RARE FINDS

Rare Disease Adverse Responses and Effectiveness For Innovative and Novel Drug Solutions

New Frontiers in Research Fund – 2024 Transformation Competition

The Problem

- Drugs for rare diseases are increasingly available in Canada

- Treated patients do not experience the same outcomes
  - Some patients have an extraordinary response
  - Some patients derive marginal benefits
  - Some patients experience serious harm

- Effective policy requires an understanding of what is possible to achieve but also what can go wrong. These two groups of patients define the Goal Posts of any drug policy

National Strategy

- *National Strategy for Rare Diseases* issued by Health Canada in March 2023
  - Improve access to new and emerging rare disease drugs
  - Establishing a robust Canadian rare disease clinical trials network
  - Help provinces and territories fund the cost rare disease drugs
  - Support early diagnoses and screening for rare disease
  - Improve collection and use of evidence to support decision-making
  - Strengthen investments in critical research and innovation in rare diseases

Project Aims

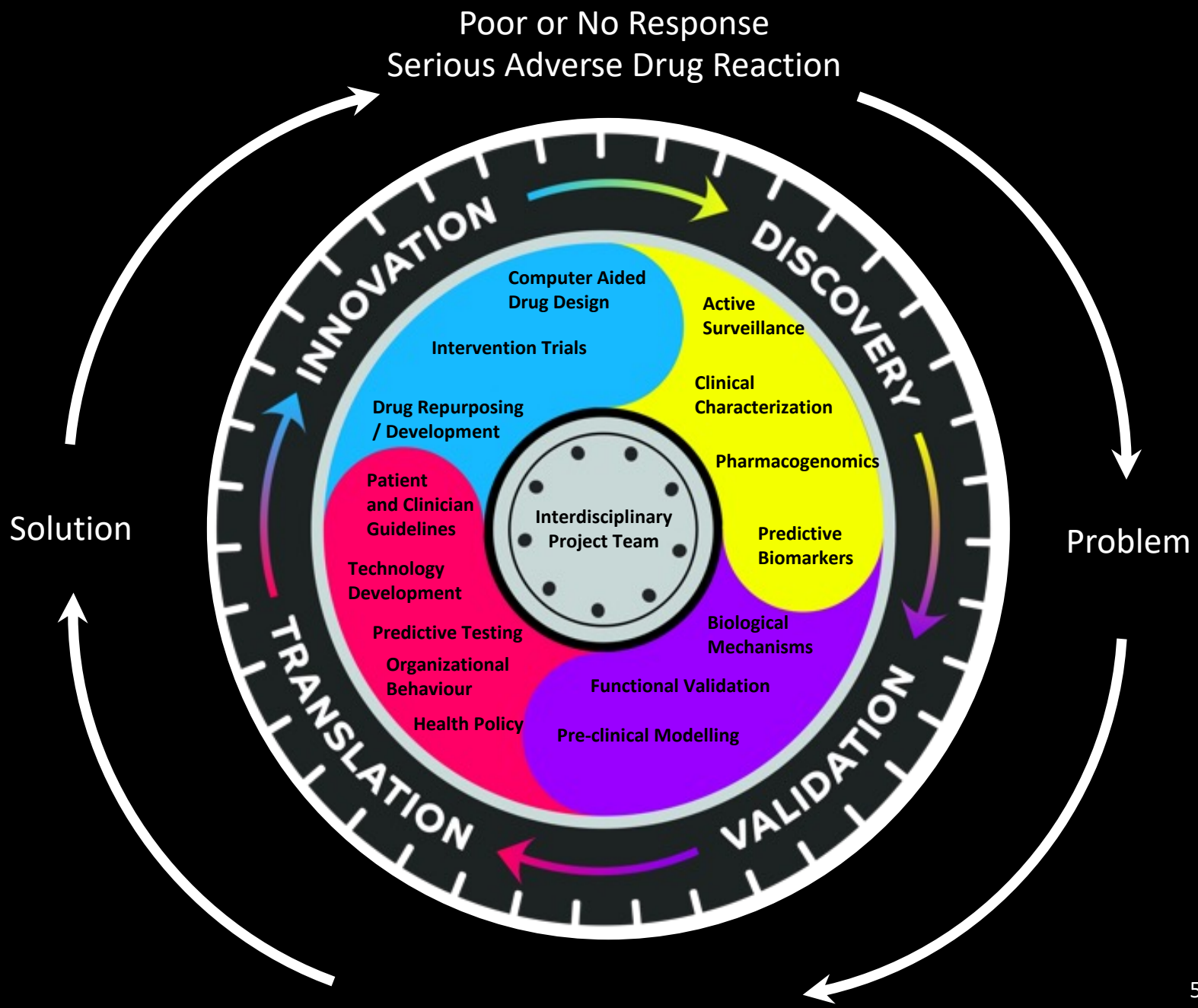
1. Identify extraordinary responders and non-responders to rare disease drugs and collect DNA for genomic analysis

