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Defining & Prioritizing Unmet Research Needs for a Deadly Disease (People & Drugs)

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Research Directions in Genetically-mediated SJS/TEN
NIH March 3-4, 2015

The SJS/TEN Five Year Vision

- Immunopathogenesis understood and diagnostic markers available
  - Providing roadmap for study of other forms of hypersensitivity
- Predictable and preventable
  - Successful pharmacogenomic screening programs
  - Successful pre-clinical screening programs for drug development & design
- Measurable decrease in morbidity and mortality
- Well established global pharmacosurveillance and collaborative networks.
- Educated providers
  - Mechanisms, prevention, recognition and treatment

SJS/TEN: What are the Unmet Needs

- Defining the phenotype and immunophenotype (including drug causality)
- Storing appropriate samples
- Collaborative networks representative across ethnicities
- Pharmacogenomic studies
- Immunopathogenesis
- Management
- Prediction and Prevention
- Capacity building for all of the above

Challenge#1: Defining the Population

- Education of providers
- Pharmacosurveillance has reporting bias and is incomplete
- Big data approaches challenges (coding and electronic health record approaches lack sensitivity and specificity)
- Challenges in retrospective causality assessment
- Infrastructure for collaborative networks

ORIGINAL RESEARCH ARTICLE

Drug Safety 2004; 27 (7): 477-487
0114-5916/04/0007-0477/$31.00/0

Evaluation of the Extent of Under-Reporting of Serious Adverse Drug Reactions

The Case of Toxic Epidermal Necrolysis

Nicole Mittmann,[1] *Sandra R. Knowles*,[2] *Manuel Gomez*,[3] *Joel S. Fish*,[3] *Robert Cartotto*[3] and *Neil H. Shear*[1,4]

Calculation of Reporting Rate

If one used the burn facility data as the denominator, 10% (25/250) of TEN cases were reported to the CADRMP. Using CIHI data as a denominator, only 4% (25/674) of TEN cases were reported to the CADRMP.

-underreporting of TEN in Canada 1995-2000
-22 burn units across Canada (14/22 responded)
-CADRMP
-Canadian Institute for Health Information discharge summaries (ICD9 695.1)

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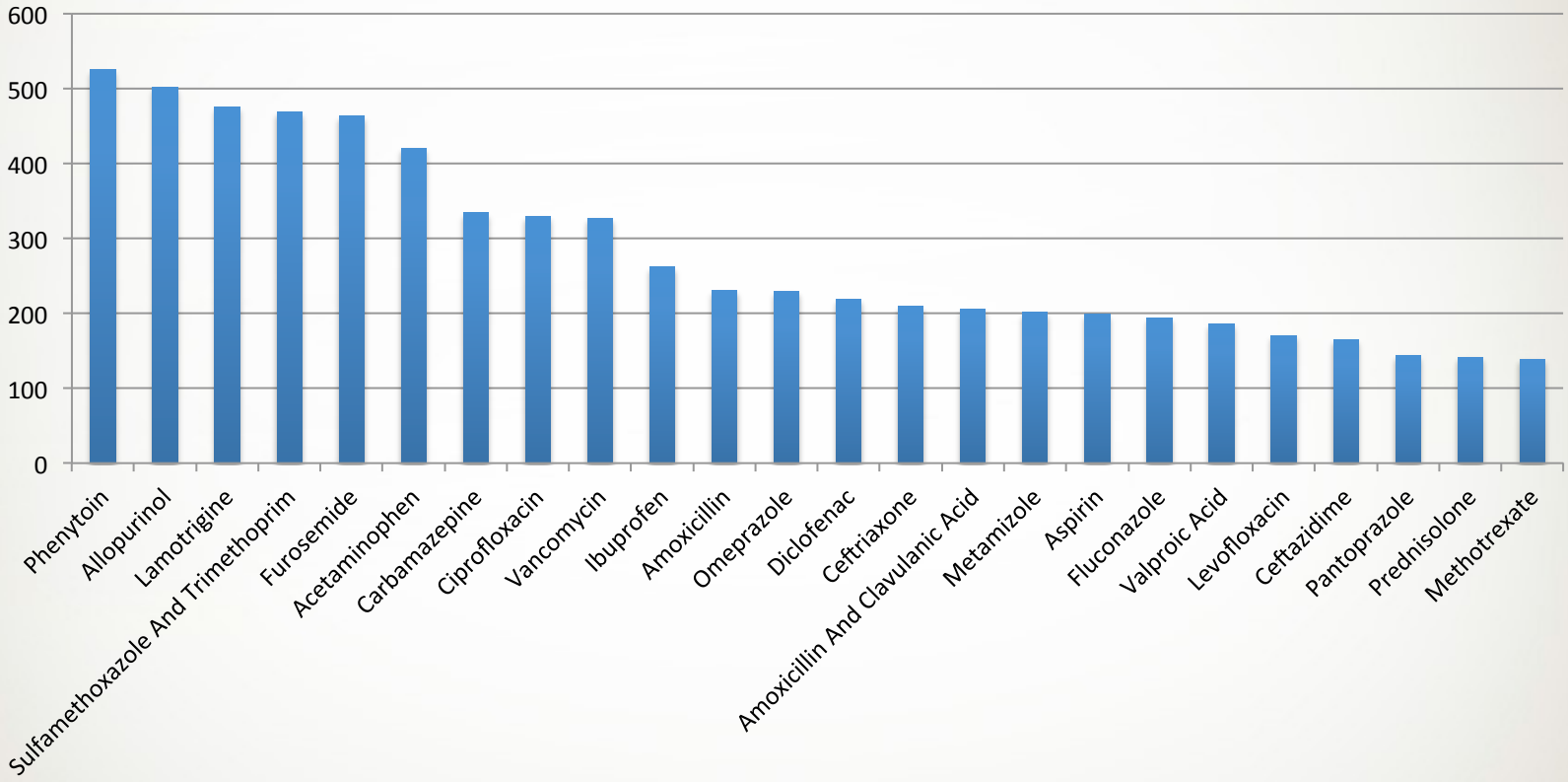
Top 25 Drugs in FAERS (TEN)*



