Institutional Leadership Perspective on Implementing Genomic Medicine Programs

William E. Evans

Director & CEO

St. Jude Children's Research Hospital

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Institutional Leadership Perspective on Implementing Genomic Medicine Programs

We started down this road at St. Jude in 1984…

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We started using somatic genome Variation to decide treatment in 1984

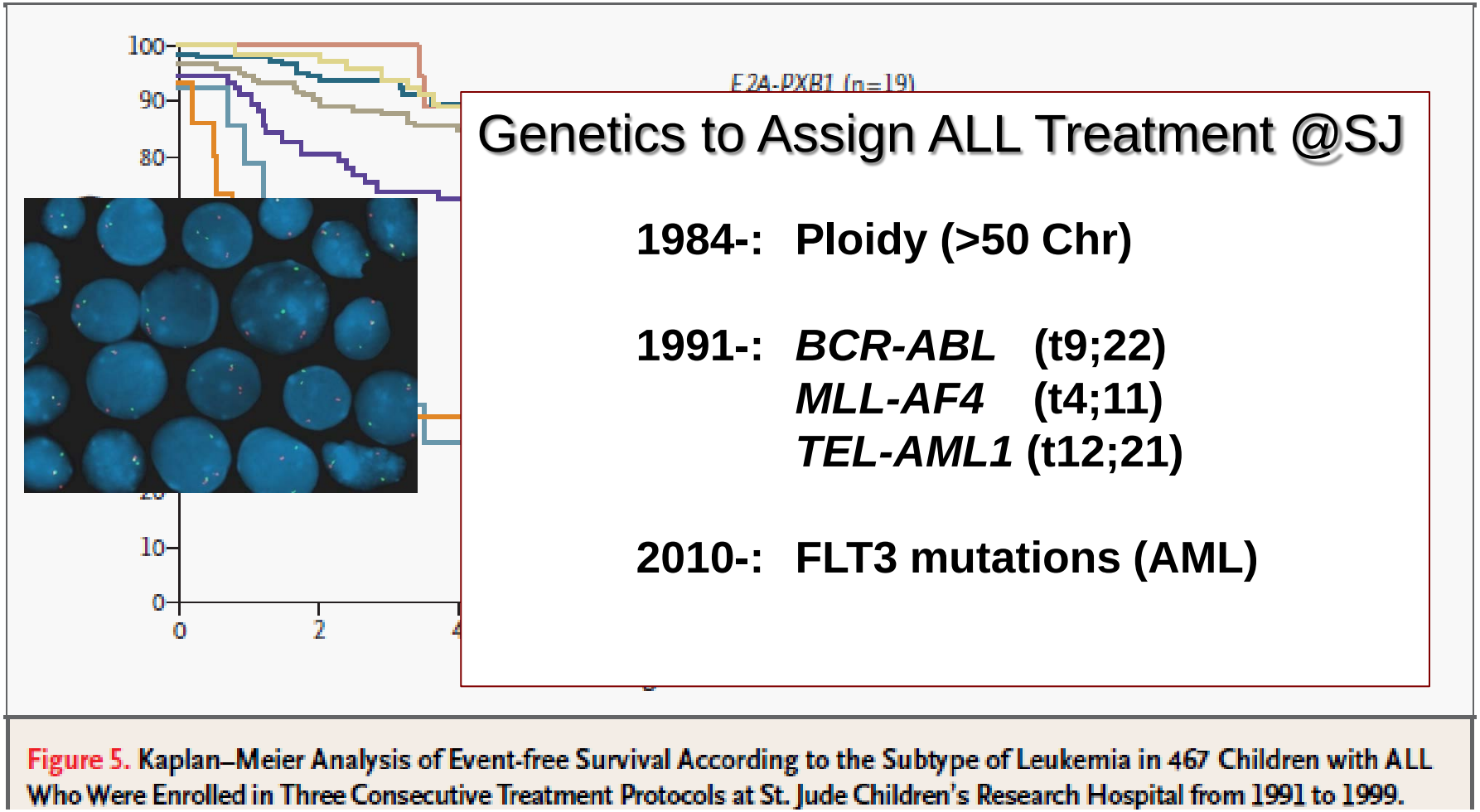
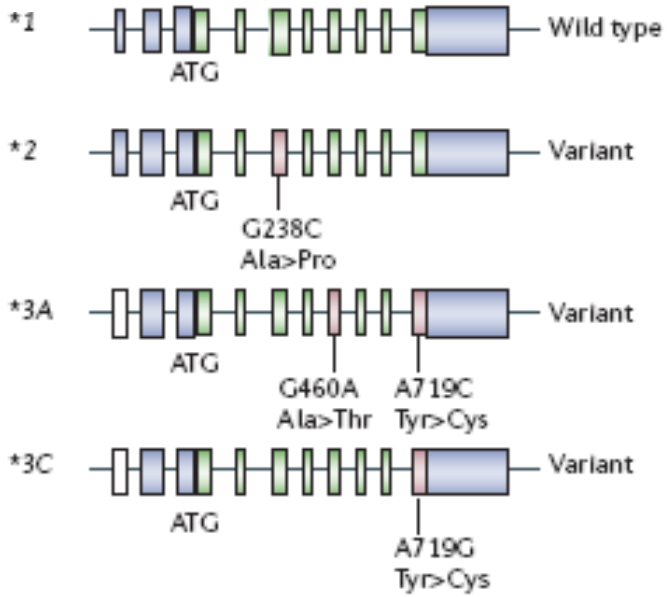


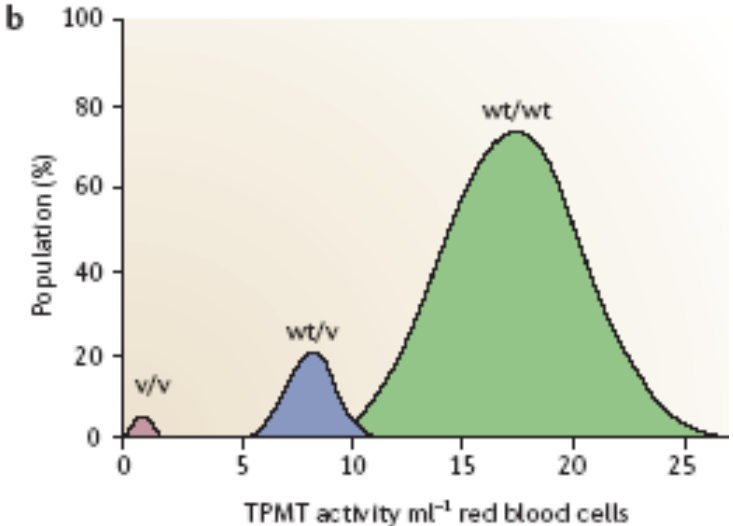
Figure 5. Kaplan–Meier Analysis of Event-free Survival According to the Subtype of Leukemia in 467 Children with ALL Who Were Enrolled in Three Consecutive Treatment Protocols at St. Jude Children's Research Hospital from 1991 to 1999.

Pui et al, *NEJM* 2004

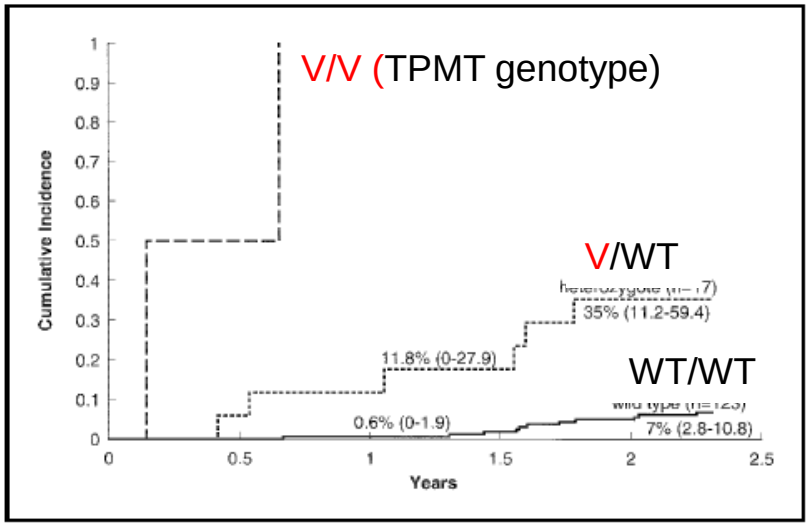
Germline Genome Variation can Influence ALL chemotherapy

