Prevention of Adverse Drug Reactions in Childhood by Identifying Predictive Genomic Markers: 
Use of Big (and Small) Data

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BC Children’s Hospital Research Institute, Vancouver
University of British Columbia
The Canadian Pharmacogenomics Network for Drug Safety has received financial support for its adverse drug reaction research from:

Canada Foundation for Innovation (CFI), Canadian Institutes of Health Research, Genome Canada, Genome British Columbia and the Provincial Health Services Authority. POPi has also received support by the University of British Columbia, Child & Family Research Institute (Vancouver), Health Canada, Michael Smith Foundation for Health Research, Eli Lilly Canada (unrestricted), Janssen Ortho Canada (unrestricted) Pfizer Canada (unrestricted) and Dynacare Next.

All industry funding was a partnership requirement of federal peer-reviewed Genome Canada research applications.

There are no patents or patents-pending for any of this work anywhere in the world.
Big Clinical Data Challenges

Population Health Data is great, but **drug outcomes** remain a limitation

- Particularly for quantifiable outcome data on specific outcomes (e.g., degree of cardiotoxicity induced by anthracyclines)
- If such data can be linked, which data?

- Pediatric echocardiography is done at baseline and throughout therapy
- Test results bounce around
  - measurement error?
  - Measured too close to anthracycline dose?
ADR Case Definitions

- Critical *a priori* need
- CTCAE definitions are rarely quantitative enough to use without modification
- Definition develops as data are collected and plan for analysis is refined
- Modifications to case definition are always needed over time as more data become available and more research is published
Pharmacoepidemiology
Big Data Methods

- Good at describing and dealing with limitations in the data
- Another approach is to go into the clinical data itself and define how best to address limitations
  - Sometimes best approach is to collect more data prospectively such that temporal relation between drug and outcome is better understood
  - Required data can be hidden in the clinical record where it is not expected
Canadian Pharmacogenomics Network for Drug Safety (CPNDS)

- Established & co-founded in 2004 by Bruce Carleton first as GATC, then CPNDS
- Pan-Canadian network with clinical surveillance and research personnel located at 13 pediatric and 13 adult hospitals and clinics across Canada
- Collects detailed information on ADRs from medical records and patients/families, other sources
- Purpose-built to find high-association pharmacogenomic biomarkers, create innovative tools (pharmacogenomic tests) to predict the likelihood of ADR risk and implement drug-safety solution strategies
CPNDS Network in Canada

**CPNDS Paediatric Surveillance Sites**
- 13 Paediatric Sites
  - 8 CPNDS
  - 5 C17 Sites

**CPNDS Adult Surveillance Sites**
- 13 Adult Sites

- VANCOUVER: CFRI/BC Children’s Hospital
- EDMONTON: Stollery Children’s Hospital
- CALGARY: Alberta Children’s Hospital
- WINNIPEG: Winnipeg Children’s Hospital
- KINGSTON: Kingston General Hospital
- LONDON: Children’s Hospital of Western Ontario
- MONTREAL: Montreal Children’s Hospital
- MONTREAL: Sainte-Justine Hospital
- OTTAWA: Children’s Hospital of Eastern Ontario
- TORONTO: Hospital for Sick Children
- HAMILTON: Hamilton Children’s Hospital
- ST. JOHN’S: Janeway Children’s Hospital
- HALIFAX: IWK Grace Health Centre
- WINNIPEG: Winnipeg Children’s Hospital
- CALGARY: Alberta Children’s Hospital
- EDMONTON: Stollery Children’s Hospital
- VANCOUVER: CFRI/BC Children’s Hospital

Adults: 3 sites-BCCA, VGH, SPH, KGH, PMH, SUN
5 MS Sites-UBC, WIN, LON, HAL, CHUM
How are Targeted ADRs identified?

- Targeted surveillance for ADRs of interest to **member institutions** and **Network Executive Steering Committee**
- Standardized case definitions
- Complete data; clinician surveillors are paid by the Network but work under contract to the Network at local sites
CPNDS ACTIVE Surveillance

- Responsive to local needs
- No local funding, despite my efforts and the alarming number of ADRs of clinical relevance
- Best way to determine ADR causation is to witness it or find temporal relations that can be further explored (e.g., ECGs before/after drug administration in two unlabeled populations receiving ondansetron)
Surveillance Tools

Clinical Characterization System Development: Case Definitions
- serious skin rashes (SJS/TEN, HSS) – data collection form
- nephrotoxicity (cisplatin)
- pancreatitis
- thrombosis
- hepatotoxicity (valproic acid)