*up to February 15, 2015

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Table 5 Details of the algorithm of drug causality for epidermal necrolysis (ALDEN)

Criterion	Values	Rules to apply	
Delay from initial drug component intake to onset of reaction (index day)	Suggestive +3	From 5 to 28 days	−3 to 3
	Compatible +2	From 29 to 56 days	
	Likely +1	From 1 to 4 days	
	Unlikely −1	>56 Days	
	Excluded −3	Drug started on or after the index day	
		In case of previous reaction to the same drug, only changes for: Suggestive: +3: from 1 to 4 days Likely: +1: from 5 to 56 days	
Drug present in the body on index day	Definite 0	Drug continued up to index day or stopped at a time point less than five times the elimination half-life[a] before the index day	−3 to 0
	Doubtful −1	Drug stopped at a time point prior to the index day by more than five times the elimination half-life[a] but liver or kidney function alterations or suspected drug interactions[b] are present	
	Excluded −3	Drug stopped at a time point prior to the index day by more than five times the elimination half-life[a], without liver or kidney function alterations or suspected drug interactions[b]	
Prechallenge/rechallenge	Positive specific for disease and drug: 4	SJS/TEN after use of same drug	−2 to 4
	Positive specific for disease or drug: 2	SJS/TEN after use of similar[c] drug or other reaction with same drug	
	Positive unspecific: 1	Other reaction after use of similar[c] drug	
	Not done/unknown: 0	No known previous exposure to this drug	
	Negative −2	Exposure to this drug without any reaction (before or after reaction)	
Dechallenge	Neutral 0	Drug stopped (or unknown)	−2 or 0
	Negative −2	Drug continued without harm	
Type of drug (notoriety)	Strongly associated 3	Drug of the "high-risk" list according to previous case–control studies[d]	−1 to 3
	Associated 2	Drug with definite but lower risk according to previous case–control studies[d]	
	Suspected 1	Several previous reports, ambiguous epidemiology results (drug "under surveillance")	
	Unknown 0	All other drugs including newly released ones	
	Not suspected −1	No evidence of association from previous epidemiology study[d] with sufficient number of exposed controls[c]	
		Intermediate score = total of all previous criteria	−11 to 10
Other cause	Possible −1	Rank all drugs from highest to lowest intermediate score	−1
		If at least one has an intermediate score >3, subtract 1 point from the score of each of the other drugs taken by the patient (another cause is more likely)	
Final score −12 to 10			

<0, Very unlikely; 0–1, unlikely; 2–3, possible; 4–5, probable; ≥6, very probable.