Began @SJ with *TPMT* in the 1990's





Cum. Incidence Hematological Toxicity

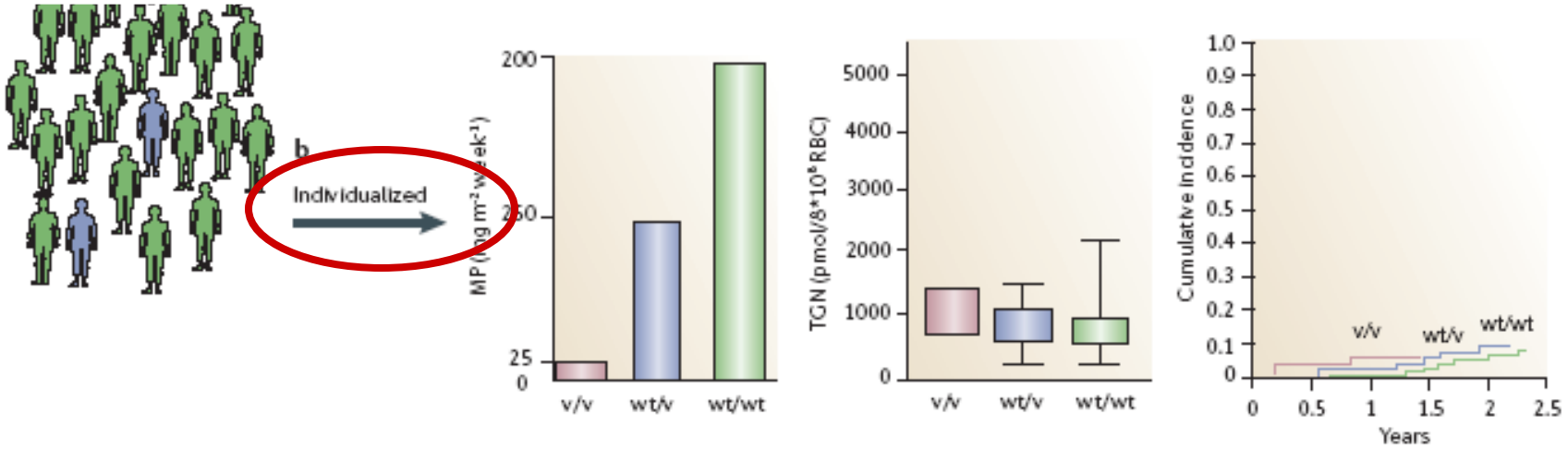


PNAS 94, 99; *AJHG* 96, *Ann Int Med* 96, *PGEN 99, JNCI* 99, *Nat Gen* 05, *CPT* 09

Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing

MV Relling[1], EE Gardner[1], WJ Sandborn[2], K Schmiegelow[3,4], C-H Pui[5], SW Yee[6], CM Stein[7], M Carrillo[8], WE Evans[1] and TE Klein[8]

Clin. Pharm. Ther., 2011



Science, Oct 2003

NEWS

Preventing Toxicity With a Gene Test

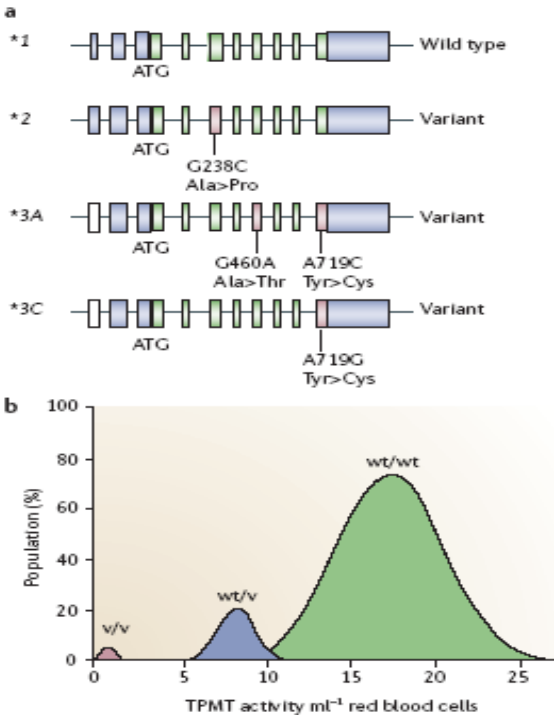
To test or not to test? That is the question clinicians are asking about screening for genes that affect how the body metabolizes drugs

But the medical community remains skeptical…

For more than 30 years, doctors have been using [illegible] cure [illegible] drug- sized by the late Gertrude Elion and George Hitchings—has saved thousands of lives. But it has a dark side. Researchers discovered more than 20 years ago that it is extremely toxic in patients with an inherited metabolic flaw. The drug can accumulate rapidly, wiping out essential bone marrow and leading to infections.

About 8 years ago, teams led by William Evans of St. Jude Children's Research Hospital in Memphis, Tennessee, and Richard Weinshilboum of the Mayo Clinic in Rochester, Minnesota, pinpointed flaws in an enzyme-producing gene called *TPMT* on chromosome 6. A DNA test became available in the 1990s. It tells patients whether they are in one of three risk categories: standard, with a copy of the normal *TPMT* gene from each parent; slightly elevated, with a deficient gene from one parent; or extremely high, with two deficient genes. People in the last category, roughly 1 in 300 Caucasians, should not receive standard 6MP therapy, physicians say. It could kill them.

community remains skeptical. Like other doubts about physicians' ability to understand test results. Such real-world headaches seem to keep pushing the human genome about how to recalibrate drug doses, and



U.S. Food and Drug Administration (FDA) seems unlikely to recommend one.

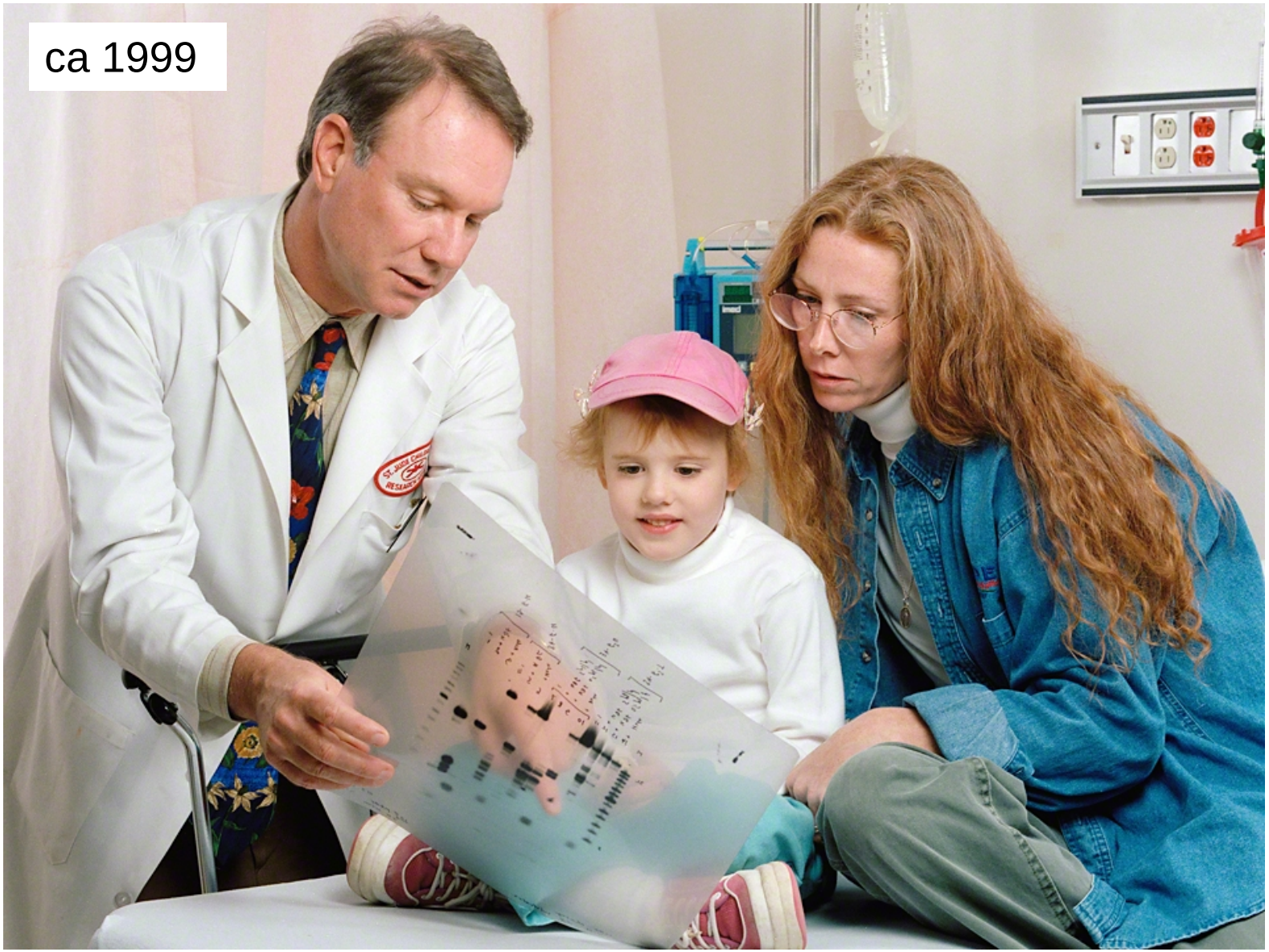
The resistance has surprised champions of genomic medicine. A leader in [illegible] an of [illegible] that [illegible] hard sell. In all, says FDA pharmacogenetic expert Larry Lesko, about 20 drug labels now mention reactions that may be influenced by genetic differences, but none recommends a gene test or related dose guidelines. Adds Altman: "Everyone thought *TPMT* would be the big one to do first. I must admit there is not a single case of a genetic variation where the standard of care is to test first. … We have not yet broken through."

Still, the *TPMT* case suggests that genomic medicine is gaining momentum, albeit slowly. Genotyping to prevent adverse drug reactions may indeed be one of the first applications to win broad acceptance, but the pace will depend a lot on how physicians respond. Patients who face risks of toxicity may be among the first to recognize the benefits, and they may bring along the doctors.