2. Identify patients who suffer specific serious drug-induced harms from rare disease drugs and those who do not suffer these harms, collect DNA

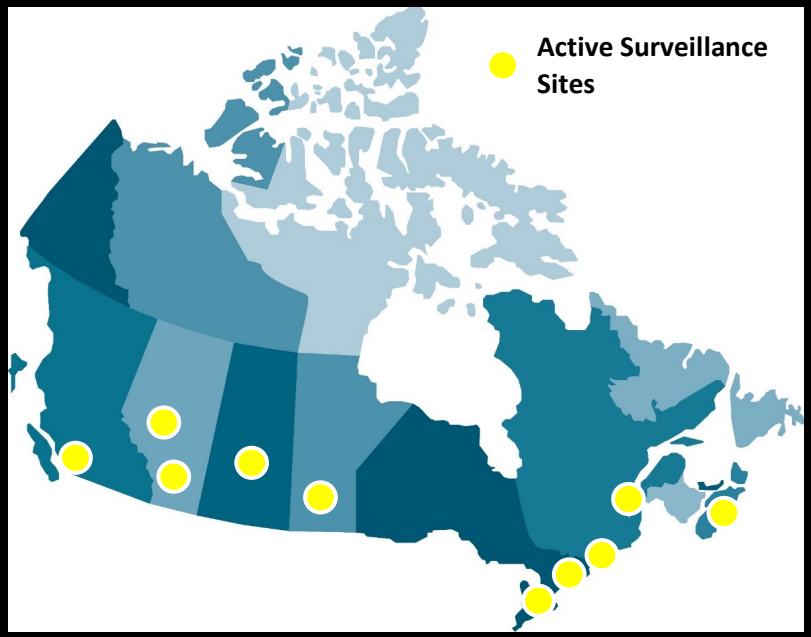
3. Conduct genomic analyses to discover predictive biomarkers strongly associated with these these outcomes

4. Use cell and animal models to validate significant genomic findings to understand the underlying mechanistic basis of these outcomes

5. Exploit findings to improve drug effectiveness across a broader range of patients and protect patients from drug-induced harms


Poor or No Response
Serious Adverse Drug Reaction
Problem
Solution
INNOVATION
DISCOVERY
TRANSLATION
VALIDATION
Computer Aided Drug Design
Intervention Trials
Drug Repurposing / Development
Active Surveillance
Clinical Characterization
Pharmacogenomics
Predictive Biomarkers
Biological Mechanisms
Functional Validation
Pre-clinical Modelling
Patient and Clinician Guidelines
Technology Development
Predictive Testing
Organizational Behaviour
Health Policy
Interdisciplinary Project Team

Feasibility – Patient Recruitment



- 10 academic health centres across Canada
- Investigators in the USA, Africa, Europe and the UK
- Many collaborating organizations