ATC, anatomical therapeutic chemical; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

[a]Drug (or active metabolite) elimination half-life from serum and/or tissues (according to pharmacology textbooks, tentative list available in complementary table), taking into account kidney function for drugs predominantly cleared by kidney and liver function for those with high hepatic clearance. [b]Suspected interaction was considered when more than five drugs were present in a patient's body at the same time. [c]Similar drug = same ATC code up to the fourth level (chemical subgroups), see Methods. [d]See definitions for "high risk," "lower risk," and "no evidence of association" in Methods, ref. 15 (detailed list available in complementary table).

Sassolas et al CPT 2010;88(1):60-67

Canada Vigilance
Summary of Reported Adverse Reactions

Report Runtime: 2015-02-24 04:31:32 PM
Initial Received Date: 1965-01-01 to 2014-09-30
Latest Received Date: N/A
Total Number of Reports: 223 Report(s)

Report Information

***AER = Adverse Reaction Report*

Adverse Reaction Report Number	Latest AER Version Number	Initial Received Date	Latest Received Date	Source of Report	Market Authorization Holder AER Number	Type of Report	Reporter Type
000052936	0	1986-02-18	1986-02-18	Hospital		Spontaneous	

Serious report?	Death:	Disability:	Congenital Anomaly:
Yes	Life Threatening:	Hospitalization:	Other Medically Important Conditions:

Patient Information

Age	Gender	Height	Weight	Report Outcome
46 Years	Female			Not recovered/not resolved

Link / Duplicate Report Information

Record Type	Link AER** Number
No duplicate or linked report.	

Product Information

Product Description	Health Product Role	Dosage Form	Route of Administration	Dose	Frequency	Therapy Duration	Indication(s)
ACETYLSALICYLIC ACID	Concomitant	NOT SPECIFIED	Oral	650.0 Milligram	As required	14.0 Day(s)	
BACTRIM ROCHE	Suspect	NOT SPECIFIED	Oral	1.0 Dosage forms	2 every 1 Day(s)	2.0 Day(s)	
DILANTIN	Suspect	NOT SPECIFIED	Oral	100.0 Milligram	3 every 1 Day(s)	20.0 Day(s)	
FERROUS GLUCONATE	Concomitant	TABLET	Oral	300.0 Milligram	3 every 1 Day(s)	15.0 Day(s)	
PHENOBARBITAL	Suspect	NOT SPECIFIED	Oral	60.0 Milligram	2 every 1 Day(s)	21.0 Day(s)	

Canada Vigilance
Summary of Reported Adverse Reactions

Initial Received Date:	1965-01-01 to 2014-09-30
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Report Information

***AER = Adverse Reaction Report*

Adverse Reaction Report Number	Latest AER Version Number	Initial Received Date	Latest Received Date	Source of Report	Market Authorization Holder AER Number	Type of Report	Reporter Type
000364879	1	2011-03-24	2011-06-14	MAH	2011063119	Spontaneous	Physician

Serious report?	Death:		Disability:		Congenital Anomaly:	
Yes	Life Threatening:	Yes	Hospitalization:	Yes	Other Medically Important Conditions:	

Patient Information

Age	Gender	Height	Weight	Report Outcome
16 Years	Female		56 Kilograms	Recovered/resolved

