. RISK	COMPARED TO AVERAGE
Obesity	★★★★	58.4%	59.0%	0.99x
Coronary Heart Disease	★★★★	24.4%	24.4%	1.00x
Breast Cancer	★★★★	12.7%	13.5%	0.94x

The Trouble with CYP2D6 genotyping

- **Copy Number Variation (CNV)**
  - **2 to 18 copies reported in humans**
  - **All copies contribute, must ensure adequate capture**
  - **Final genotype scoring (Gaedick)**
- **Pseudogene**
  - **CYP2D7**
- **Sequencing coverage**
- **Use caution, understand the assay before accepting the genotype**

Show me the money (esoteric)

Resource Utilization

Personnel: One pharmacist dedicated at 80 percent effort, with dedicated bioinformatics (15 percent), and intermittent ISD support.

IT and other infrastructure: Up front build upon existing EMR infrastructure. Estimated at a combined 40 hours from various ISD personnel.

Supply Expense: None

Return on Investment: By March 2013, we had run 84 TPMT samples pre-emptively at a cost of $55,200 (we saved $19,000 by bringing the assay in house). Nine samples (10.7 percent) have returned with a variant requiring dosage adjustment. Without dose adjustment, the patients could have experienced severe myelosuppression requiring hospitalization. The average length of stay for an ADR requiring hospitalization (no ICU) is four days, or about $14,000. Thus, the total cost from the ADRs could have been as high as $126,000. **The net savings of avoiding the ADRs is estimated at $70,800 from this single drug/gene pair.**

******AVERAGE ADR modeling. No way to know for sure. All in theory.**

Show me something other than the money

Recognized Intangible Benefits

Our staff have a greater appreciation of the role that a person's genetics can play in medication tolerance. We have identified an area of unlimited possibility for ISD, prescriber, nursing, laboratory and pharmacist involvement as we move into the future of personalized medicine, particularly as it relates to pediatrics.

The Future

- **Platform migration to whole exome/whole genome sequencing**
  - Data handling, storage in current EMR system is unlikely to be possible
  - Cross-reference genes that have both a pharmacogenetic implication and a disease modifying implication
    - Example: SCN5A – gated sodium channel, long QT, lidocaine (anti-arrhymythic).
  - Secondary (incidental) findings
  - Consent policies and online capture
  - Data sharing (genotype/phenotype/outcome data)
  - Revisible reporting
  - Patient portal
    - Return of result- telehealth- policies need to be put in place
    - Reimbursement, State lines

The Ultimate Goal

- **Complete "safe med" system**
  - Incorporates all known med safety data related to the patient, including but not limited to:
    - PGx, biomarkers, drug-drug interactions, drug-food interactions with intelligent design (cannot be 20 different alerts).

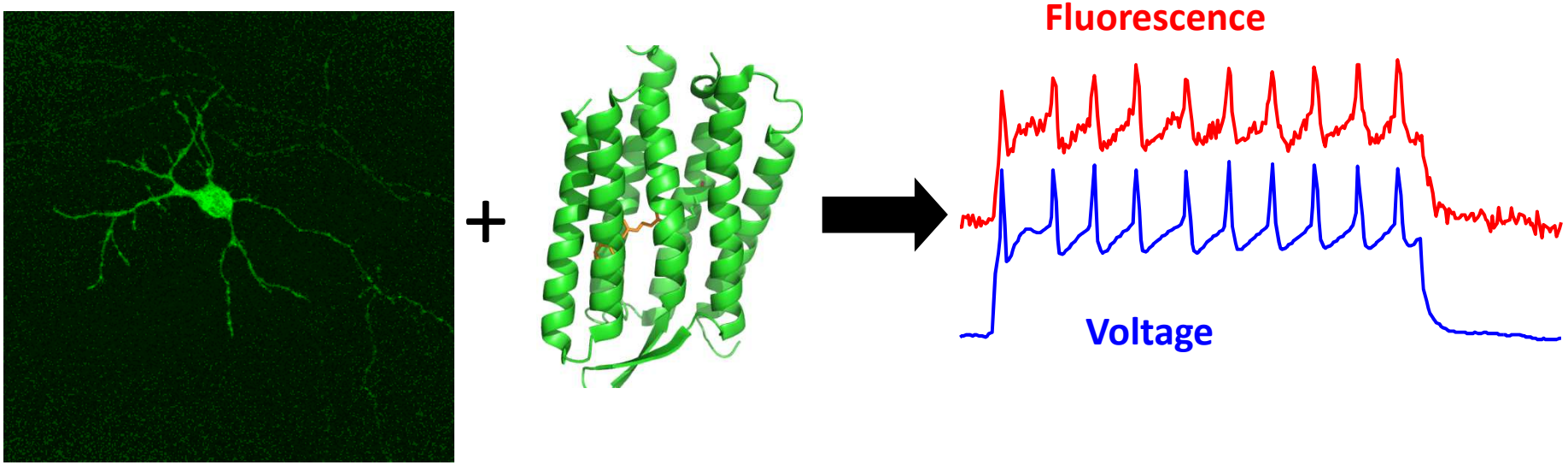
- **Life long data must be always available when relevant and NOT encounter based**
  - Can't see results across the continuum. Right now, the NICU genetic test can't be seen in Pain Clinic
  - Was designed that way, couldn't handle data before, didn't want to propagate errors.

