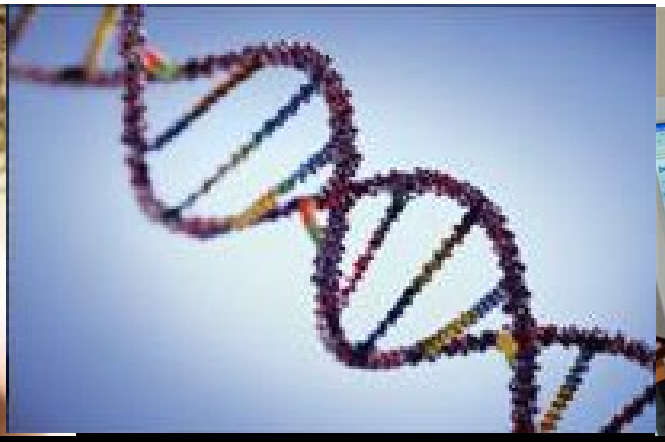
Canadian Pharmacogenomics Network for Drug Safety

UBC

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


Using the Human Genome to Understand Medication Response

Dr. Bruce Carleton

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MedSafe Clinics, BC Children's and St Paul's Hospitals

Senior Clinician Scientist, BC Chlldren's Hospital Research Institute

Vancouver, CANADA

Land Acknowledgement

Today’s word is *reconciliation*

E lau hoe, mai na wa'a; i ke ka, i ka hoe, i ka hoe, i ke ka; pas aku i ka’aina

Overarching Goals
of the CPNDS Precision Medicine Network

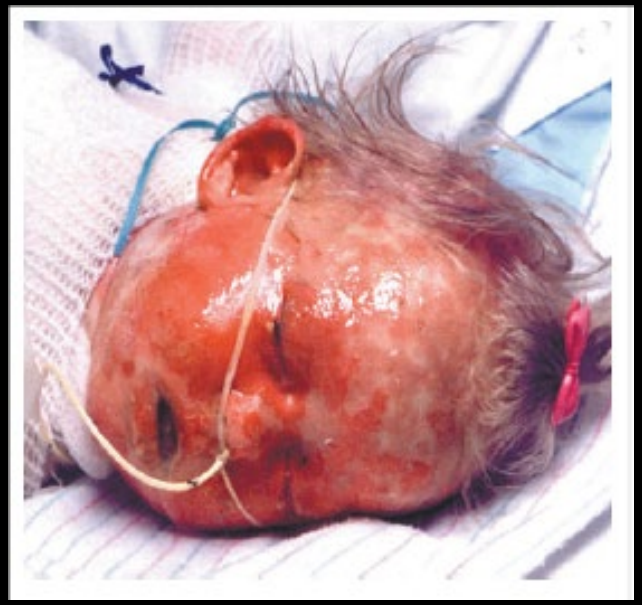
Make the lives of children better

Survive and Thrive

Optimize drug therapy to achieve its best outcomes possible for every patient

Avoid harmful outcomes from medication use

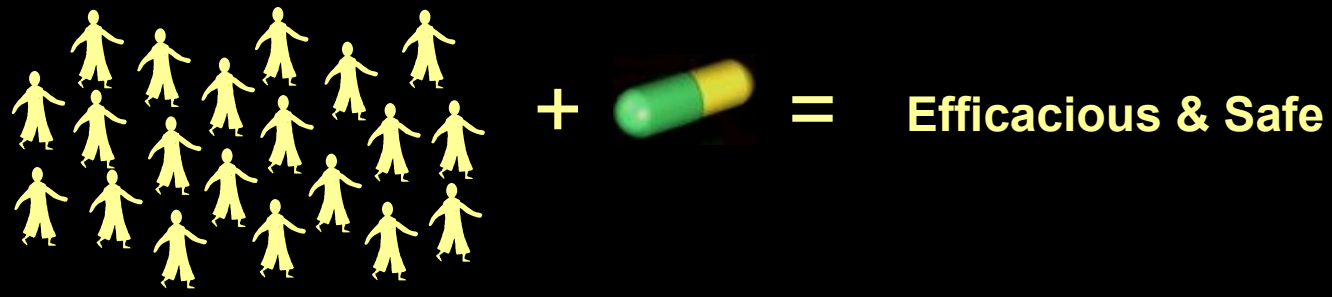
Individual variability in drug response can have serious consequences



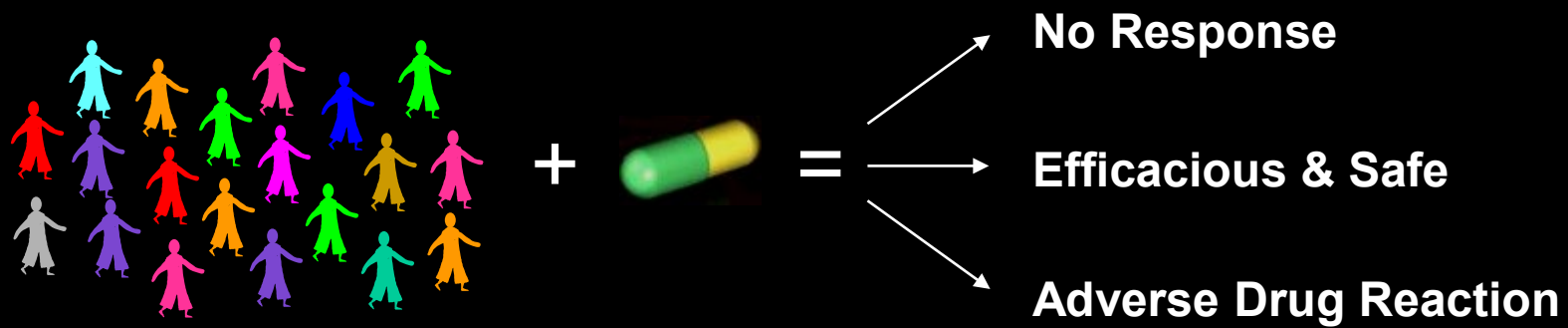
Stevens-Johnson Syndrome (SJS)
Adverse Drug Reaction

Paradox of Modern Drug Development

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



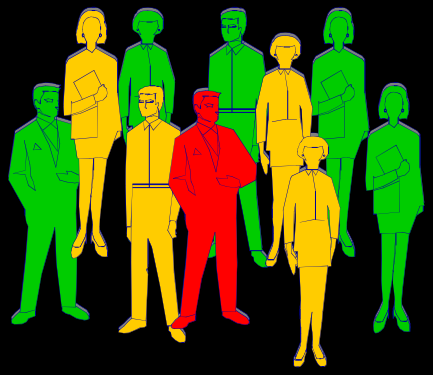
2. Physicians treat ***individual*** patients who can <u>vary widely</u> in their response to drug therapy