Link / Duplicate Report Information

Record Type	Link AER** Number
Duplicate	000372420
Duplicate	000336902

Product Information

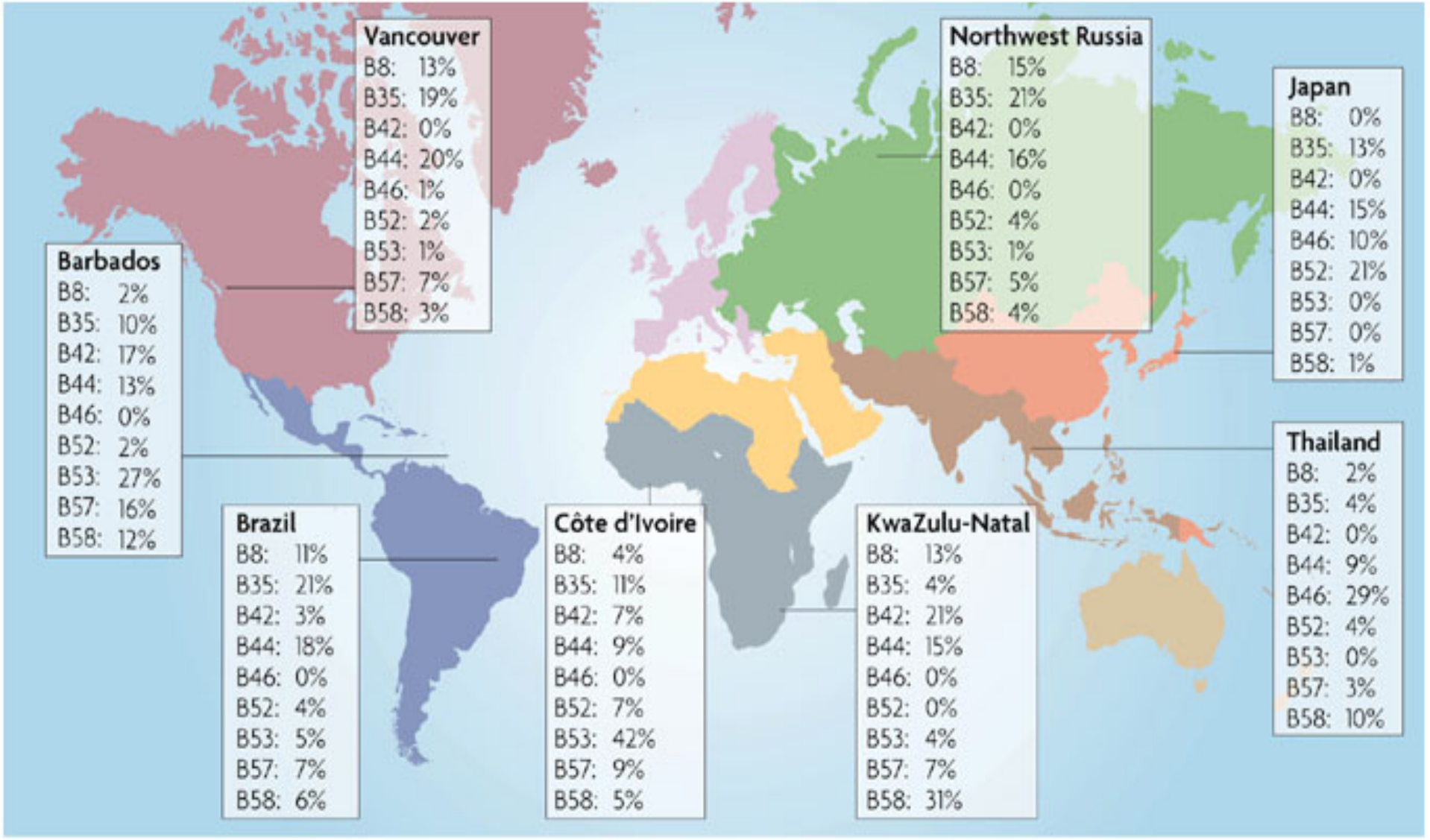
Product Description	Health Product Role	Dosage Form	Route of Administration	Dose	Frequency	Therapy Duration	Indication(s)
ADVIL IBUPROFEN TAB 200MG	Suspect	TABLET	Unknown	4800.0 Milligram	Total	334.0	Product used for unknown indication
APO-CLINDAMYCIN	Suspect	CAPSULE	Oral	300.0 Milligram	4 every 1 Day(s)	7.0 Day(s)	Peritonsillar abscess

Challenge#2: Biological Samples

- Require robust phenotyping
- Prospective collection of sufficient material
- Few electronic health records paired with biological samples
- Both DNA and cellular banking ideal however resources intrastructure and expertise for latter often lacking
- **Tissue specific samples** - blister fluid and PBMCs (acute time points)

Challenge#3: Pharmacogenomic Studies

- Require robust phenotyping with appropriate reference and control populations (founder effect)
- Should provide roadmap for translation as well as insights into pathogenesis



#Cases needed to Establish Risk

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

[a]Number of cases required to achieve 80% power to reject the null hypothesis of no association at 2×10^{-5} and 10^{-7} test-wise significance levels (see text) with 200 clinical matched/population controls. Assumed linkage disequilibrium between genetic risk factor and best SNP marker is $r^2 = 0.7$. Power calculations not provided for multigenic/multiallelic risk factors.

[b]Allele frequency of the ADR susceptibility variant.

