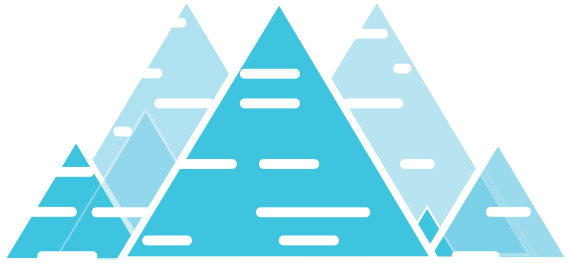


PERSONALIZED MEDICINE

SUMMIT

TRANSFORMING THE PRACTICE OF MEDICINE

June 7-9th 2015, UBC, Vancouver, BC

Be part of the Personalized Medicine Revolution

personalizedmedsummit.com

#PMSummit2015

Development of pharmacogenomic predictors of severe adverse drug reactions to chemotherapy from the treatment of pediatric cancer.

Colin Ross, MSc PhD

University of British Columbia, Assistant Professor

Depts. of Paediatrics and Medical Genetics, Div. Translational Therapeutics

Scientist, Child & Family Research Institute

CIHR New Investigator

Canada Foundation for Innovation
Fondation canadienne pour l'innovation

GenomeBritishColumbia

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

Canadian Gene Cure Foundation
Fondation Canadienne Gène Cure

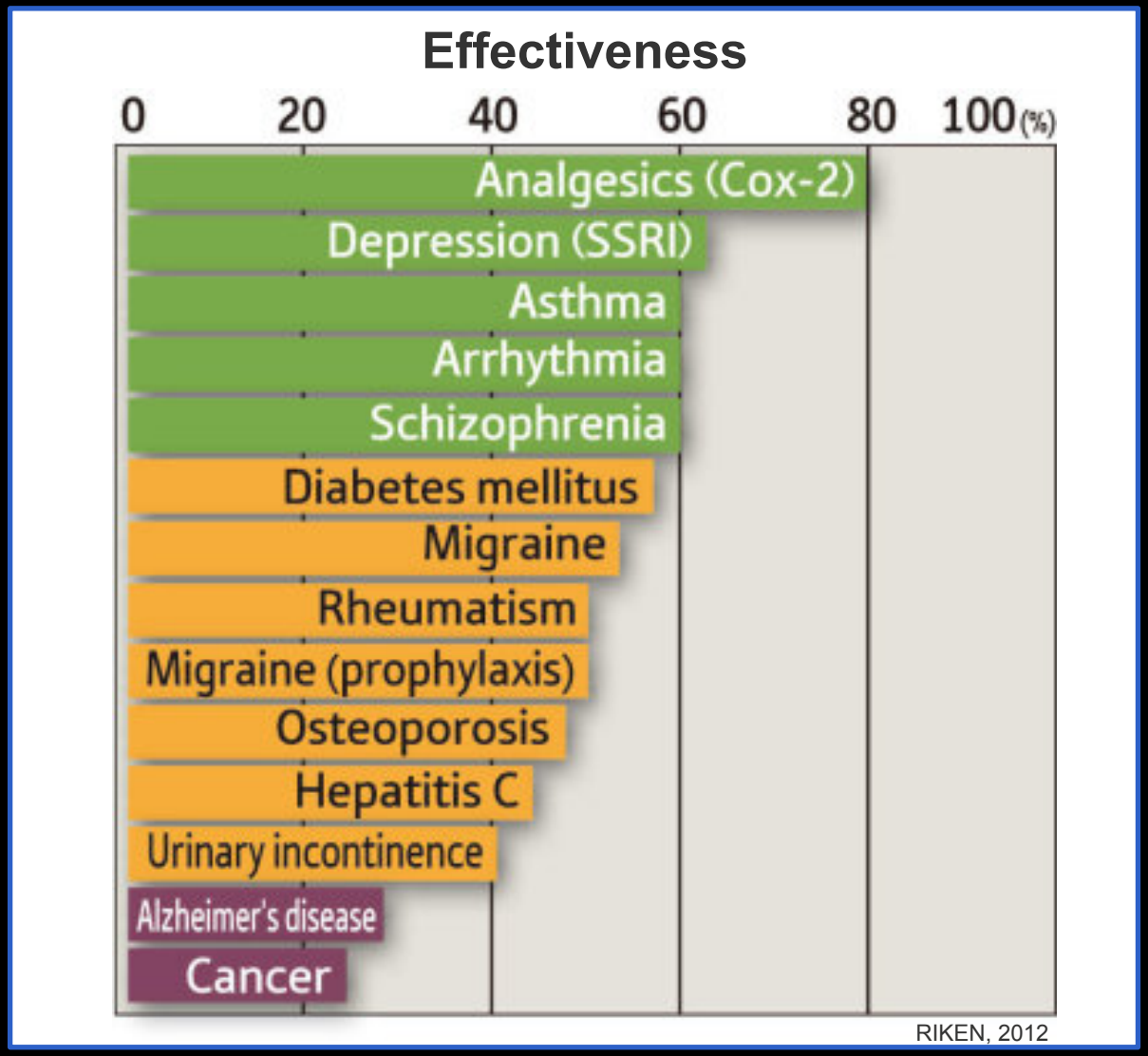
NIH
National Institutes of Health

The Ideal Medication

Effectively treats or prevents disease