Clinical Characterization Quality Assurance

Site quarterly reporting

Training Logs: Site visitation and training
## Standardized data collection

<table>
<thead>
<tr>
<th>Rash</th>
<th>Diagnostics</th>
</tr>
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<tbody>
<tr>
<td><strong>Morphology:</strong></td>
<td><strong>Blood count:</strong></td>
</tr>
<tr>
<td>Typical targets</td>
<td>Yes □ No □</td>
</tr>
<tr>
<td>Raised atypical targets</td>
<td>Result:</td>
</tr>
<tr>
<td>Flat atypical targets</td>
<td></td>
</tr>
<tr>
<td>Macules with/without blisters</td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

**Description:**

% BSA affected:
% BSA skin detachment:
Duration of eruption:

**Photographs:** Yes □ No □

<table>
<thead>
<tr>
<th>Mucous membrane involvement</th>
<th>Other organ manifestations</th>
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<tr>
<td><strong>Yes □ No □</strong></td>
<td>Lung:</td>
</tr>
<tr>
<td><strong>Yes □ No □</strong></td>
<td>Yes □ No □</td>
</tr>
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<td><strong>Yes □ No □</strong></td>
<td>Description:</td>
</tr>
<tr>
<td><strong>Yes □ No □</strong></td>
<td>CNS:</td>
</tr>
<tr>
<td><strong>Yes □ No □</strong></td>
<td>Yes □ No □</td>
</tr>
<tr>
<td><strong>Yes □ No □</strong></td>
<td>Description:</td>
</tr>
<tr>
<td><strong>Yes □ No □</strong></td>
<td>Heart:</td>
</tr>
<tr>
<td><strong>Yes □ No □</strong></td>
<td>Yes □ No □</td>
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<td><strong>Yes □ No □</strong></td>
<td>Description:</td>
</tr>
<tr>
<td><strong>Yes □ No □</strong></td>
<td>Muscle:</td>
</tr>
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<td><strong>Yes □ No □</strong></td>
<td>Yes □ No □</td>
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<td><strong>Yes □ No □</strong></td>
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<td><strong>Yes □ No □</strong></td>
<td>Gl tract:</td>
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<td>Yes □ No □</td>
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<td><strong>Yes □ No □</strong></td>
<td>Description:</td>
</tr>
<tr>
<td><strong>Yes □ No □</strong></td>
<td>Thyroid:</td>
</tr>
<tr>
<td><strong>Yes □ No □</strong></td>
<td>Yes □ No □</td>
</tr>
<tr>
<td><strong>Yes □ No □</strong></td>
<td>Description:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infections/Virus reactivation</th>
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<tbody>
<tr>
<td>HIV</td>
<td>Yes □ No □ Not assessed □</td>
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</tr>
<tr>
<td>HHV-6</td>
<td>Yes □ No □ Not assessed □</td>
<td></td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>Yes □ No □ Not assessed □</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Could take 4-5 hours, or up to 4-5 days to complete clinical characterizations
### DNA Information

<table>
<thead>
<tr>
<th></th>
<th>Sample collected</th>
<th>Collection method</th>
<th>Date sent to CMMT</th>
<th>Courier tracking/bill of lading #</th>
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<tbody>
<tr>
<td>Patient</td>
<td>Blood ○, Saliva ○, Buccal Swab ○</td>
<td>○</td>
<td>21/02/2012 21-Feb-2012</td>
<td>□ □</td>
</tr>
<tr>
<td>Mother</td>
<td>Yes ○, No □</td>
<td>Blood ○, Saliva ○, Buccal Swab ○</td>
<td>21/02/2012 21-Feb-2012</td>
<td>□ □</td>
</tr>
<tr>
<td>Father</td>
<td>Yes ○, No □</td>
<td>Blood ○, Saliva ○, Buccal Swab ○</td>
<td>□ DD-MM-YYYY</td>
<td>□ □</td>
</tr>
</tbody>
</table>

### Patient Information

1. **Date of birth:** 25-05-1998
   - 25-May-1998
   - **Age at time of enrolment:** 13.7 years

1.2 **Height:** inches 130.8 cm
   - Body Surface Area: 0.93 m²

1.3 **Weight:** lbs 24 kg

1.4 **Country of Ancestry:**
   - Patient: Ire/Germ/Eng ▼
   - Mother: Ireland/German ▼
   - Father: Germany/Englan▼
   - Maternal grandmother: Ireland ▼
   - Paternal grandmother: Germany ▼
   - Maternal grandfather: Germany ▼
   - Paternal grandfather: England ▼