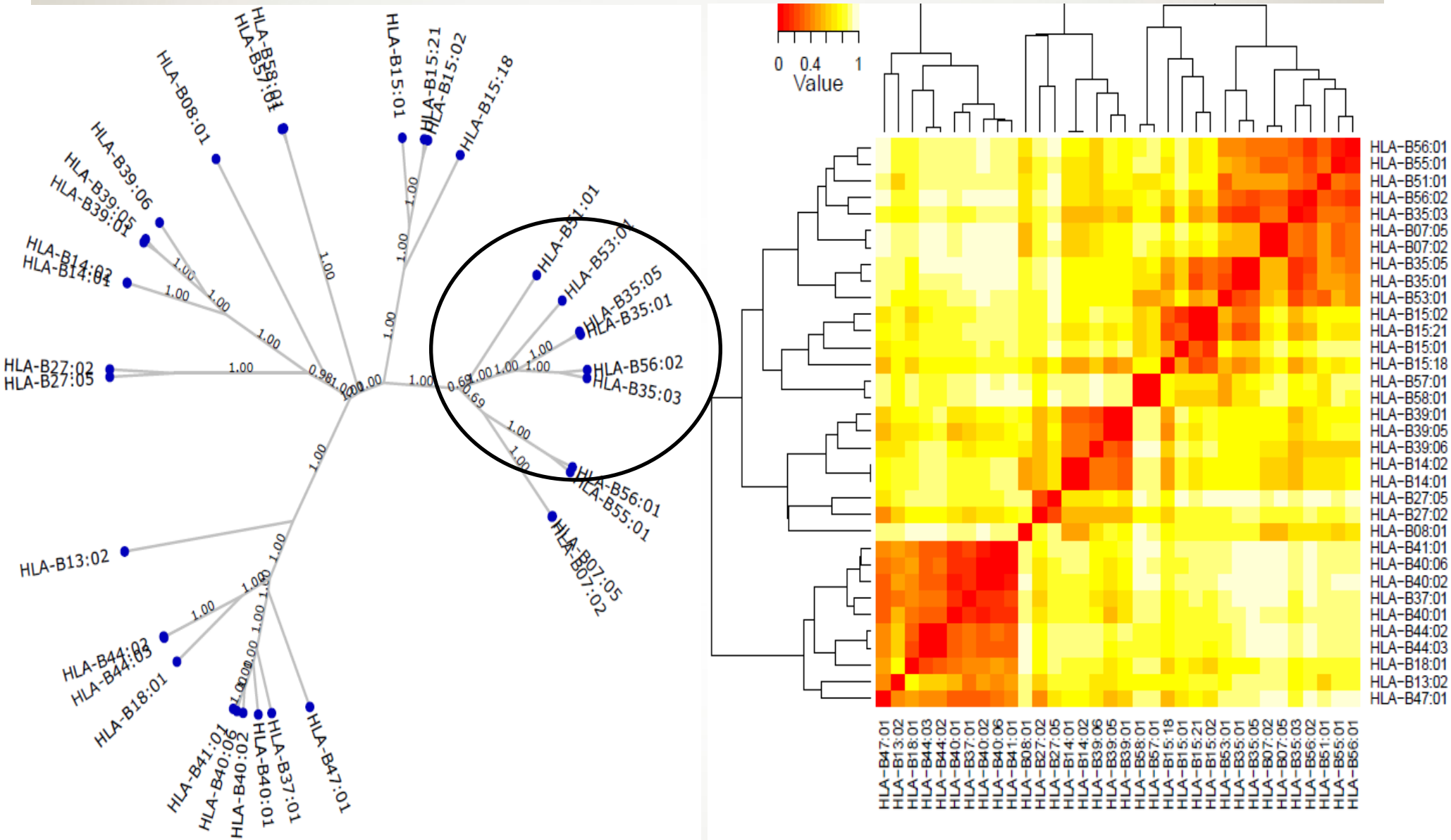
[c]Genetic effect is the estimate of the GRR for those homozygous for the susceptible genotype compared to the low-risk homozygotes.

[d]Frequency of the *CYP2E1*1* and *NAT2* slow acetylator homozygous genotype.

[e]Estimated cumulative frequency of TPMT-deficient alleles.