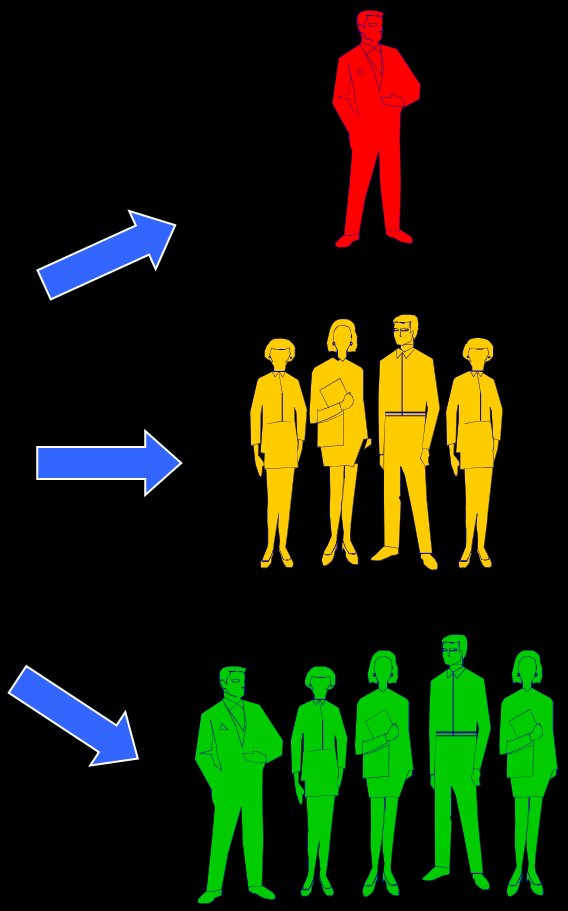
Pharmacogenomics

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

All Patients with Same Diagnosis



10% risk of adverse reaction



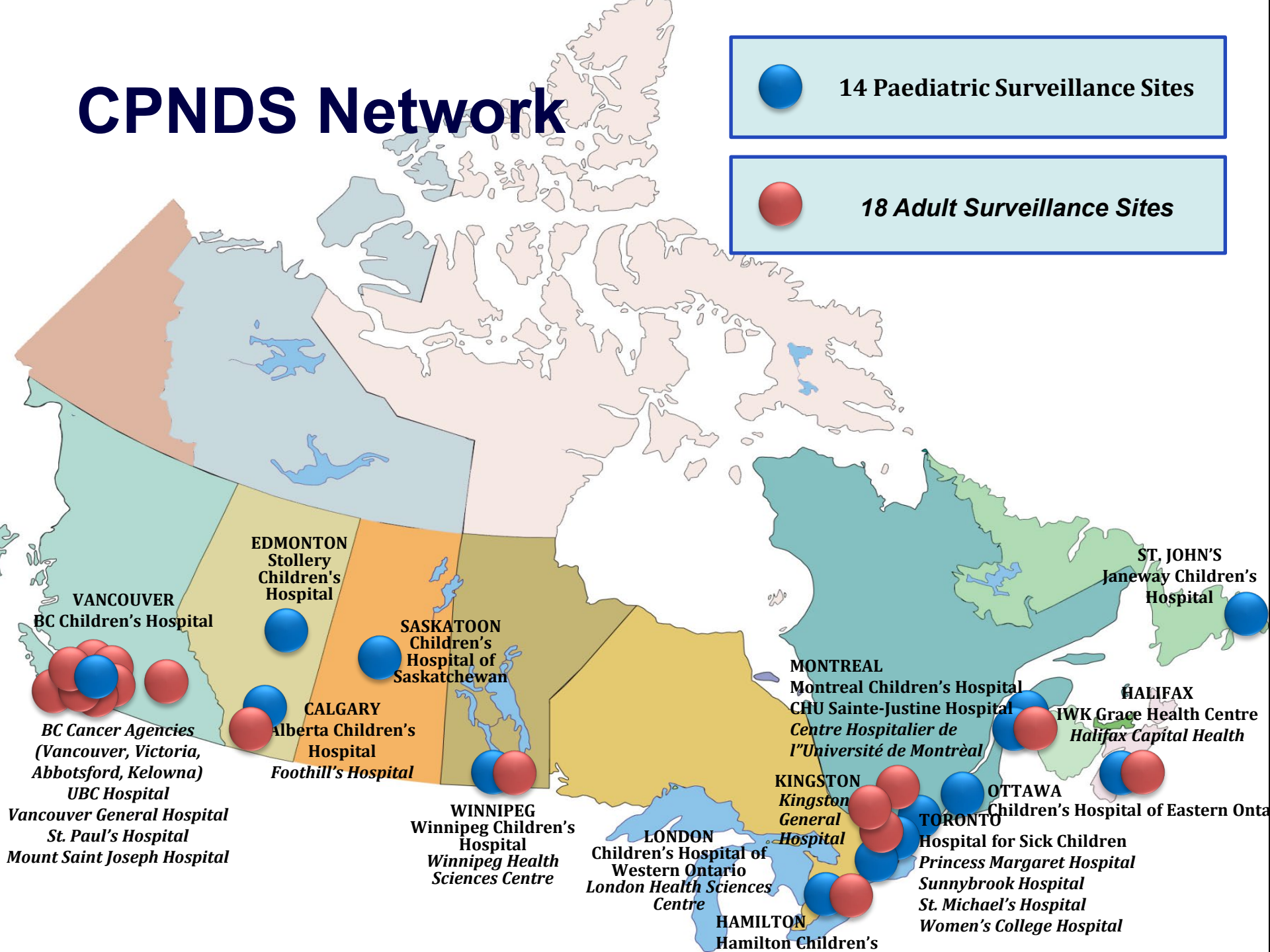
Pharmacogenetic Profile:

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

CPNDS Network



CPNDS Biomarker Discovery Strategy

1. Identify children with ADRs & matched controls

2. Collect DNA samples (blood/ saliva)

3. Detailed patient clinical character-ization

4. Screen genetic variants

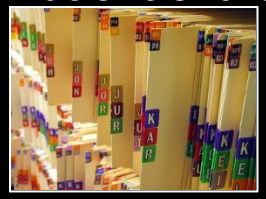
5. Replication

ADR cases

Matched controls

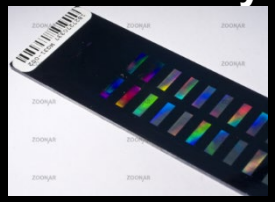
Patient blood/ saliva

Patient charts

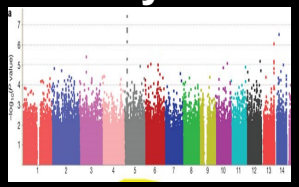


Clinical data

Custom ADME Array



Statistical Analyses

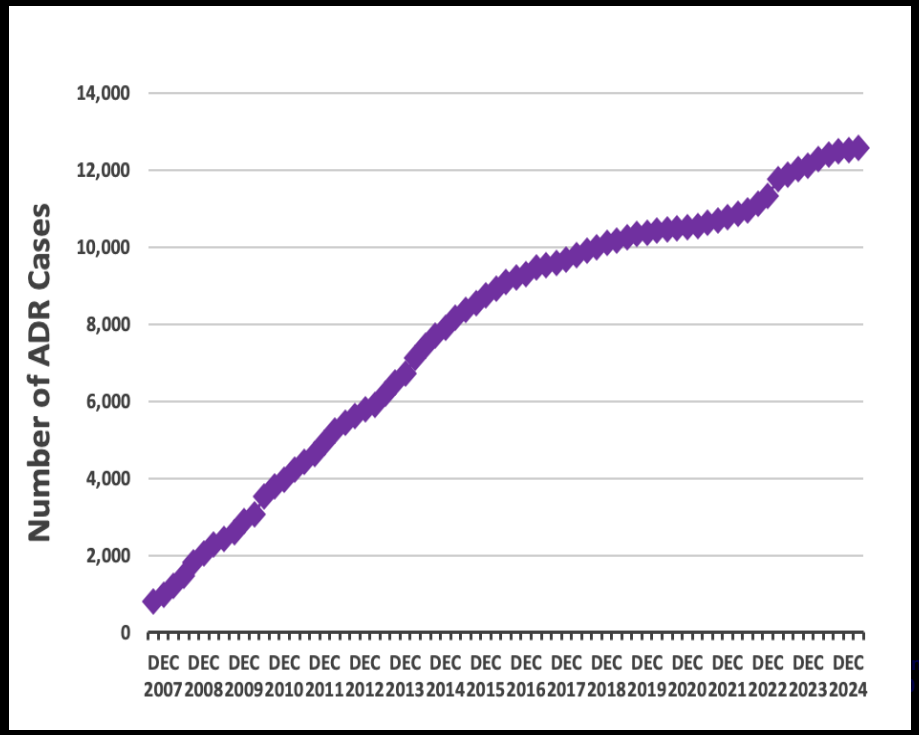


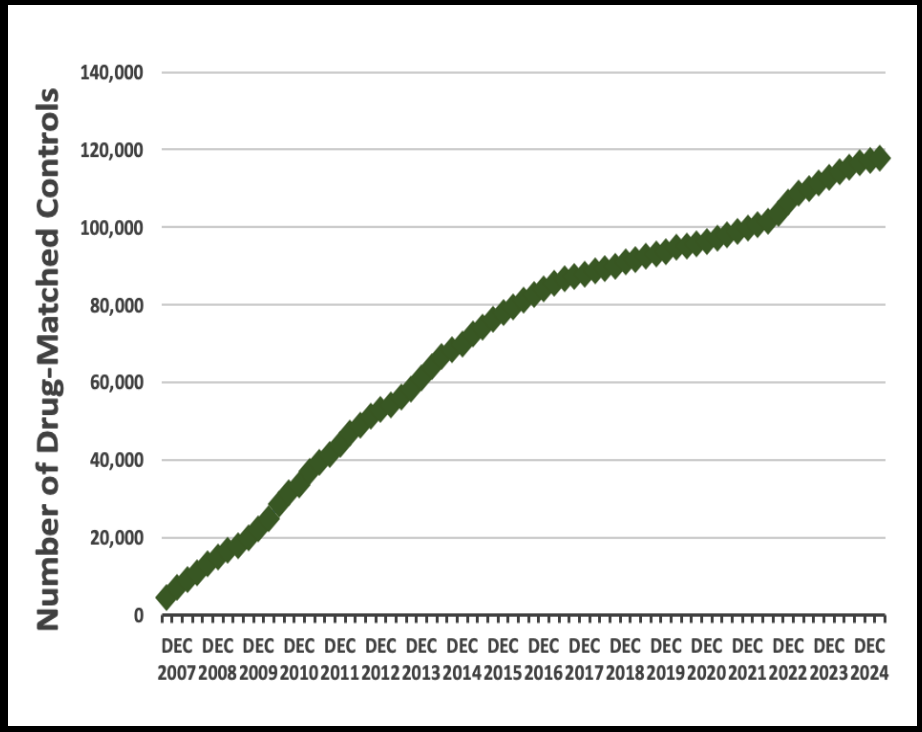
ADR cases & controls

Assay DNA samples

Statistical Analyses

Recruitment of ADR cases and drug-matched controls in Canada

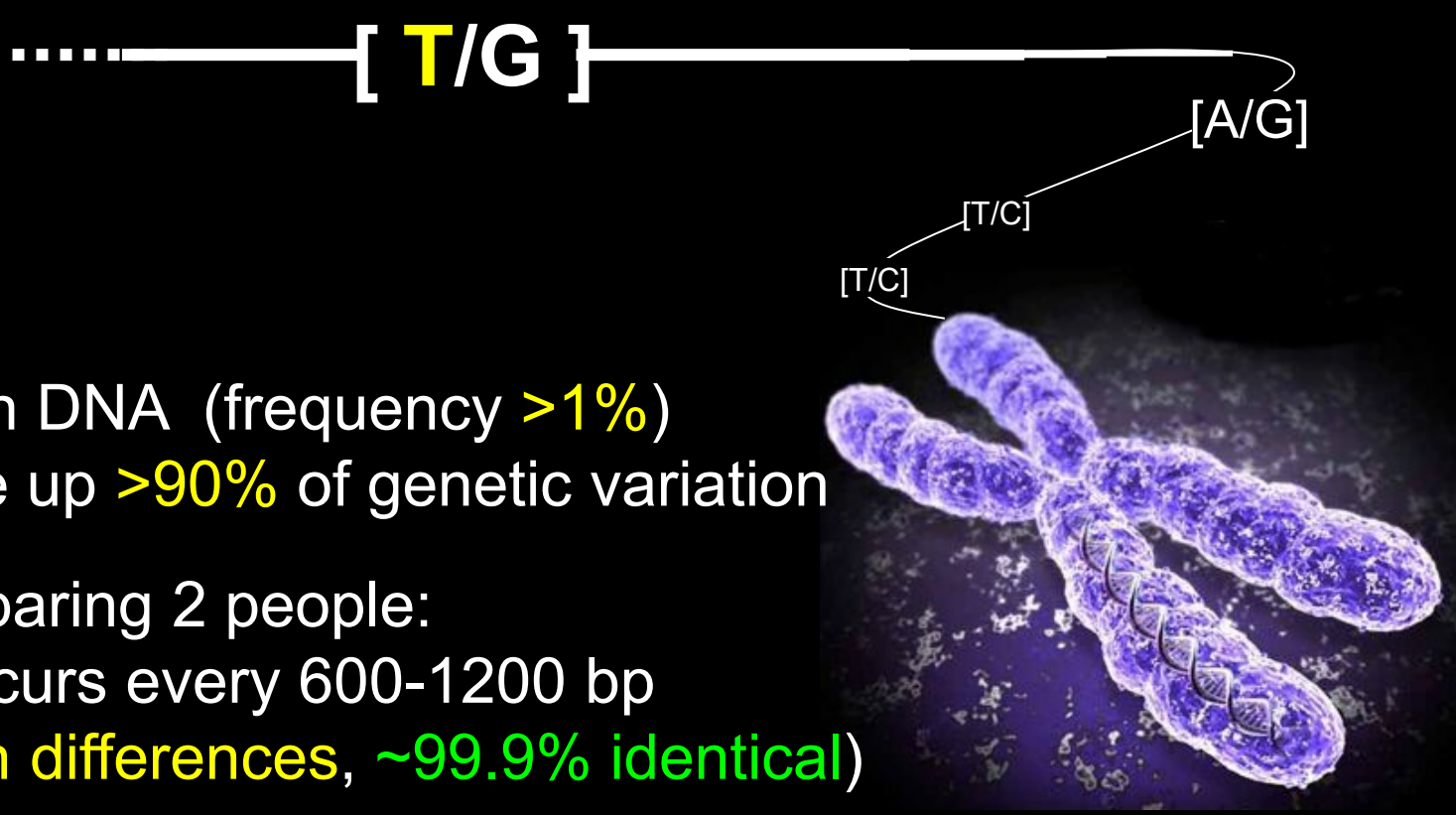




12,565
ADR cases

117,945
Drug-matched controls

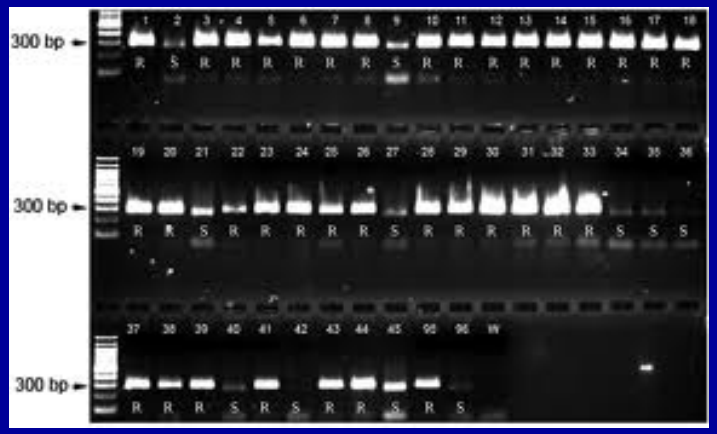
Single Nucleotide Polymorphisms (SNP)



- Variations in DNA (frequency >1%)
- SNPs make up >90% of genetic variation
- When comparing 2 people:
  1 SNP occurs every 600-1200 bp
  (= 5million differences, ~99.9% identical)
- More than 15 Million known SNPs
- 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