1.5 **Sex:** Male ○, Female □, Unknown □

**Notes:**
- Diagnosed with high risk T-cell acute lymphoblastic leukemia in December 2006
- Protocol AALL0434, Arm C (December 2006 to September 2008)
- Modified Protocol 0232 (September to November 2008)
- Protocol BMT ASCT0431 (December 2008 to January 2009)

- Vincristine given: Total cumulative dose: 51mg/m²
- Anthracyclines given: Total cumulative dose: 275mg/m²
- Radiation given: Total body radiation, 1200cGy (December 2008)
  - Cranial radiation, 1200cGy (September 2007)
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<tr>
<th>Generic Name</th>
<th>Tobramycin</th>
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<tbody>
<tr>
<td>Dose</td>
<td>35-40 mg q8h</td>
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<tr>
<td>Total daily dose</td>
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</tr>
<tr>
<td>Dose/kg</td>
<td></td>
</tr>
<tr>
<td>Combination Product</td>
<td>Yes</td>
</tr>
<tr>
<td>Route used</td>
<td>Oral, IV, IM, SC, Other</td>
</tr>
<tr>
<td>Indication</td>
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</tr>
<tr>
<td>Brand Name</td>
<td></td>
</tr>
<tr>
<td>Manufacturer</td>
<td></td>
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<tr>
<td>Therapeutic Class</td>
<td>Antibiotic-Aminoglycoside</td>
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<tr>
<td>Notes</td>
<td>Intermittent: 09/11/09-11/11/09, 11/12/09-21/12/09, 27/01/10-11/02/10</td>
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<table>
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<tr>
<th>Generic Name</th>
<th>Vancomycin</th>
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<td>150-200 mg q6-8h</td>
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<tr>
<td>Total daily dose</td>
<td></td>
</tr>
<tr>
<td>Dose/kg</td>
<td></td>
</tr>
<tr>
<td>Combination Product</td>
<td>Yes</td>
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<tr>
<td>Route used</td>
<td>Oral, IV, IM, SC, Other</td>
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<tr>
<td>Therapy Dates:</td>
<td>From 29/01/2010, 29-Jan-2010, to 13/08/2010, 13-Aug-2010, Duration 196 days</td>
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<tr>
<td>Indication</td>
<td></td>
</tr>
<tr>
<td>Brand Name</td>
<td></td>
</tr>
<tr>
<td>Manufacturer</td>
<td></td>
</tr>
<tr>
<td>Therapeutic Class</td>
<td>Antibiotic</td>
</tr>
<tr>
<td>Notes</td>
<td>Intermittent: 29/01/10-10/02/10, 21/04/10-23/04/10, 18/05/10-22/05/10, 11/08/10-13/08/10</td>
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</tbody>
</table>
Recruitment of ADR cases and drug-matched controls in Canada

Severe ADR case reports

- Number of ADR Reports
- Y-axis: 0 to 10,000
- X-axis: Dec 2005 to Dec Jun 2017

- 9,537 ADR case reports

Drug-matched controls

- Number of Control Reports
- Y-axis: 0 to 90,000
- X-axis: Dec 2005 to Dec Jun 2017

- 86,818 Drug-matched controls
Human Genome: ~3 billion nucleotides. Typed out 1 per mm = 3,000 km long
Human Genome: ~3 billion nucleotides. Typed out 1 per mm = 3,000 km long x 2 copies.
Single Nucleotide Polymorphisms (SNP)

Variations in DNA (frequency >1%)
SNPs make up >90% of genetic variation

When comparing 2 people:
  1 SNP occurs every 1200 bp approx
  (= 5 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
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 Exome and genome sequencing
1. Identify children with ADRs & matched controls
2. Collect DNA samples (blood/saliva)
3. Detailed patient clinical characterization
4. Screen genetic variants
5. Replication

ADR cases
Matched controls

Patient blood/saliva

Patient charts

Clinical data

Custom ADME Array

Statistical Analyses

Statistical Analyses

ADR cases & controls
Assay DNA samples
Statistical Analyses
What Data are Missing?