Nelson et al Pharmacogenomics J 2009;9:23-33

Delayed Serious T-cell mediated Cutaneous Reactions



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B*57:01, B*58:01, B*56:01, B*59:01, B*55:01, B*44:03, B*39:01, B*37:01, B*27:05, B*35:01/5, B*18:01, B*13:01, B*15:02, A*31:01, C*04:01

HLA-B*57:01 Screening Translational Roadmap

Abacavir causes abacavir hypersensitivity (ABC HSR) in 5-8%	**1998**
↓	
Two independent groups publish strong association between ABC HSR and HLA-B*5701 in predominantly Caucasian populations	**2002**
↓	
Apparent low sensitivity of HLA-B*5701 in non-white populations questions generalizability	**2002-2004**
↓	
Clarity added to the "false positive clinical diagnosis " of ABC HSR, **observational studies**	**2002-2008**
↓	
Patch testing is a highly specific for "true" ABC HSR	**2000-2005**
↓	
Randomised clinic trial using patch testing confirms utility of HLA-B*5701 and **case-control study** shows generalizability across ethnicity	**2008**
↓	
Widespread uptake into clinic in developed world, incorporation into treatment guidelines, test reimbursed	**2008**

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HLA SJS/TEN Translational Roadmap

DRUG IDENTIFIED AS CAUSE OF SJS/TEN

HLA association identified

Define relevance, generalizability across different populations
Labelling, Black box warning

Number needed to test to prevent one case dependent on prevalence of disease, HLA allele and positive predictive value

TRANSLATION INTO CLINICAL PRACTICE

100% NPV

HLA screening prior to drug prescription

Prevention of SJS/TEN cases

Define immunopathogenesis mechanisms of incomplete positive predictive value

Structural, biochemical functional relationship between HLA/immune receptor + drug

Preclinical prediction
Influence drug development design

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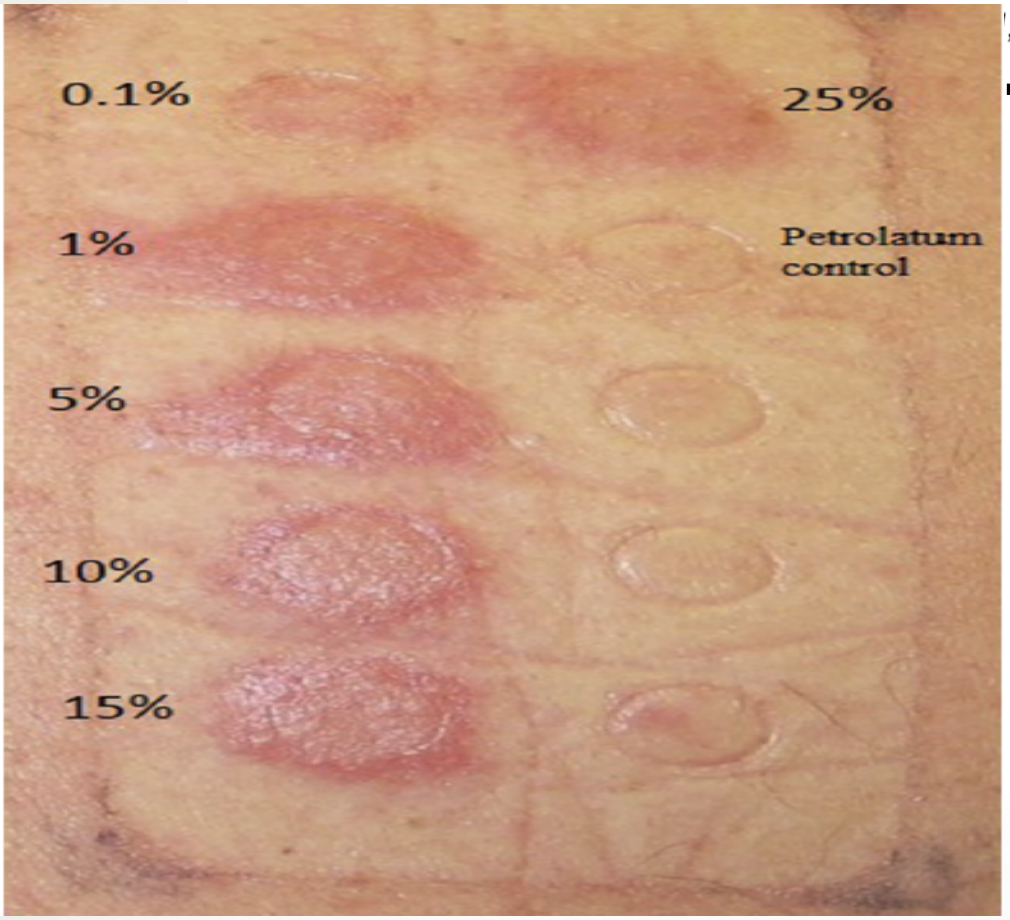
Challenge#4: Immunopathogenesis