No advice, thanks

The question of whether to add an advisory on gene testing to the 6MP package label is now before FDA. The agency's new administrator, Mark McClellan, has said that one of his top five priorities is to raise the profile of genomics in FDA decisions. Partly because of McClellan's interest, says Lesko, the agency is taking a

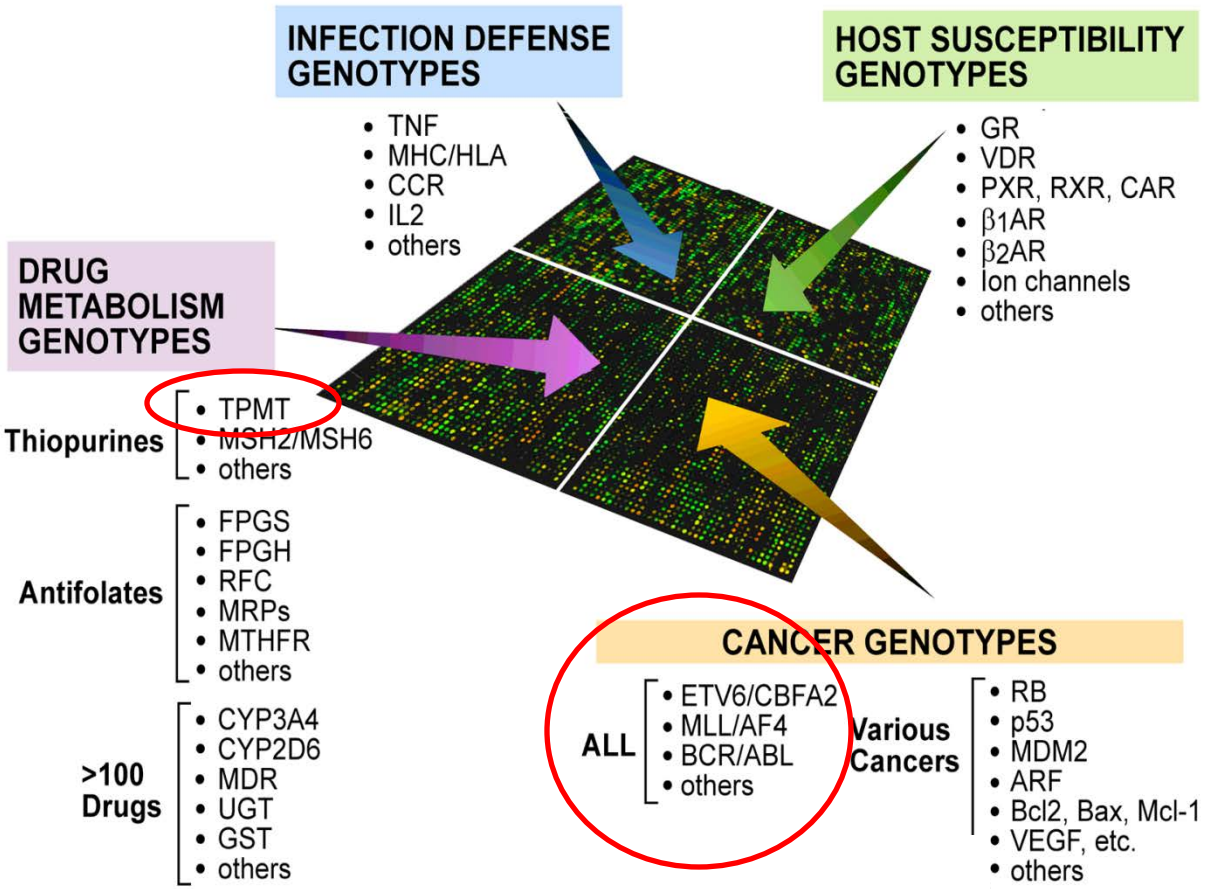
Technology has improved but translation is lagging……..



GENOME
REVIEW

Pharmacogenomics: Translating Functional Genomics into Rational Therapeutics

William E. Evans* and Mary V. Relling



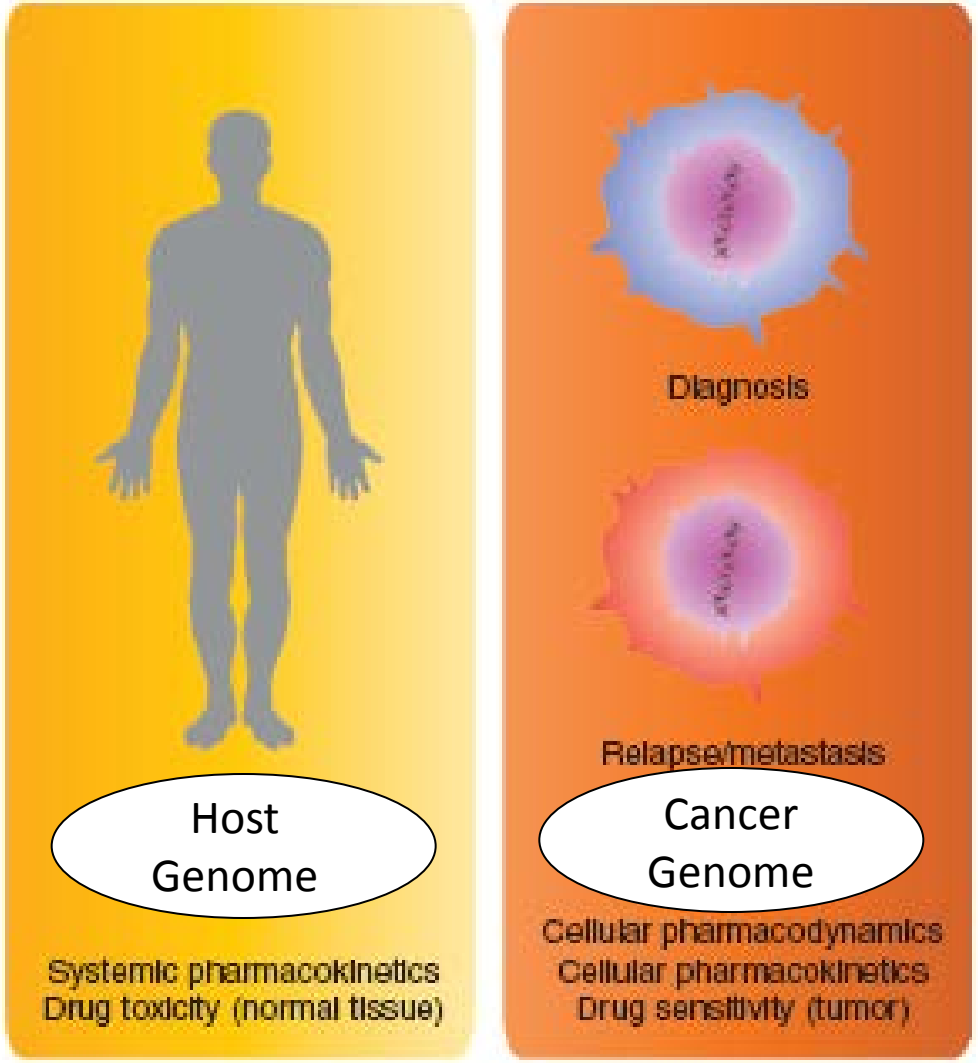
Evans and Relling, *Science*, 1999

Academic System Rewards Discovery More than Translation

Germline

- MP & *TPMT*
- MTX & *SLCO1B1*
- Asp & allergy
- Steriods & ON
- GWAS & MRD
- GWAS & EFS

(*PNAS, AJHG, AIM, Nat Gen., JCI, Blood*)



Somatic

- MTX & *RFC, GGH*
- MP & *MSH2*
- IC50 Rx & ALL GEP
- WGS (PCGP)

(*NEJM, JCI, AJHG, Can. Cell, Nat. Gen., Nat Med., Nature*)

What are we doing to *translate* genomics into clinical practice @SJ?

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Pediatric Cancer Genome Project
Washington University in St. Louis
School of Medicine

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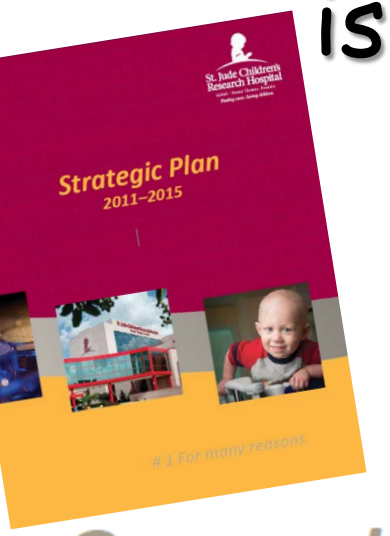
Genomics to individualize therapy is an institutional priority @SJ



2011-2015 Strategic Plan

Overarching Goals and Objectives

Our Strategic Plan has been developed to accelerate progress in our treatment and research programs, toward the accomplishment of several overarching organizational goals, including:

1. To push the collective cure rates for childhood cancer to 90% in the next decade.
2. To enhance our status as the leading patient care center for children with cancer, sickle cell disease and selected infectious diseases.
3. To be the leading discovery-oriented research center for pediatric cancer genomics and pediatric cancer biology.
4. To be a model center for translating biomedical discoveries into innovative treatment strategies for childhood cancer, sickle cell disease and other catastrophic diseases in children.

From our Strategic Plan 2011-2015

The promise of 'individualized medicine" can only be fully realized if the vast amount of complex medical, genetic, laboratory and pharmaceutical data can be presented to clinicians in real time with evidence-based decision support tools to affect clinical decision making in real time.

So, How Much? *

Patient Care	$ 10M – 20M
Research	$150M – 200M
	$160M – 220M

* Guesstimate of annual spend on genetics
Total annual operating budget $625M

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What we are currently doing to translate…..?

