Introduction to Pharmacogenomics for Clinicians: *Pharmacogenomics of Adverse Drug Reactions*  

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1. Clinical trials provide evidence of efficacy and safety at usual doses in *populations*.
99.9% identical
No one size fits all
99.9% identical

0.1% different

~3 million differences in each person
Paradox of Modern Drug Development

1. Clinical trials provide evidence of efficacy and safety at usual doses in populations

2. Physicians treat individual patients who can vary widely in their response to drug therapy

- Safe & Effective
- No Response
- Adverse Drug Reaction
Adverse Drug Reactions

- 5th leading cause of death in the USA
  - Over 100,000 fatal ADRs in hospitalized patients each year
  - Over 2,000,000 serious ADRs in hospitalized patients (6.7%)/yr

- ADRs cause 7% of all hospital admissions (UK)

- ADR Health care costs: $78-177 billion annually (USA)
  - Exceeds the annual cost of medications

- ADRs cause an average 2 day increase in hospital stays

- 95% of all ADRs are unreported
“12% of patients rushed to Vancouver General Hospital have adverse reactions to medications.”

50% of newly approved therapeutic health products have **serious ADRs**, discovered only after the product is on the market

(Health Canada, 2007)
ADRs in Children
Increased Risk of Severe ADRs in Children

- 11-15% of hospitalized children have an ADR\(^1-3\)
- ADRs cause 22% of admissions in pediatric cancer patients\(^4\)
- 30% of ADRs in hospitalized children are severe causing long-term disability or death\(^4\)
- 26,000 children die each year from ADRs in USA\(^5\)
- Gross lack of knowledge about ADRs in children

We Can’t Treat Children Like Adults

Increased Risk of Severe ADRs in Children

- >75% of approved drugs used in children are untested in pediatric populations
- Young children cannot evaluate or express their own response to medications
- Pediatric dosage forms not available
- Children metabolize drugs differently than adults
Patient genotype is currently an unknown factor in the prescribing of medicines.
How Can The Causes of Variability be Unraveled?
The Canadian Pharmacogenomics Network for Drug Safety

Michael Hayden & Bruce Carleton

**Hypothesis**

- Genetic polymorphisms in drug metabolism genes underlie a significant portion of concentration-dependent ADRs in children.

**Goal**

- To develop genotype-based dosing guidelines to predict safety and avoid severe ADRs in children.
Goal is to predict safety and avoid potential complications, not to make effective drugs difficult to obtain for patients.
ADR Surveillance
Over 95% of ADRs are not reported

2 studies identified patients being treated for drug-induced T.E.N. in burn units

Q: What % of these ADRs were reported?

4% ADR Reporting

2.5% ADR Reporting
Canadian Pharmacogenomics Network for Drug Safety

- CPNDS Active Surveillance Sites
- Canadian Pediatric Surveillance Sites
- C17 Pediatric Oncology Sites

Locations:
- VANCOUVER: Children's & Family Research Institute & B.C. Children's Hospital
- EDMONTON: Stollery Children's Hospital
- CALGARY: Alberta Children's Hospital
- WINNIPEG: Winnipeg Children's Hospital
- MONTREAL: Sainte-Justine Hospital
- OTTAWA: Children's Hospital of Eastern Ontario
- TORONTO: Hospital for Sick Children
- HALIFAX: IWK Grace Health Centre
- HAMILTON: Children's Hospital
- EDMONTON: Stollery Children's Hospital
- LONDON: Children's Hospital of Western Ontario
- CALGARY: Alberta Children's Hospital
- WINNIPEG: Winnipeg Children's Hospital
- LONDON: Children's Hospital of Western Ontario
- MONTREAL: Sainte-Justine Hospital
Recruitment of ADR Cases and Drug-Matched Controls
Genomic Analyses
Association Study