CORD Canadian Organization for Rare Disorders

Cystic Fibrosis Canada | CF CanACT FK ÉCLAIR

Rare Disease Foundation

ICHOM International Consortium for Health Outcomes Measurement

James Lind Alliance Priority Setting Partnerships

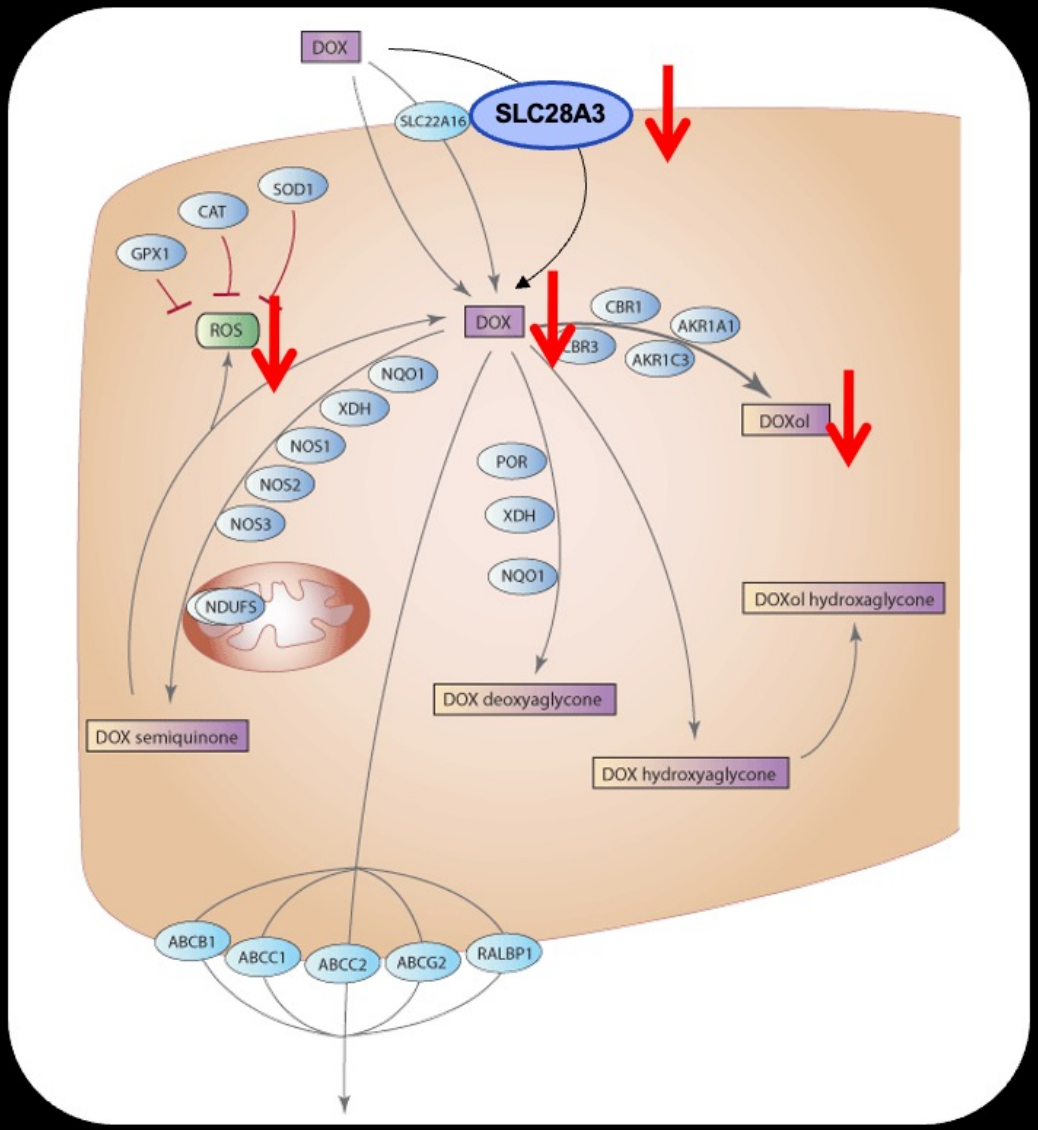
Canadian Pharmacogenomics Network for Drug Safety