- **A lot**
  - QoL impacts, longitudinal outcomes
  - Especially in pediatrics
    - Outcomes should be measured in yrs, not months

- **Systems Pharmacology is needed**

- **Networks of interactions**
  - Drug-protein, protein-protein, cell signaling
  - Physiological (at cellular, tissue, organ and whole body levels)

- **Even bigger data are needed!**
If the Purpose of Surveillance is to Improve Patient Care…

- Buy-in from clinicians is critical for quantity AND quality of data submitted
- Surveillors need to know HOW the data are being used to improve reporting details
- Detailed reporting can fill in missing gaps from epidemiological databases
- Active surveillance can help confirm epidemiological findings such that practice change is more likely to occur
Small Data Solutions for Big Data

- Active surveillance both retrospective and prospective to ensure proper granularity of data is captured
- Directed by relevant public health needs

These two things address data limitations

- Get whatever data you desire or need
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
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


Lipshultz et al. *Heart*. 2008;94(4):525-33
Classification of Anthracycline-Cardiotoxicity

**Controls**
- n=266
- No cardiotoxicity, SF ≥30%, ≥5yr follow-up

**ADR Cases**
- n=78
- **Grade 1 toxicity:**
  - Shortening fraction 27-30% or
  - Resting ejection fraction 50-60%
- **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*
$SLC28A3 + UGT1A6 +$ Clinical Variables for Risk Prediction of Anthracycline Cardiotoxicity

- Low Risk (50%)
- Intermediate Risk (30%)
- High Risk (19%)

ROC: AUC (SNPs + Clinical) = 0.76
1st GWAS of Anthracycline Cardiotoxicity uncovers RARG

Stage 1 & 2 – Discovery & Replication, European Patients

- Canada: 280 patients
- The Netherlands: 96 patients
- Combined: 376 patients

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>O.R.</th>
<th>P-value</th>
<th>O.R.</th>
<th>P-value</th>
<th>O.R.</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RARG</td>
<td>rs2229774</td>
<td>6.0</td>
<td>4.1x10^-8</td>
<td>4.1</td>
<td>0.0043</td>
<td>4.9</td>
<td>1.2x10^-9</td>
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Stage 3 – Replication, Worldwide: (N = 80; 19 cases, 61 controls)

- Africans: 11 patients
- Hispanics: 23 patients
- First Nations: 15 patients
- East Asians: 31 patients

<table>
<thead>
<tr>
<th>Variant</th>
<th>O.R.</th>
<th>P-value</th>
<th>O.R.</th>
<th>P-value</th>
<th>O.R.</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2229774</td>
<td>9.5</td>
<td>0.026</td>
<td>12.3</td>
<td>0.052</td>
<td>9.9</td>
<td>0.012</td>
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## Novel Biomarker in Adult Patients

Adult Cancer Patients from BCCA, VGH and SPH  
N = 73 patients: 41 cases and 32 drug-matched controls

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>O.R.</th>
<th>P-value</th>
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<tbody>
<tr>
<td><strong>RARG</strong></td>
<td><strong>rs2229774</strong></td>
<td><strong>11.0</strong></td>
<td><strong>0.0064</strong></td>
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### Genetic Biomarker

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant Function</th>
<th>MAF Cases</th>
<th>MAF Controls</th>
<th>P-value</th>
<th>Odds Ratio (95%CI)</th>
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<tbody>
<tr>
<td><strong>RARG</strong></td>
<td><strong>rs2229774</strong></td>
<td>0.073</td>
<td>0</td>
<td>0.0067</td>
<td>1.5 x 10^{16}</td>
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</tbody>
</table>

Logistic Regression Analysis (Additive Model)

- Without Covariates
- Adjusting for Dose

Manuscript in Preparation
A coding variant in RARG confers susceptibility to anthracycline-induced cardiotoxicity in childhood cancer

Folefac Aminkeng¹,²,¹³, Amit P Bhavsar²,³,¹³, Henk Visscher¹,⁴, Shahrad R Rassoolzadeh⁵, Yulina¹,¹³, Long W Lee⁶,⁷,⁸, Liam R Brunham⁶, Huib N Caron⁷, Elvira C van Dalen⁷, Leontien C Kremer⁷, Helena J van der Pal⁷,⁸, Ursula Amstutz²,³,¹², Michael J Rieder⁹, Daniel Bernstein¹⁰, Bruce C Carleton²,³,¹¹,¹⁴, Michael R Hayden¹,²,⁶,¹⁴, Colin J D Ross¹–³,¹¹,¹⁴ & The Canadian Pharmacogenomics Network for Drug Safety Consortium¹⁵
Personalized Medicine Program (PMP):
Implementation of a Pharmacogenomic ADR Prevention Program in British Columbia