Has no adverse effects

Medications are Not Effective in All Patients



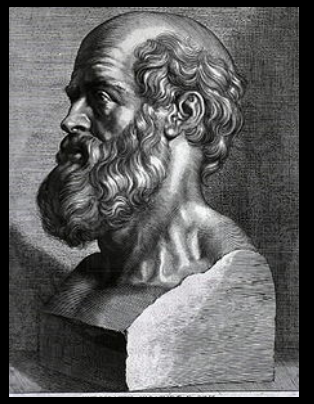
In susceptible patients, medications can cause severe adverse drug reactions (ADRs)

Stevens-Johnson Syndrome (SJS)

Personalized Medicine ➡ Genomic Medicine

- **Hippocrates (370 BC)**

  "Different [medications] for different patients, for the sweet ones do not benefit everyone, nor do the astringent ones, nor are all the patients able to drink the same things"



- **Paracelcus (1541 AD)**

  "All things are poison and nothing is without poison, only the dose permits something not to be poisonous."

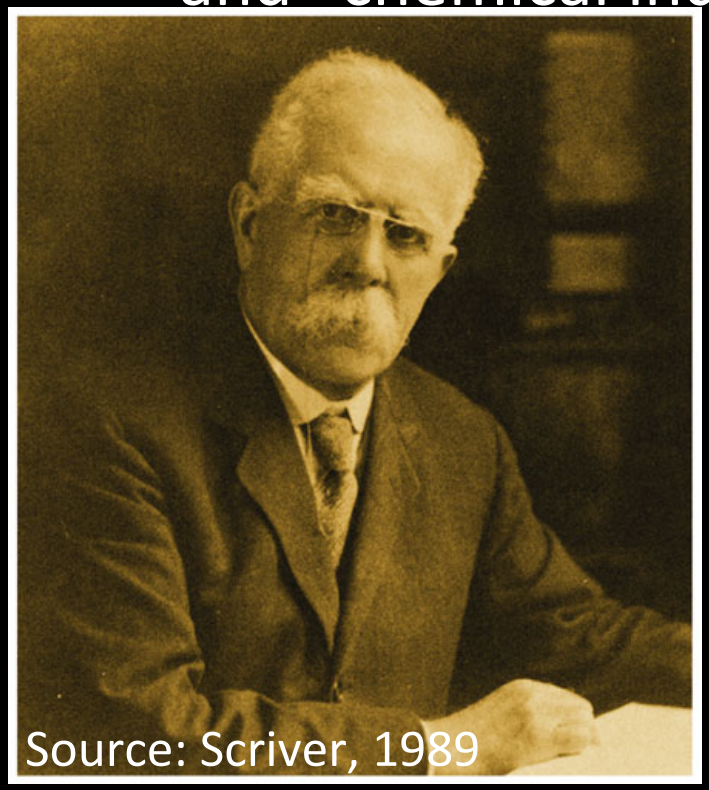
- **Sir William Osler (1849-1919)**

  "If it were not for the great variability among individuals, medicine might as well be a science and not an art."

  "The good physician cares for the disease, the great physician cases for the patient."