Patients with a specific, well-defined, severe ADR

Control Unaffected Patients that received same medication
Association Study

Patients with a specific, well-defined, severe ADR

Control Unaffected Patients that received same medication

Odds Ratio = 16
P value = 0.02
Gene Classification Examples

Phase I Metabolizing Enzymes: CYP1A1, CYP2B6, ALDH2
Phase II Metabolizing Enzymes: UGT2B7, GSTM1, NAT1, COMT
Receptors / Drug Targets: VDR, PPARG, CETP
Transporters: ABCB1, ABCC1, ABCC2
Transcription factors: HNF4A, STAT3, NR1I2
Immunity: HLA variants
Ion Channels: SCN5A, KCNH2, KCNQ1
Others: EPHX1, FMO1, PTGS1

ADME/Tox Genes SNP Arrays

Current: 3072 SNP array
Other options: 6144 to 1.1 million SNP arrays

1536 HapMap derived haplotype tag SNPs
1536 Altered enzyme activity common non-synonymous, literature validated rare non-synonymous, synonymous coding SNPs
Illumina SNP Genotyping

20 million beads on one slide
Illumina SNP Genotyping

DNA target capture probe affixed to bead:
50 bp complementary to SNP region
Illumina SNP Genotyping

Complementary DNA from Patient DNA bound to probe
Illumina SNP Genotyping

Single-nucleotide extension (biochemical reaction)

Bead
Slide

[G]

[G - C]
**Illumina SNP Genotyping**

- Single-nucleotide product fluorescently labeled
- Individual with “T” genotype at this site
Illumina SNP Genotyping

1.2M Chip (1.2 million SNPs)
2 Samples/Chip

[T/T]  [T/G]  [G/G]
Raw Fluorescence Intensity Data

SNP #1 (480 samples)

Genotype Text Output

SNP 1  AA
SNP 2  TT
SNP 3  GG
SNP 4  GC
30 replicate assays for each SNP
Raw SNP Data (n = 480)

Reproducibility >99.99%

- 16 miscalls out of 178,860 genotype calls (58 patient DNA replicates)
- 0 miscalls out of 50,688 genotype calls (16 control DNA replicates)
1 Sequencing Center (2004)

- 100 Sequencers
- Size: Factory
- 125 million bases/year
- 27 years to sequence 3.5 billion bases

1 High-Throughput DNA Sequencer (2009)

- Size: Bench-top
- 500 million bases/day/machine
- 1 week to sequence 3.5 billion bases
In Progress:

- Codeine-induced infant mortality
- Cisplatin-induced deafness
- Anthracycline-induced cardiotoxicity
- Life-threatening skin reactions
- Vincristine-induced neuropathy
- Statin-induced muscle toxicity
- Interferon-β toxicity
- Warfarin-induced bleeding/thrombosis
Codeine
The American Academy of Pediatrics and major authoritative texts list codeine as compatible with breastfeeding

– Briggs et al., 2005; Pediatrics, 2001
Codeine-Induced Adverse Reaction

Case Report

- A new mother was given Tylenol #3 for obstetric pain relief
  - Given a standard dose (60 mg every 12 hours)
- Mother complained of significant drowsiness
  - Codeine dose cut in half (30 mg every 12 hours)
- Infant showed poor feeding
- Infant died on day 13 due to respiratory failure

Follow-up Analysis:

- Maternal milk from last day of the baby’s life contained morphine at 10-20x higher levels than expected (87 ng/ml)
- Infant’s blood contained lethal levels of morphine (70 ng/ml)
Identified genetic variants associated with a lethal adverse reaction to codeine in newborns

Mother’s Genotype:
- **CYP2D6** gene duplication
- **UGT2B7*2/*2**

Outcome:
- Accumulation of morphine in breast milk (10-20x more than normal)
- Breast milk fed to infant
- Infant died at 13 days of age
- Lethal levels of morphine accumulated in the infant causing CNS depression, respiratory failure, and death

Infants exhibiting decreased alertness while breastfeeding from mothers taking codeine (n = 17 cases, 55 controls) (compared to the period after codeine was discontinued)

All infants with combined CYP2D6-UM and UGT2B7*2/*2 exhibited severe neonatal toxicity and required medical intervention.

