

Is It Time for Personalized Medicine in Patient Care?

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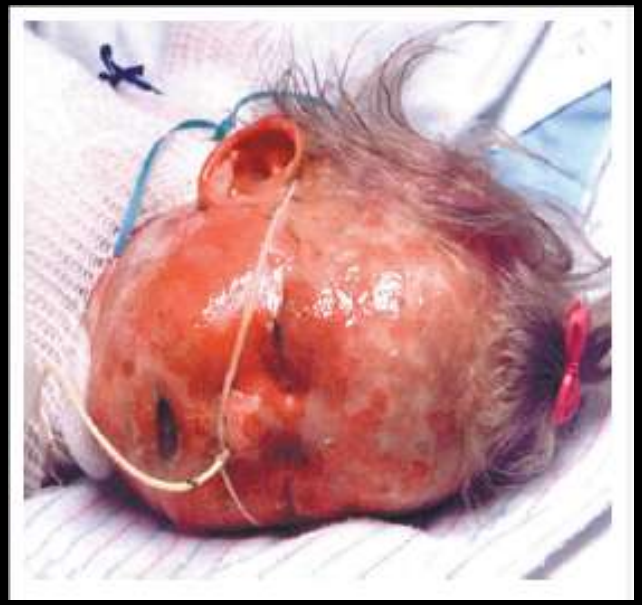
Individual variability in drug response can have serious consequences



Stevens-Johnson Syndrome (SJS)
Adverse Drug Reaction

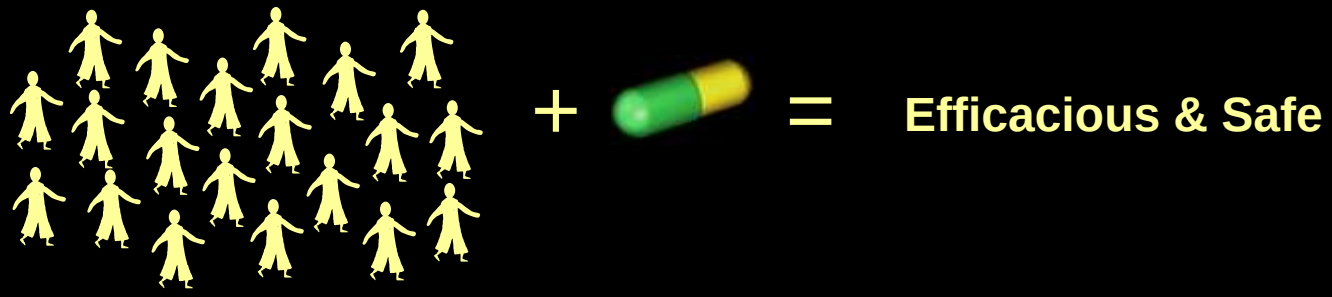
Adverse Drug Reactions

- 4-6th leading cause of death in the USA[1]
- Health care costs: $137-177 billion annually (USA)[2-3]
- Cause 7% of all hospital admissions[4]
- Cause serious reactions in over 2,000,000 hospitalized patients (6.7%) each year in the USA[1]
- Cause fatal reactions in over 100,000 hospitalized patients each year in the USA[1]
- **50%** of newly approved therapeutic health products have ***serious ADRs,*** discovered only after the product is on the market (Health Canada, 2007)
- **95%** of all ADRs are unreported

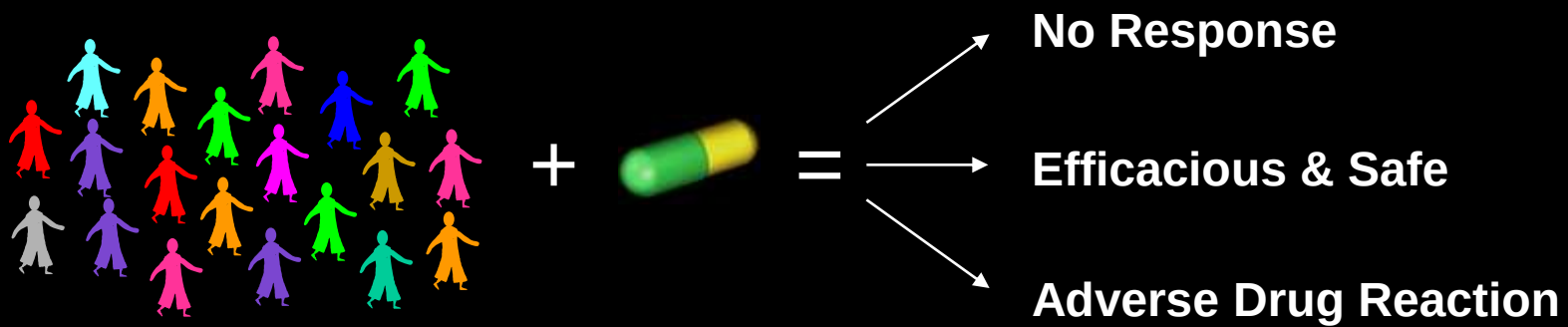
1. Lazarou et al, *JAMA*, 1998
2. Johnson et al, *Arch Intern Med* 1995
3. Ernst et al, *J. Am. Pharm. Assoc*. 2001
4. Pirmohamed et al, *BMJ*, 2004
5. MjoÈrndal et al, EACPT3, 1999
6. Moore et al., 2007

Paradox of Modern Drug Development

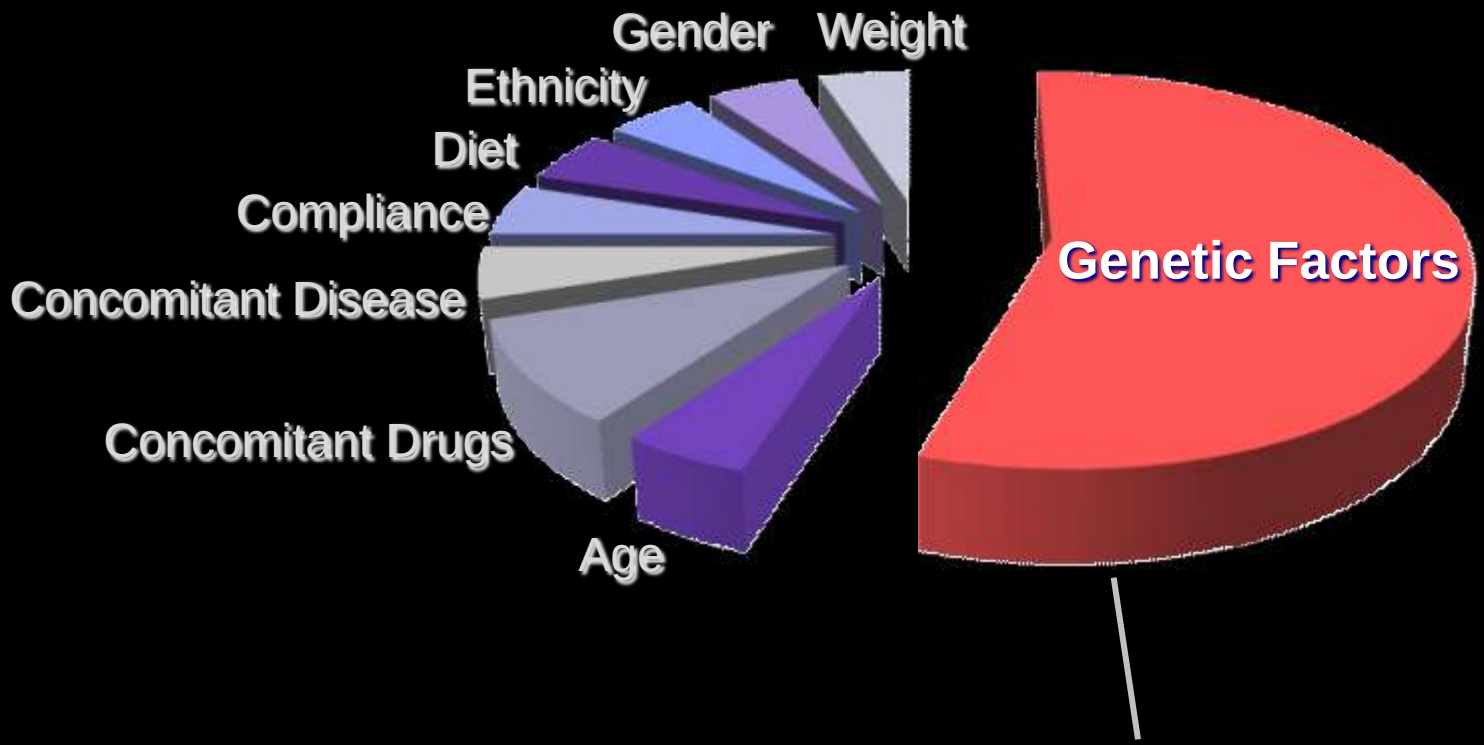
1. Clinical trials provide evidence of efficacy and safety at <u>usual doses</u> in ***populations***



2. Physicians treat ***individual*** patients who can <u>vary widely</u> in their response to drug therapy



Factors Contributing to Variability in Drug Response

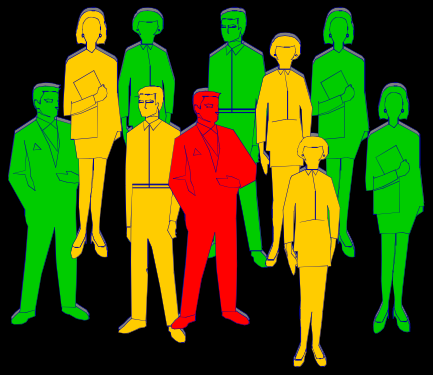


Patient genotype is currently an unknown factor in the prescribing of medicines

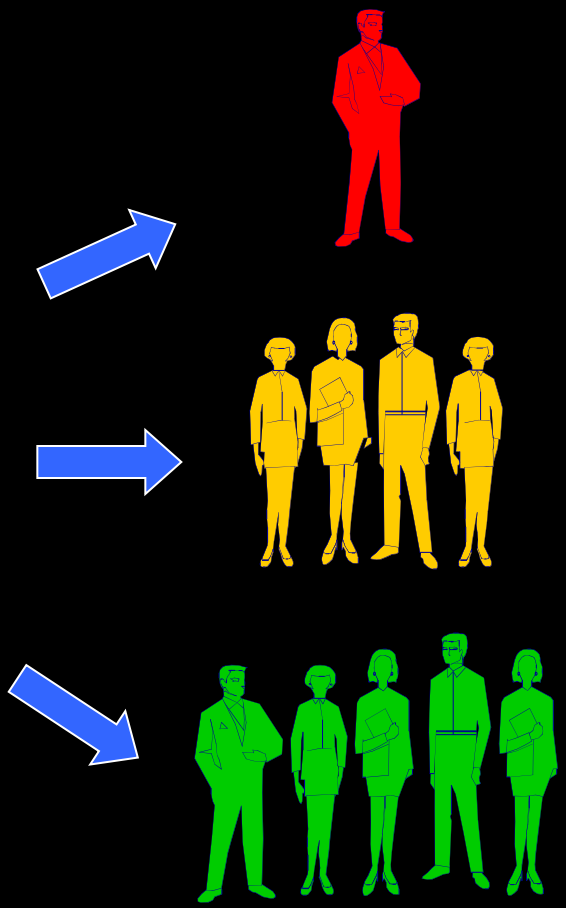
Pharmacogenomics

- 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

Low risk of ADR (0%):

treat with conventional dose

Health Systems Need to Move Us from Serious Medical Problems to Solutions

Research and Development Methods/Outputs

- Identify patients with ADRs
- Identify ‘matched’ patients on same medications, without ADRs
- Look for genetic variation in key drug biotransformation genes
- Inform new-drug development
- Develop new dosing guidelines
- Focus on drug outcomes – benefit AND risk

The Canadian Pharmacogenomics Network for Drug Safety (CPNDS) Plan

Hypothesis

- Genetic polymorphisms in drug biotransformation genes underlie a significant portion of concentration-dependent ADRs

Goal

- To develop genotype-based dosing guidelines to predict harm and avoid severe ADRs