Sir Archibald Garrod (1857-1936)

- Successor to Osler at Oxford
- "Father of Biochemistry, Inborn Errors of Metabolism"
- "Pioneer of Pharmacogenetics", and "chemical individuality" (1902)



Source: Scriver, 1989

"Every active drug is a poison when taken in large enough doses; and in some subjects a dose which is innocuous to the majority of people has toxic effects, whereas others show exceptional tolerance of the same drug"

Genomic Medicine

Incorporate genomic information to improve the safety and effectiveness of patient treatment

Strategies for Genomic Medicine

- Gene-Targeted Therapeutics
- Diagnostic Genome-Sequencing
- Identify Good Responders To a Medication
- Identify Patients at High Risk of an ADR

Strategies for Genomic Medicine

Gene-Targeted Therapeutics

Diagnostic Genome-Sequencing

Identify Good Responders To a Medication

Identify Patients at High Risk of an ADR

Glybera®

- "Road-block buster"

Important Factors:

- Extreme (severe)
- Focused program

Strategies for Genomic Medicine

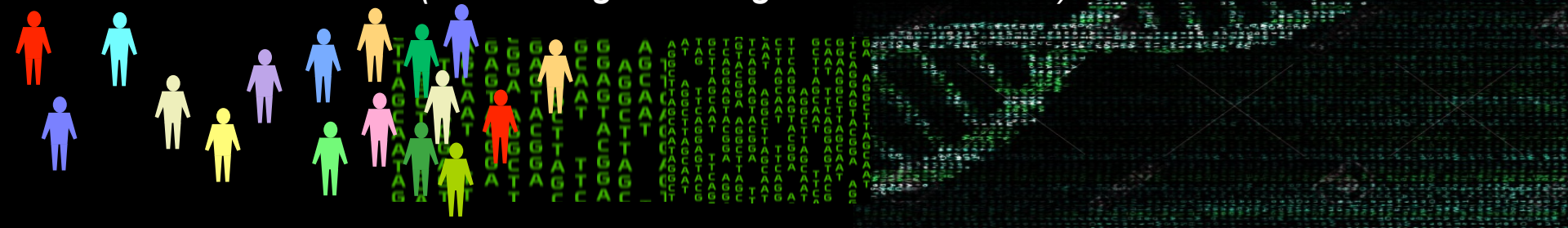
Gene-Targeted Therapeutics	**Diagnostic Genome-Sequencing**	Identify Good Responders To a Medication	Identify Patients at High Risk of an ADR

TIDE BC

CAUSES Clinic

Pilot Clinical Genome Sequencing Program for BC Children's Hospital

(TIDE Program Diagnosis Rate: 89%)



Strategies for Genomic Medicine

Gene-Targeted Therapeutics	Diagnostic Genome-Sequencing	**Identify Good Responders To a Medication**	Identify Patients at High Risk of an ADR

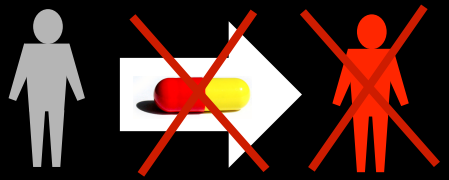
Strategies for Genomic Medicine

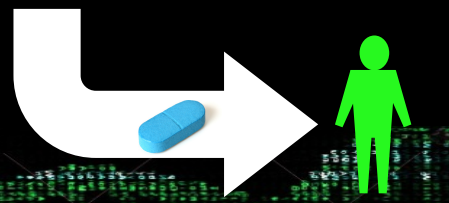
Gene-Targeted Therapeutics

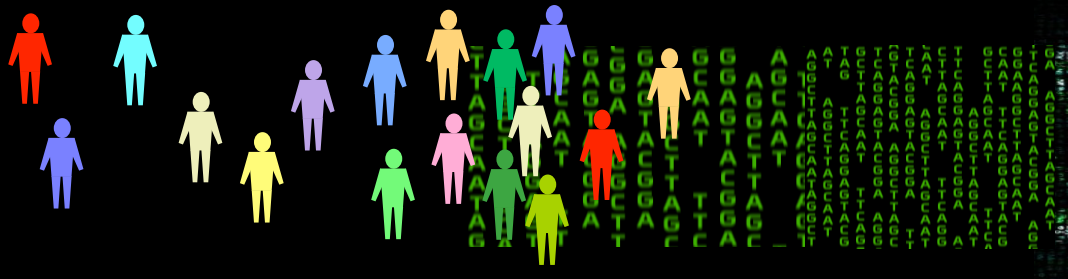
Diagnostic Genome-Sequencing

Identify Good Responders To a Medication

Identify Patients at High Risk of an ADR







Genomic factors can predict who will develop an adverse drug reaction

Stevens-Johnson Syndrome (SJS)