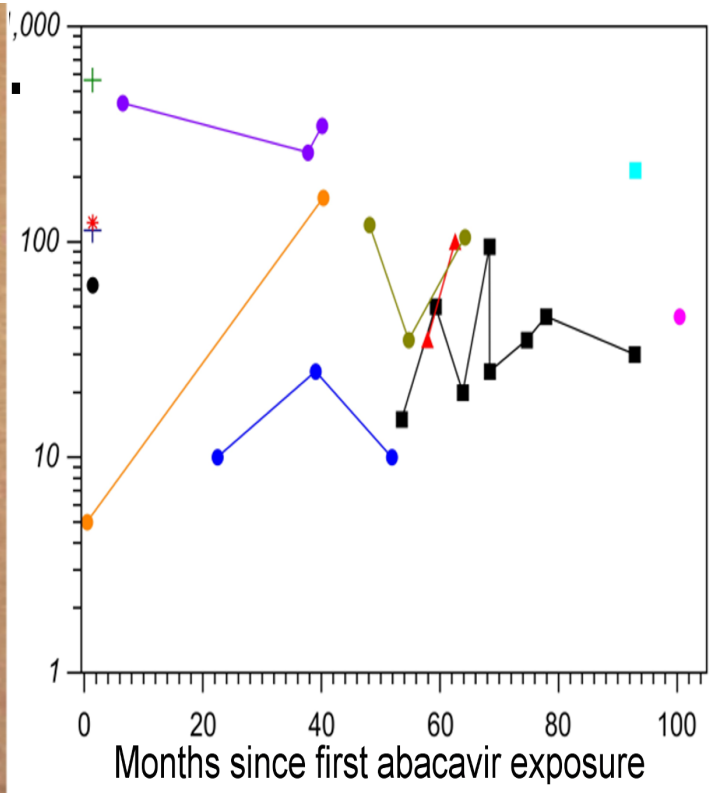
- Insights from *in vitro* and *in vivo* studies
- Broader insights into immunopathogenesis of other drug hypersensitivity syndromes and inflammatory/ autoimmune/allergic diseases
- Therapeutic targets
- Prediction (includes pre-clinical), prevention, diagnosis