CPNDS Biomarker Discovery Strategy

1. Identify patients with ADRs & matched controls

2. Collect DNA samples (blood/ saliva)

3. Detailed patient clinical character-ization

4. Screen genetic variants

5. Replication

ADR cases

Matched controls

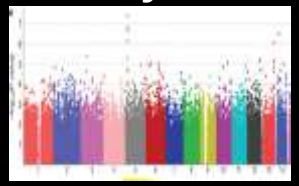
Patient blood/ saliva

Patient charts

Clinical data

Custom ADME Array

Statistical Analyses

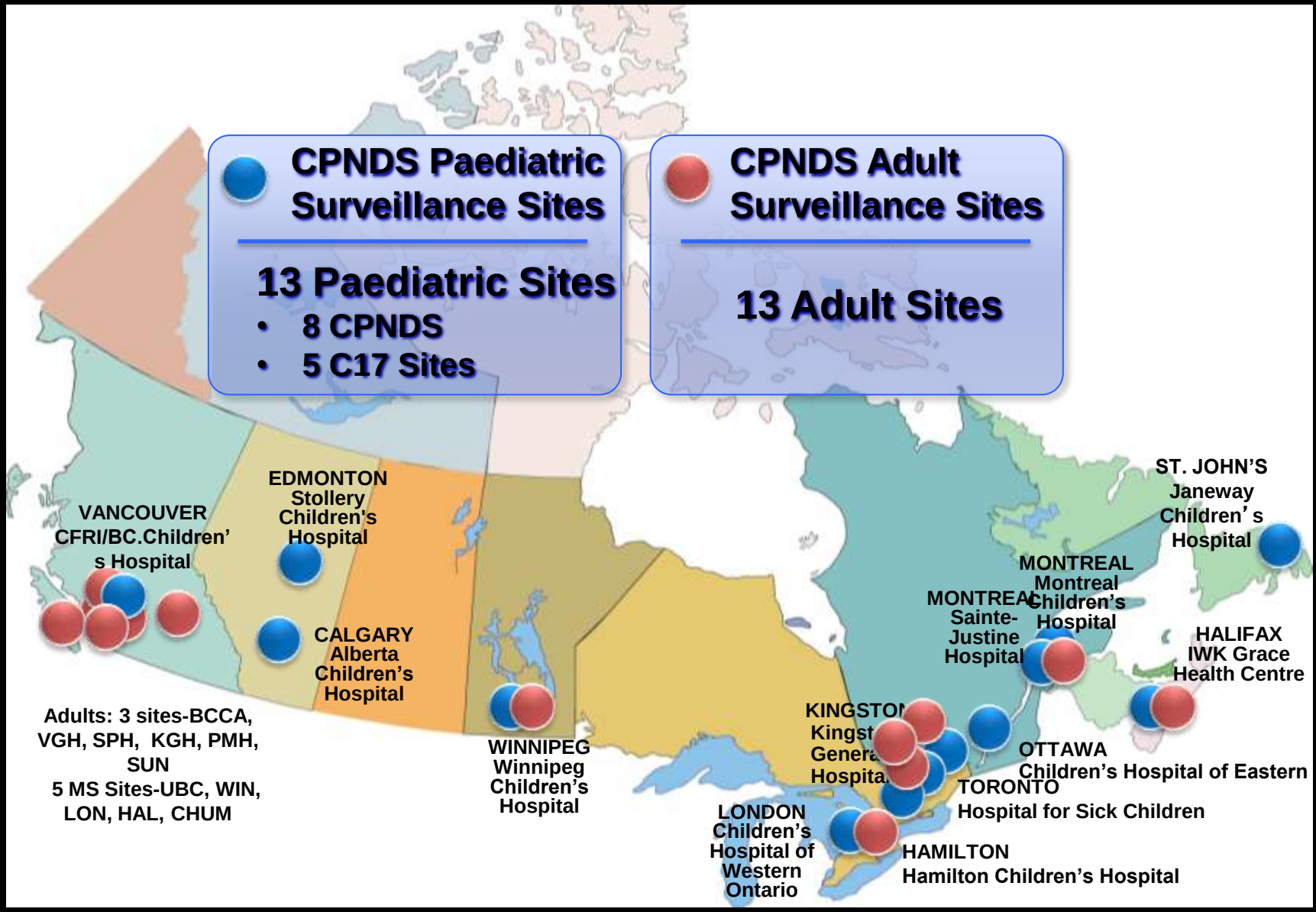


ADR cases & controls

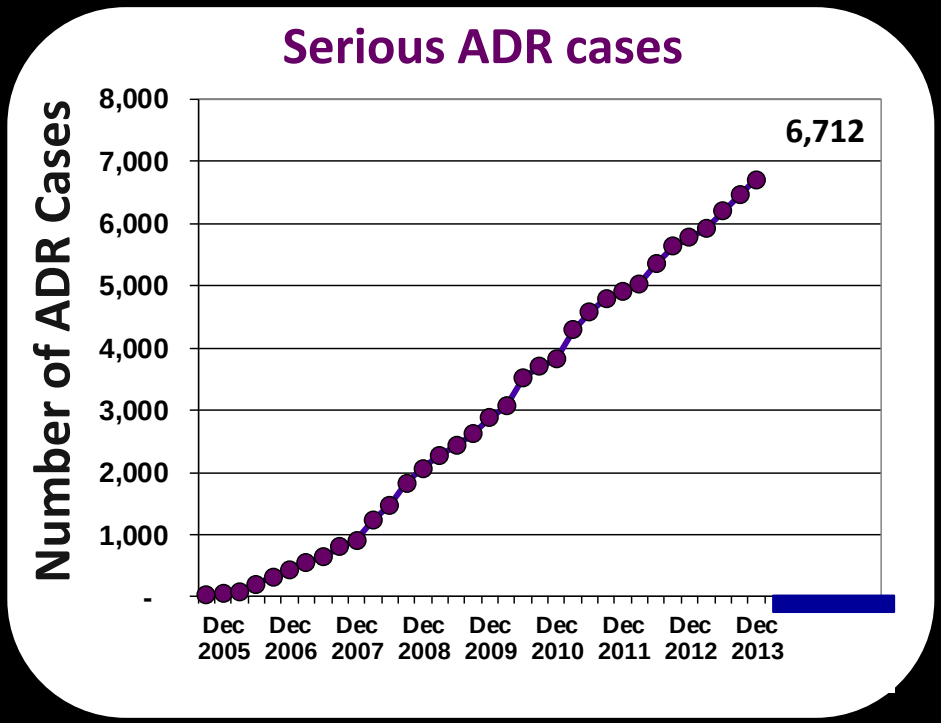
Assay DNA samples

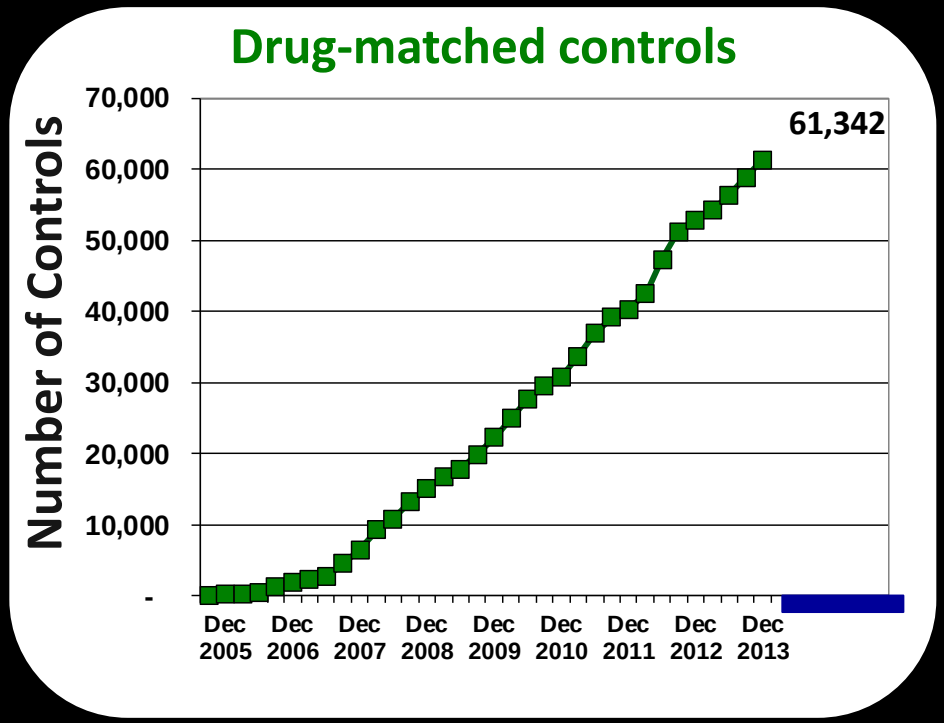
Statistical Analyses

CPNDS Network in Canada



Recruitment of ADR cases and drug-matched controls





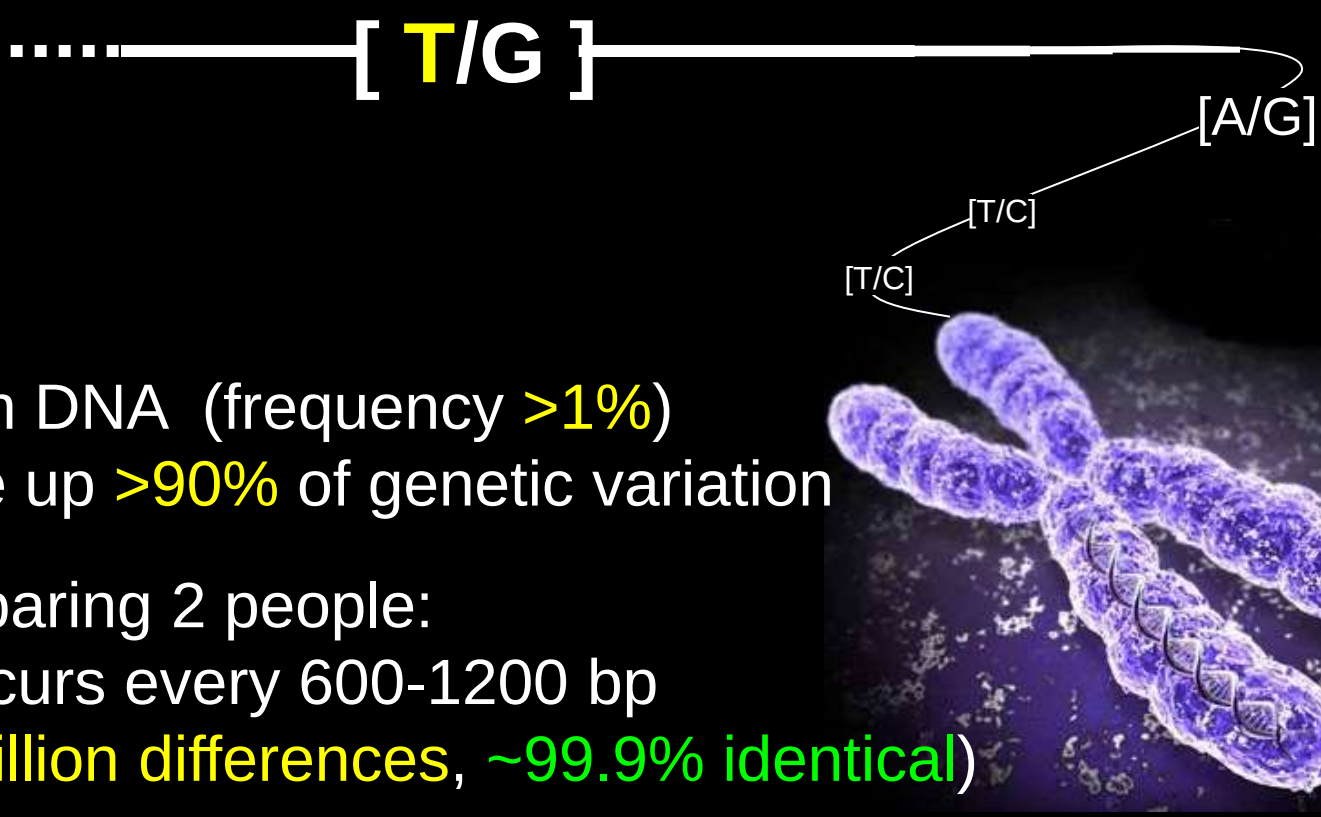
>6,700 ADR cases

>61,000 drug-matched controls

Could take 4-5 hours, or up to 4-5 days to complete clinical characterizations

We are 99.9% genetically identical

Single Nucleotide Polymorphisms (SNP)



- Variations in DNA (frequency >1%)
- SNPs make up >90% of genetic variation
- When comparing 2 people:
  1 SNP occurs every 600-1200 bp
  (= 5-10 million differences, ~99.9% identical)
- 14.7 Million known SNPs (January 2009)
- SNPs can alter the amino acid sequence of the encoded protein as well as alter RNA splicing and transcription
- New technology can test > 24 million SNPs per day

Illumina Sentrix™ Array Matrix

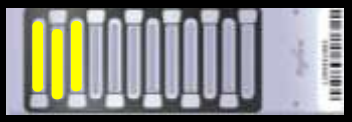
ADME/Tox Genes SNP Arrays

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

Versions:

Initial: **2k ADME SNP panel *(220 genes)***

Phase II: 4.6k ADME *(300 genes)*
or 1.2M genome-wide scan



Current: 10k ADME & 2.5-5M+ arrays
Genome Sequencing

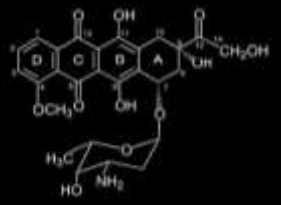
Anthracycline Case Report

- A previously healthy 10-year-old presented with abdominal mass
- Biopsy confirmed neuroblastoma
- Patient began standard doxorubicin chemotherapy protocol
  - Cumulative dose: 300 mg/m^2

Case Report

- A previously healthy 10-year-old child presented with neuroblastoma to B.C. Children's Hospital
- Began doxorubicin chemotherapy
- Prior to last cycle of treatment, child became unwell during a routine CT scan at BC Children's Hospital
  - Intubated and rushed to ICU
  - **Developed serious cardiac dysfunction, virtually no cardiac output**
  - **Child placed on extracorporeal membrane oxygenation (ECMO)** ***(heart-lung machine)***
  - **Child received a heart transplant**
  - **First transplanted heart rejected**
  - **Child received a second heart transplant**
- Child is currently cancer remission

Anthracyclines



- Doxorubicin, Epirubicin, Daunorubicin, Idarubicin
- Administered to 70% all childhood cancer patients
- Adjuvant chemotherapy for 50-90% of breast cancer
  - 22,000 patients/year in Canada
- At least **970,000 patients** receive each year (N. America)

Highly effective

- Introduction of anthracyclines contributed to improved childhood cancer survival: from 30% in 1960s to >80% today


NDC 63323-101-61 100161
DOXOrubicin HCl
INJECTION, USP
200 mg (2 mg/mL)
FOR IV USE ONLY
STERILE, ISOTONIC SOLUTION
100 mL
Multiple Dose Vial
Rx only
Preservative Free
Discard unused portion.
Each mL contains: Doxorubicin hydrochloride 2 mg; sodium chloride 9 mg for isotonicity; Water for Injection q.s. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment.
Usual Dosage: Before administering, read insert for complete prescribing and product information.
WARNING: Severe cellulitis, vesication and
NDC 63323-883-30 88330
DOXOrubicin HCl
INJECTION, USP
50 mg (2 mg/mL)
FOR IV USE ONLY
STERILE, ISOTONIC SOLUTION
25 mL
Single Dose Vial
Rx only
NDC 63323-683-10 88310
DOXOrubicin HCl
INJECTION, USP
20 mg (2 mg/mL)
FOR IV USE ONLY
STERILE, ISOTONIC SOLUTION
10 mL
Single Dose Vial
Rx only
NDC 63323-883-05 88305
DOXOrubicin HCl
INJECTION, USP
10 mg (2 mg/mL)
FOR IV USE ONLY
STERILE, ISOTONIC SOLUTION
5 mL
Single Dose Vial
Rx only

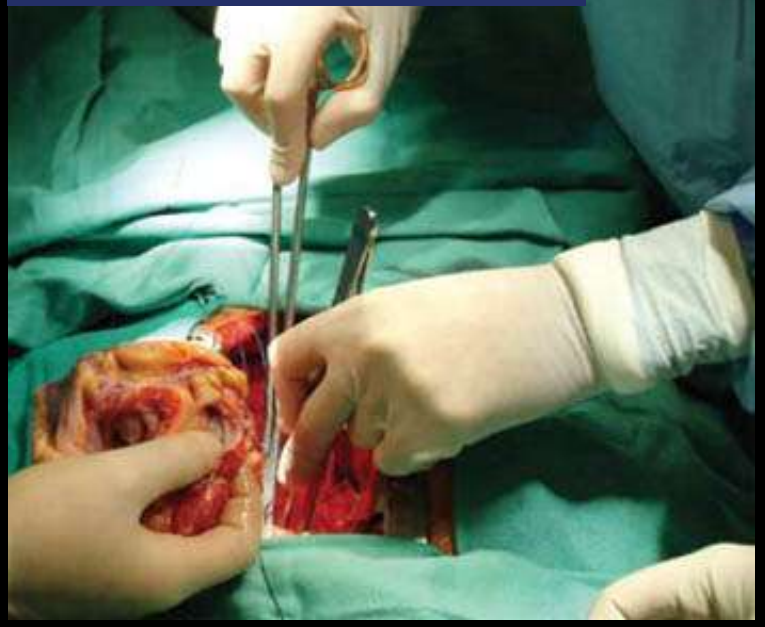
Anthracycline-Induced Cardiotoxicity

- 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 doses <300 mg/m^2
  - While some patients tolerate >1000 mg/m^2
- 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 Agency 2010)

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

ECMO Unit

Cardiac Transplant



Anthracycline-induced Cardiotoxicity

- Most important risk factor is high cumulative dose
- However there is no absolute safe dose
- Large inter-individual variability suggests genetic susceptibility

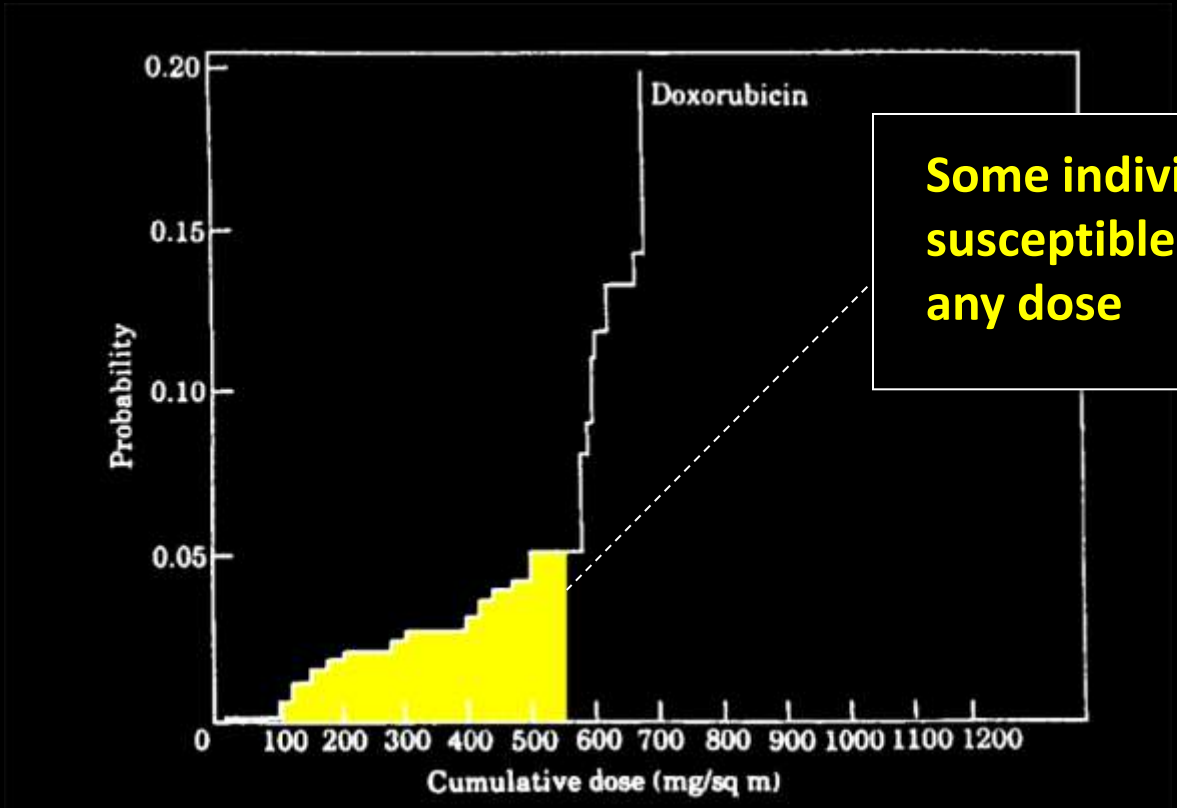


Figure adopted from: Launchbury & Habboubi. *Cancer Treat Rev*. 1993;19(3):197-228