CAPRI Canadian Alliance of Pediatric Rheumatology Investigators

When Good Drugs Cause Harm

- 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

Potential mechanism of SLC28A3



Reduced SLC28A3 expression

Less anthracycline into cell

Less ROS and toxic alcohol metabolites

Less toxicity

Validation of SLC28A3 in iPSC cardiomyocytes

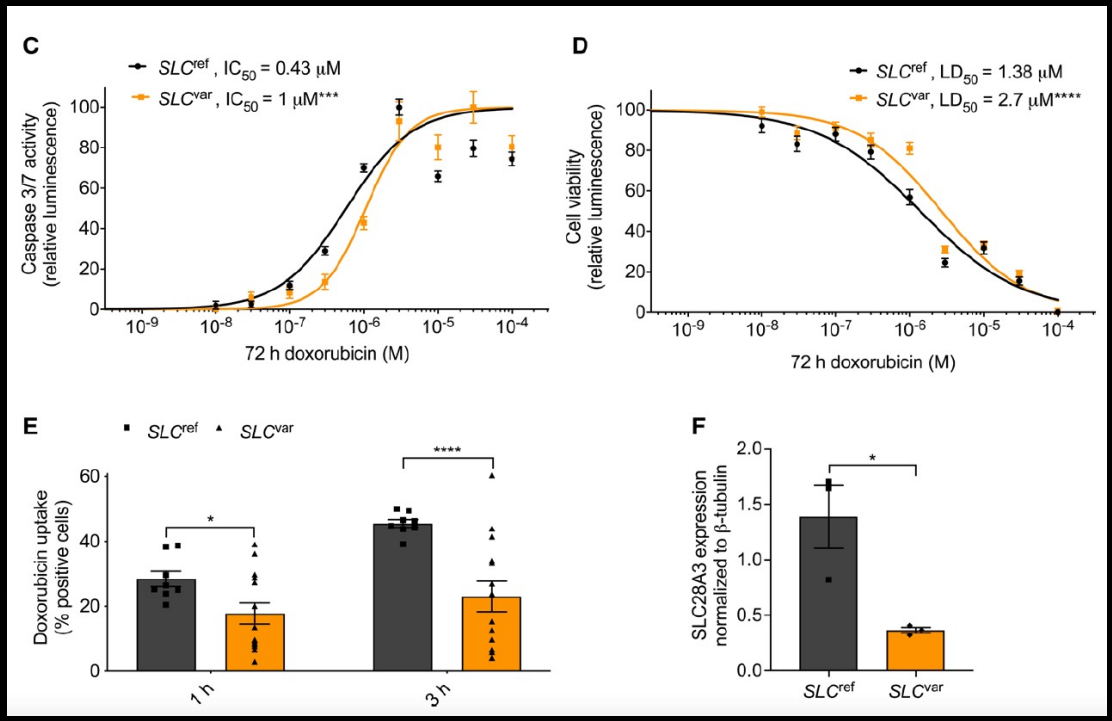
SLC28A3 variant cells exhibits increased viability when exposed to doxorubicin

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

Circulation. 2022 | Volume 145, Issue 4: 279–294, originally published December 7, 2021,

- Patient-derived iPSC cardiomyocytes
- *SLC28A3*$^{\textbf{rs11140490}}$ 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



Project Team – Areas of Research

SSHRC CRSH	NSERC CRSNG	CIHR IRSC
Health Law & Policy	Machine Learning	Genetics
Game Theory	Bioinformatics	Pharmacology
Knowledge Translation	Information Systems	Clinical Practice
Economics		Rare Diseases
Behaviour Change		Biology

Novelty of Approach

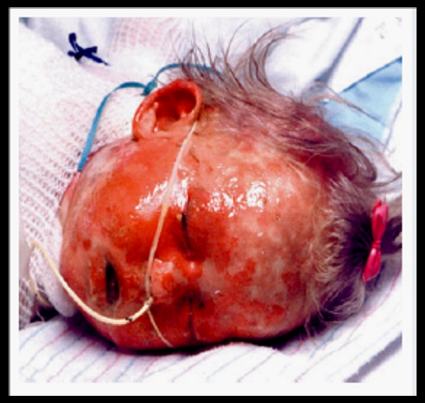
- Extraordinary response: what makes this possible?
  - Convey this benefit to more patients
- Serious harm: why does this happen?
  - Predict and prevent in future treated patients

