Institutional Leadership Perspective on Implementing Genomic Medicine Programs

William E. Evans
Director & CEO
St. Jude Children’s Research Hospital
Institutional Leadership Perspective on Implementing Genomic Medicine Programs

We started down this road at St. Jude in 1984...
We started using somatic genome variation to decide treatment in 1984.

1984-: Ploidy (>50 Chr)

1991-: BCR-ABL (t9;22)
MLL-AF4 (t4;11)
TEL-AML1 (t12;21)

2010-: FLT3 mutations (AML)
Germline Genome Variation can Influence ALL chemotherapy
Began @SJ with TPMT in the 1990's

Cum. Incidence Hematological Toxicity

V/V (TPMT genotype)

V/WT

WT/WT

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 Relling¹, EE Gardner¹, WJ Sandborn², K Schmiegelow³,⁴, C-H Pui⁵, SW Yee⁶, CM Stein⁷, M Carrillo⁸, WE Evans¹ and TE Klein⁸

Clin. Pharm. Ther., 2011
But the medical community remains skeptical...

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.

For more than 30 years, doctors have been using drugs to cure diseases. The late Gertrude Elion and George Hitchings—two scientists who had a huge impact on medicine—have 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.

U.S. Food and Drug Administration (FDA) seems unlikely to recommend one. The resistance has surprised champions of genomic medicine. A leader in the field, says, “The idea that this is a 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........

c.a. 1999
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)


At Least Two Genomes of Importance in Every Cancer Patient

Host Genome
- Systemic pharmacokinetics
- Drug toxicity (normal tissue)

Cancer Genome
- Cellular pharmacodynamics
- Drug sensitivity (tumor)
What are we doing to translate genomics into clinical practice @SJ?
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? **

<table>
<thead>
<tr>
<th>Category</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Care</td>
<td>$10M – 20M</td>
</tr>
<tr>
<td>Research</td>
<td>$150M – 200M</td>
</tr>
<tr>
<td></td>
<td>$160M – 220M</td>
</tr>
</tbody>
</table>

* Guesstimate of annual spend on genetics

Total annual operating budget $625M
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)

PAAR4Kids
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.

TPMT genotype data is recommended before using a thiopurine (mercaptopurine, thioguanine, and azathioprine). A TPMT genotype test result does not appear to be available for this patient. Please consider ordering a TPMT genotype test to help guide prescribing.
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.

**WARNING**

This patient has an active entry on the problem list for TPMT deficiency, the enzyme responsible for the metabolism of mercaptopurine, azathioprine, and thioguanine. Patients with TPMT deficiency MAY require REDUCED doses of these drugs, please refer to PK consult under PKN Tests tab regarding the correct dosage, or if necessary, page a Clinical Pharmacist.

**Alert Action**
- [ ] Cancel entry
- [ ] Dose altered accordingly
- [ ] Modify
***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
How and When to Take Genomics to Clinic?

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

2. Prioritization
   - Pleiotropy
     - Pathway analyses
     - Plausibility
     - Frequency
     - Generalizability
     - Effect size

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

4. Clinical Integration
   - PGRN consensus
   - Prospective trials
   - Routine patient care

PAAR4Kids: Pharmacogenomics of Anticancer Agents Research in Children

www.pharmacogenetics.org
Clinical Integration is independent of who made the discoveries and even of “the” disease state.

- PGRN consensus
- Prospective trials
- Routine patient care

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

- Other trials
- Other murine models
- Superoxide dismutase
- Inflammation

- Pleural effusion
- Pathologic
- Planning
- Frequency
- Generalizability
- Effect size
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MV Relling¹, EE Gardner¹, WJ Sandborn², K Schmiegelow³⁴, C-H Pui⁵, SW Yee⁶, CM Stein⁷, M Carrillo⁸, WE Evans¹ and TE Klein⁸

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

SA Scott¹, K Sangkuhl², EE Gardner³, CM Stein⁴⁵, J-S Hulot⁶⁷, JA Johnson⁸⁹¹⁰, DM Roden¹¹¹², TE Klein² and AR Shuldiner¹³¹⁴

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

JA Johnson¹, L Gong², M Whirl-Carrillo², BF Gage³, SA Scott⁴, CM Stein⁵, JL Anderson⁶, SE Kimmel⁷⁸⁹, MTM Lee¹⁰, M Pirmohamed¹¹, M Wadelius¹², TE Klein² and RB Altman²¹³

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**
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
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
• 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

- Determine eligibility for migrating individual test results

- **Initial Genes:**
  - *TPMT*
  - *CYP2D6*
The process

Pt enrolled

DNA genotyped

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

Most genotypes remain in research database

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

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

Ongoing evaluations of data by experts

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

Evaluation of decision support flags at least annually
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
**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 research participants and clinicians.
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 involves many factors. One key factor is the likelihood that the test results will influence the course of treatment. Ideally, tests should be moved into practice only if the test results consistently impact the choice of medication.
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 diplotype (their choice)
• Automated letter to PATIENTS [Parents] (their choice)
• General information and video on website
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 caregivers 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.

![Gene Metabolizer Chart]

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)

You are here
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

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

Scaling up to Whole Genome

PCGP Steering Committee

St. Jude Children's Research Hospital

Pediatric Cancer Genome Project

Washington University in St. Louis
School of Medicine
PCGP Whole Genomes Sequenced (through Nov, 2011)

193 cases completed
246 cases by Dec 2011

492 whole genomes in 2 years
The pace of sequencing is increasing, the cost is dropping

(Whole Genomes Seeded per Day in PCGP)
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

Process

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 and other health professionals will be more knowledgeable of genomics, but most will not be self-sufficient……

There will therefore continue to be a need for systems and experts to help translation successfully to the clinic

Genomics will be a growing component of diagnosis and treatment decisions, but never the only approach

E. Schadt, et al, 2011
SJ Pharmaceutical

Mary Relling
Kris Crews
Shane Cross
William Evans
Christian Fernandez
Cyrine Haidar
Kevin Hicks
James Hoffman
Nancy Kornegay
Pam McGill
Emily Melton
Alejandro Molinelli
Colton Smith
Cathy Suggs
Mark Wilkinson
Wenjian Yang

SJ Biostatistics

Alicia Huettel
Cheng Cheng
Deqing Pei

St. Jude MDs

Paula Condy
Lisa Walters
Terri Kuehner
Sheri Ring
Shannon Gibbs

Scott Howard
Jerry Shenep
Ching-Hon Pui
Alberto Pappo
Sima Jeha
Aditya Gaur
Ulrike Reiss
Alicia Huettel

CPIC members

CPIC members

Teri Klein
Alan Shuldiner
Julie Johnson
Russ Altman
Dick Weinshilboum
Wolfgang Sadee

PG4KDS

MCW

Keith Kunkel
Don Baker
Charlie Hurmiz
Kiran Bobba

PG4KDS

ED

PG4KDS

PGRN
Pharmacogenomics of ALL @ SJCRH
A TEAM SPORT