Acute Lymphoblastic Leukemia (example)

- Rx defined based on **somatic** genome variation
  - ✓ Ploidy/karyotype
  - ✓ Chromosomal Translocations (PCR, FISH, etc)
  - ✓ Target gene mutations (e.g., JAK2)

- Drug selection/dosing based on **inherited** variation (PG4KDS protocol)
  - ✓ DMET array (UW)
    - TPMT (6MP)
    - CYP2D6 (codeine)
    - Others (e.g., CY2C19, VKOR1)

PGRN

PAAR4Kids

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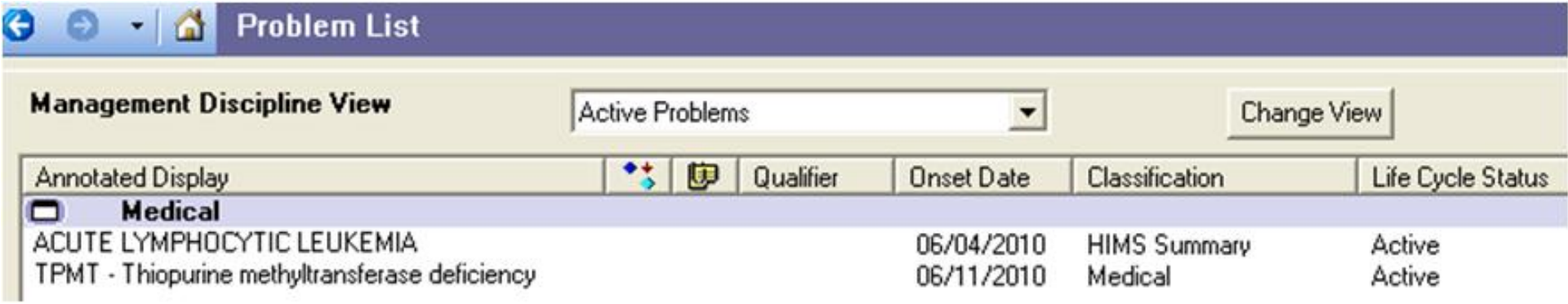
High-risk genotypes are put into Problem List of EMR

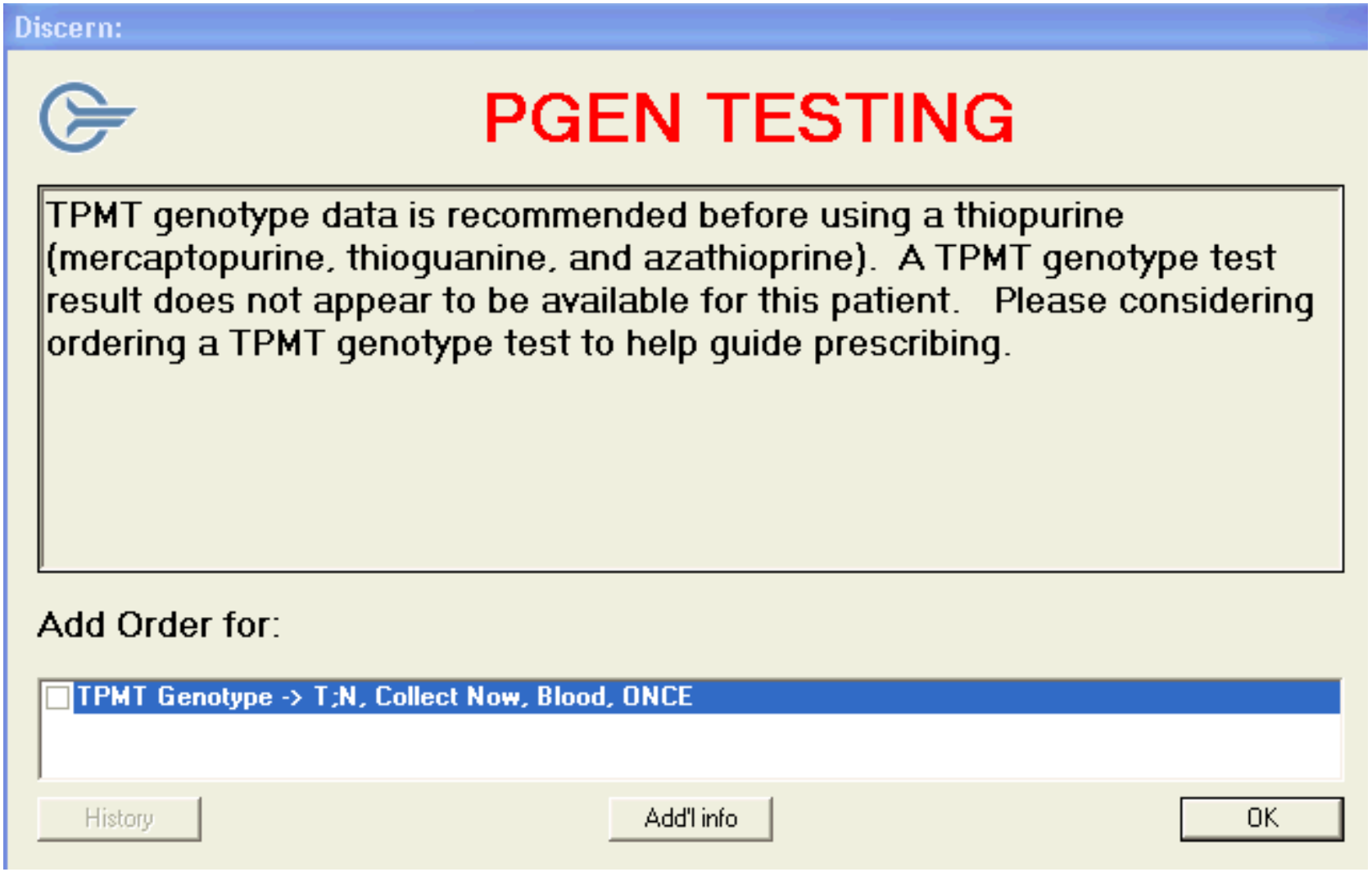


Customized Decision support "behind the scenes":

Links high-risk genotypes to thiopurine prescribing and administration

We alert clinicians of the need to genotype

For all patients enrolled on ALL protocol

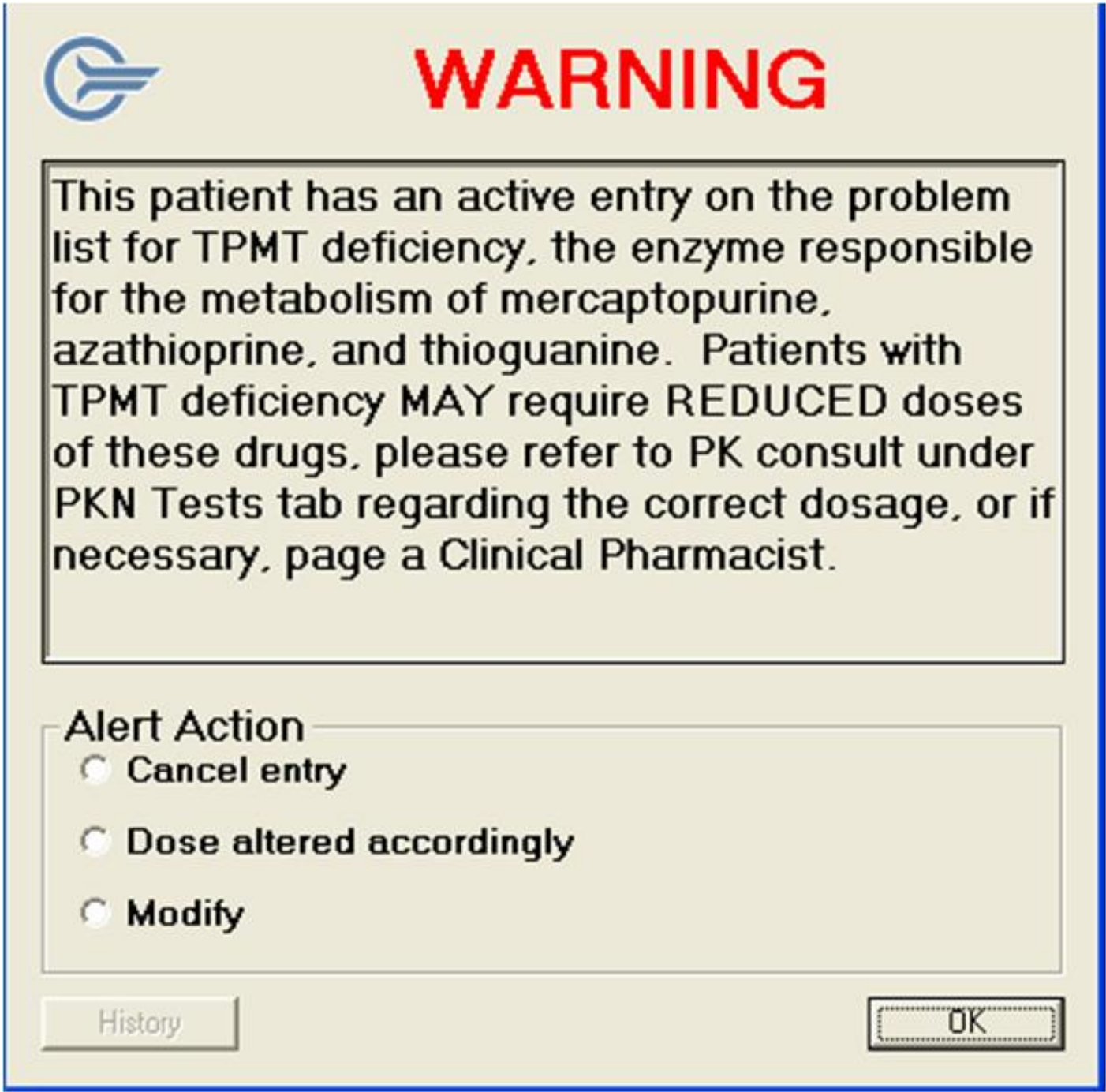


Pharmacy notified if “PGEN Rx” ordered

TPMT pharmacogenetic test alert to pharmacists

(Mercaptopurine) was just ordered on _____ Primary Service: LE Clinic. However, a **TPMT genotype test does not appear to have been ordered for this patient.** Please follow up to be certain a TPMT genotype test is ordered and used to guide thiopurine prescribing. The clinician who ordered the thiopurine received a similar alert to prompt a TPMT genotype order. This email is sent to the Clinical Pharmacy On Call email group. If you are following this patient, please follow up to be certain a TPMT genotype test is ordered and used to guide thiopurine prescribing. (The email is also sent to Kris Crews and James Hoffman for PG4KDS tracking purposes)