- Rare disease drug policy needs Goal Posts for policy development that will allow health policy to be derived that conveys the most benefit to patients

- Alleviate financial burdens by better understanding in whom the drugs work best (optimal to treat) or cause harm (avoid treatment)

Priority Rare Disease Drugs

Drug or Drug Class	Rare Disease	Outcome of Interest	Estimated # (%) of Children in Canada		
			Extraordinary Responders	Non-responders	Serious Harm
Anthracyclines	Pediatric Cancer	Heart Failure	Not applicable	Not applicable	49 (5%)
Elexacaftor/ Tezacaftor/ Ivacaftor	Cystic Fibrosis	Extraordinary Response	200 (5%)	180 (4.5%)	Not applicable
Rituximab	Dermatomyositis Vasculitis, SLE	Persistent Hypogammaglobulinemia	Not applicable	Not applicable	19 (20%)
Bisphosphonates	Chronic Recurrent Multifocal Osteomyelitis	Extraordinary Response	160 (40%)	80 (20%)	Not applicable
Agalsidase beta Migalastat	Fabry's disease	Extraordinary Response	*** (**%) 110 (22%)	120 (24%) 295 (59%)	Not applicable



HLA-B*15:02 association with Carbamazepine-induced SJS

SJS is rare –

Annual incidence: 0.4 - 2 cases/million in Europe

2 - 8 cases/million in Asia

Chung et al (2004)

- Identified a genetic variant HLA-B*1502 associated with Stevens-Johnson syndrome
- Odds Ratio: >2,500
- Discovered initially with only 44 patients
- Allele frequency : **5-20%** in South East Asian populations

April 1, 2004

nature

Medical genetics

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 Stevens–Johnson syndrome induced by carbamazepine, a drug commonly prescribed for the treatment of seizures. It should be possible to exploit this association in a highly reliable test to predict severe adverse reaction, as well as for investigation of the pathogenesis of Stevens–Johnson syndrome.

We studied 44 patients with carbamazepine-induced Stevens–Johnson syndrome

The Pharmacogenomics Journal (2009) 9, 23–33

Genome-wide approaches to identify pharmacogenetic contributions to adverse drug reactions

ORIGINAL ARTICLE

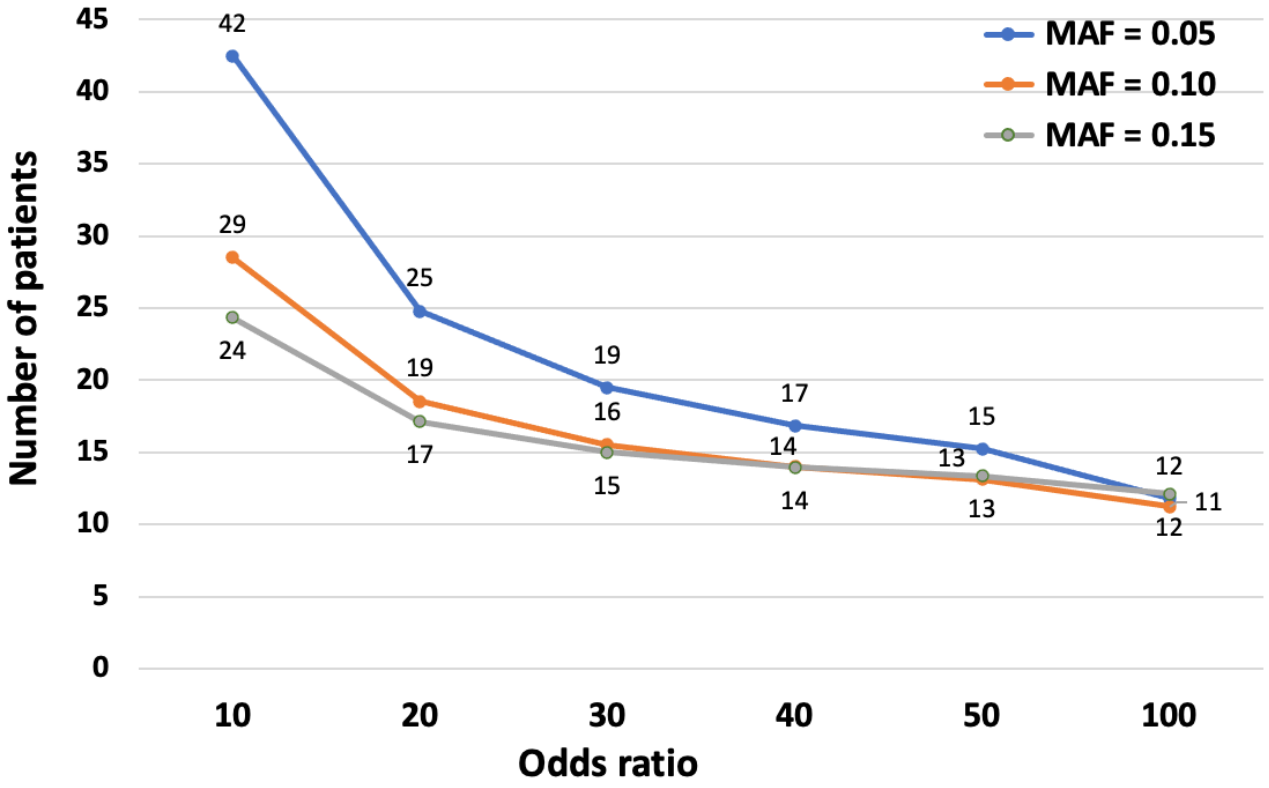
Table 1 Examples of established genetic ADR risk factors