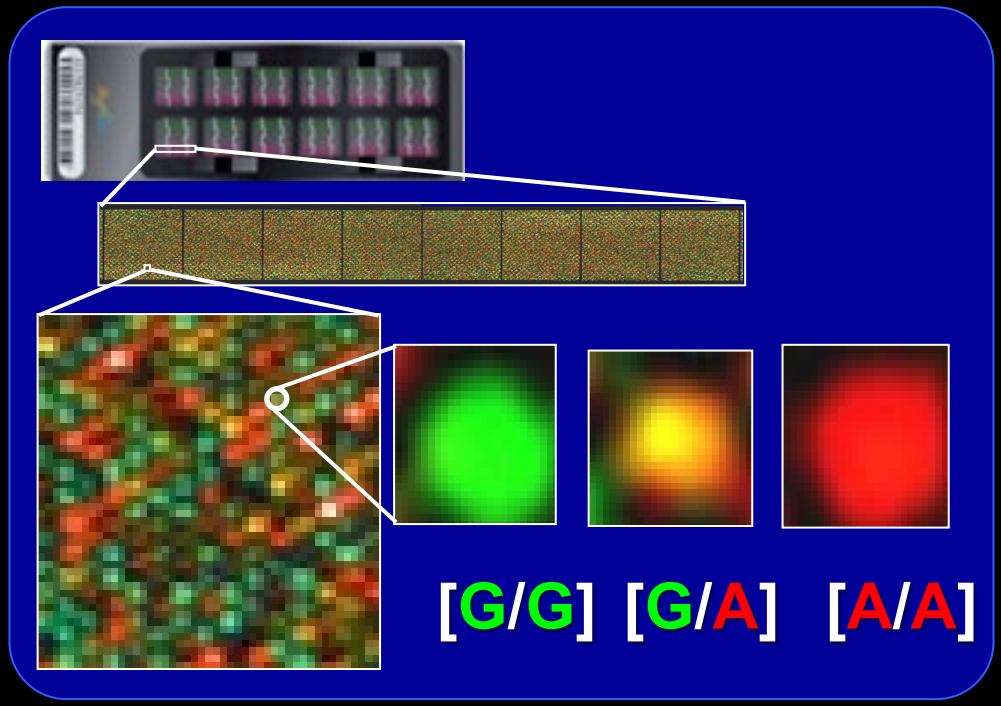
Advances in Genomics Technology

Year 2002



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

Year 2017



2 days to genotype
1 million variants
Throughout the genome
Cost: ~$50

Codeine-Induced Infant Mortality

- **Initial Case Report**:
- A new mother was given a standard dose of Tylenol #3 for obstetric pain relief
- Complained of significant drowsiness and constipation; dose reduced by 50%
- Infant showed poor feeding
- Infant died on day 13 due to respiratory failure

- **Follow-up Analysis:**
- Infant's blood contained lethal levels of morphine (70 ng/ml)
- Coroner brings case to GATC
- Maternal milk contained 87 ng/ml of morphine (10-20x expected)

Identified genetic variants associated with lethal reaction to codeine in newborns

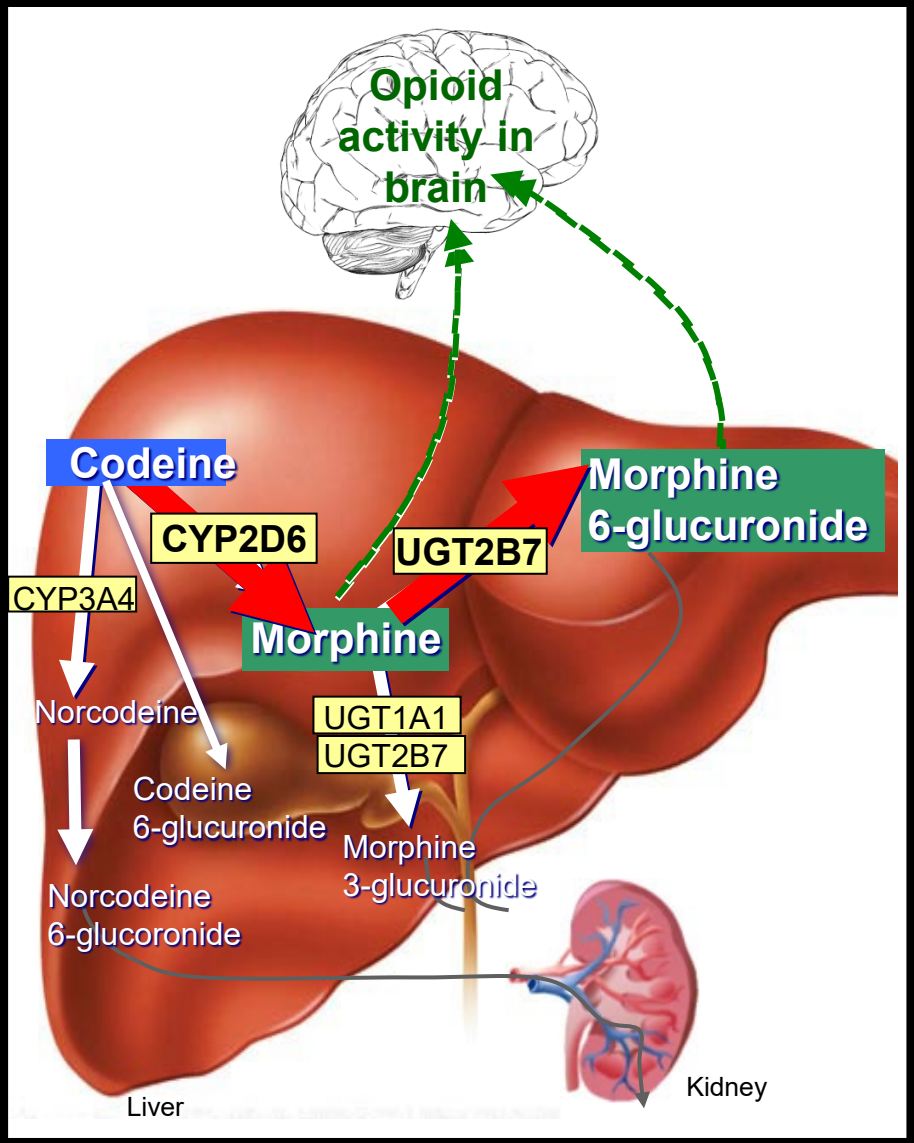
Mother's Genotype:

CYP2D6 gene duplication

UGT2B7*2/*2

Outcome:

- Accumulation of morphine in breast milk
- Breast milk fed to infant
- Accumulation of morphine in infant caused CNS depression, respiratory failure, and death



Koren et al, *Lancet*, 2006

Prior to Our Work

- *The American Academy of Pediatrics and "Drugs in Pregnancy in Lactation", the major reference guide to fetal and neonatal risk, list codeine as compatible with breastfeeding*

  – Briggs et al., 2005; Pediatrics, 2001

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

(340,000 births, 73% breastfed, 52% mothers receive codeine post-childbirth,1.4% risk genotype)


GREATER TORONTO EDITION - WEATHER: SUNNY, HIGH 19. MAP AND DETAILS, S6

S&P/TSX COMPOSITE 12,328.21 ▲ 34.01

THE GLOBE AND MAIL

CANADA'S NATIONAL NEWSPAPER ● FOUNDED 1844 ● GLOBEANDMAIL.COM ● WEDNESDAY, MAY 10, 2006

Codeine can turn toxic in nursing mothers

May 10, 2006

FDA drug label change and public health advisories


FDA

U.S. Food and Drug Administration

U.S. Department of Health and Human Services

FDA Warning on Codeine Use by Nursing Mothers

May Increase Chance of Serious Side Effects in Infants

The U.S. Food and Drug Administration (FDA) is concerned that nursing infa
ultra-rapid metabolizers of codeine. The agency has reviewed all available inf
who died from morphine overdose. The morphine levels in the mother's milk
showed that the mother was an ultra-rapid metabolizer of codeine.