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>O.R.</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6-UM (ultrametabolizer)</td>
<td>17.8%</td>
<td>1.8%</td>
<td>11.6</td>
<td>0.036</td>
</tr>
<tr>
<td>CYP2D6-UM + UGT2B7*2/*2</td>
<td>11.8%</td>
<td>0%</td>
<td>Infinity</td>
<td>0.050</td>
</tr>
</tbody>
</table>
FDA drug label change and public health advisories

Health Canada Public Advisory

Aug. 21, 2008

Estimated 1846 newborn infants are at risk for this codeine ADR each year in Canada

(340,000 births, 73% breastfed, 52% mothers receive codeine post-childbirth, 1.4% risk genotype)
Additional Cases of Infant Toxicity from Codeine from Literature

35 reports of breastfeeding infants with ADRs to codeine, including:
- Unexplained severe drowsiness
- Apnea
- Bradycardia
- Cyanosis
Currently Performing Randomized Controlled Trial

Prospective study to test the benefit of a diagnostic test to prevent codeine ADRs in infants

Study Design:

- **Prospective Screening for CYP2D6-UM Predictive Variants**
  - N = 300
  - Prospective Screening for CYP2D6-UM Predictive Variants
  - + Test
    - N = 12 (est.)
    - Receive Ibuprofen or Naproxen post-partum
  - - Test
    - N = 288 (est.)
    - Standard Care: Receive codeine & monitoring for CNS depression ADR

- **Control Group** (standard care)
  - N = 300
  - Control Group (standard care)

- **Standard Care:**
  - Receive codeine & monitoring for CNS depression ADR

- **Compare Outcomes**
  - Adverse events
  - Adequate pain relief?
  - Cost of ADRs
  - Hospitalization
  - Cost of care
  - Cost of Screening
  - Outcome of therapy/survival
  - Treatment Compliance
  - Validity of Diagnostic Test

- **Retrospective genetic screening for CYP2D6-UM**
ADRs in Chemotherapy
Cancer Survival has Improved, but Survivors often Left with Lifelong Consequences of Severe ADRs

82% of children beat cancer

Survivors are often left with lifelong health consequences
By KRISTEN THOMPSON
April 10, 2008 02:24

More children are surviving cancer than ever before, according to statistics released yesterday by the Canadian Cancer Society. But experts are finding that survival often carries lifelong health consequences.

Seven-year-old Casey Wright, from Maple Ridge, is among the 82 per cent of children diagnosed with cancer who survive thanks to progress in treatments — an 11 per cent increase in the past 15 years.

But he also represents the two-thirds of survivors who have to live with chronic or late-occurring health effects.

Casey Wright, 7, hugs his sister Jemma, 9, during lunch hour yesterday at Maple Ridge elementary as their mother, Kim, discusses his recovery from a malignant brain tumour.
Pediatric Oncology:

- 1 in 750 young adults are survivors of childhood cancer

- 75% of cancer survivors suffered at least 1 ADR

- 40% of cancer survivors have had a severe ADR (life-threatening, or disabling)

- 25% of cancer survivors suffer 5 or more ADRs

Geenan et al, *JAMA*, 2007
Pharmacogenomics

- Avoid adverse drug reactions
- Maximize drug efficacy for individual patients

All Patients with Same Diagnosis

10% risk of adverse reaction

Pharmacogenetic Profile:

- **High risk of ADR (50%)**: treat with alternative drug or dose
- **Moderate risk of ADR (12.5%)**: treat with alternative drug or dose, or increased monitoring
- **Low risk of ADR (0%)**: treat with conventional dose
Canadian Pharmacogenomics Network for Drug Safety

CPNDS Active Surveillance Site

Canadian Pediatric Surveillance

C17 Pediatric Oncology Sites
Bedside-to-Bench-to-Bedside

- Patients & Clinicians
- Commercialization Committee
- ADR Surveillance
- PGx Research Core
- PK & Functional Validation Core
- Knowledge Translation Core
- Knowledge Dissemination
- Ethical, Legal, Social Issues
- Health Economics
- Training
- ADR-Associated Markers
- ADR Diagnostic Test
- ADR Test
- Ethical, Legal, Social Issues
- Bedside-to-Bench-to-Bedside
Canadian PGx Network for Drug Safety

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