Drug	*Adverse drug reaction*		*Genetic risk factor*			*Cases required*[a]	
	Reaction	*Prevalence*	*Risk allele*	*Frequency*[b]	*Effect*[c]	2×10^{-5}	10^{-7}
Gefitinib[6]	Diarrhea	0.28	*ABCG2* Q141K	0.07	5	29/101	47/>150
Isoniazid[7]	Hepatotoxicity	0.15	CYP2E1*1 & NAT2 slow Ac	0.13[d]	7		
Irinotecan[8,9]	Neutropenia	0.20	UGT1A1*28	0.32	28	17/36	26/58
Abacavir[10]	Hypersensitivity reaction	0.05	HLA-B*5701	0.04	36	10/13	15/19
Tranilast[11]	Hyperbilirubinemia	0.12	UGT1A1*28	0.30	48	28/37	42/54
6-Mercaptopurine[12]	Neutropenia, other toxicity	0.12	*TPMT**2,*3A, *3B,*3C	0.05[e]	49		
Allopurinol[13]	Severe cutaneous adverse reactions	<0.001	HLA-B*5801	0.15	678	13/13	19/19
Carbamazepine[14]	Stevens–Johnson syndrome	<0.001	HLA-B*1502	0.04	1023	6/6	9/9

In the condition of clinical matched controls / population controls

In a variety of adverse event prevalence scenarios, only **9 to 47 cases** are required to obtain 80% power and a significant *P*-value of 1×10^{-7} when performing clinical matched control comparisons.