The NEW ENGLAND JOURNAL of MEDICINE

HLA-A*3101 and Carbamazepine-Induced Hypersensitivity Reactions in Europeans

Mark McCormack, B.A., Ana Alfirevic, M.D., Ph.D., Stephane Bourgeois, Ph.D.,
John J. Fa
Graeme J. S
Pa
Maria
G
Saud Alh
Erin L. Hei
Werner Pi
Sa
Panos Delo

4 May 2000 international weekly journal of science

nature

A marker for Stevens–Johnson syndrome

Stevens–Johnson syndrome and the related disease toxic epidermal necrolysis are life-threatening reactions of the skin to particular types of medication[1–3]. Here we show that there is a strong association in Han Chinese between a genetic marker, the human leukocyte antigen *HLA–B*1502*, and

Genomic factors can predict who will develop an adverse drug reaction

Stevens-Johnson Syndrome (SJS)

The NEW ENGLAND JOURNAL *of* MEDICINE

HLA-A*3101 and Carbamazepine-Induced Hypersensitivity Reactions in Europeans

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nature

International weekly journal of science

4 May 2000

A marker for Stevens–Johnson syndrome

Stevens–Johnson syndrome and the related disease toxic epidermal necrolysis are life-threatening reactions of the skin to particular types of medication[1–3]. Here

nature publishing group — ARTICLES

HLA-A*31:01 and HLA-B*15:02 as Genetic Markers for Carbamazepine Hypersensitivity in Children

U Amstutz[1–3], CJD Ross[1,3,4], LI Castro-Pastrana[5], MJ Rieder[6–8], NH Shear[9], MR Hayden[4], BC Carleton[1–3] and the CPNDS Consortium

- **High predictive (Odds Ratios >10)**
- **Phenotyping critical**
- **Do not require thousands of patients to identify predictive genomic factors**

ADRs are a significant problem in the treatment of cancer

Canada: > 700,000 cancer survivors
USA: > 10,000,000 cancer survivors

- 75% of cancer survivors suffer $\geq$ 1 ADR
- **40% of cancer survivors have a severe ADR (life-threatening, or disabling)**

1. Geenan et al, *JAMA*, 2007
2. Mitchell et al, 1988

Anthracycline chemotherapy-induced heart toxicity

Anthracyclines

- e.g., Daunorubicin, Doxorubicin,
- Highly effective cancer therapy
- Significantly increased childhood cancer survival rates
- Today, administered to 60-70% of childhood cancer patients (leukemias & solid tumors)
- Adults: breast cancer, sarcoma, lymphoma, leukemia, and others
- Over 900,000 patients receive each year

Case Report from Dr. Rod Rassekh

- Previously healthy 8-year-old child presented with neuroblastoma to B.C. Children's Hospital

- Began doxorubicin chemotherapy

Case Report

- Previously healthy 8-year-old child presented with neuroblastoma to B.C. Children's Hospital

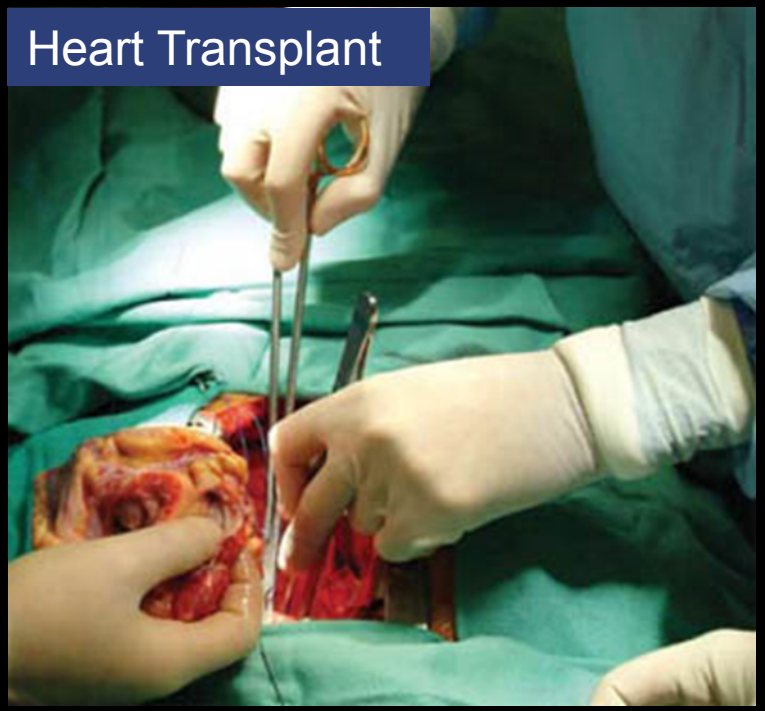
- Began doxorubicin chemotherapy
- Prior to last cycle of treatment, visited B.C. Children's Hospital for routine CT scan, but became unwell during scan