- **Each site should not need to develop and institute their own rules**
  - A core set of rules based on consensus guidelines (i.e. CPIC) that may be further customized by the sites
  - Ability to update in (relatively) real time

PGx Research at BCH

Adam E. Cohen

Chemistry and Chemical Biology
and Physics
Harvard University

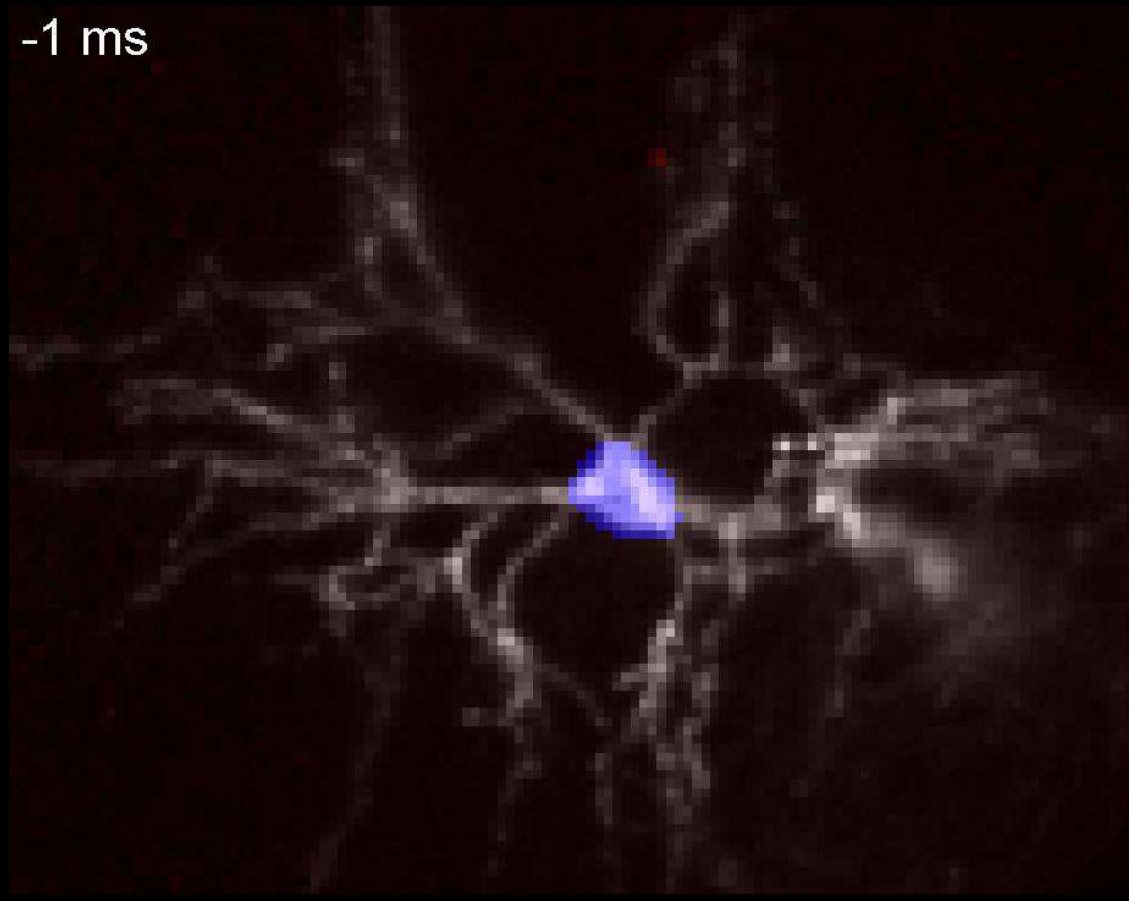


All-optical electrophysiology

3 key technologies:

1. Optogenetic tools for simultaneous stimulation and imaging
2. Advanced microscopy
3. Sophisticated software

Click here →

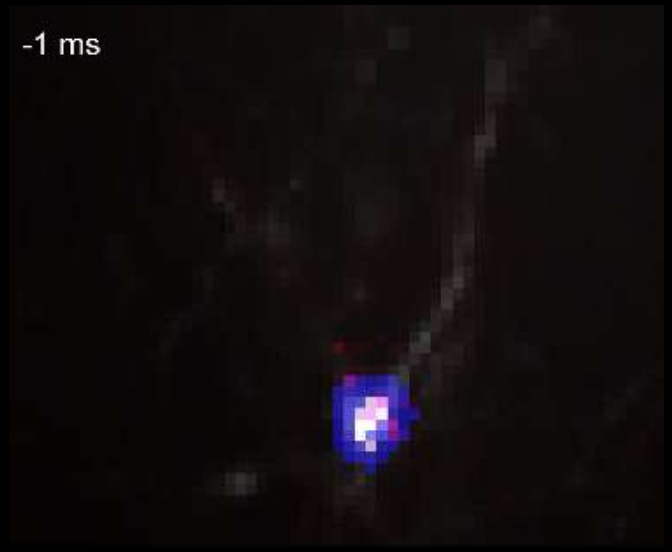


Mouse neuron expressing the “Optopatch” genetic construct. Optical stimulation at the cell body (blue) excites Channelrhodopsin. This causes the neuron to fire. An Archaerhodopsin-based voltage indicator converts this activity into fluorescence. Using custom microscopes and software, we follow the electrical propagation at 100,000 frames/s. Precision of about 1 mV in a 1 kHz bandwidth.

Imaging voltage in human cells

Human induced pluripotent stem cell (hiPSC)-derived neurons and cardiomyocytes are emerging as a promising model for studying disease. These cells can be derived from individuals with mutations associated with many diseases, or engineered to express disease-associated genes. **A key bottleneck in adoption of this technology has been the difficulty in electrophysiological characterization. New HMS created technology provides electrophysiology data with ~100x speedup and vastly more information compared to patch clamp recordings.**

Optopatch in a hiPSC-derived neuron

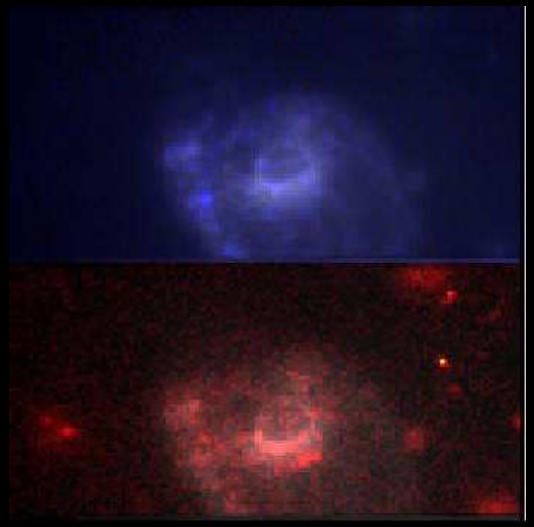


Click here

← →

Video at 20,000 frames/s showing electrical propagation in a human neuron. A flash of blue light to the cell body caused the neuron to fire, which manifested as a wave of red fluorescence.