"Our best advice to physicians prescribing codeine-containing products to nu
Sandra Kweder, M.D., deputy director of the Office of New Drugs in FDA's Ce
physicians before taking any codeine containing products."

Codeine is an ingredient found in prescription and non-prescription medicines
(metabolized) to morphine. Some people, due to their genetic makeup, meta
metabolizers, are more likely to have higher-than-normal levels of morphine i
usual levels of morphine in breast milk.

According to the FDA, nursing mothers have used codeine safely for many y
relievers for nursing women and their babies. However, to raise awareness of
manufacturers of prescription codeine medicines to include information about
information about this issue on the FDA website for healthcare providers and

Nursing mothers taking codeine (or other narcotic pain relievers) should know
three hours and should not sleep for more than four hours at a time. Signs of
breathing difficulties or limpness.

The chance of being an ultra-rapid metabolizer varies among different populat
metabolizers, the risk of having an adverse event when taking codeine is not
There is a FDA-cleared test to check for ultra-rapid metabolism, but there is
alone may not correctly predict if a mother's breast milk will have too much n

Mothers and babies gain many health benefits from breastfeeding. When a n
is important for healthcare professionals and nursing women using codeine o

For more information, go to Use of Codeine Products in Nursing Mothers

Aug 17, 2007

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About Health Canada

Use of Codeine Products by Nursing Mothers

Advisory

OTTAWA - Health Canada is advising the public, especiall
very rare but serious health risk to breastfed babies pose
Once ingested, codeine is converted by the body into mor
codeine into morphine more rapidly and completely than o
mothers who rapidly metabolize codeine may be at increas
due to higher-than-expected morphine levels in breast mil

Codeine is found in prescription and non-prescription prod
treat coughs. Despite the common use of codeine product
reports of adverse events in infants are rare. However, a
information is important because in severe cases, infant d

Health Canada recommends nursing mothers take the follo
the risk of morphine exposure in breastfed babies:

Aug. 21, 2008


VANCOUVER EDITION ▮ THURSDAY, AUGUST 21, 2008

VARIABLY CLOUDY, HIGH 18 LOW 14

THE GLOBE AND MAIL

CANADA'S NATIONAL NEWSPAPER

HEALTH ▮ 'YOU CANNOT CONTINUE TO GIVE IT LIKE CANDIES'

Codeine can prove toxic for breastfed babies

Study highlights risk in mother's milk

Nationwide outbreak spurs massive meat recall

August 20, 2009

The NEW ENGLAND JOURNAL of MEDICINE

361;8 AUGUST 20, 2009

Codeine, Ultrarapid-Metabolism Genotype, and Postoperative Death

- 2 year old boy
- Received tonsillectomy for sleep apnea
- Received standard codeine dose
- Died of respiratory depression
- High levels of morphine in blood (32 ng/ml)
- Boy carried CYP2D6 gene duplication

PEDIATRICS

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

More Codeine Fatalities After Tonsillectomy in North American Children

Lauren E. Kelly, Michael Rieder, John van den Anker, Becky Malkin, Colin Ross, Michael N. Neely, Bruce Carleton, Michael R. Hayden, Parvaz Madadi and Gideon Koren

Pediatrics; originally published online April 9, 2012;

"…These cases demonstrate that analgesia with codeine or other opioids that use the CYP2D6 pathway after adenotonsillectomy may not be safe in young children with obstructive sleep apnea syndrome."

Drug Label Change

Feb. 22, 2013 FDA New Black Box Warning

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communication

Safety review update of codeine use in children; new *Boxed Warning* and *Contraindication* on use after tonsillectomy and/or adenoidectomy

This update is in follow-up to the FDA Drug Safety Communication: Codeine use in certain children after tonsillectomy and/or adenoidectomy may lead to rare, but life-threatening adverse events or death issued on 8/15/2012.

Safety Announcement

[2-20-2013] The U.S. Food and Drug Administration (FDA) is updating the public about new actions being taken to address a known safety concern with codeine use in certain children after tonsillectomy and/or adenoidectomy (surgery to remove the tonsils and/or adenoids). Deaths have occurred post-operatively in children with obstructive sleep apnea who received codeine for pain relief following a tonsillectomy and/or adenoidectomy. Codeine is converted to morphine by the liver. These children had evidence of being ultra-rapid metabolizers of codeine, which is an inherited (genetic) ability that causes the

THE WALL STREET JOURNAL.

U.S. NEWS | February 20, 2013, 7:16 p.m. ET

FDA Warns on Codeine Use for Children

Calls for Removal of Codeine

Globe & Mail August 20, 2009

SECTION L THURSDAY, AUGUST 20, 2009

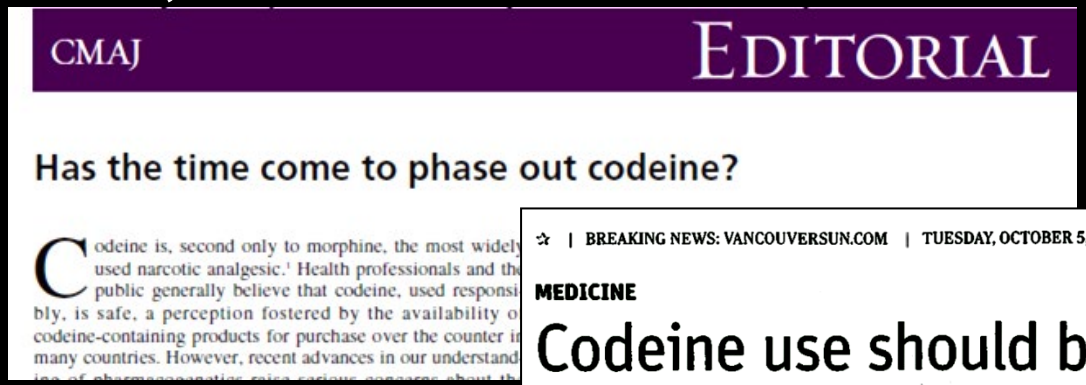
Globe Life

STUDY || PAINKILLERS

Codeine may be fatal to children after tonsil surgery

BY ANDRÉ PICARD
PUBLIC HEALTH REPORTER

CMAJ, Oct. 2010



CMAJ EDITORIAL

Has the time come to phase out codeine?