Case Report

- During CT scan:
  - Developed serious cardiac dysfunction with virtually no cardiac output
- Intubated and rushed to ICU
- Placed on extracorporeal membrane oxygenation (ECMO) for 3 weeks
- 1 year later received a heart transplant
- First transplanted heart rejected
- Child received a second heart transplant
- Currently in cancer remission

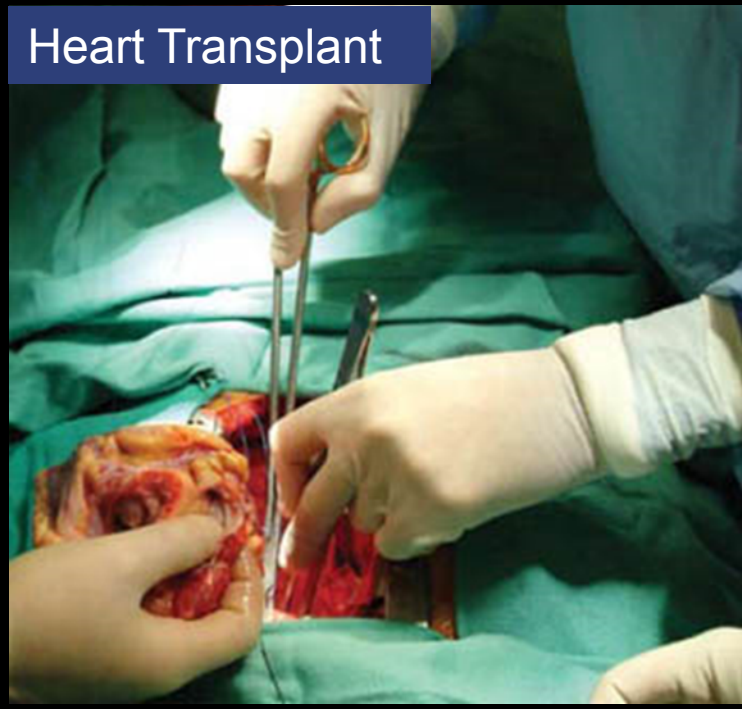
ECMO Unit

Heart Transplant



Anthracycline-Induced Cardiotoxicity

- **Since 1967, recognized that anthracyclines can cause fatal cardiac toxicity** (Tan et al., *Cancer*, 1967)
- **5-16% of patients suffer serious cardiomyopathy and heart failure**
  - **Toxicity can occur at low doses <100 mg/m²**
  - **While some patients tolerate >1000 mg/m²**
- **May require intra-ventricular assist device or heart transplant**
- **Increased severity in children, especially less than 4 years old**
- **72% mortality rate for severe cases (BC Cancer 2010)**



Kremer et al. *N Engl J Med*. 2004; Canadian Cancer Statistics 2007; Mariotto et al. *J Natl Cancer Inst*. 2002

Why does one patient develop cardiotoxicity, while another patient does not?