CaViar: A Ca^{2+} and Voltage Indicator



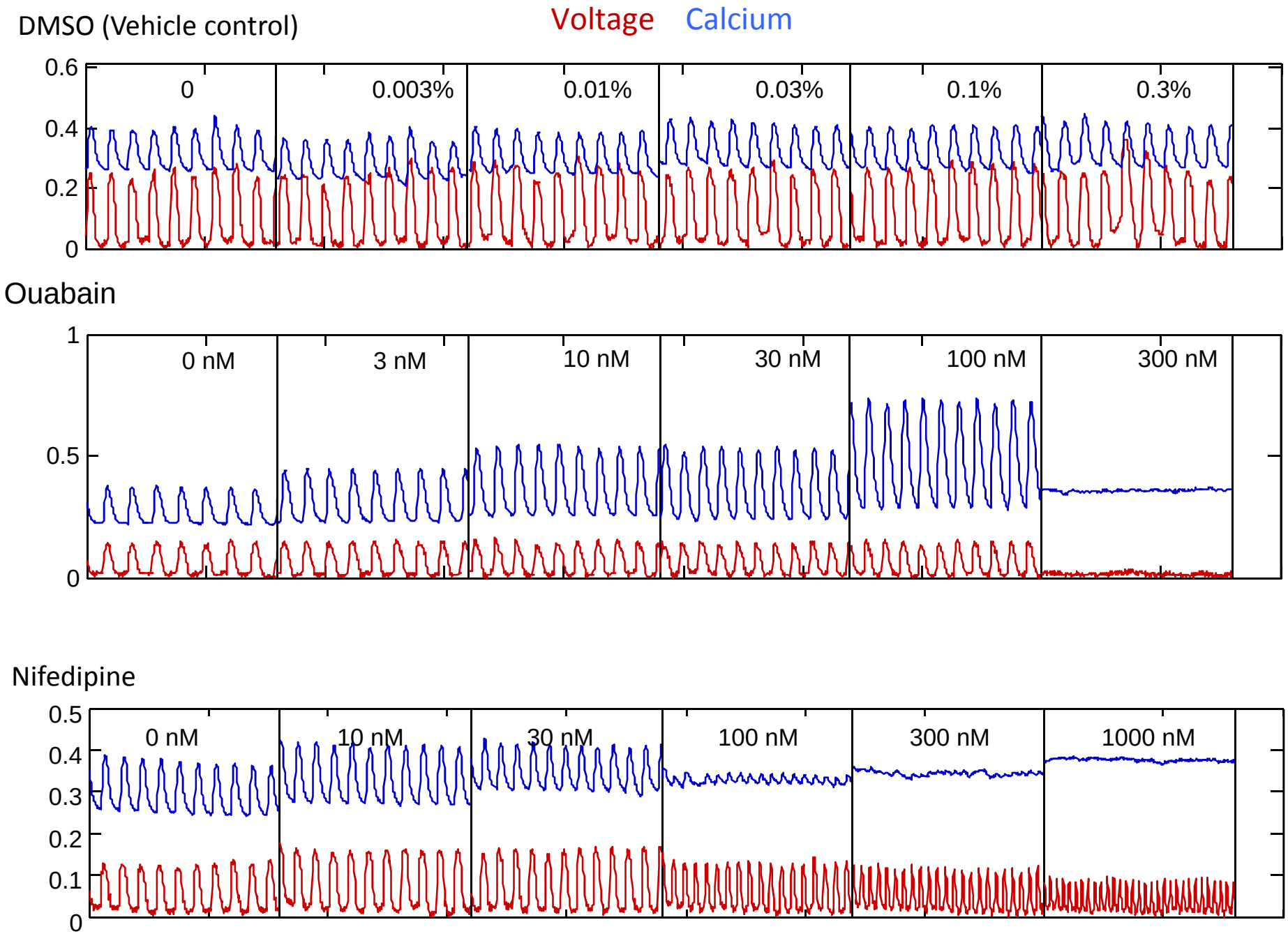
Ca^{2+}

Voltage

Simultaneous monitoring of Ca^{2+} and voltage in a single hiPSC-derived cardiomyocyte. “Calcium sparks” appear as flashes in the Ca^{2+} channel.

Example application: Cardiac safety testing

In the following slides we show examples of 2 drugs (+ DMSO vehicle control) and their effect on electrical (red) and calcium (blue) dynamics in single human iPS-derived cardiomyocytes. Each drug was tested at 5 – 7 concentrations, in 30 – 40 cells at each concentration. This screen took ~4 hours to run. With manual patch-clamp this would have taken several months.


DMSO (Vehicle control)
Voltage
Calcium
0.6
0.4
0.2
0
0
0.003%
0.01%
0.03%
0.1%
0.3%
Ouabain
1
0.5
0
0 nM
3 nM
10 nM
30 nM
100 nM
300 nM
Nifedipine
0.5
0.4
0.3
0.2
0.1
0
0 nM
10 nM
30 nM
100 nM
300 nM
1000 nM

Ex vivo Modeling -- v 2.0

- V 1.0 PLUS:
- Demonstrate optogenetic 'phenotype' of derived neuronal networks
- Demonstrate that optogenetic patterns are also
  - Reproducibly differentiating between nls and unique mutations
  - Affected by drugs
  - Useful to diagnose and select therapies for individual patients

In Kirby-Bauer testing, white wafers containing antibiotics are placed on a plate of bacteria. Circles of poor bacterial growth surround some wafers indicating susceptibility to the antibiotic.

Conclusions

- BCH has retooled its infrastructure to incorporate pharmacogenomics data at the beside
- This approach has yielded successes in less than 18 months
- BCH is actively pursuing *Ex Vivo* modeling with the goal of high throughput screening

The CPS Team

- Shannon Manzi, PharmD
- Jared Hawkins, PhD
- Catherine Clinton, MSGC
- David Margulies, MD
- Wendy Wolf, PhD
- Catherine Brownstein, PhD

Thank you

- St. Jude's Hospital
- Medical College of Wisconsin
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- Shannon Manzi, PharmD
- Cohen Lab
- Eggan Lab
- Research Connection team
- Harvard Center for Biomedical Informatics (CBMI)