Codeine is, second only to morphine, the most widely
used narcotic analgesic.[1] Health professionals and th
public generally believe that codeine, used responsi
bly, is safe, a perception fostered by the availability o
codeine-containing products for purchase over the counter i
many countries. However, recent advances in our understand

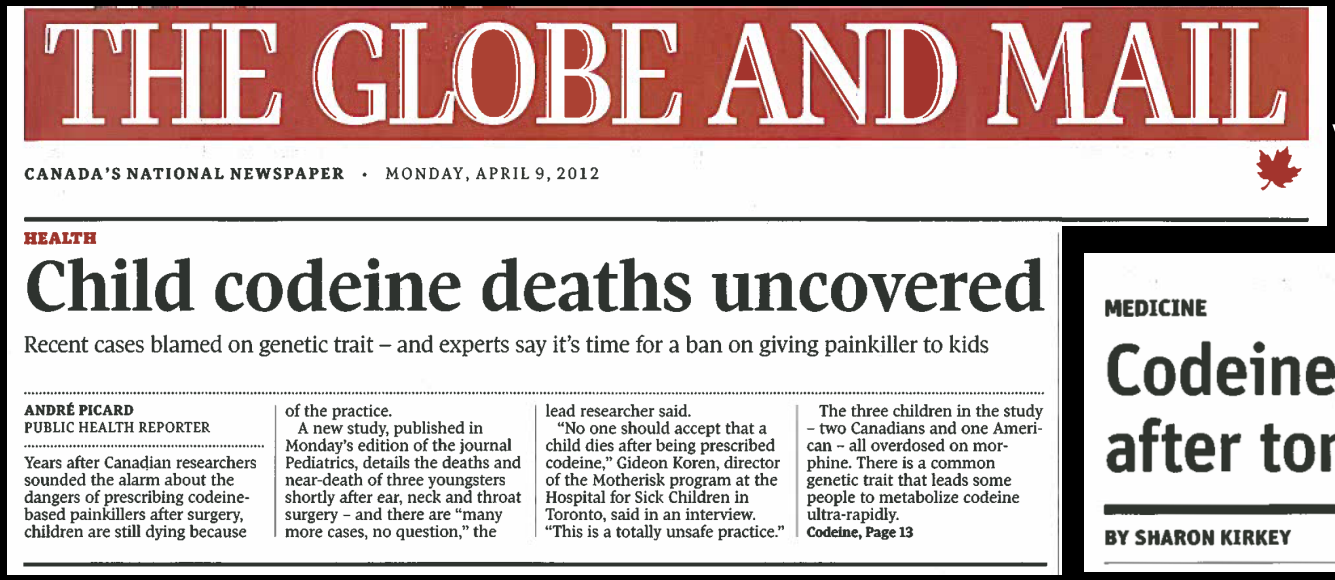
Globe & Mail October 5, 2010

☆ | BREAKING NEWS: VANCOUVERSUN.COM | TUESDAY, OCTOBER 5, 2010

MEDICINE

Codeine use should be halted, journal says

Cover Globe & Mail April 9, 2012



THE GLOBE AND MAIL

CANADA'S NATIONAL NEWSPAPER • MONDAY, APRIL 9, 2012

HEALTH

Child codeine deaths uncovered

Recent cases blamed on genetic trait – and experts say it's time for a ban on giving painkiller to kids

ANDRÉ PICARD
PUBLIC HEALTH REPORTER

Years after Canadian researchers sounded the alarm about the dangers of prescribing codeine-based painkillers after surgery, children are still dying because of the practice.

A new study, published in Monday's edition of the journal Pediatrics, details the deaths and near-death of three youngsters shortly after ear, neck and throat surgery – and there are "many more cases, no question," the lead researcher said.

"No one should accept that a child dies after being prescribed codeine," Gideon Koren, director of the Motherisk program at the Hospital for Sick Children in Toronto, said in an interview. "This is a totally unsafe practice."

The three children in the study – two Canadians and one American – all overdosed on morphine. There is a common genetic trait that leads some people to metabolize codeine ultra-rapidly.

Codeine, Page 13

Vancouver Sun April 10, 2012

MEDICINE

Codeine can kill kids after tonsil surgery

BY SHARON KIRKEY

are kids who, except for the sleep apnea, are healthy kids. They should have a life

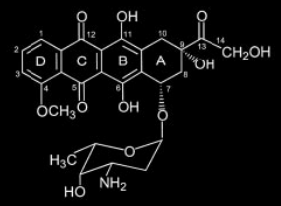
Anthracycline Case Report

- A previously healthy 10-year-old presented with abdominal mass
- Biopsy confirmed neuroblastoma
- Patient began standard doxorubicin chemotherapy protocol
  - Cumulative dose: 250 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
Preservative Free
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
Preservative Free
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
Preservative Free

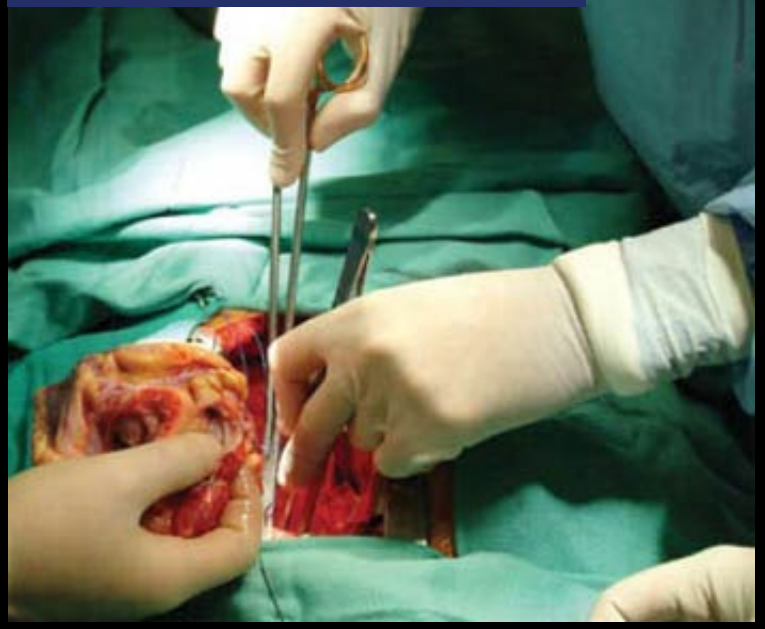
Anthracycline-Induced Cardiotoxicity

- 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

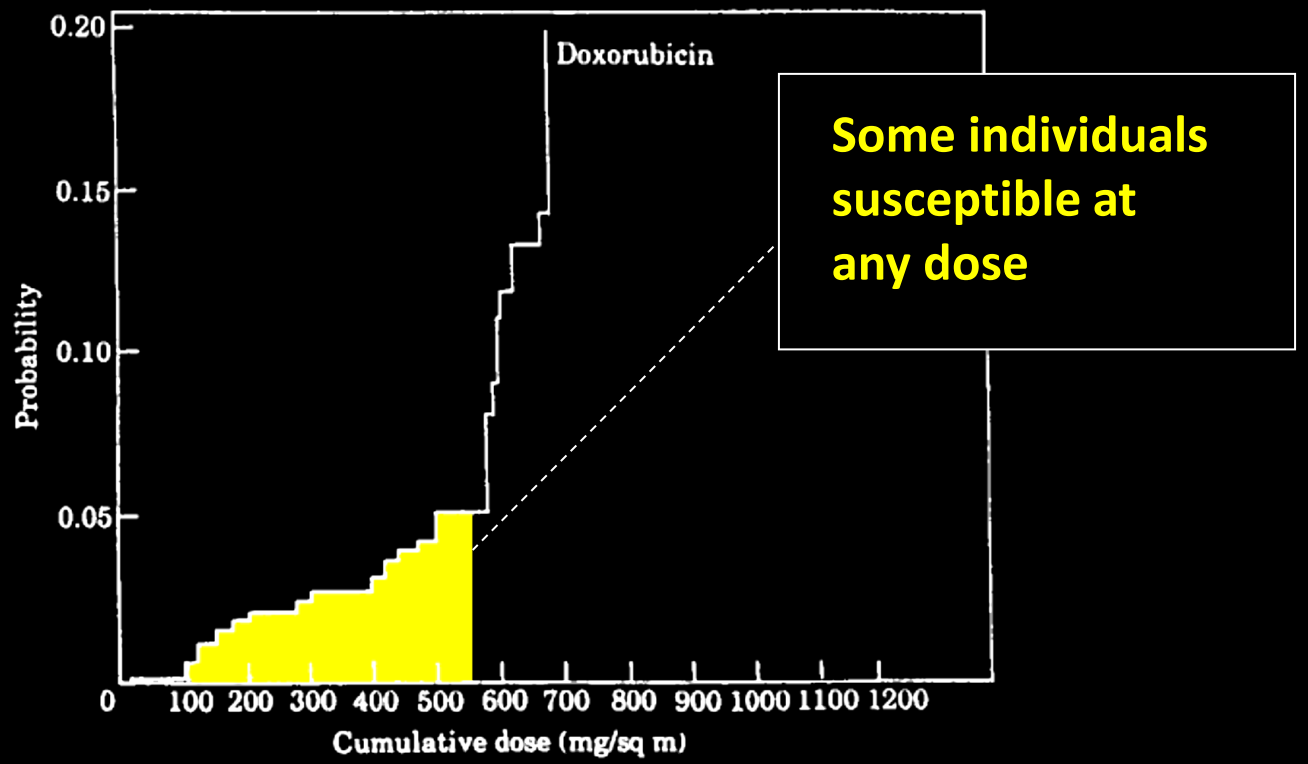


Figure adopted from: Launchbury & Habboubi. *Cancer Treat Rev*. 1993;19(3):197-228