Strategy to Identify Genomic/Clinical Factors of Drug Response

Identify children with ADRs & matched controls → Collect DNA samples (blood/ saliva) → Detailed patient clinical character-ization → Genomic Analyses to identify ADR risk variants → Replication & Functional Validation

ADR cases

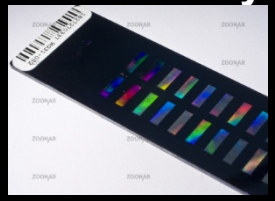
Matched controls

Patient blood/ saliva

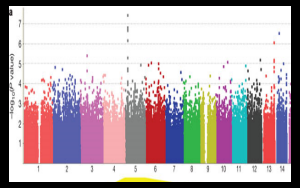
Patient charts

Clinical data

Custom GWAS Array



Statistical Analyses



Fine-Mapping & Imputation

Replication:

ADR cases & controls → Statistical Analyses

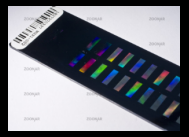
Functional Validation:

In vitro, in vivo analyses → Assay drug response

Study Design

Stage 1 Discovery → **740k Genome-wide Array** → **Stage 2 Replication** → **Stage 3 Replication** → **Functional Validation**

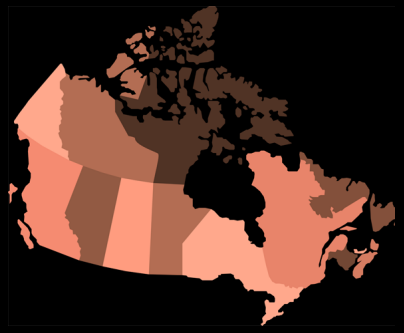
Canadian patients of European Ancestry



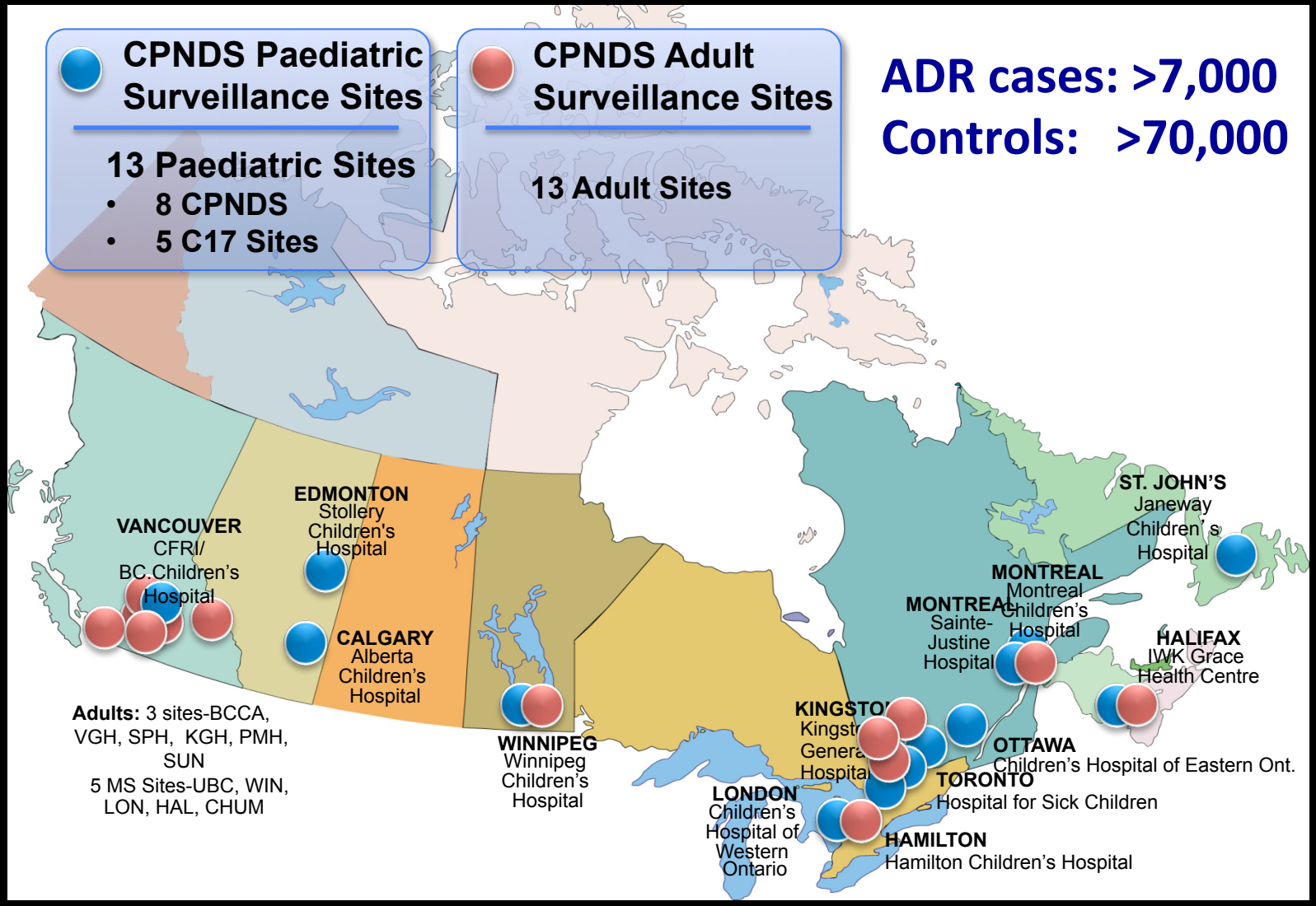
Dutch patients of European Ancestry

Patients of Worldwide Ancestries

Cell models



Stage 1: Canadian Discovery Cohort
CPNDS ADR Surveillance Network



Dr. Bruce Carleton, UBC, CFRI

Classification of Anthracycline-Cardiotoxicity

Controls n=383

- **No cardiotoxicity,** SF ≥30%, ≥5yr follow-up

- **Grade 1 toxicity**:
  - Shortening fraction 27-30% or

ADR Cases n=73

- **Grade 2 toxicity**: **Moderate to Severe cardiotoxicity**
  - Shortening fraction ≤ 24% or
- **Grade 3 toxicity**: **Symptomatic congestive heart failure**
  - Shortening fraction < 15% or
- **Grade 4 toxicity: Congestive heart failure requiring heart transplant or ventricular assist device**