Serious Drug-induced Harm Sample Sizes

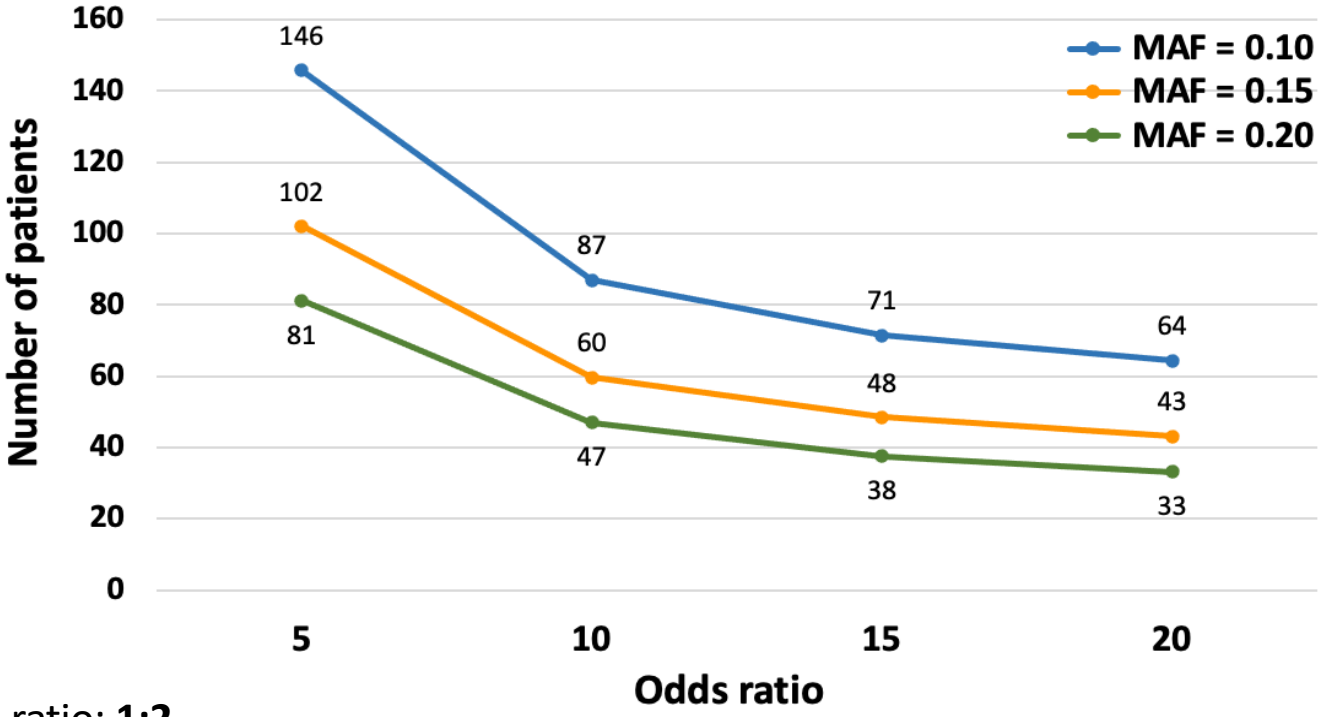


Assumptions –

Case-to-control ratio: **1:10**

Significant GWAS *P*-value: 5×10^{-8}; Additive genetic model

Extraordinary Responders and Nonresponders Sample Sizes

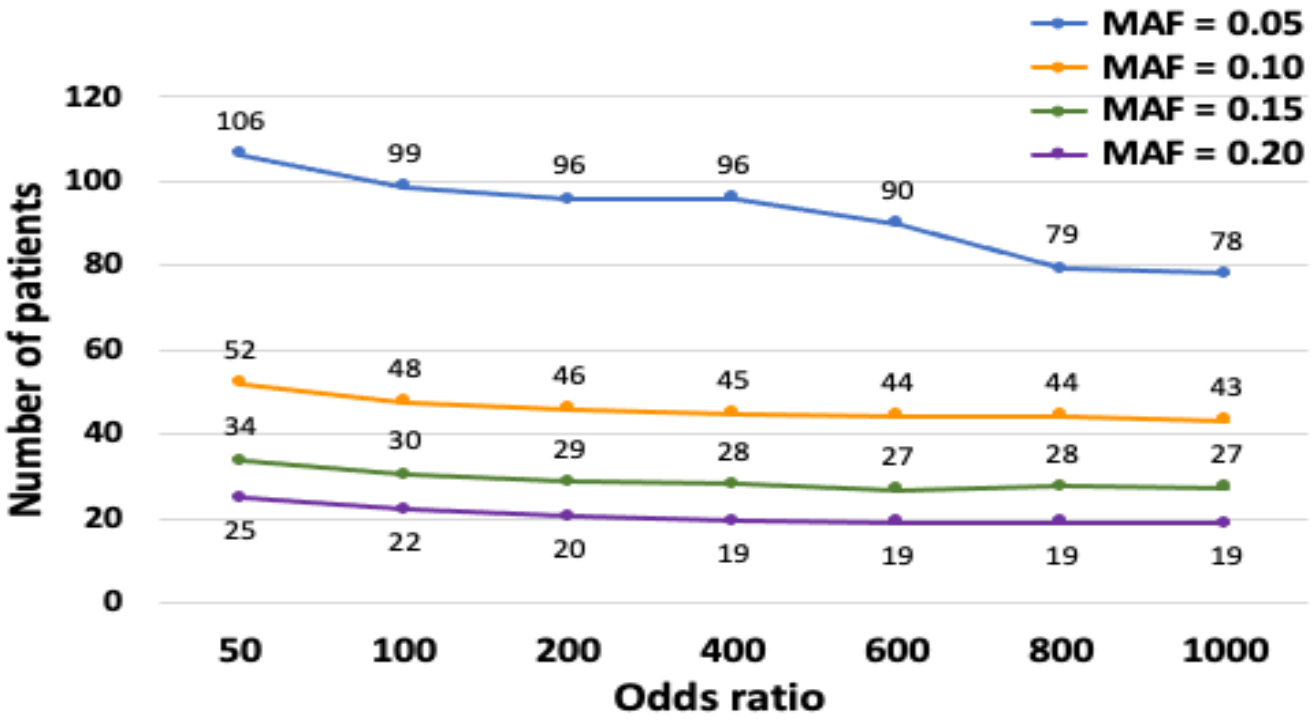


Assumptions –

Case-to-control ratio: **1:2**

Significant GWAS *P*-value: 5×10^{-8}; additive genetic model

Extraordinary Responders and Nonresponder Sample Sizes



Assumptions –

Case-to-control ratio: **1:2**

Significant GWAS *P*-value: 5×10^{-8}; additive genetic model

Endorsed By

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- Nicole Mittman, Vice President, Canadian Agency for Drugs and Technologies in Health
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Canadian Pharmacogenomics Network for Drug Safety

International Collaborations

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Canadian Pharmacogenomics Network for Drug Safety

Extra Slides

Project Deliverables

1. Understand clinical, genomic and psychosocial differences between patients for five priority rare disease drugs.
2. Develop predictive tools to improve drug safety, effectiveness and quality of life for up to five priority rare disease drugs.