The EMR warns clinicians when they order a drug for which genotype should be used to guide therapy



TPMT Pharmacogenetic Clinical Consults

PHARMACOGENETICS CONSULT FOR
TPMT GENOTYPE

Sample for TPMT Genotype Obtained: $SAMPLE_DT_TM
PG4KDS TPMT Genotype Result: *1/*3C

This result signifies that this patient has one copy of a wild-type (high activity) allele and one copy of a non-functional (low activity) allele. This patient is predicted to have intermediate TPMT activity. The patient is at risk for myelosuppression with normal doses of drugs in the thiopurine class (6-mercaptopurine, 6-thioguanine or azathioprine), and thus reduced starting doses may be needed. Some experts recommend lower doses of thiopurines in heterozygotes because these patients may be at a higher risk of thiopurine-related late secondary cancers. For 6-mercaptopurine and azathioprine, consider starting at 30-70% of the normal dose. For example, a normal dose of 6-mercaptopurine (e.g., 75 mg/m2/day) should be reduced to 20-50 mg/m2/day. A normal dose of azathioprine (e.g., 2-3 mg/kg/day) should be reduced to 0.6 - 2.0 mg/kg/day. For thioguanine reduce the normal dose by 30-50%.

Titrate thiopurine doses based on myelosuppression. In the setting of myelosuppression, and depending on other therapy, emphasis should be on reducing thiopurine doses over other agents. Allow 2-4 weeks to reach steady-state after each dosage adjustment. For drug monitoring, consider obtaining a thiopurine metabolite plasma concentration.

For more information about how TPMT activity influences thiopurine dosing please go to www.stjude.org/pg4kds.

Comments: none_

Shane Cross, Pharm.D., page 0920

How and When to Take Genomics to Clinic?

4

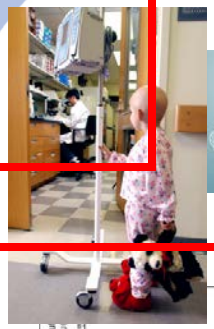
- PGRN consensus
- Prospective trials
- Routine patient care

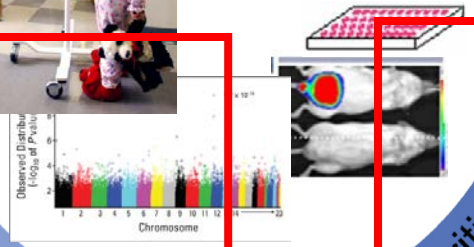
3

- Other trials
- Other diseases
- Murine models
- Surveys of liver, HapMap LCLs
- In vitro mechanisms

Clinical Integration

Validation





Discovery/Replication

Prioritization

- Prospective clinical trials (COG and St. Jude)
- Antileukemic, PK, and adverse effect phenotypes
- Inherited and leukemia cell genomic variation
- Nongenetic covariates

1

- Pleiotropy
- Pathway analyses
- Plausibility
- Frequency
- Generalizability
- Effect size

2

PAAR4Kids: Pharmacogenomics of Anticancer Agents Research in Children

www.pharmacogenetics.org

PGRN

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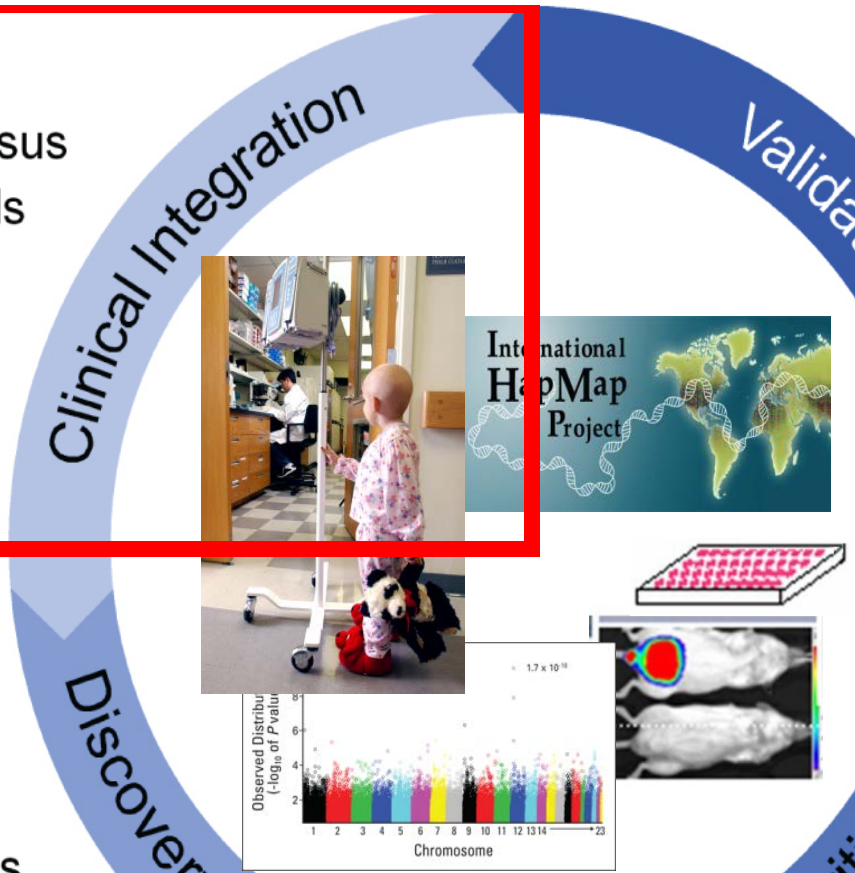
Clinical Integration is independent of who made the discoveries and even of "the" disease state

4

- PGRN consensus
- Prospective trials
- Routine patient care



- Prospective clinical trials (COG and St. Jude)
- Antileukemic, PK, and adverse effect phenotypes
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Clinical implementation of pharmacogenomics: overcoming genetic exceptionalism

Mary V Relling*, Russ B Altman, Matthew P Goetz, William E Evans

***Lancet Onc.* 2010**

CPIC Queen

Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing

MV Relling[1], EE Gardner[1], WJ Sandborn[2], K Schmiegelow[3,4], C-H Pui[5], SW Yee[6], CM Stein[7], M Carrillo[8], WE Evans[1] and TE Klein[8]

Clin Pharmacol Ther.

PharmGKB

Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450-2C19 (*CYP2C19*) Genotype and Clopidogrel Therapy

SA Scott[1], K Sangkuhl[2], EE Gardner[3], CM Stein[4,5], J-S Hulot[6,7], JA Johnson[8,9,10], DM Roden[11,12], TE Klein[2] and AR Shuldiner[13,14]

Clinical Pharmacogenetics Implementation Consortium Guidelines for *CYP2C9* and *VKORC1* Genotypes and Warfarin Dosing

JA Johnson[1], L Gong[2], M Whirl-Carrillo[2], BF Gage[3], SA Scott[4], CM Stein[5], JL Anderson[6], SE Kimmel[7,8,9], MTM Lee[10], M Pirmohamed[11], M Wadelius[12], TE Klein[2] and RB Altman[2,13]

CYP2D6/ codeine *in press*

Barriers to integration of pharmacogenetic tests into clinical care in USA

- **Fragmentation** of health-care systems---esp over a lifetime
- Health-care delivery system and incentive structures are focused on **"sick care"** and not prevention
- **Modest evidence** of clinical utility or cost effectiveness--coupled with excessively high requirements **(genetic exceptionalism)**
- **Complexity** of the underlying laboratory results
- Lack of use of computational **decision support** in all of medicine
- Need for **pre-emptive testing**

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Fewer Barriers at St. Jude

- We cover all patient care costs
- We provide all medications for 5000 high-risk patients per year
  - ~ 80% have cancer
  - ~20% have sickle cell, HIV
- Patient care and research extensively interwoven
- Multi-disciplinary team approach to patient care (since 1962)
- Integrated, comprehensive EMR with customized decision support

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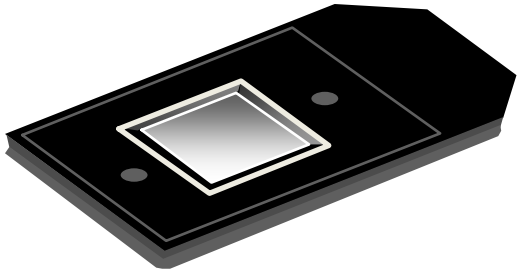
Ability to genotype many loci on CLIA-approved array is ~~coming~~ here and allows for pre-emptive genotyping