Wouters et al. *Br J Haematol.* 2005;131(5):561-78
Lipshultz et al. *Heart*. 2008;94(4):525-33

Classification of Anthracycline-Cardiotoxicity

Controls n=266

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

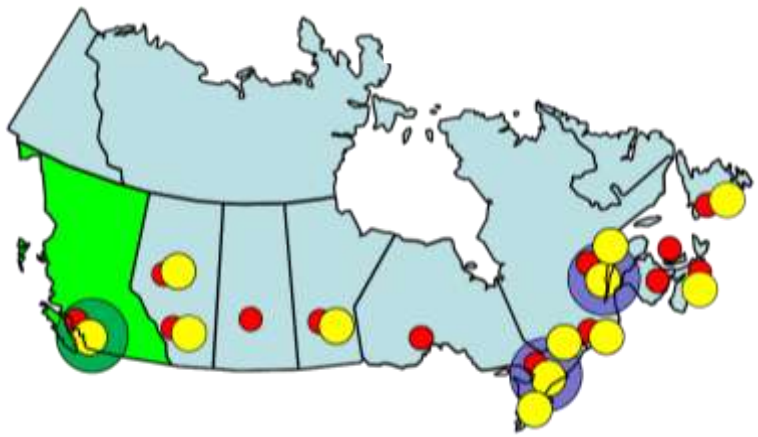
- **Grade 1 toxicity:**
  - Shortening fraction 27-30% or
  - Resting ejection fraction 50-60%

ADR Cases n=78

- **Grade 2 toxicity: Moderate to severe cardiotoxicity**
  - Shortening fraction < 15% or Shortening fraction 15-26%
  - or resting ejection fraction 40-50%
- **Grade 3 toxicity: Symptomatic congestive heart failure**
  - Shortening fraction < 15% or
  - Resting ejection fraction < 40%
- **Grade 4 toxicity: Congestive heart failure requiring heart transplant or ventricular assist device**
  - Resting ejection fraction < 20%

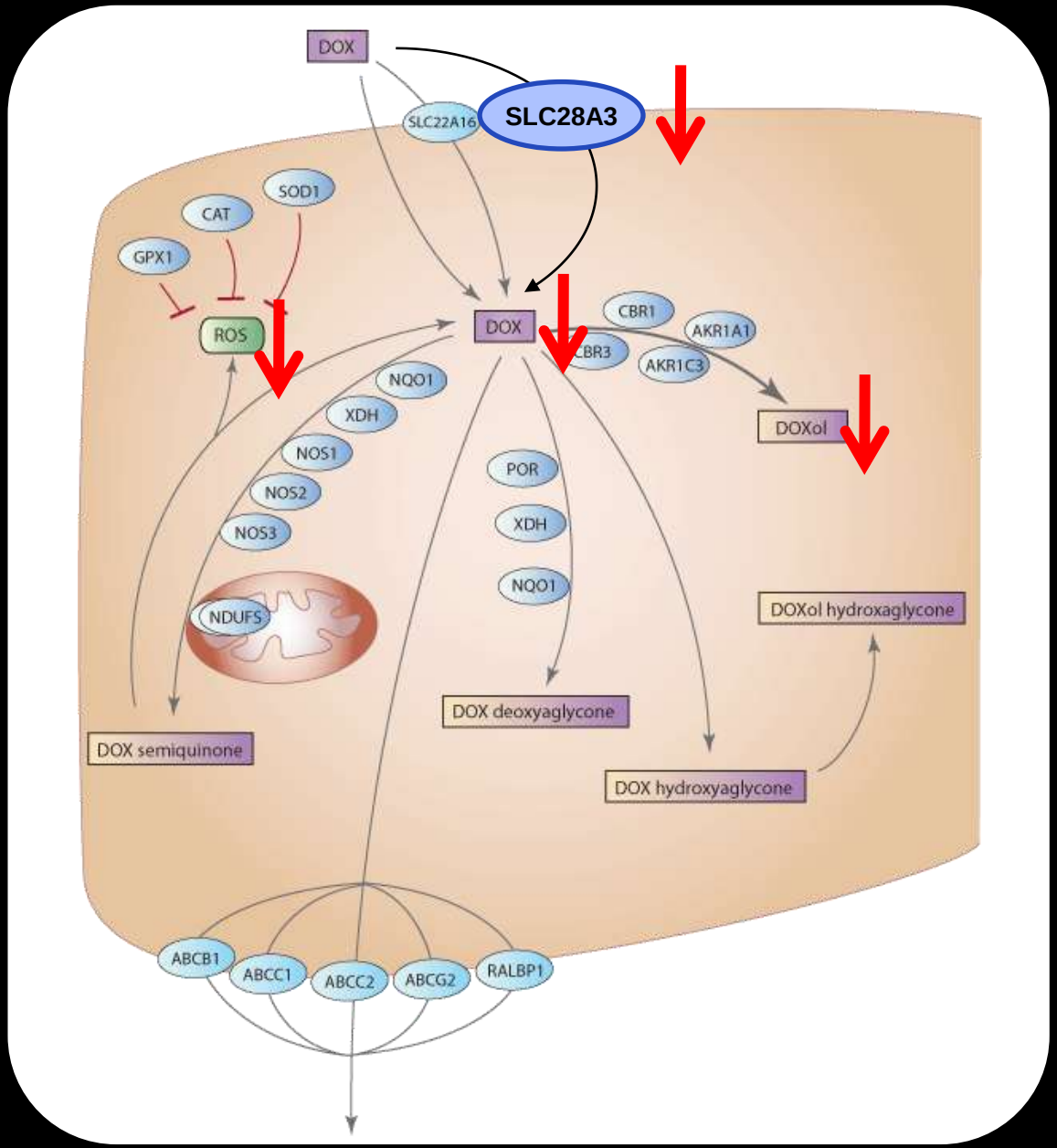
Modified National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 *With modified Grade 1 from 24-30% SF to 27-30% SF*

Replication of *SLC28A3* in a third independent Dutch cohort from Amsterdam



Gene	Discovery OR	Discovery P-value	Canada Replication OR	Canada Replication p-value	Dutch Replication OR	Dutch Replication p-value	Combined OR	Combined p-value
SLC28A3 L461L	0.29	0.0071	0.33	0.0072	0.46	0.05	0.36	1.6 E-5
	n = 156		n = 188		n = 177		n = 521	

Potential mechanism of SLC28A3



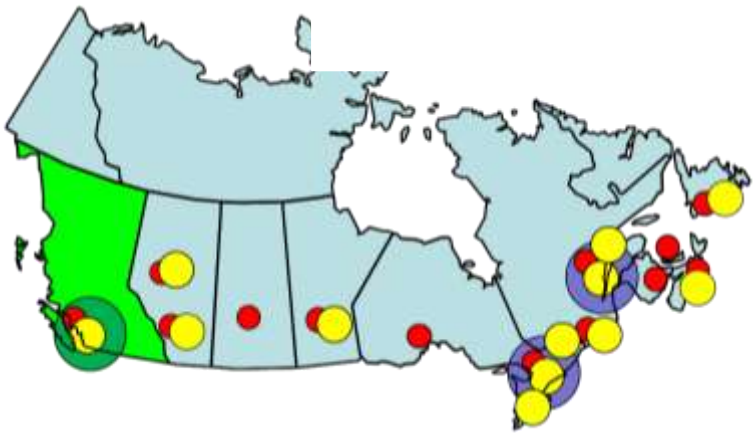
Reduced SLC28A3 expression

Less anthracycline into cell

Less ROS and toxic alcohol metabolites

Less toxicity

Replication of *UGT1A6* synonymous variant in a third independent Dutch cohort



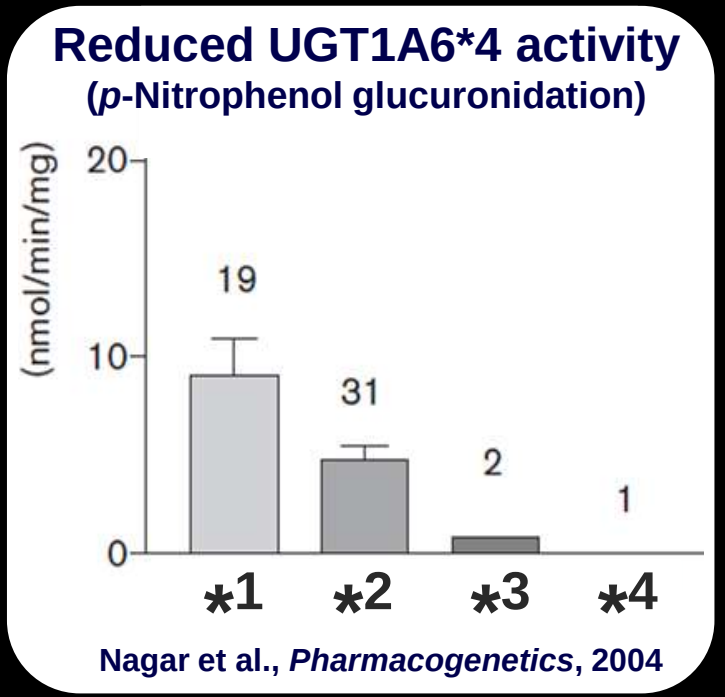
Risk Allele Frequency

Controls: 1.9%
Cases: 6.4%

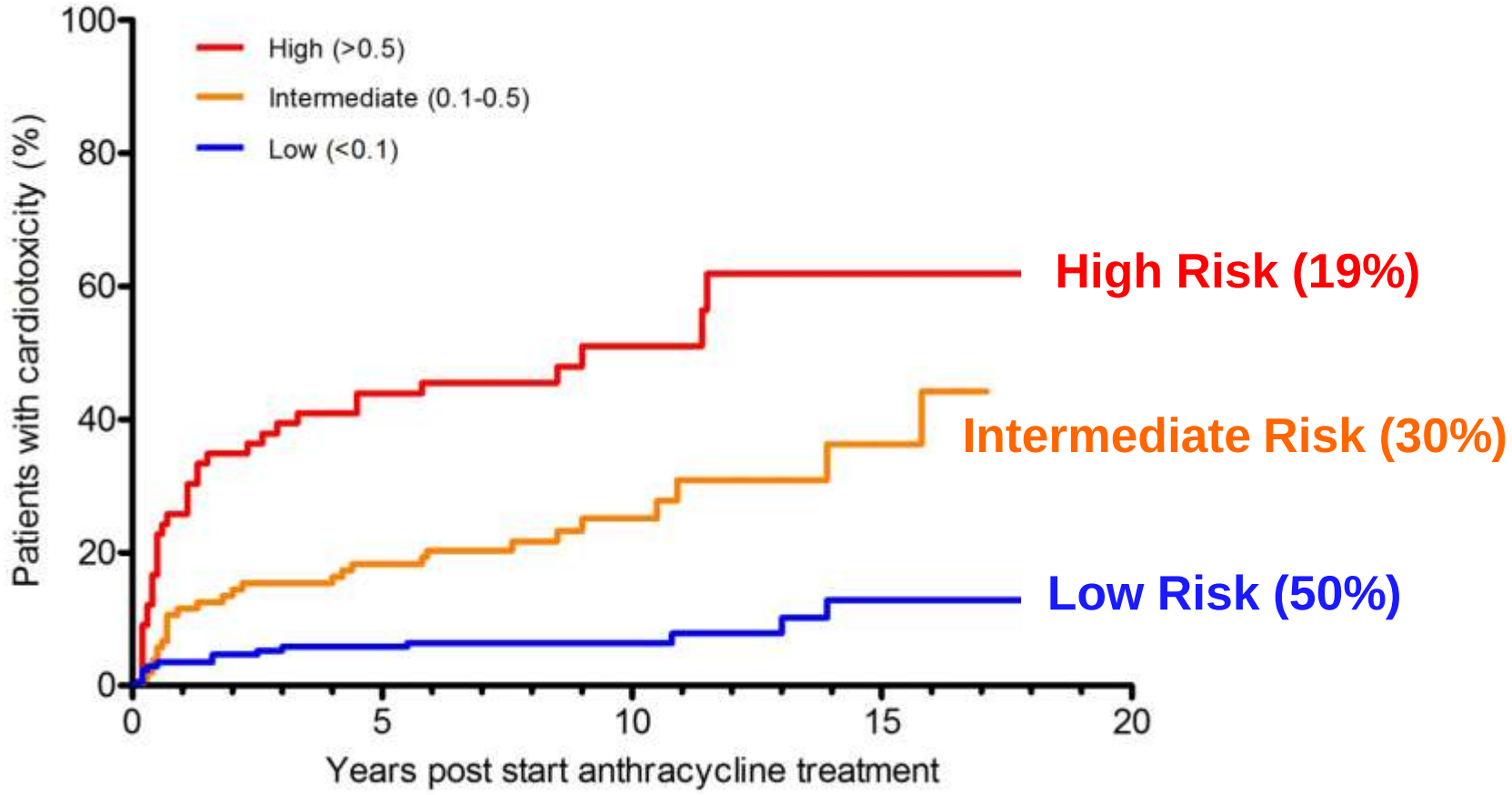
Gene	Discovery OR	Discovery P-value	Canada Replication OR	Canada Replication p-value	Dutch Replication OR	Dutch Replication p-value	Combined OR	Combined p-value
UGT1A6 V209V	4.1	0.040	4.0	0.07	7.98	0.0062	4.3	2×10^{-4}
	n = 156		n = 188		n = 177		n = 521	

Potential mechanism of UGT1A6

- **UGT1A6: UDP glucuronosyltransferase 1A6** glucuronidates many different substrates
- Synonymous Val209Val variant tags the *UGT1A6**4b* haplotype: S7A/L105L/R184S/V209V
- ***UGT1A6**4 has 30-100% reduced enzyme activity***
  - Nagar et al., *Pharmacogenetics*, 2004; Krishnaswamy et al, *J Phar Exp Ther*, 2005
- Parent anthracycline compounds not glucuronidated, but metabolites undergo glucuronidation
- Altered glucuronidation may lead to accumulation of drug or metabolites



SLC28A3 + *UGT1A6* + Clinical Variables for Risk Prediction of Anthracycline Cardiotoxicity



Cdn Cohorts

ROC: AUC (SNPs + Clinical) = 0.76

Clinical Options for Personalized Anthracycline Therapy

Depending on risk prediction, clinician could take different actions:

Low Risk

- Echocardiogram follow-up as usual

Intermediate Risk

- Intensify echocardiogram follow-up

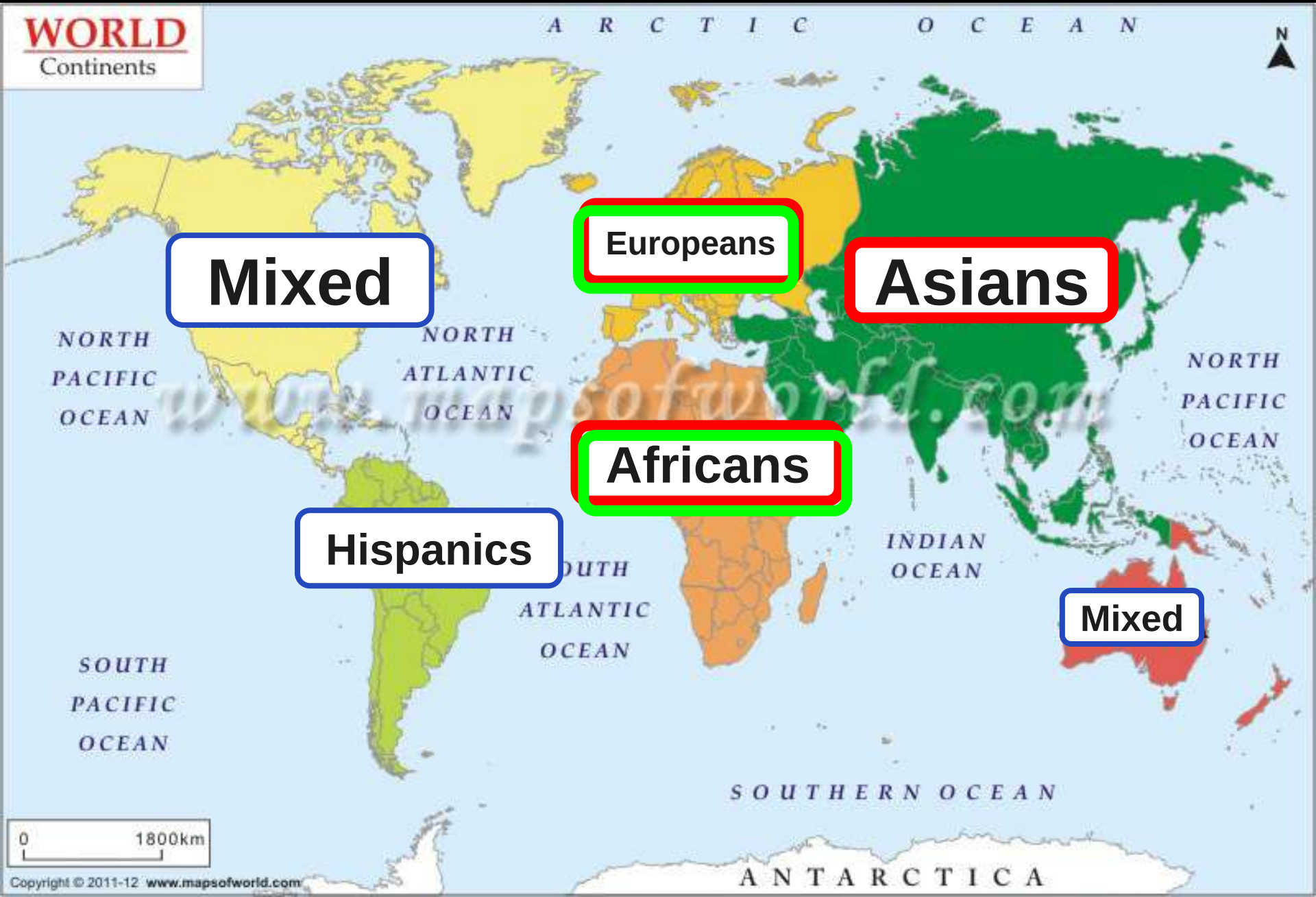
  e.g. patients in rural centres often miss appointments

High Risk

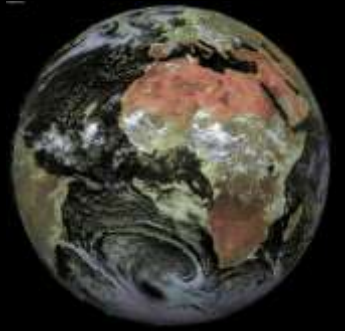
- Alternative medication (e.g. mitoxantrone) or dose
- Add cardioprotectant (e.g. dexrazoxane)
- Start treatment with ACE-inhibitors or beta-blockers to prevent further damage

One Race But Many Variations

Genetic Ancestral Populations



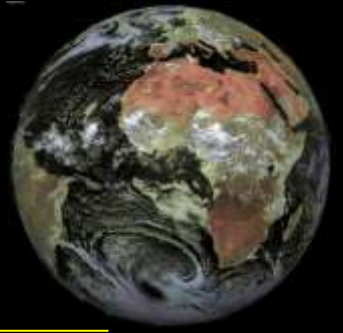
Pharmacogenomic Diversity Project Aims



- **Elucidate the pharmacogenomic diversity within African populations**
- **Identify the genetic causes of drug response differences between different ethnic populations**

Canadian Pharmacogenomics Network for Drug Safety

Study Population



1. Two genetic ancestries (Africans and Europeans) n = 1330

2. African Ancestry Populations n = 372

3. European Ancestry Population n = 958

4. Genetic Ancestry ascertained by PCA

Canadian Pharmacogenomics Network for Drug Safety

Analysis of 4500 Pharmacogenomic Variants in 15 African Subpopulations

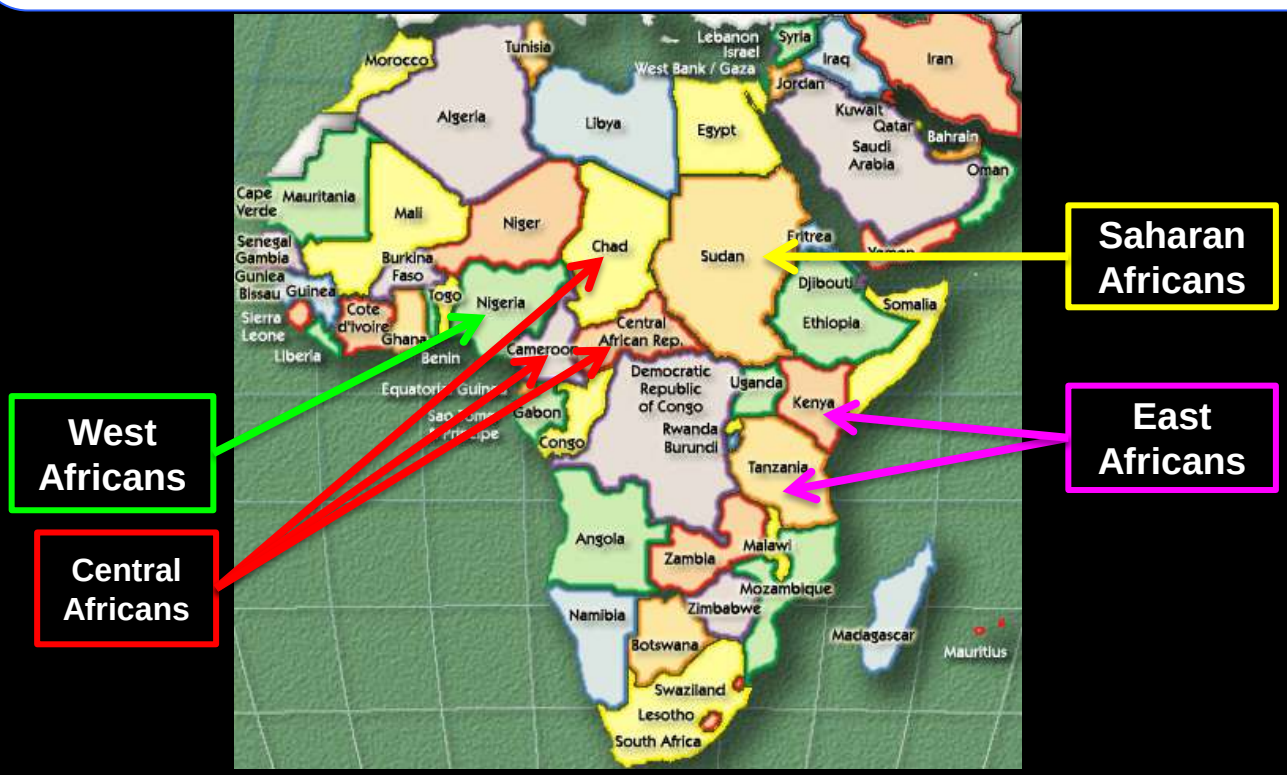
The Pharmacogenomics Journal (2013), 1–11

www.nature.com/tpj

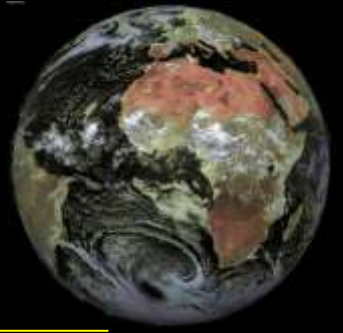
ORIGINAL ARTICLE

Higher frequency of genetic variants conferring increased risk for ADRs for commonly used drugs treating cancer, AIDS and tuberculosis in persons of African descent

F Aminkeng[1], CJD Ross[2], SR Rassekh[3], LR Brunham[1,4], J Sistonen[1,5], M-P Dube[6], M Ibrahim[7], TB Nyambo[8], SA Omar[9], A Froment[10], J-M Bodo[11], S Tishkoff[12,13], BC Carleton[2,13] and MR Hayden[1,4], The Canadian Pharmacogenomics Network for Drug Safety Consortium[14]



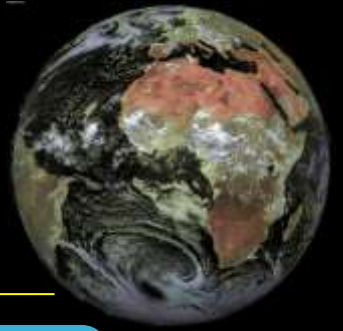
African Populations Diversity Panel



Population Name	Pop Code	n (total 281)	Country	Region	Subsistence
Fulani	CAFU	19	Cameroon	Central Africa	Herder
Lemande	CALM	19	Cameroon	Central Africa	Farmer
Mada	CAMD	19	Cameroon	Central Africa	Farmer
Bakola Pygmy	CAPL	19	Cameroon	Central Africa	Hunter-gatherer
Bulala	CHBU	16	Chad	Central Africa	Farmer (with fishing)
Boni	KEBN	19	Kenya	Eastern Africa	Hunter-gatherer
Borana	KEBR	19	Kenya	Eastern Africa	Herder
Luo	KELO	19	Kenya	Eastern Africa	Herder
Sengwar	KESN	19	Kenya	Eastern Africa	Hunter-gatherer
Yoruba	NGYR	19	Nigeria	Western Africa	Farmer
Beja	SDBA/SDHD	19	Sudan	Saharan Africa	Herder
Datog	TZDT	19	Tanzania	Eastern Africa	Herder
Hazda	TZHZ	19	Tanzania	Eastern Africa	Hunter-gatherer
Iraqw	TZIQ	19	Tanzania	Eastern Africa	Mixed farmer
Sendawe	TZSW	18	Tanzania	Eastern Africa	Hunter-gatherer

Pharmacogenomic Analysis

The Strategy



African Ancestry

European Ancestry

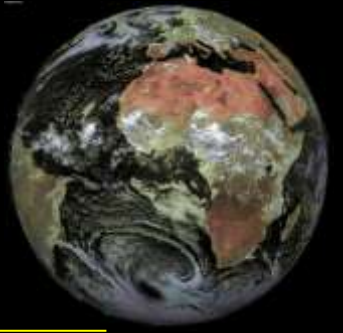
WHO Model List of Essential Medicines

PGX Differences AFR vs. EUR

1. Cancer Chemotherapy
2. Antiretrovirals
3. Anticoagulants
4. Other Drugs

Canadian Pharmacogenomics Network for Drug Safety

Pharmacogenomic Analysis



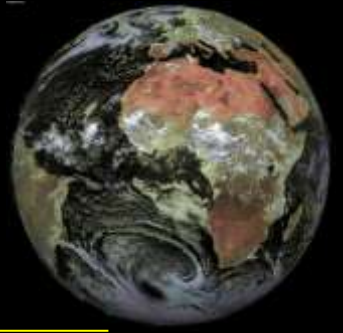
Anthracyclines & Related Compounds

- Known toxicity problems include severe cardiotoxicity and heart failure in up to 16% of treated patients

- African Americans have a higher rate of cardiotoxicity after doxorubicin (7%) vs. Caucasian population (2.4%) ($p<0.027$, odds ratio 2.93) - *Hasan et al., J Natl Med Assoc. 96:196-199. 2004*

- African Americans have a 1.7-fold greater relative risk of cardiotoxicity – *Marsh et al., J Clin Oncol. 15:1544–521. 1997*

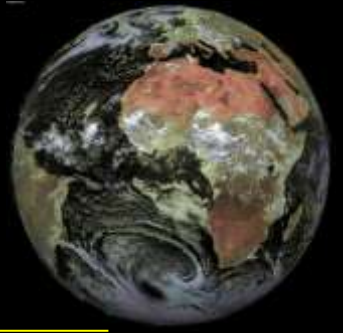
Pharmacogenomic Analysis



Anthracyclines

PGX Gene Variant	AFR Ancestry %MAF	EUR Ancestry %MAF	*P*
Selected Risk Variants			
UGT1A6 **rs17863783**	**12.0**	**2.8**	**9.8E-015**
ABCC1 rs4148350	13.5	5.4	2.1E-007
ABCB1 rs2235047	18.2	2.5	3.8E-036
ABCB11 rs10497346	24.7	9.3	2.3E-020

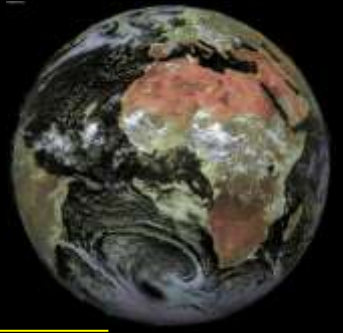
Pharmacogenomic Analysis



Anthracyclines

PGX Gene Variant	AFR Ancestry %MAF	EUR Ancestry %MAF	*P*
Selected Protective Variants			
SLC22A17 rs4982753	5.7	25.2	8.4E-025
SULT2B1 rs10426377	17.5	27.4	4.7E-004
SLC28A3 rs4877847	44.4	54.2	4.4E-002

Pharmacogenomic Analysis

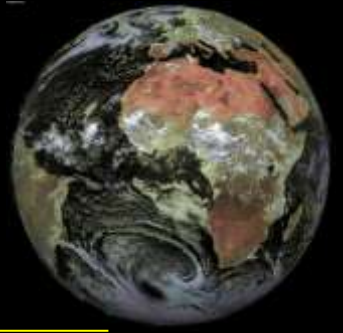


Cisplatin and Platinum Compounds

- Ototoxicity, nephrotoxicity, neutropenia, neurotoxicity

	European Ancestry	African-American	P-value	Reference
Cisplatin toxicity	8.3%	47.6%	0.007	Shord et al, *Anti-Canc Drugs* 2006
"Increased cisplatin toxicity in South African patients vs. patients from western countries"				Nyongesa et al, Int J Gyn Cancer, 2006
"40% lower maximum tolerable dose in South African population"				Nyongesa et al, Int J Gyn Cancer, 2006

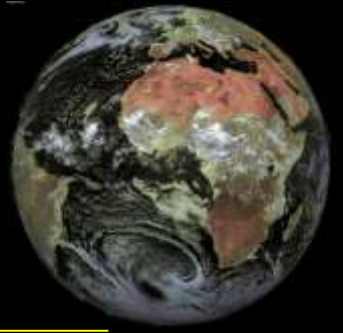
Pharmacogenomic Analysis



Cisplatin

PGX Gene Variant	AFR Ancestry %MAF	EUR Ancestry %MAF	*P*
Risk Variant			
TPMT rs12201199	48.9	6.7	6.5E-129
COMT rs9332377	32.7	16.8	5.4E-014

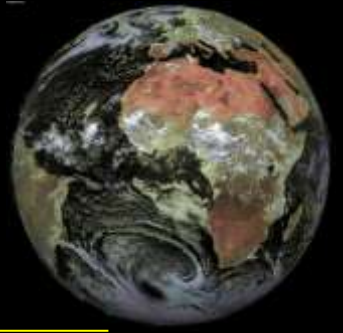
Pharmacogenomic Analysis



Vinca Alkaloids

- **Vincristine**, vinblastine, vindesine, and vinorelbine.
- The main adverse effects of vincristine are peripheral neuropathy, hyponatremia, constipation and hair loss
- **34.8% of Caucasians** experienced vincristine-related neurotoxicity compared with only **4.8% of African Americans (P = 0.007)** - *Renbarger et al, 2008. Pediatr Blood Cancer; 50:769–71.*

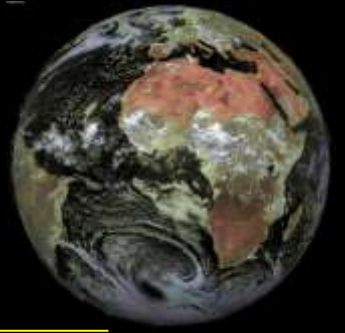
Pharmacogenomic Analysis



Vincristine

PGX Gene Variant	AFR Ancestry %MAF	EUR Ancestry %MAF	*P*
Risk Variant			
NOS3 rs1799983	4.9	33.8	8.5E-012

Pharmacogenomic Analysis



PGX of Antiretroviral Drugs

- Increased frequency of low activity variants may increase drug accumulation and the frequency and risk of drug toxicity in African patients

What We Know About Drug Response

There are patient-specific differences in drug response. One drug is not ideal for all patients.