- ADRs: Cisplatin-induced ototoxicity
  Anthracycline-induced cardiotoxicity
- Sites: BC Children’s Hospital, BCCA, and VGH

CPGs Prepared → Tests Developed → Patients Tested → Results Delivered → Ongoing Follow-up

- Education
- Interviews
- Workshops
- Focus Groups
- Cost-effectiveness
Pediatric Anthracycline Cardiotoxicity Risk Prediction Tool

- **14% Risk**
  - (~23% of population.
  - Risk estimate based upon 139 patients. Includes carriers of protective SLC28A3 variant.)

- **21% Cardiotoxicity Risk**
  - (~60% of population.
  - Risk estimate based upon 356 patients. Includes non-carriers, and carriers of 1 risk + 1 protective variant).

- **39% Cardiotoxicity Risk**
  - (~13% of population.
  - Includes carriers of 1+ RARG and 1+ UGT risk variants)

- **45% Cardiotoxicity Risk**
  - (~20% of population.
  - Risk estimate based upon 11 patients.
  - Includes carriers of 2 RARG risk variants)

- **89% Cardiotoxicity Risk**
  - (~2% of population.
  - Risk estimate based upon 9 patients.
  - Includes carriers of 80% 1+ RARG and 1+ UGT risk variants)
Potential 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 or dose
  - Add cardioprotectant (e.g. dexrazoxane)
  - Start treatment with ACE-inhibitors or beta-blockers to prevent further damage
Functional Validation of Pharmacogenetic Biomarkers

RESEARCH ARTICLE
Pharmacogenetic variants in TPMT alter cellular responses to cisplatin in inner ear cell lines

Amit P. Bhavsar1,2*, Erandika P. Gunaretnam1,2,3, Yuling Li2,3, Jafar S. Hasbullah2,4, Bruce C. Carleton2,3, Colin J. D. Ross1,2*
Aim: Explore the impact of pharmacogenetic variants in *TPMT* on cellular responses to cisplatin

Approach:

1. Express *TPMT* variants in murine inner ear cell lines (HEI-OC1 and UB/OC-1)

2. Monitor the impact of *TPMT* variants on cisplatin response in these cell lines by measuring:
   - Cytotoxicity (MTT assay)
   - Activation of a sensitive cisplatin-response gene (*TLR4*)
Results: TPMT variants expressed in cells, and as expected, TPMT*3A is unstable in cell culture.

Western blot of HA-epitope tagged TPMT constructs:
- *3B (Ala154Thr)
- *3C (Tyr240Cys)
- *3A (Ala154Thr, Tyr240Cys)

- TPMT*3A is especially unstable

Normalized protein expression:
- Reduced protein levels of *3B and *3A
Results: TPMT*3A expression sensitizes cells to cisplatin cytotoxicity compared to *1 (wild-type)

- TPMT*3A-expressing cells have cellular phenotypes consistent with higher effective cisplatin concentrations.
Results: TPMT *3A expressing cells exhibit a significantly greater response to cisplatin, as measured by TLR4, a sensitive marker of cisplatin-response

- TLR4 is a sensitive cisplatin biosensor:
  - *TLR4* expression is induced by increasing cisplatin concentrations

- TPMT*3A-expressing cells exhibit significantly increased TLR4-response to cisplatin
  - Consistent with higher effective cisplatin concentrations in TPMT*3A expressing cells
Cisplatin Functional Validation Summary

- Multiple independent \textit{in vitro} cisplatin phenotypes altered by genetic variations in \textit{TPMT} gene

- Validates a cisplatin-TPMT drug-gene interaction

- Functionally validates the pharmacogenomic association between TPMT variants and cisplatin ototoxicity:
  - \textit{TPMT}*-3A-expressing cells have cellular phenotypes consistent with higher effective cisplatin concentrations
  - Suggests TPMT is involved in cisplatin metabolism
  - We postulate that a nephrotoxic glutathione-derived cisplatin-thiol conjugate\textsuperscript{1,2} could act as a TPMT substrate

Concerns for the Future

National and international networks are needed
  – Particularly in childhood or rare diseases

No real funding options for sustained funding of international networks
  – Need longitudinal Big Data for outcomes, particularly in childhood cancer where late effects of drugs are an increasing concern
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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Department of Paediatrics, Faculty of Medicine
University of British Columbia

bcarleton@popi.ubc.ca