3. Create a mechanism and framework to assess, respond and solve complex problems associated with rare disease therapy and facilitate decision-making for patients, clinicians and health regulators/authorities.
4. Establish a databank of clinical, genomic and environmental data to catalyze global research of rare disease therapy

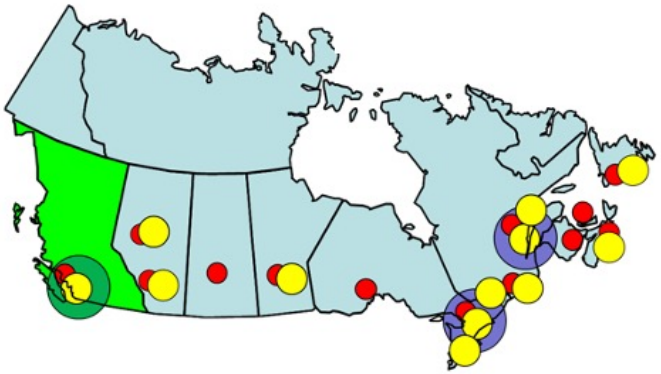
Benefits to End Users

- **Patients**
  - Individualized drug therapy delivered via predictive pharmacogenetic testing to enhance effectiveness and prevent harm
- **Clinicians**
  - Individualized drug benefit-risk assessment for their patients
- **Regulators**
  - Interdisciplinary framework to delineate Goal Posts for drug policy of rare disease drugs
- **Drug Plans**
  - Cost effective health spending that conveys the most benefit to patients

Benefits to Canada & World

- Reduce health care costs associated with rare disease drug-induced harm and non-response
- Exploit scientific understanding of “extraordinary responders” to enhance rare disease drug effectiveness
- Place Canada as a world leader in precision medicine for rare disease therapy
- International resource for researchers and stakeholders for rare disease drug biomarker discovery, validation and innovation

SLC28A3 Protective Against Anthracycline-Induced Cardiotoxicity



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	

Project Team

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