What We are Now Figuring Out

Pharmacogeneticic biomarkers can help tailor therapy for an individual patient

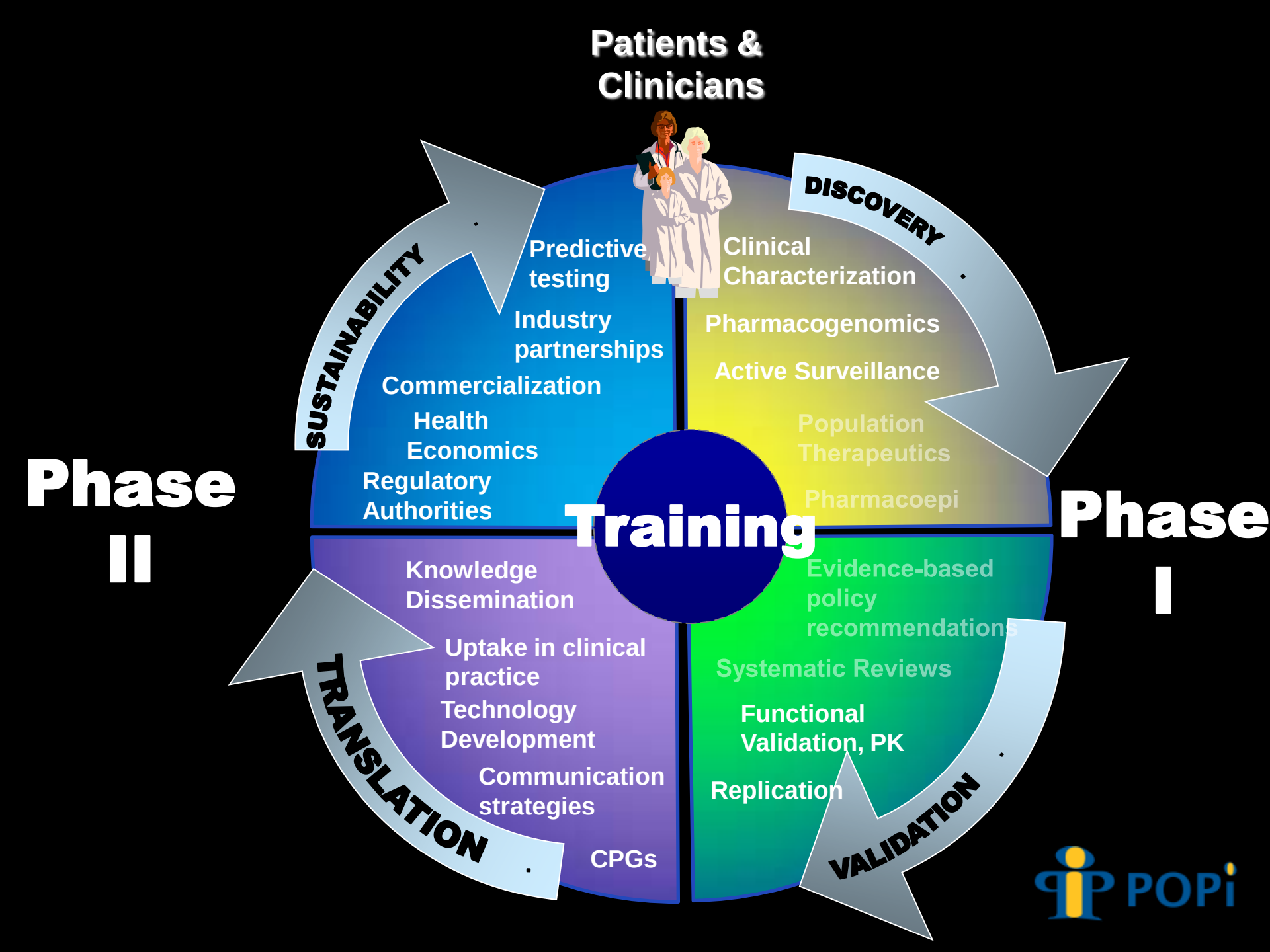
What We Can Achieve

-Better risk/benefit information for individual patients

-Improved attainment of therapeutic objectives

-Avoidance of harm

-Rationale for the need of a range of therapeutic options to meet patient needs


Patients & Clinicians
DISCOVERY
Clinical Characterization
Pharmacogenomics
Active Surveillance
Population Therapeutics
Pharmacoepi
Phase I
VALIDATION
Evidence-based policy recommendations
Systematic Reviews
Functional Validation, PK
Replication
TRANSLATION
Knowledge Dissemination
Uptake in clinical practice
Technology Development
Communication strategies
CPGs
SUSTAINABILITY
Predictive testing
Industry partnerships
Commercialization
Health Economics
Regulatory Authorities
Phase II
Training
POPi

Canadian Pharmacogenomics Network for Drug Safety

POPi
Pharmaceutical Outcomes & Policy Innovations

UBC
a place of mind

BC Children's Hospital
An agency of the Provincial Health Services Authority

Women's
BC Women's Hospital & Health Centre

CMMT
Centre for Molecular Medicine and Therapeutics

Child & Family Research Institute

CIHR IRSC

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

Canada Foundation for Innovation
Fondation canadienne pour l'innovation

BC Cancer Agency
Care + Research

Vancouver Coastal Health
Promoting wellness. Ensuring care.

Providence Health Care
How you want to be treated.

Canadian Gene Cure Foundation
Fondation Canadienne Gène Cure

BCCGN
British Columbia Clinical Genomics Network

GenomeBritishColumbia

Cinvestav

SEP - CONACYT
Consejo Nacional de Ciencia y Tecnología
M É X I C O

IMSS

Canadian Dermatology Foundation
www.cdf.ca

CHEO
Children's Hospital of Eastern Ontario
Centre hospitalier pour enfants de l'est de l'Ontario

Princess Margaret Hospital

University of Toronto

Toronto SickKids

MOTHERISK
Treating the mother – protecting the unborn

Children's Hospital
London Health Sciences Centre

Stollery Children's Hospital Foundation

Children's Hospital
Health Sciences Centre Winnipeg

IWK Health Centre

CHU Sainte-Justine

Western
Education

University of Calgary

McMaster Children's Hospital

KGH
Kingston General Hospital

Université de Montréal

St. Michael's
Inspired Care. Inspiring Science.

Pfizer

Alberta Children's Hospital

Women's College Hospital

Sunnybrook
Health Sciences Centre

L'Hôpital de Montréal pour enfants
The Montreal Children's Hospital
Centre universitaire de santé McGill
McGill University Health Centre

Janeway

Candlelighters
Childhood Cancer Foundation

Children's Mercy Hospitals & Clinics
www.childrensmercy.org

Indiana University
School of Medicine

Stanford University

Lucile Packard Children's Hospital at Stanford

Health Canada
Santé Canada

Canadian Pharmacogenomics Network for Drug Safety

CPNDS International Surveillance Sites and Collaborations

CPNDS & Collaborations

CPNDS Planned/Potential Collaborations

Canadian Pharmacogenomics Network for Drug Safety

At the Child & Family Research Institute
Children's & Women's Health Centre of British Columbia
Vancouver, CANADA

Contact/Questions

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Chair, Division of Translational Therapeutics
Department of Pediatrics, Faculty of Medicine
University of British Columbia

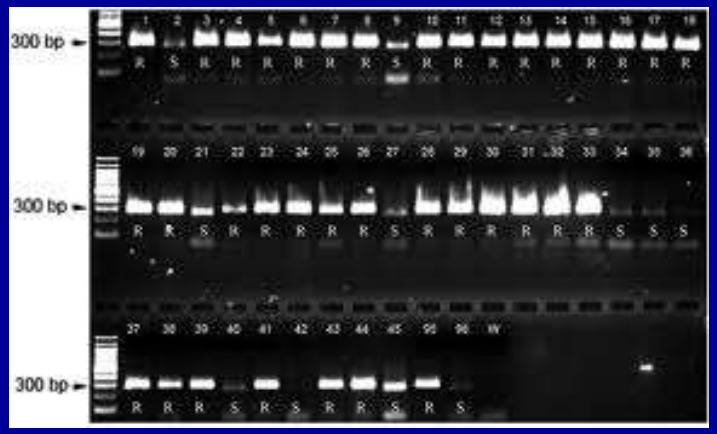
bcarleton@popi.ubc.ca

Canadian Pharmacogenomics Network for Drug Safety

Additional Slides

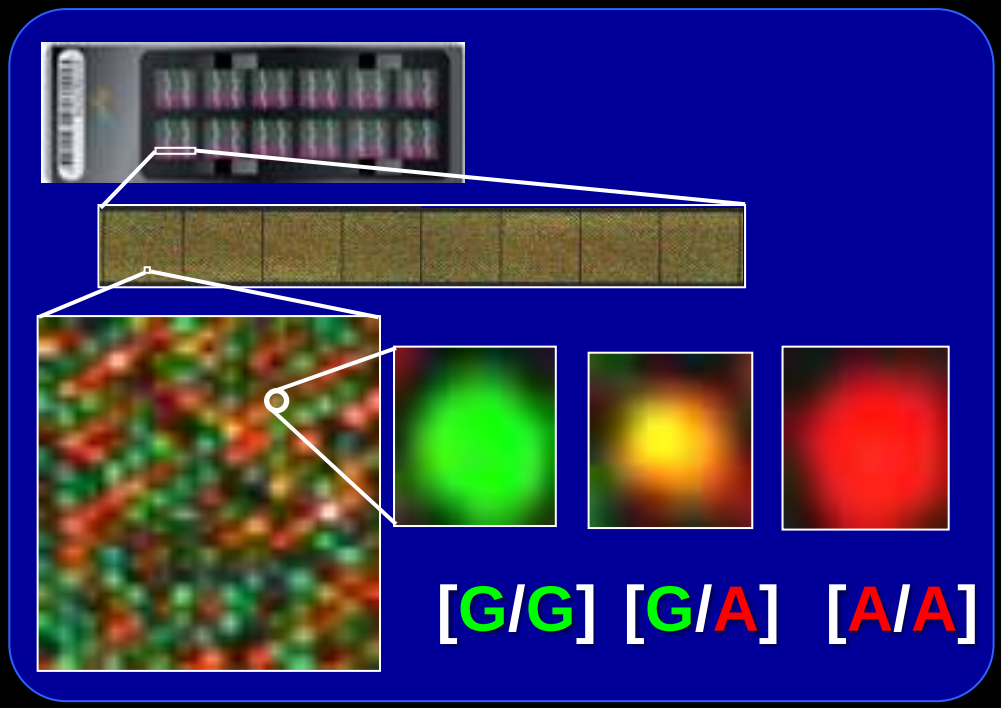
Advances in Genomics Technology

Year 2002



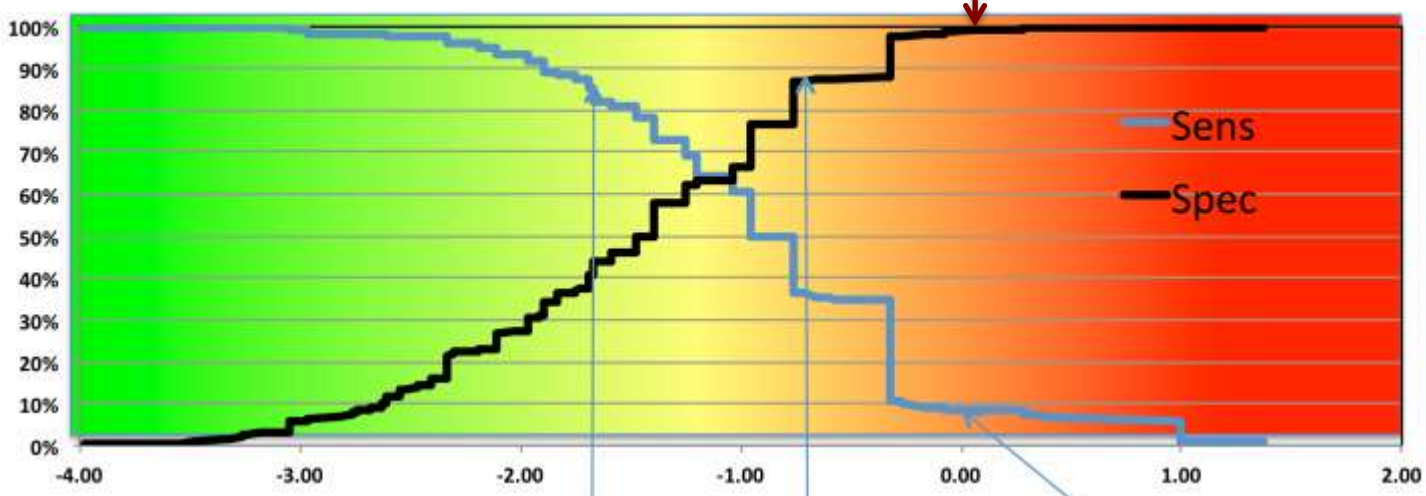
12+ years to genotype
1 million variants
throughout the genome
Cost: $2.7 billion

Year 2013



2 days to genotype
1 million variants
Throughout the genome
Cost: ~$250

Patient IND701701



Low Risk Cutoff
Sens: 85%
Spec: 40%
PPV: 30%
NPV: 90%

High Risk Cutoff
Sens: 37%
Spec: 88%
PPV: 47%
NPV: 82%

LOW RISK
34% of Population
10% Risk of Cardiotoxicity

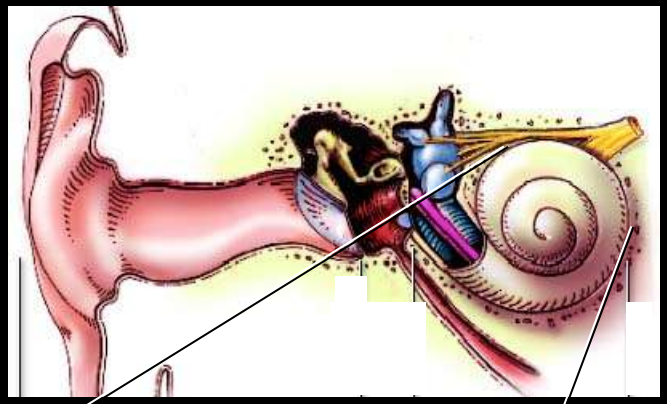
INTERMEDIATE RISK
47% of Population
25% Risk of Cardiotoxicity

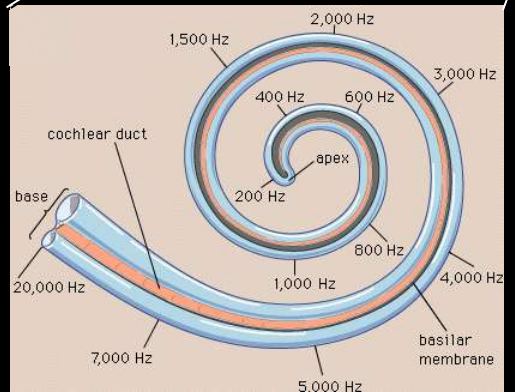
HIGH RISK
18% of Population
47% Risk of Cardiotoxicity

VERY HIGH RISK
3% of Population
70% Risk of Cardiotoxicity

Cisplatin

- Drug of choice for solid tumours including hepatoblastoma, ovarian, CNS, osteosarcoma, neuroblastoma, lung, bladder, head and neck tumors
- **1,000,000 new patients** receive cisplatin each year (N. America & Europe)
- Causes permanent hearing loss
- 10-38% of patients
- Increased frequency and severity in children
  - **28%-61%** of children 5-14 develop severe hearing loss
  - **38%-62%** of children <5 yrs old develop severe hearing loss (Li et al, 2004)
- B.C. Children's Hospital: 37% of patients developed grade 3-4 deafness since 2005





Cisplatin Case Studies

Case 1

- 14 yrs old
- Osteosarcoma of right proximal tibia
- Diagnosed Nov 2000
- Chemotherapy:
  - Cisplatin
  - Doxorubicin
  - Methotrexate
- Alive and Well