  - Resting ejection fraction < 20%

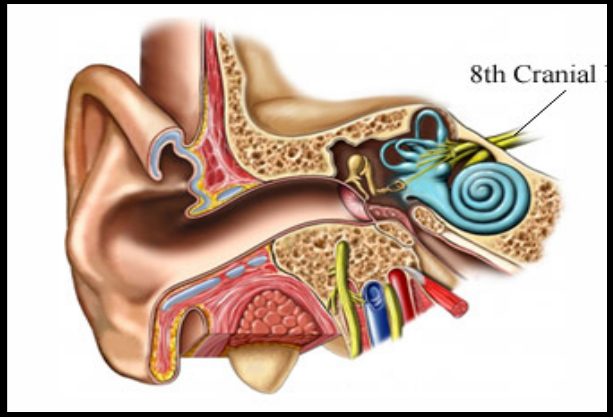
Modified National Cancer Institute Common Terminology Criteria for Adverse Events v3.0
With modified Grade 1 from 24-30% SF to 27-30% SF

Cisplatin-induced hearing loss

Cisplatin-induced Hearing Loss

- Cisplatin is a widely used chemotherapeutic agent for the treatment of solid tumours
  - Highly effective in both adults and children

- Limitations for clinical application:
  - Nephrotoxicity
  - Neurotoxicity
  - **Severe bilateral hearing loss**
    - 10-25% of adults
    - 40-60% of children



- Sensorineural hearing impairment
  - Permanent and progressive
  - Lifetime cost: $400,000 to $500,000 per patient for grade 3-4 hearing loss

Candidate-Gene Studies of Cisplatin-induced Ototoxicity identified variants in *TPMT, COMT, ABCC3*

ADME Panel: 220 Genes (~2000 SNPs)
Captures genetic variation in key genes involved in drug absorption, distribution, metabolism, excretion (ADME) and toxicity

A) Discovery, Replication #1 (n=162)

Genetic variants in *TPMT* and *COMT* are associated with hearing loss in children receiving cisplatin chemotherapy

Colin J D Ross[1,2,11], Hagit Katzov-Eckert[1,2,11], Marie-Pierre Dubé[3], Beth Brooks[4], S Rod Rassekh[5], Amina Barhdadi[3], Yassamin Feroz-Zada[3], Henk Visscher[1,2], Andrew M K Brown[3,6], Michael J Rieder[7], Paul C Rogers[5], Michael S Phillips[3,6], Bruce C Carleton[2,8,9] Michael R Hayden[1,2] & the CPNDS Consortium[10]

Ross et al. *Nature Genetics* (2009)

B) Replication #2 (n=155)