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**

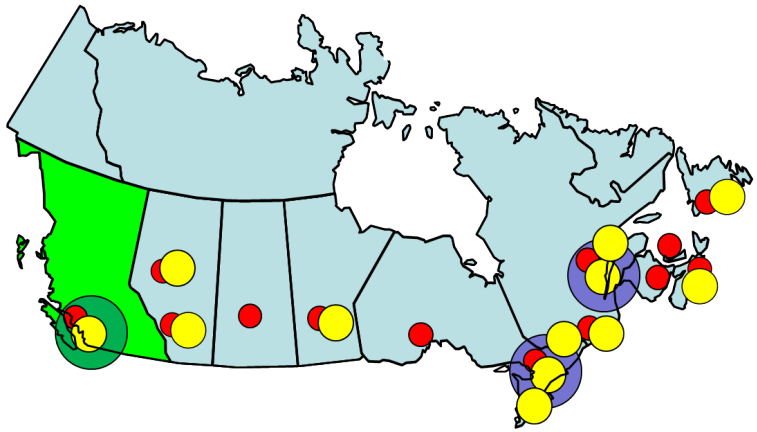
- **Grade 1 toxicity:**
  - Shortening fraction 27-30% or
  - Resting ejection fraction 50-60%

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%

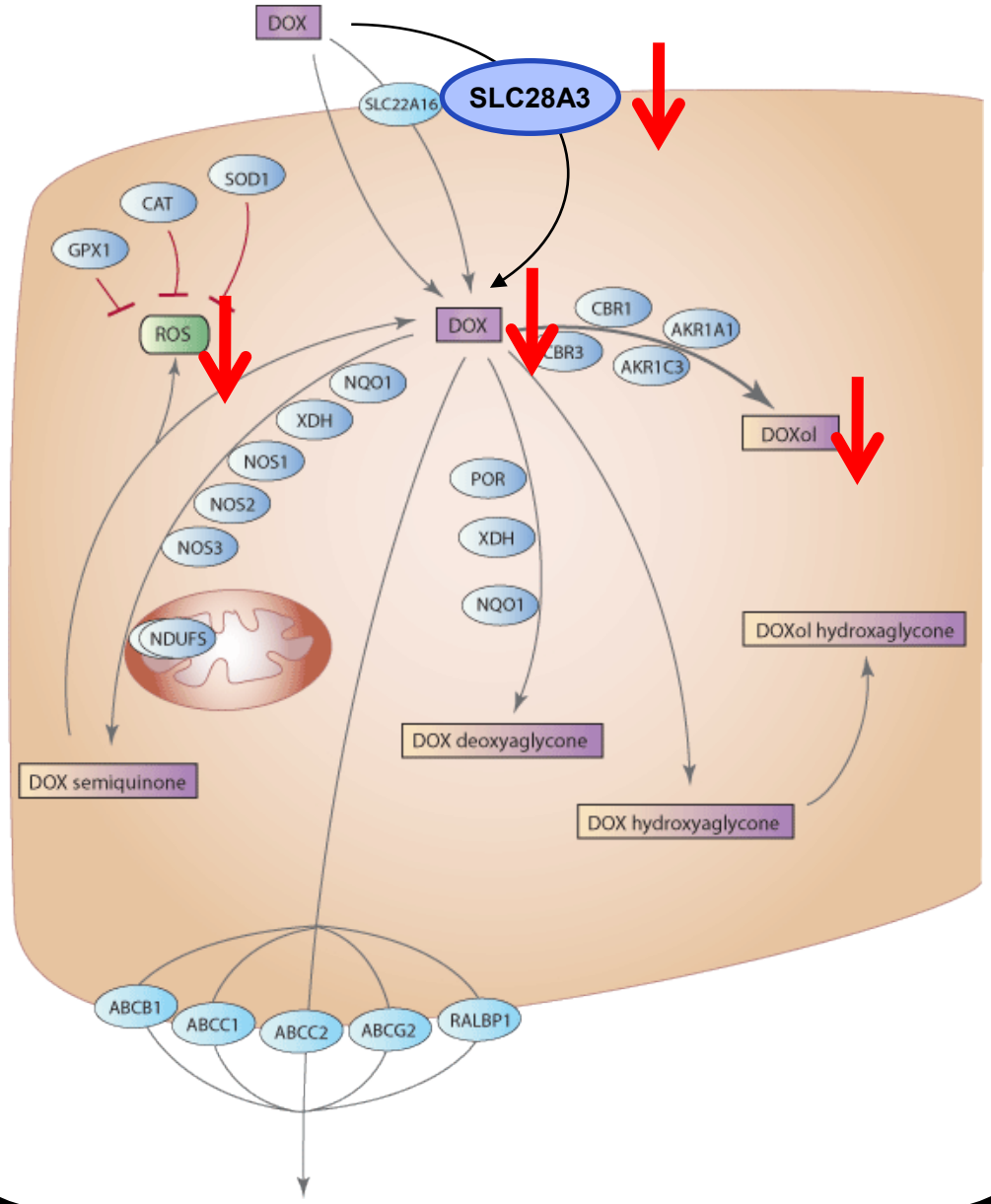
Modified National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 *With modified Grade 1 from 24-30% SF to 27-30% SF*

Further 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	

Mechanism of SLC28A3



Reduced SLC28A3 expression

Less anthracycline into cell

Less ROS and toxic alcohol metabolites

Less toxicity

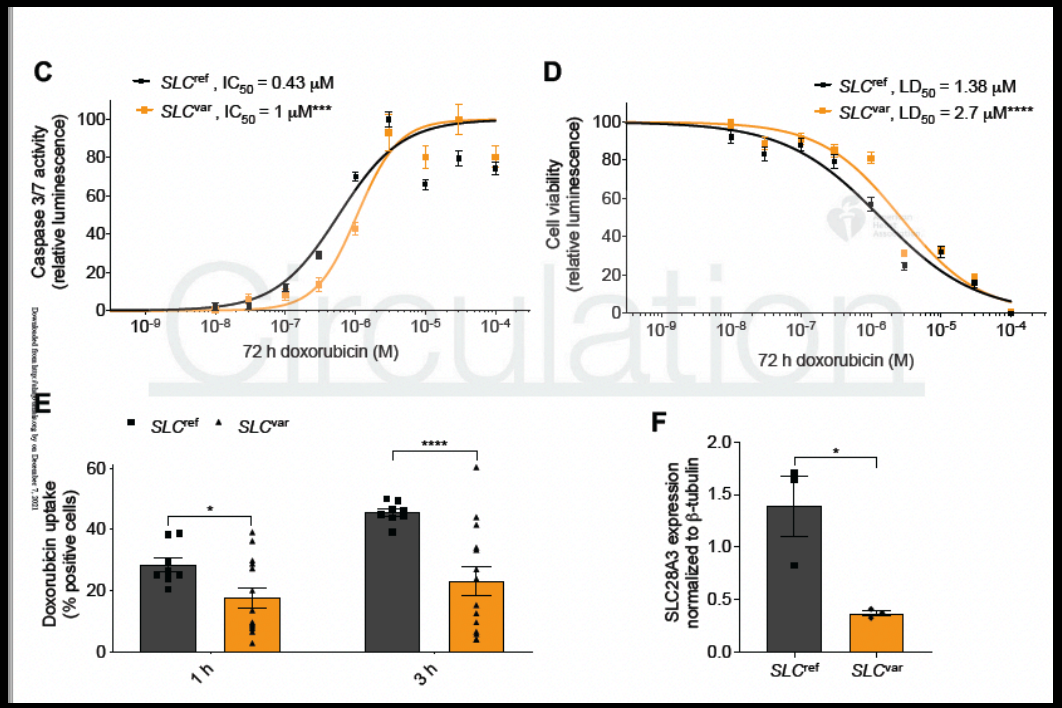
Validation of SLC28A3 in a patient iPSC heart cells