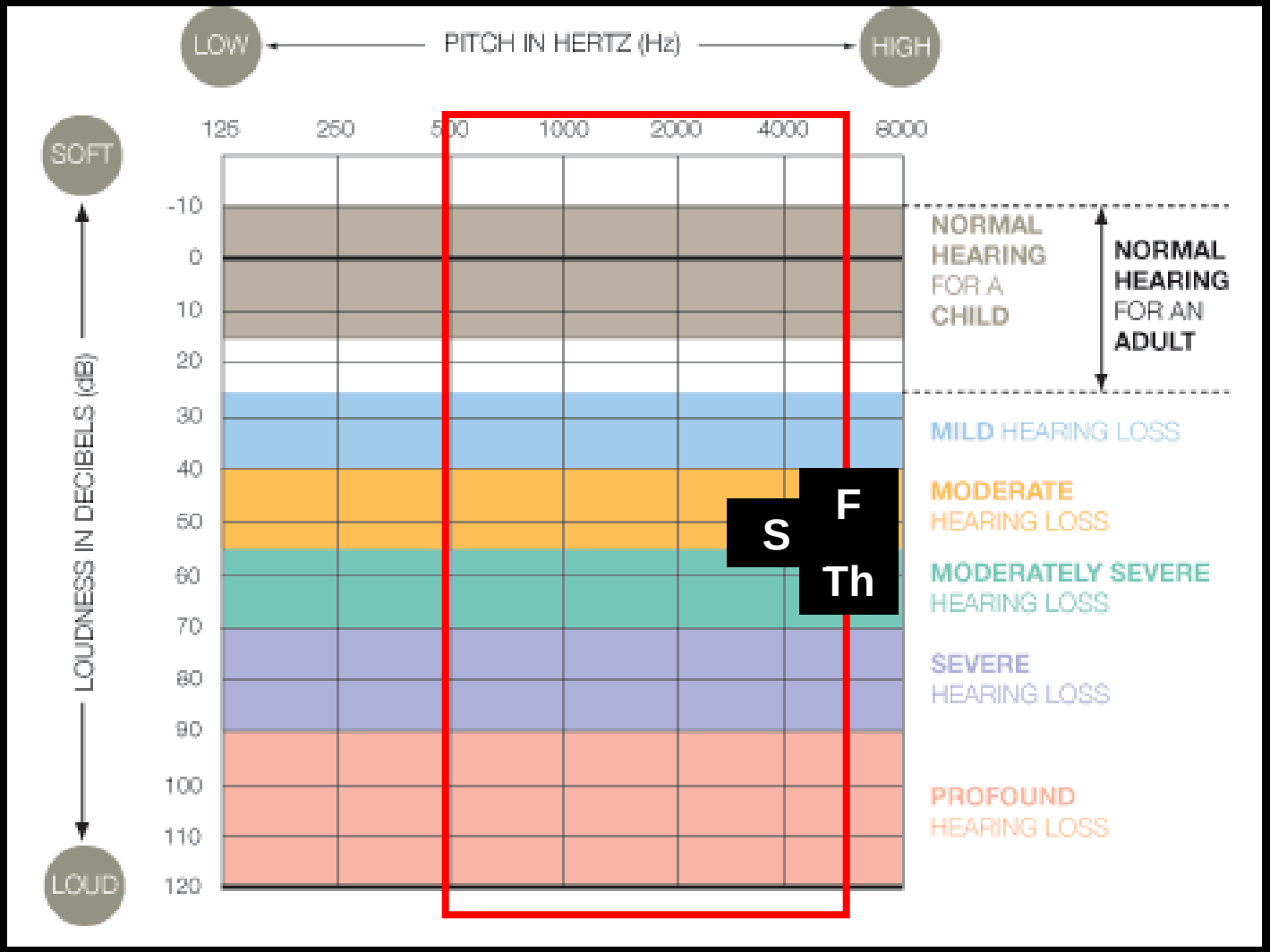
Case 2

- 12 yrs old
- Osteosarcoma of right proximal tibia
- Diagnosed Oct 1998
- Chemotherapy:
  - Cisplatin
  - Doxorubicin
  - Methotrexate
- Alive and Well

Cisplatin Case Studies

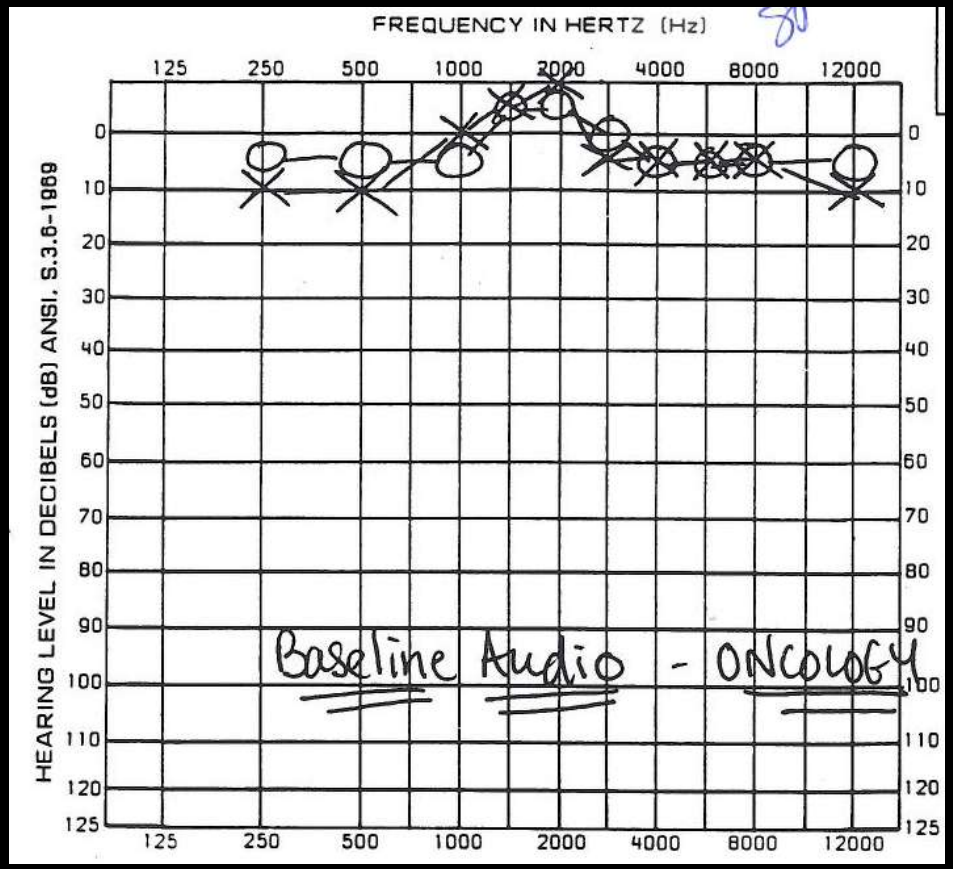
- Cases sound similar
  - Same tumor
  - Same protocol
  - Same good outcome from cure point of view
- However :
  - Significant difference in Audiograms
  - Case 2 needed last 2 doses of cisplatin held due to significant hearing loss
  - Case 2 needs hearing aids

Audiogram

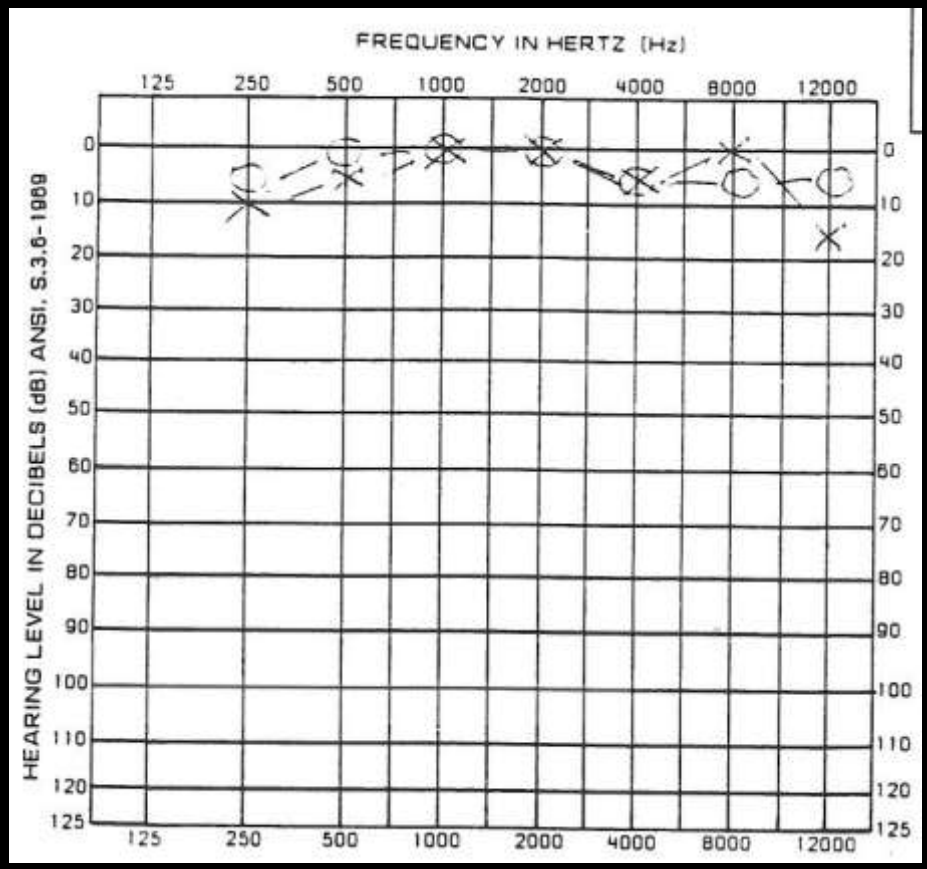


Slide from “League for the Hard of Hearing” - http://www.lhh.org/about_hearing_loss/understanding/audiogram.html