Replication of *TPMT* and *ABCC3* Genetic Variants Highly Associated With Cisplatin-Induced Hearing Loss in Children

K Pussegoda[1,2], CJ Ross[1,2,3], H Visscher[1,2], M Yazdanpanah[1,2,4], B Brooks[5], SR Rassekh[2,6], YF Zada[7], M-P Dubé[7], BC Carleton[2,3,8], MR Hayden[1,2] and the CPNDS Consortium

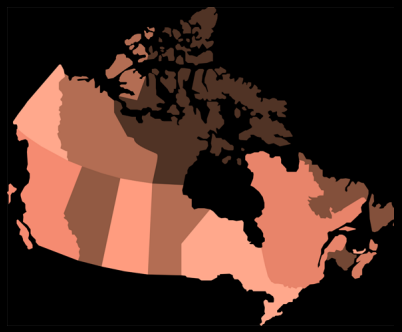
Pussegoda et al. *Clinical Pharmacology and Therapeutics* (2013)

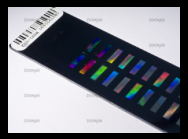
Can we identify additional genetic variants involved in cisplatin-induced hearing loss in children using a genome-wide analysis approach?

Study Design

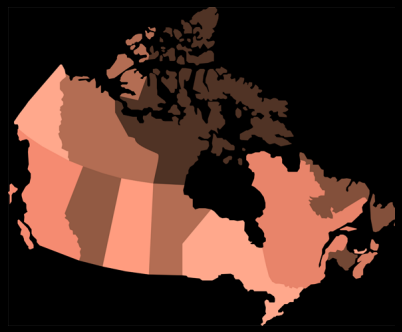
Stage 1 Discovery → **740k Genome -wide Array** → **Stage 2 Replication** → **Functional Validation**

Canadian patients





Canadian patients



Cell models

Implementation of a Pilot ADR Prevention Program in British Columbia

Genome BritishColumbia

Provincial Health Services Authority
Province-wide solutions. Better health.

Implementation of a Pilot ADR Prevention Program in British Columbia

Implementing Pharmacogenetic Testing for:

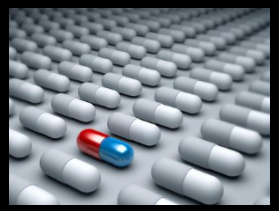
- Anthracycline-induced heart failure
- Cisplatin-induced deafness

Site: B.C. Children's Hospital

Bruce Carleton, UBC/CFRI/BCCH
Rod Rassekh, BCCH/CFRI/UBC
Colin Ross, UBC/CFRI
Paul Rogers, BCCH/CFRI/UBC
George Sandor, BCCH
Francois Dionne, UBC
Michael Hayden, UBC/CMMT/CFRI
Michael Rieder, UWO
Claudette Hildebrand
Pediatric Oncologists of B.C.

Overview of Project

1. **Developed clinical practice guidelines.**
2. **Implemented an ADR prevention program for two predictive pharmacogenetic tests** at the Regional Cancer centres across B.C. beginning at B.C. Children's Hospital.
3. **KEY GOAL: To determine how the PGx tests are perceived and utilized by patients, physicians, and families** before and after administration of the test.
4. Evaluating the **cost-effectiveness** of the pharmacogenetic tests.
5. Lay the groundwork for a **pharmacogenomic ADR prevention** program.



Potential Clinical Options for Personalized Anthracycline Therapy

Depending on predicted risk, clinicians can take different actions:

Low Risk

- Echocardiogram follow-up as usual

Intermediate Risk

- Intensify echocardiogram follow-up

  e.g. patients in rural centres often miss appointments

High Risk

- Alternative medication (e.g. mitoxantrone) or dose
- Add cardioprotectant (e.g. dexrazoxane)
- Begin early treatment with ACE-inhibitors or beta-blockers to prevent further damage

Summary

- Identified genetic variants that are predictive of anthracycline-cardiotoxicity
- Identified genetic variants that are protective against cisplatin-hearing loss
- Functional studies to validate the mechanistic basis of these ADRs and explore new interventions
- Pilot implementation program ongoing in B.C.

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Previous Lab Members:
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Michael Rieder, UWO
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Edmonton: Paul Grundy, Kent Stobert, Bev Wilson, Sunil Desai, Linda Churcher, Terence Chow
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