- Affy DMET array: over 1 million features to interrogate 1900 polymorphisms in 225 genes
- For the same money we spend on 2 genes, we can interrogate 225 genes
  - ❖ Makes pre-emptive genotyping a possibility



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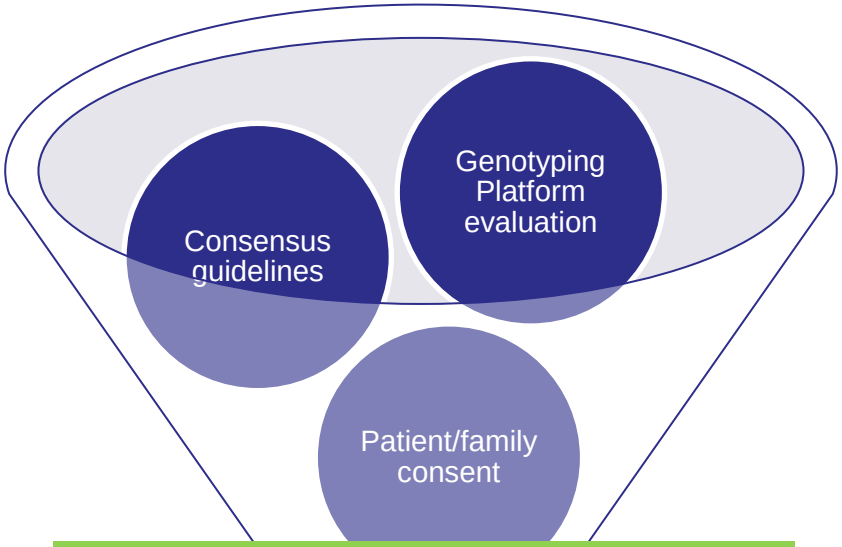
- Use **array** to test for 225 genes (1900 SNPs)
- Use a **defined process** to move one gene/drug pair at a time into medical record
- Use **decision-support** in EMR for prescribing



Initial Genes:
TPMT
CYP2D6

Determine eligibility for migrating individual test results

Process for migrating PG data to medical record

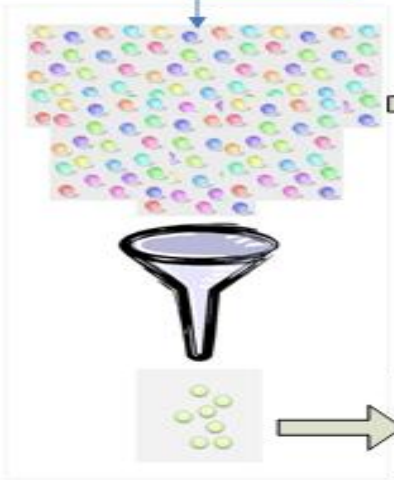
The process

Pt enrolled

DNA genotyped

Genotypes classified as clinically eligible genotypes (CEGs), research only, conflict, or suspect

Ongoing evaluations of data by experts



Most genotypes remain in research database

Evaluation of genotype/drug phenotype, and genotype/ incidental findings, at least annually

A small fraction of CEGs that meet threshold for Clinical Pharmacogenetic Loci

Clinical Pgen Loci genotypes posted as lab results in medical record with basic Pgen consult

Evaluation of decision support flags at least annually

Subset of selected genotypes linked to drug orders, problem list via Decision Support

PGEN4Kids

From Array to EMR

CLIA Lab runs DMET array

Pharm. Sci. Research databases (1900 SNPs/225 genes)

Firewall

1 gene/drug at a time

Into EMR
Clinical Data repository

PG4KDS

CLINICAL IMPLEMENTATION OF PHARMACOGENETICS at ST. JUDE

Why do this under a protocol?

Goal: migrate pharmacogenetic tests from laboratory (array-based) into routine patient care, preemptively

Why a research protocol?

- DMET done per **CLIA**, but process is **complicated** from lab results to clinically actionable recommendations
- Need process for **withholding/sharing** results
- Need **consent** for:
  - Withholding results
  - Incidental findings

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PG4KDS

Protocol Objectives

Long term goal is to use proactive pharmacogenomic testing as the **standard of care** for all St. Jude patients.

Primary Objective

Estimate the proportion of patients who have high-risk or actionable pharmacogenetic results entered in their electronic medical record (EMR)

Secondary Objectives

Use systematic procedures to prioritize and migrate pharmacogenomic tests to the EMR.

Incorporate clinical **decision support** tools linking test results to medication use, and assess their level of use.

Assess attitudes and concerns of res ticipants and clinicians

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Non-Therapeutic Protocol

PG4KDS: Clinical Implementation of Pharmacogenetics

Type of Protocol/Clinical Study

Supportive Studies: Genetics

Description

Pharmacogenetics is the study of how genes affect a person's response to drugs. This field combines pharmacology (the science of drugs) and genetics (the study of genes and their functions) with the goal of making medications safer and more effective by tailoring medications based on a person's genetic makeup.

Gene tests are used in pharmacogenetics. Over time, scientists are discovering which of these gene tests are so important that they should move from the research lab into the patient's medical record, where they would be available to the doctors and other care givers to see the test results, and to use the information when they give the patient the drug.

The process for deciding which tests to move from the research lab into the patient medical record

Related Topics

PG4KDS - Priority Genes

Video: PGEN4Kids Educational Video

Mary V. Relling, PharmD

With just 2 genes, >15% of unselected patients have high-risk genotypes

- CYP2D6 poor metabolizers (10%)
- CYP2D6 ultra-rapid metabolizers (2.6%)
- TPMT heterozygote or homozygote variant (10%)

"Delivery" of Genetic Information

- Moved to review queue for trained pharmacists (competencies) to finalize
- Posted to EMR
  - One gene at a time
  - As each gene is prioritized, it moves to EMR for all past and future pts
- Point-of-care decision support alerts
- Automated email to MD for high risk diplotypes (their choice)
- Automated letter to PATIENTS [Parents] (their choice)
- General information and video on website

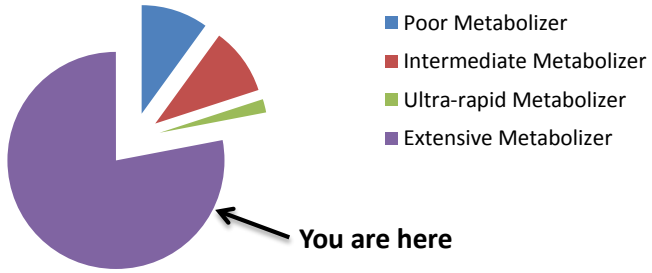
For patients (parents) who request a letter about their genotype results (e.g., *CYP2D6*)

Dear _____,

During your/your child's treatment at St. Jude Children's Research Hospital, you chose to participate in the PGEN4Kids study (PG4KDS). As a part of this study, a test was performed to look for variations in certain genes. A gene refers to a part of the DNA, and variations in genes may affect how well you/your child respond to or whether you/your child have side effects from specific medicines.

You agreed to have hundreds of your/your child's genes tested for variations. Over time, scientists are discovering which of these gene tests are important enough to add to your/your child's medical record. Once a gene test is added to the medical record, doctors and other care givers can see the results and use the information when prescribing medicines for you/your child. Each time a gene test result is placed into your/your child's St. Jude Children's Research Hospital medical record, you chose to receive a letter notifying you of the result. Because your genes stay the same even as you age, the results may affect how doctors prescribe medicines for you/your child over your whole lifetime. You may want to share this information with your/your child's other doctors outside of St. Jude, who may not have easy access to all of the information in the St. Jude medical record.

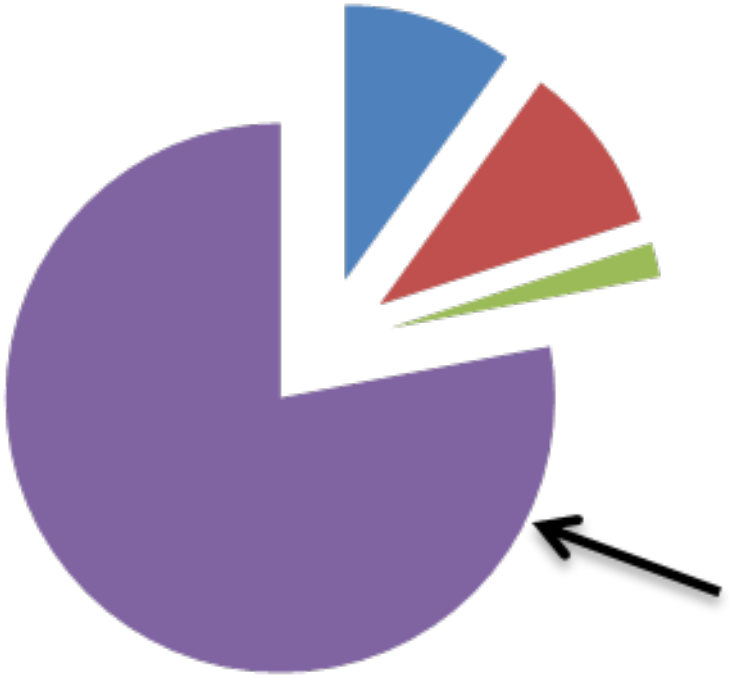
You are receiving this letter to inform you that the cytochrome P450 2D6 (CYP2D6) gene test was recently moved into your/your child's medical record. Based on your results, you are predicted to be an extensive metabolizer. This means you have normal CYP2D6 enzyme activity. You have the same gene status as most other people; about 78 % of people are extensive metabolizers, as shown in the chart below.