Case 1

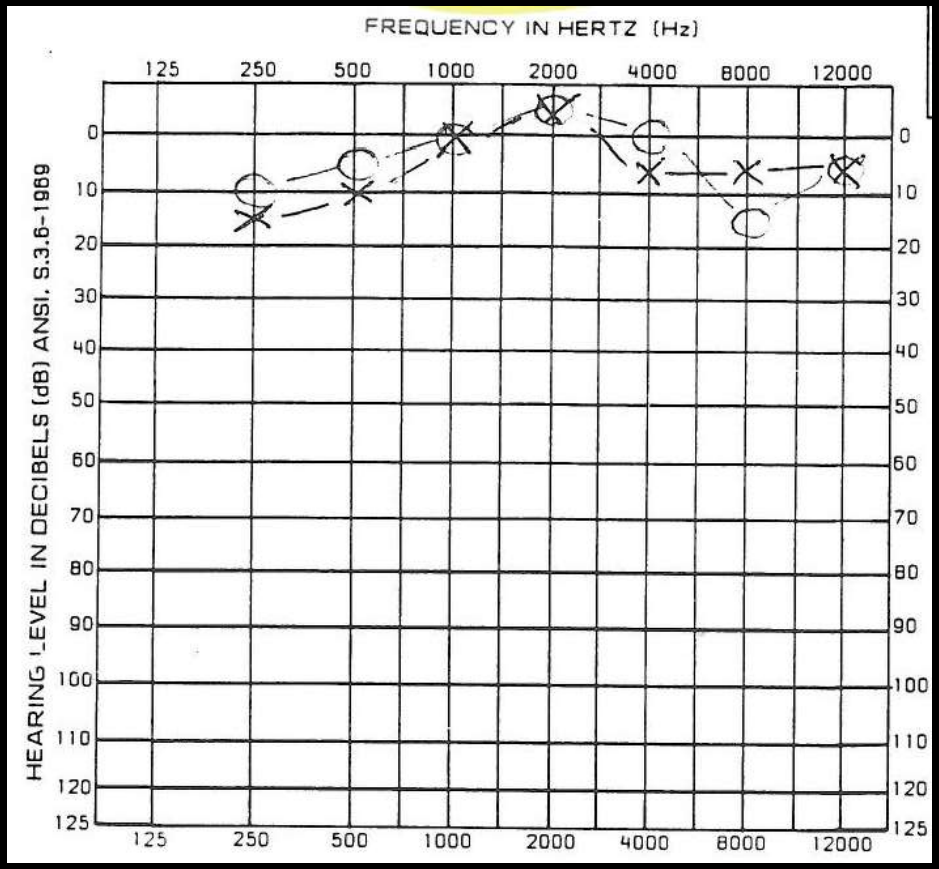


Case 2

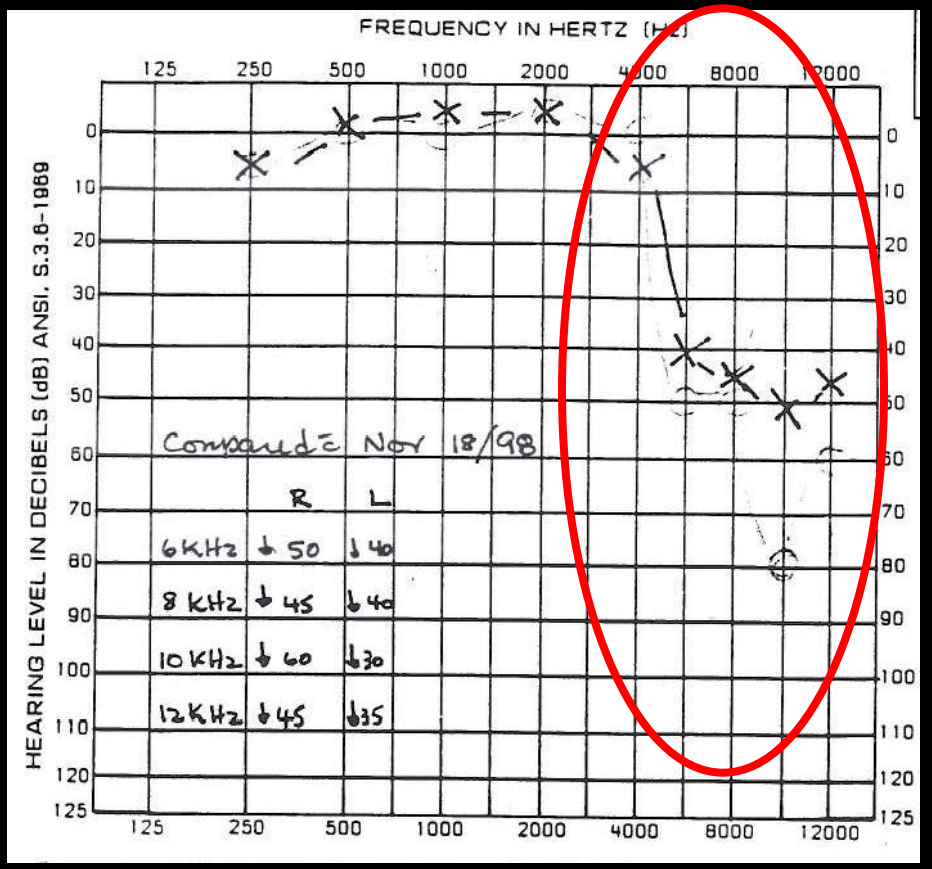


BASELINE STUDIES

Case 1



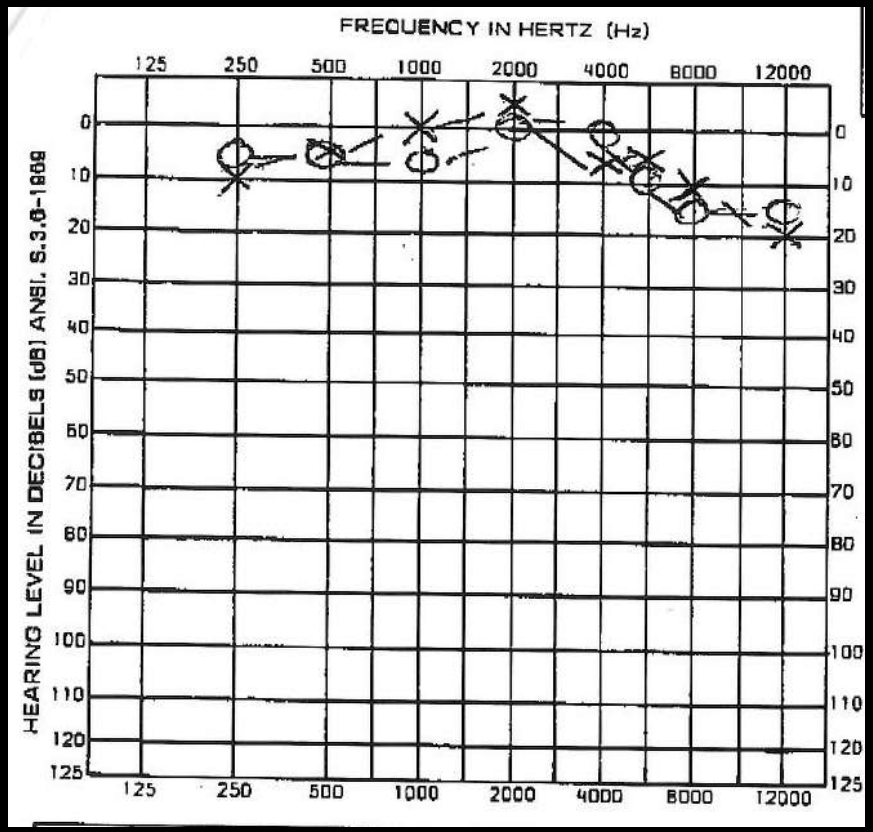
Case 2



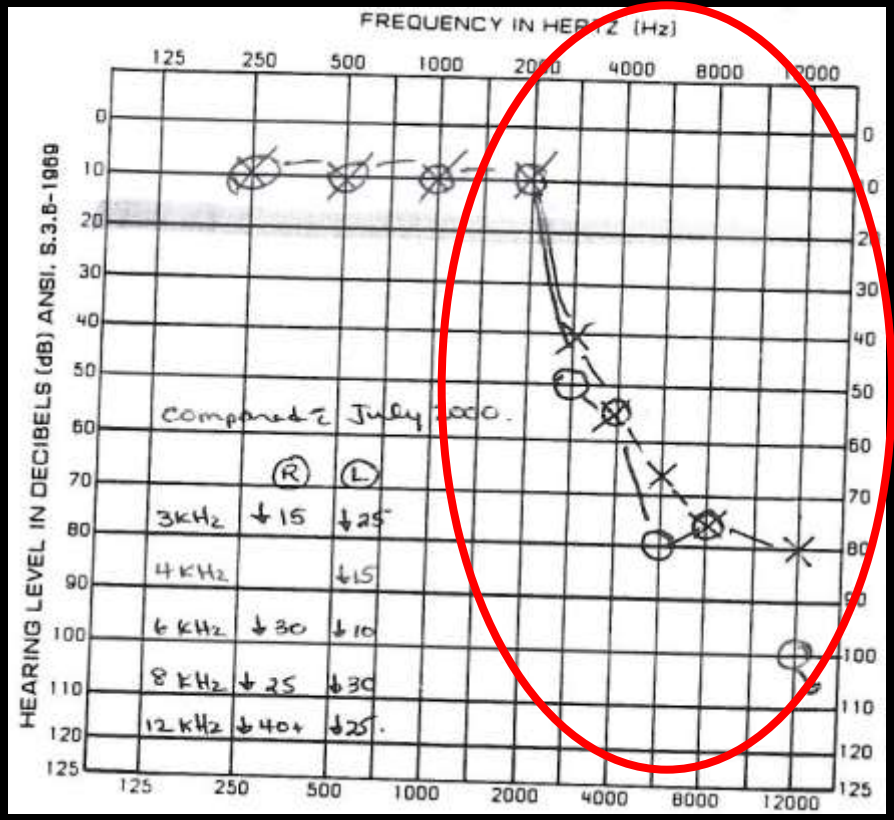
MIDPOINT OF THERAPY

(AFTER 2 CYCLES OF CISPLATIN)

Case 1



Case 2



CURRENT STUDIES

- Why does one child get hearing loss with cisplatin, while another does not?

Cisplatin-ADR Patient Recruitment

- 162 pediatric patients with hepatoblastoma, brain tumor, germ cell tumours, neuroblastoma, osteosarcoma

Classification of Cisplatin ADR Cases and Controls

Controls

- **Grade 0: Normal Hearing**
  Hearing threshold of 20 dB or less (within normal range) at all frequencies

n = 56

- **Grade 1 Hearing Loss: Mild High Freq. Loss**
  Minimum hearing threshold of 20-25 dB (4000 Hz and above)

ADR Cases

- **Grade 2 Hearing Loss: Moderate High Freq. Loss**
  May require speech therapy or intervention with hearing aid
  Minimum hearing threshold of 25-39 dB (4000 Hz and above)
- **Grade 3 Hearing Loss: Severe Hearing Loss**
  Requires intervention with hearing aid
  Minimum hearing threshold of 25-39 dB (2000 Hz and above)
- **Grade 4 Hearing Loss: Deafness**
  Requires intervention with cochlear implant
  Minimum hearing threshold of 40dB or more (1000Hz and above)

n = 106

Identified Genetic Variants Associated with Cisplatin-Induced Deafness

Combined Discovery + Replication (n = 162)

Gene	SNP	Cases	Controls	O.R.	P-value
TPMT	Intron	23.6%	1.8%	16.8	2.2 x 10(-4)*
COMT	Intron	29.2%	7.1%	5.5	1.8 x 10(-4)*

1. Loss of TPMT: Increased Cisplatin Toxicity
   - Cisplatin binds purines → DNA cross-linking → Cell death
   - TPMT normally inactivates purine-compounds (e.g. cisplatin)

2. Loss of COMT: Increased Cisplatin Toxicity
   - COMT and TPMT both use 'S-adenosyl-L-methionine' substrate
   - Accumulation of SAM substrate is toxic in the presence of cisplatin

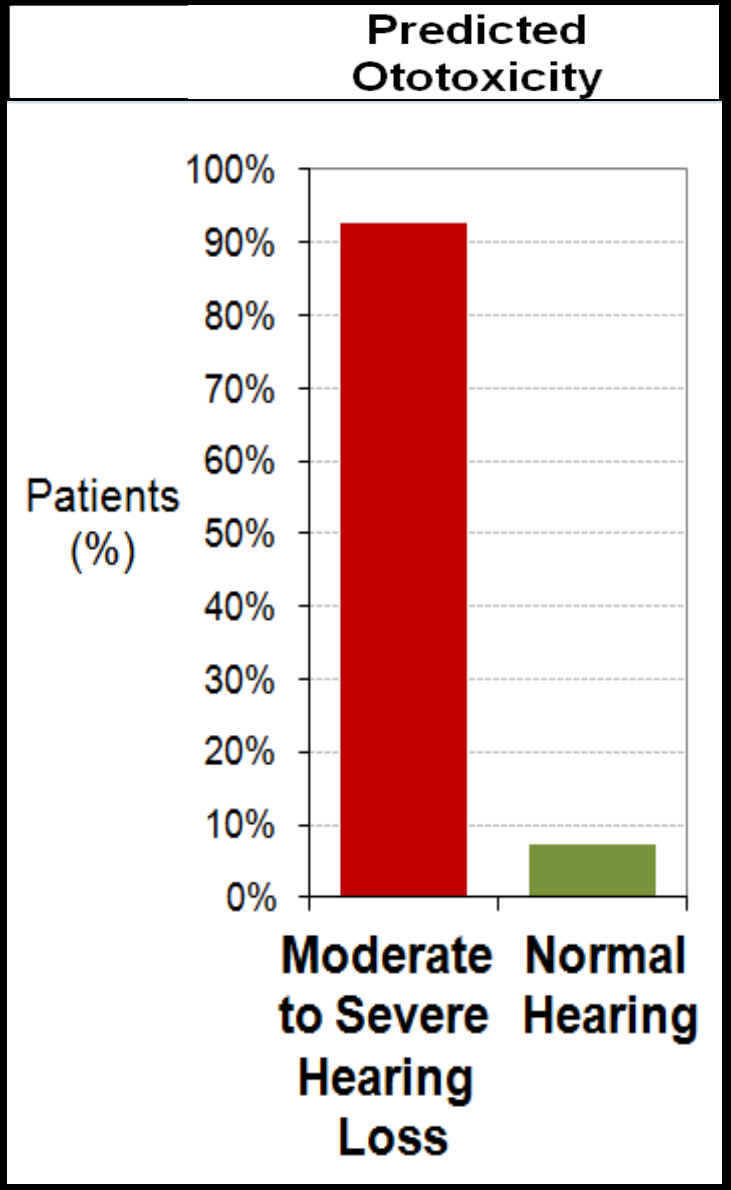
Combining Top 2 SNPs in *TPMT* and *COMT* Identifies 48% of Cisplatin Ototoxicity Cases with High Specificity

	Deaf Cases	Normal Hearing Controls
Combined TPMT/COMT	48.1%	7.1%

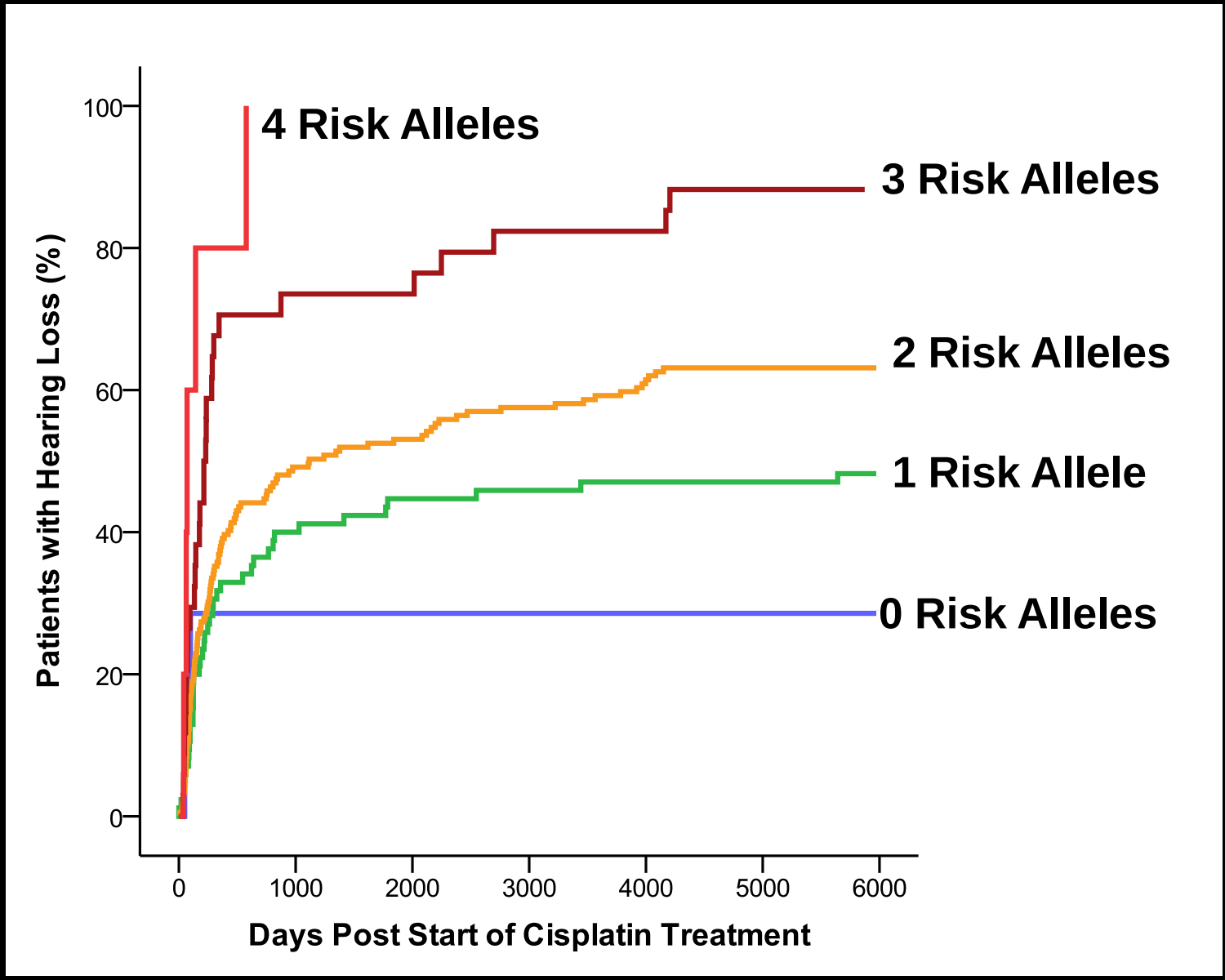
Odds ratio	p-value
12.1	3.4×10^{-8}

Sensitivity:	Specificity:
48.1%	92.9%

PPV:	NPV:
92.7%	48.6%



Increasing numbers of risk alleles means increased severity, frequency, and earlier onset of hearing loss



Drug Label Change

FDA changed the cisplatin drug label warning of the pharmacogenomic risk of deafness in susceptible patients

January 30, 2012

In cooperation with the Food and Drug Administration (FDA), and as a service to our members, ACCP will periodically distribute information about newly approved therapies or significant changes to approved therapies. This helps the FDA to inform professionals in the patient care arena of recent approvals in a timely manner. Included in the e-mail from the FDA will be a link to the product label, which will provide the relevant clinical pharmacology information on the indication, contraindications, dosing, and safety. In sending this information, ACCP does not endorse any product or therapy and does not take any position on the safety or efficacy of the product or therapy described.

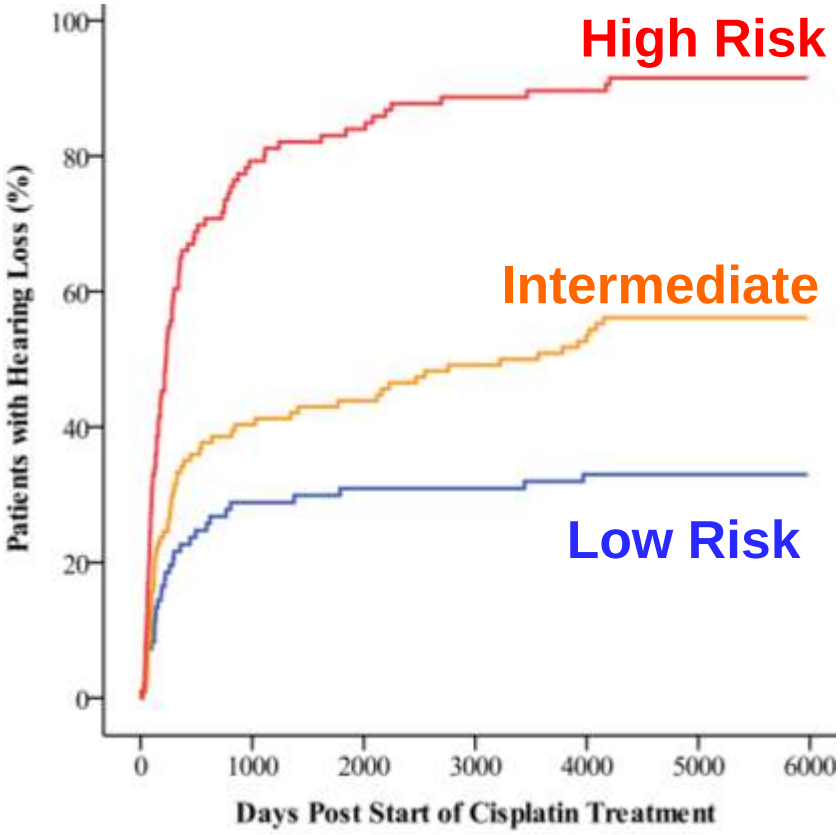
Pharmacogenetic changes to the FDA-approved PLATINOL® (cisplatin) label include safety update regarding cisplatin-induced hearing loss in children

The FDA updated the PLATINOL® (cisplatin) product label on December 29, 2011 to include new safety information pertaining to the association of variants in the thiopurine S-methyltransferase (TPMT) gene and an increased risk of cisplatin-induced ototoxicity in children. Cisplatin was originally approved as PLATINOL® by the FDA in 1978 and is currently indicated for the treatment of metastatic testicular tumors, metastatic ovarian tumors, and advanced bladder cancer. Cisplatin's toxicity profile includes risk for ototoxicity. Ototoxicity is manifested by tinnitus and high-frequency hearing loss which is often bilateral, typically irreversible, and can be progressive despite cessation of cisplatin. Hearing loss can occur following a single cisplatin dose, but tends to become more frequent and severe following repeated dosing. Ototoxic effects may be related to peak plasma concentrations of cisplatin. While cisplatin-induced ototoxicity can occur in both adults and children, its prevalence in children is estimated to be as high as 60% and the ototoxic effects can be particularly devastating on a child's cognitive, speech, language, and

Replication of *TPMT* and *ABCC3* genetic variants highly associated with cisplatin-induced hearing loss in children.

Clinical Pharmacology & Therapeutics

Kusala Pussegoda[1,2], Colin J Ross[1,2,5,10], Henk Visscher[1,2,10], Mojgan Yazdanpanah[1,2,3], Beth Brooks[4], S Rod Rassekh[2,5], Yassamin Feroz Zada[6], Marie-Pierre Dubé[6], Bruce C Carleton[2,7,8], Michael R Hayden[1,2] & the CPNDS Consortium[9]



Kaplan-Meier curve of cisplatin-induced hearing loss in three different risk groups.

(*TPMT* rs12201199, *COMT* rs4646316 and *ABCC3* rs1051640).