SLC28A3 variant exhibits increased cell viability when exposed to doxorubicin

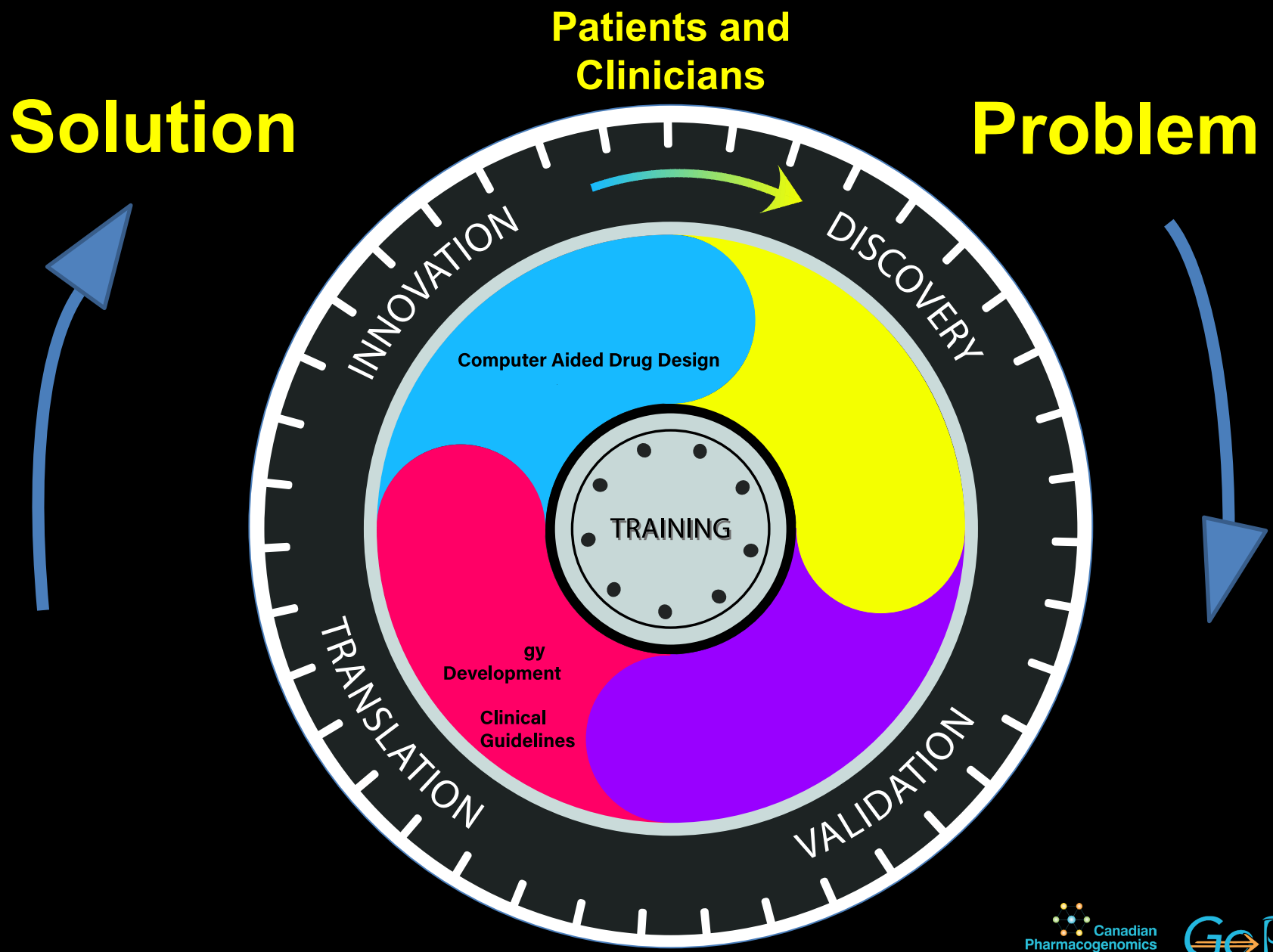
Identification of Drug Transporter Genomic Variants and Inhibitors That Protect Against Doxorubicin-Induced Cardiotoxicity

Tarek Magdy , Mariam Jouni , Hui-Hsuan Kuo , Carly J. Weddle , Davi Lyra-Leite , Hananeh Fonoudi , Marisol Romero-Tejeda , Mennat Gharib , Hoor Javed , Giovanni Fajardo , Colin J.D. Ross , Bruce C. Carleton , Daniel Bernstein and Paul W. Burridge

https://doi.org/10.1161/CIRCULATIONAHA.121.055801
Circulation. 2022;145:279–294



- Patient-derived iPSC cardiomyocytes
- *SLC28A3*^{rs11140490} exhibits:
  - 2.0-2.3-fold higher LD_{50} (P<0.0001) when exposed to doxorubicin
  - **2-fold reduced doxorubicin uptake into cells**
  - 3-fold reduced expression



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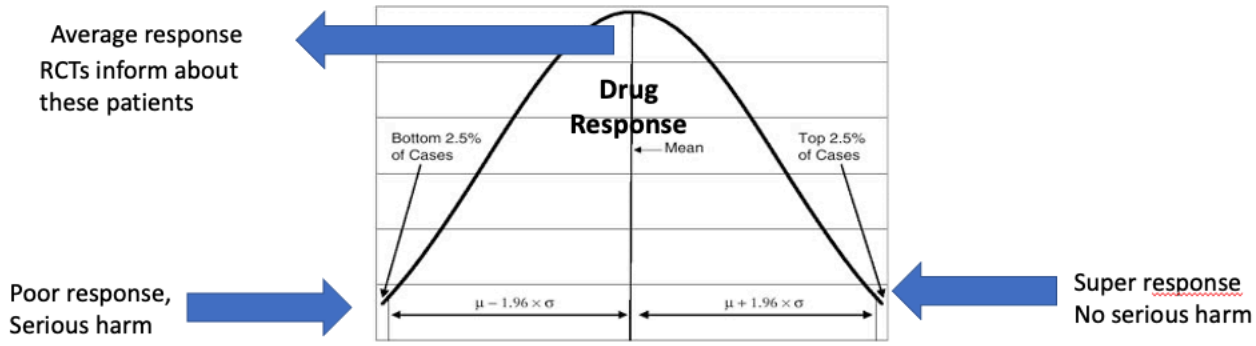
Study the Tails!

The Extraordinary Responders Project

Figure. Studying the extremes of drug therapy outcomes to better understand response and harm



Considerations:

- Outcomes may overlap or might not be sustainable over time
- Heterogeneous disease experience makes meaningful measurement of benefit/harm difficult over short time periods
- Both clinical and genomic investigations can lead to understanding the biological and mechanistic basis of outcomes

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