The exact percent of each group varies by ethnicity.

CYP2D6 metabolizes many different medicines, including codeine and some other pain relief medicines, some antidepressants and other psychiatric medicines, and beta blockers (used for heart conditions and high blood pressure). Your/your child's CYP2D6 gene test result suggests that for most medicines there is no reason to selectively adjust the dose of medicines metabolized by CYP2D6 enzymes. For information on how to understand your/your child's

A letter for each genotype
(at least for now)



Poor Metabolizer

Intermediate Metabolizer

Ultra-rapid Metabolizer

Extensive Metabolizer

You are here

http://beta.web.stjude.org/news/relling/jl3404_PGEN4Kids.html

St. Jude Family Advisory Council (Alicia Huettel et al)

- Great diversity of opinion

  From “why are you telling me this” to “I want to decide when this goes in record”
- High level of interest
- Helped to put together educational DVD
- Will remain engaged in protocol

Scaling up to Whole Genome

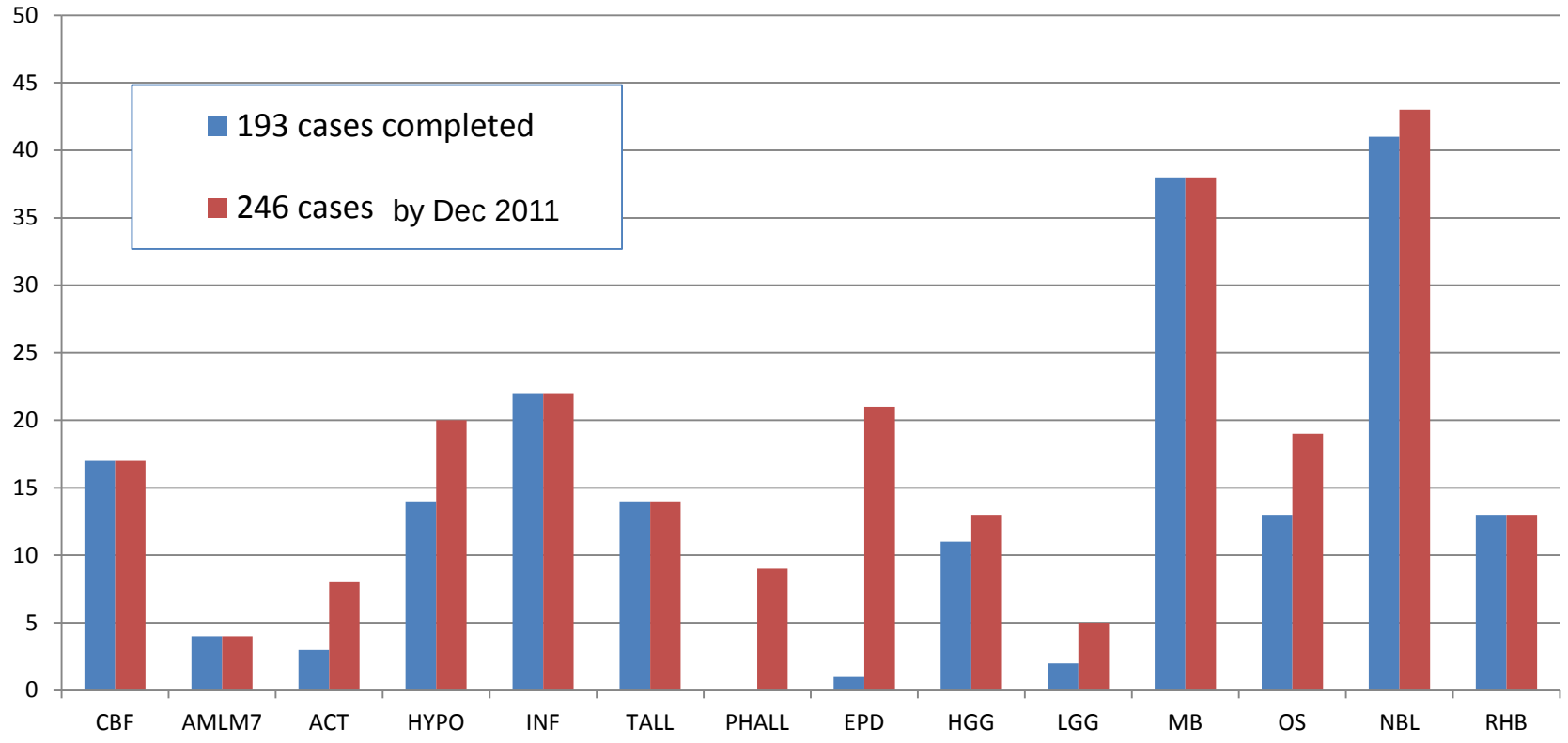
St. Jude Children's Research Hospital
ALSAC · Danny Thomas, Founder

Pediatric Cancer Genome Project

Washington University in St. Louis
School of Medicine

PCGP Steering Committee

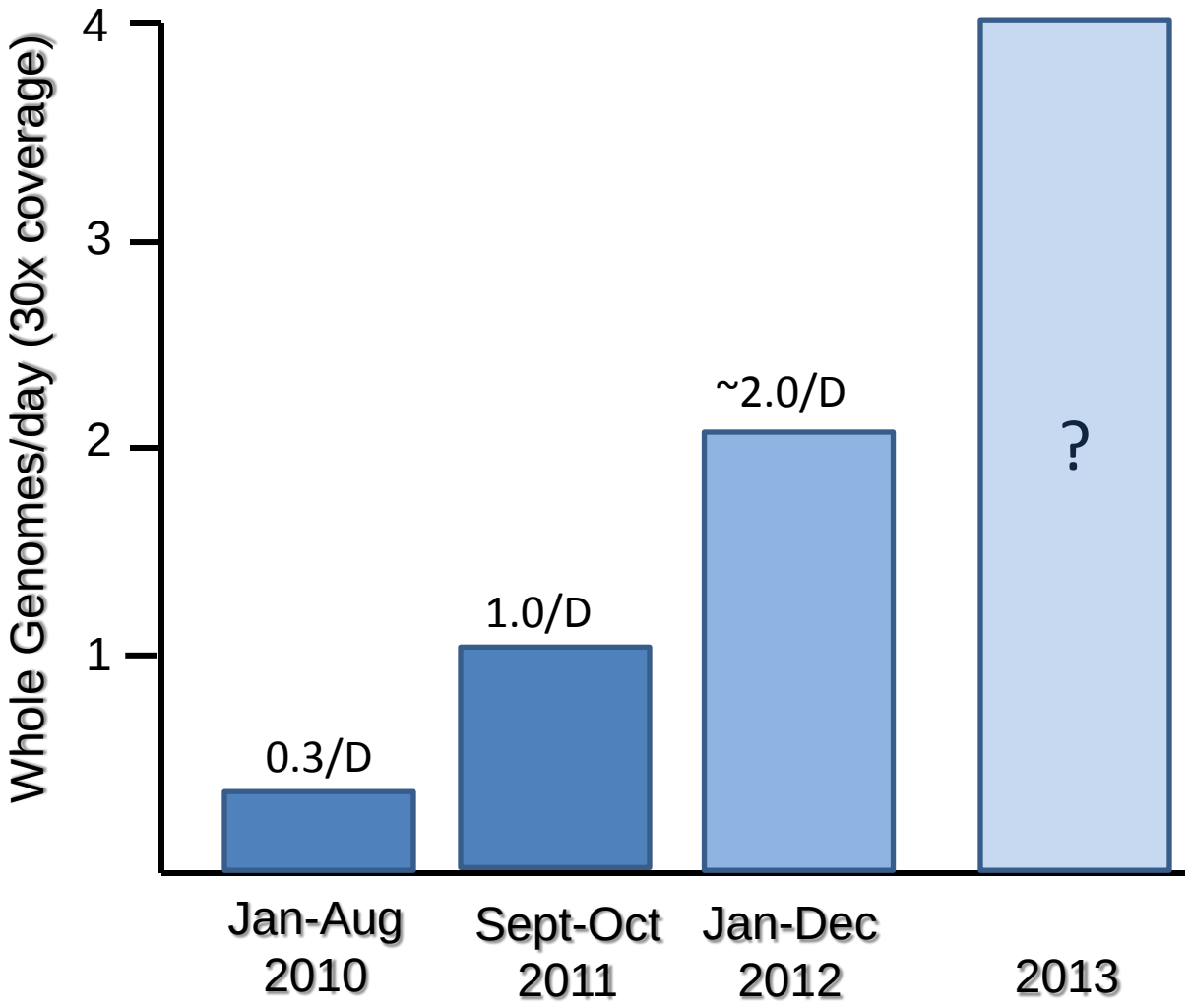
PCGP Whole Genomes Sequenced
(through Nov, 2011)



492 whole genomes in 2 years

The pace of sequencing is increasing, the cost is dropping

(Whole Genomes Sequenced per Day in PCGP)