(P_{trend}=3.4x10^{-19}).

What Next?
Patient Predicted to be at High Risk for Cisplatin-Induced Ototoxicity

What is done now without a predictive test:

Protocol	Treatment	Ototoxicity	Intervention
Osteosarcoma	Doxorubicin & cisplatin	Grade 2	**Reduce cisplatin 50%**
		Grade 3+	**Discontinue cisplatin**
CNS tumors	Cisplatin, Etoposide, + Vincristine	Grade 2	**Reduce cisplatin 50%**
		Grade 3+	**Discontinue cisplatin**
Neuroblastoma	Doxorubicin + cisplatin	Grade 3+	**Discontinue cisplatin**

New Treatment Options with Pharmacogenetic Personalized Medicine

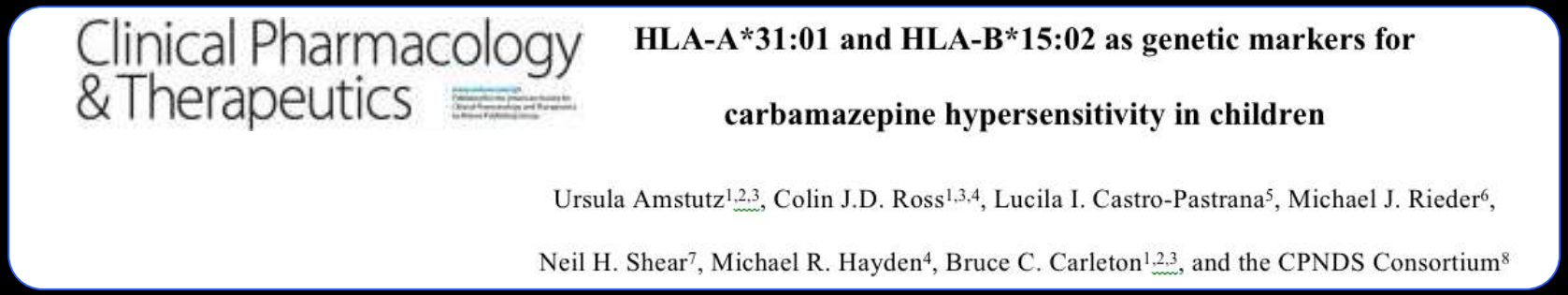
- Alternative medications (i.e. carboplatin?)
- Modified cisplatin dose
- Increase monitoring in high risk patients
- Protective strategies to prevent cisplatin-ototoxicity (e.g. sodium thiosulfate)

Implementing cisplatin PGx testing would save an estimated $16 million/yr in Canada

- Dionne et al, *Pharmacogenomics Journal*, 2011

Highlights of Research Publications

Recent Key Publication:

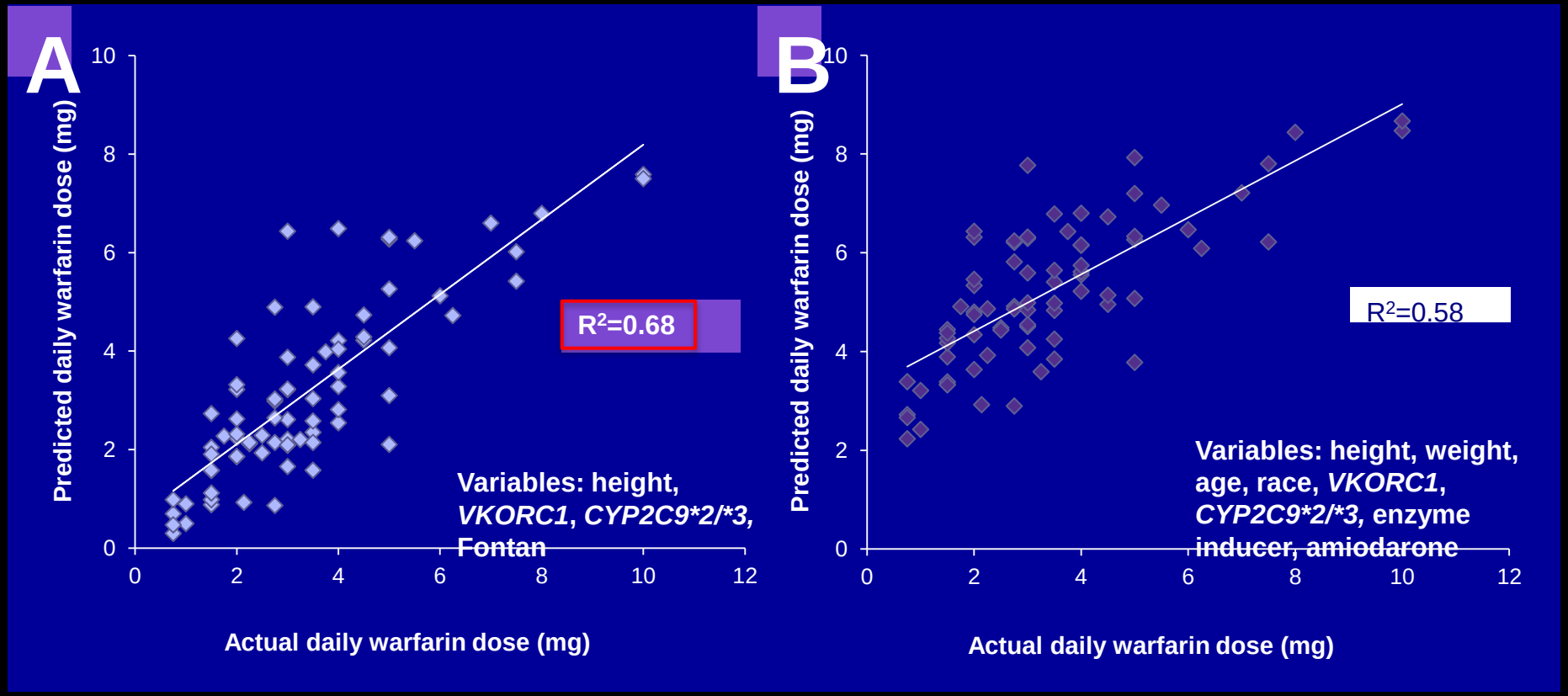


"…HLA-A*31:01 was significantly associated with CBZ-HSS (OR: 26.4, p=0.0025) and maculopapular exanthems (OR: 8.6, p=0.0037)… HLA-B*15:02 was associated with CBZ-SJS (OR: 38.6, p=0.002)...

…first study to demonstrate the association of HLA-A*31:01 with CBZ hypersensitivity in children… highlighting the importance HLA-A*31:01 as a predictive biomarker across various ancestries

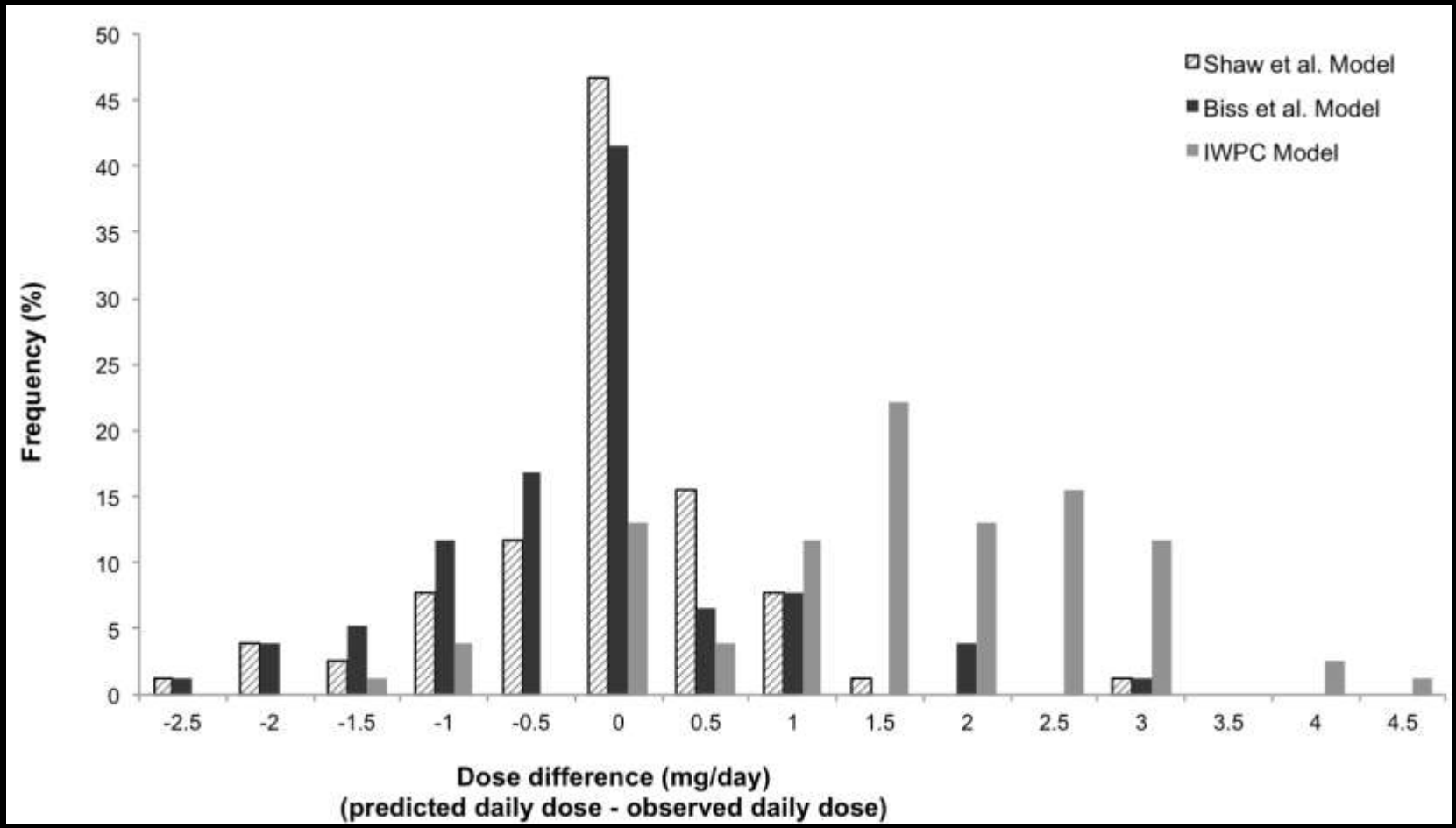
Results: Dose prediction model

Compared the performance of a (A) pediatric-derived dosing model (Biss et al., 2012) and an (B) adult-derived dosing model (IWPC, 2008) when predicting the required dose in children



Pediatric-derived model was significantly more accurate when predicting optimal dose (p=0.023)

Results: Dose prediction model



Pediatric-derived model slightly under-estimated the required dose, while the IWPC model over-estimated the required dose in our cohort of patients

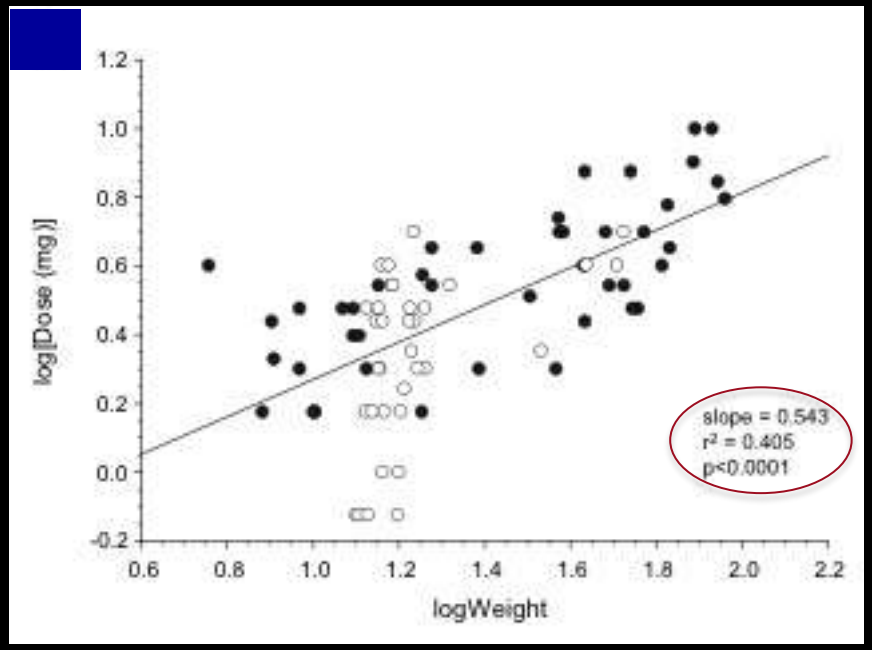
Results: Dose prediction model for warfarin in Children

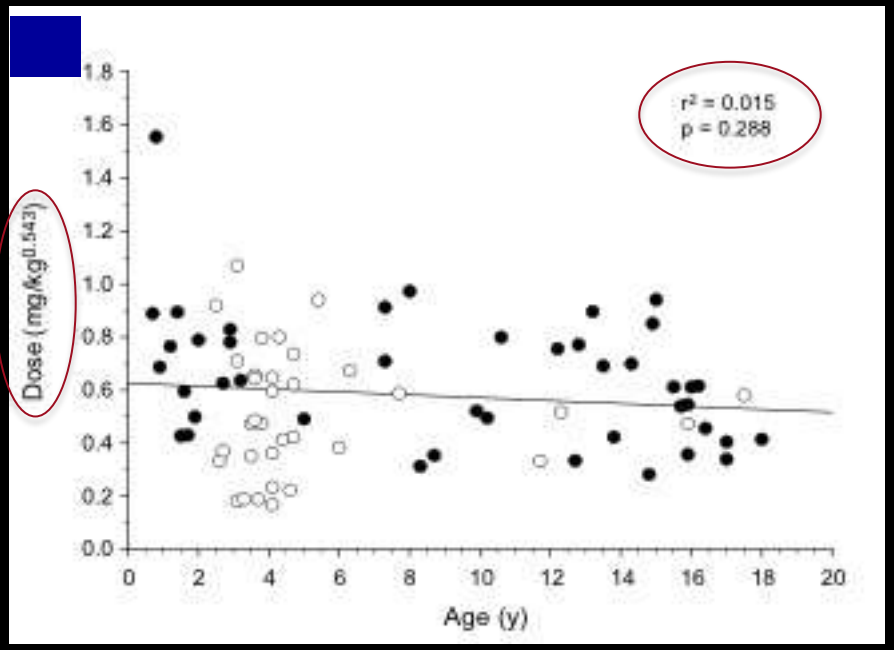
Contribution of *VKORC1* and *CYP2C9* genotypes and clinical factors to multivariate regression model for predicting therapeutic warfarin dose in children (mg)

x variable	Univariate R^2	Contribution to model, %	*p*-value
Weight	52.8	52.8	<0.001
VKORC1	17.2	12.2	<0.001
*CYP2C9*2*	0.04	1.0	0.078
*CYP2C9*3*	7.8	7.9	<0.001
Fontan	17.9	2.4	0.015
Full Model	--	**76.3**	<0.001

Regression Equation:
Square root of dose = 1.71 +0.014 [weight] – 0.257[VKORC1 variant alleles] – 0.127[CYP2C9 *2 alleles] – 0.463[CYP2C9 *3 alleles] – 0.161[Fontan]

Results: Allometric Scaling & Dose





- **Log[dose] plotted against log[weight] gives a slope of 0.543**
- **Allometric scaling using 0.543 as an exponent helps to eliminate the effect of age on dose (r^2=0.015)**

Results: Allometric Scaling & Dose

Contribution of *VKORC1* and *CYP2C9* genotypes and clinical factors to multivariate regression model for predicting therapeutic warfarin dose in children (mg/kg^0.543)

x variable	Contribution to model, %	*p*-value
VKORC1	20.8	<0.001
*CYP2C9*3*	15.6	<0.001
Heart Valve	7.9	0.003
*CYP2C9*2*	2.3	0.081
Full Model	46.6	<0.001

Using allometric scaling increases the contribution of genetics to dose variability from 21.1% to 38.7%

Results: Therapeutic dose

- **Both *CYP2C9* and *VKORC1* significantly influenced required warfarin dose in children**
- **Larger percentage of dose variability was explained by clinical and genetic factors (76.3%) in children than in adult studies**
- **Validated the performance of a pediatric pharmacogenetic dosing model**
- **Results suggest that a pediatric-specific dosing model should be used in children to avoid over-anticoagulation**