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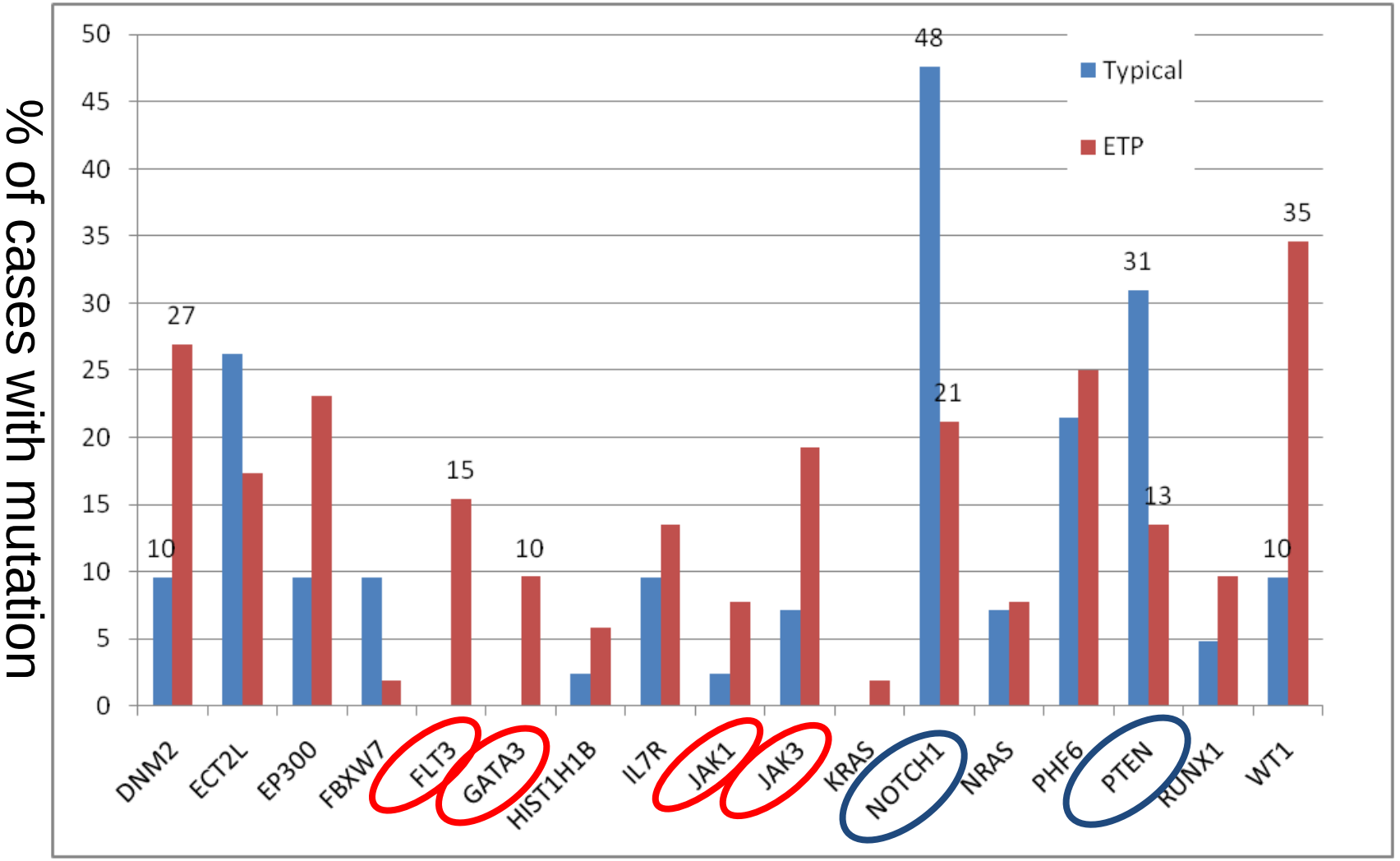
Different mutations in ETP vs T-ALL

Typical T-ALL (42 cases) and ETP ALL (52 cases)



Nature, in press 2011

How will we deal with >20K genes & >3M variants/pt? (e.g., WGS)

WGS (CLIA)

Research databases
(20K genes, ~3M SNPs/pt (~15% novel)

Firewall

What goes in?

Into EMR
Clinical Data repository

Where to from here?

Next 10 years:

Whole genome sequencing will be **feasible and affordable** (< $1000 per genome)

There will be steady **expansion** of valid pharmacogenomic traits

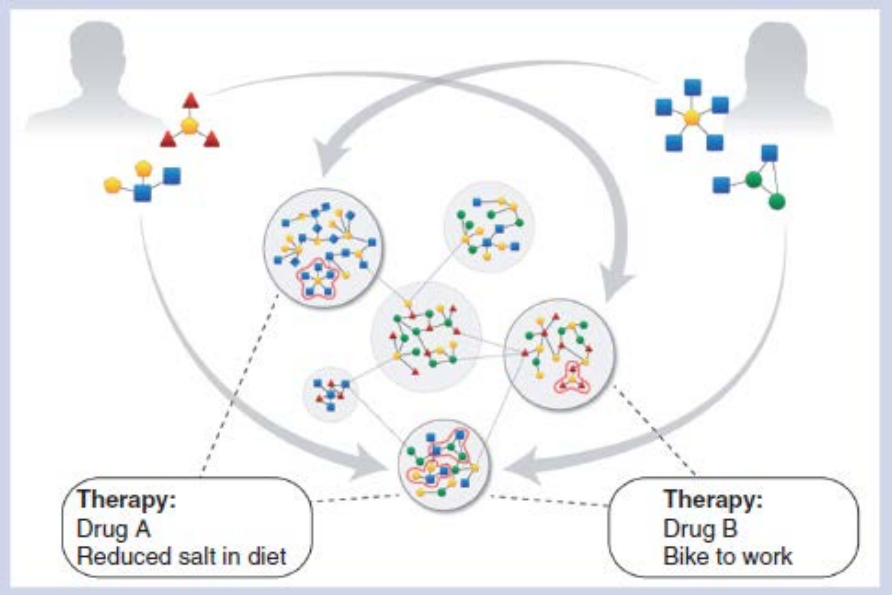
Increasingly, pharmacogenomic traits will be **polygenic** and **involve rare variants**

More **sophisticated polygenic models** will be required to define and translate

Medical, pharmacy a
knowledgeable of ge **nt…….**

There will therefore **perts** to
help translation succ

Genomics will be a **g** **eatment** decisions, but
never the only appro



E. Schadt, et al, 2011

SJ Pharmaceutical

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Kevin Hicks
James Hoffman
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Pam McGill
Emily Melton
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Paula Condy
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PG4KDS

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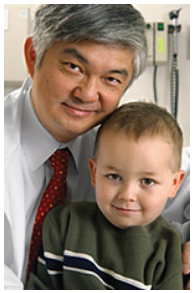
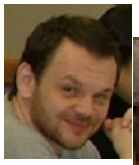
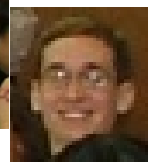
Finding cures. Saving children.

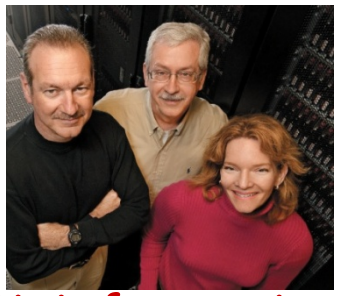
Medical College of Wisconsin

PGRN

Pharmacogenomics of ALL @ SJCRH
A TEAM SPORT

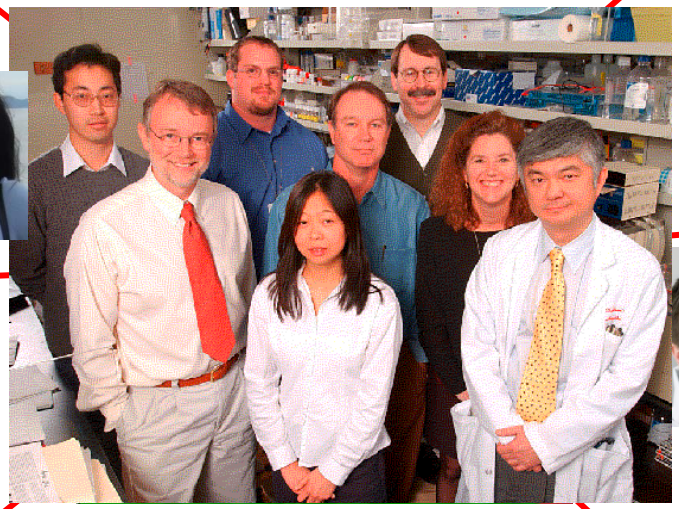



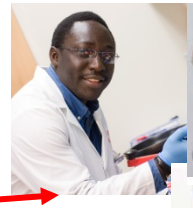


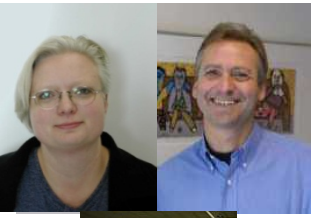
Faculty colleagues

Bioinformatics

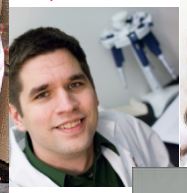


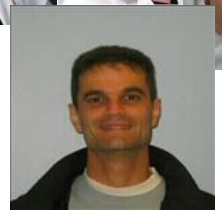




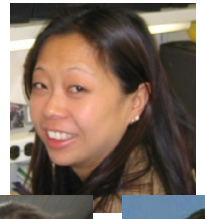
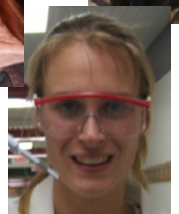
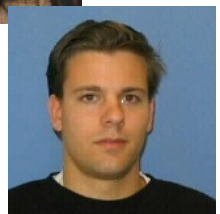






Post-docs




Students

Research RNs

PAAR4Kids

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