Long-lasting Immunity



Abacavir patch test

Phillips et al AIDS 2002, 2005



Abacavir gamma-interferon ELISpot Responses

Lucas et al PLoS One 2015;10(2):e0117160

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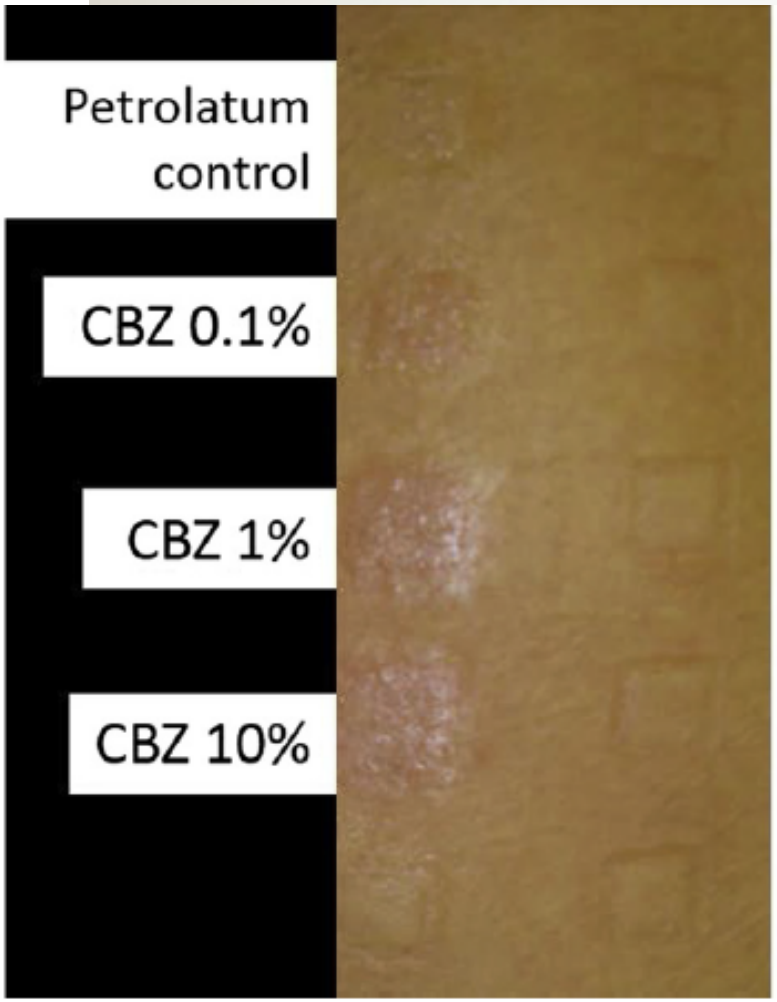
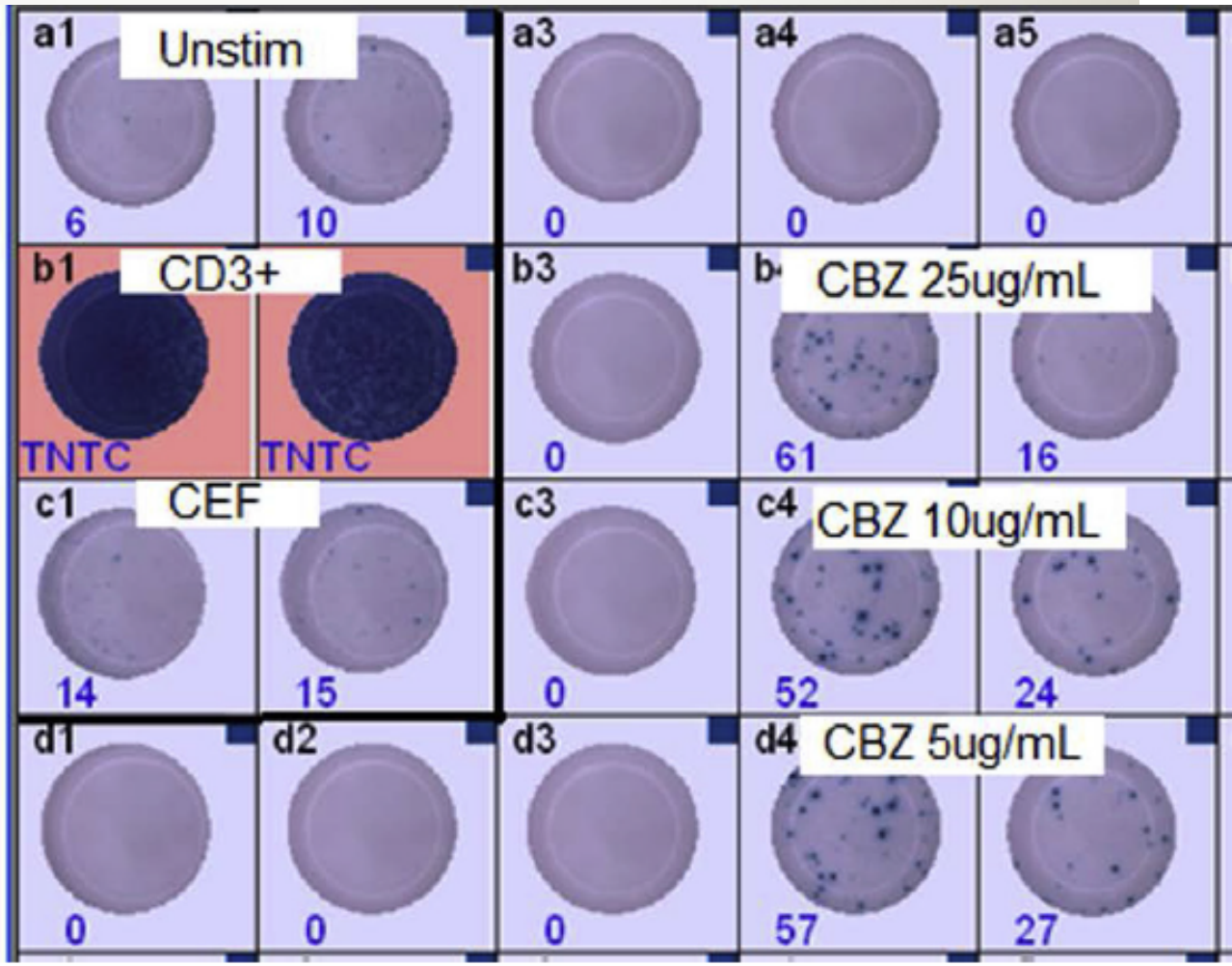
Long-lasting Immunity





Patch + 9 year post- CBZ TEN

ELISpot > 17 years post CBZ TEN

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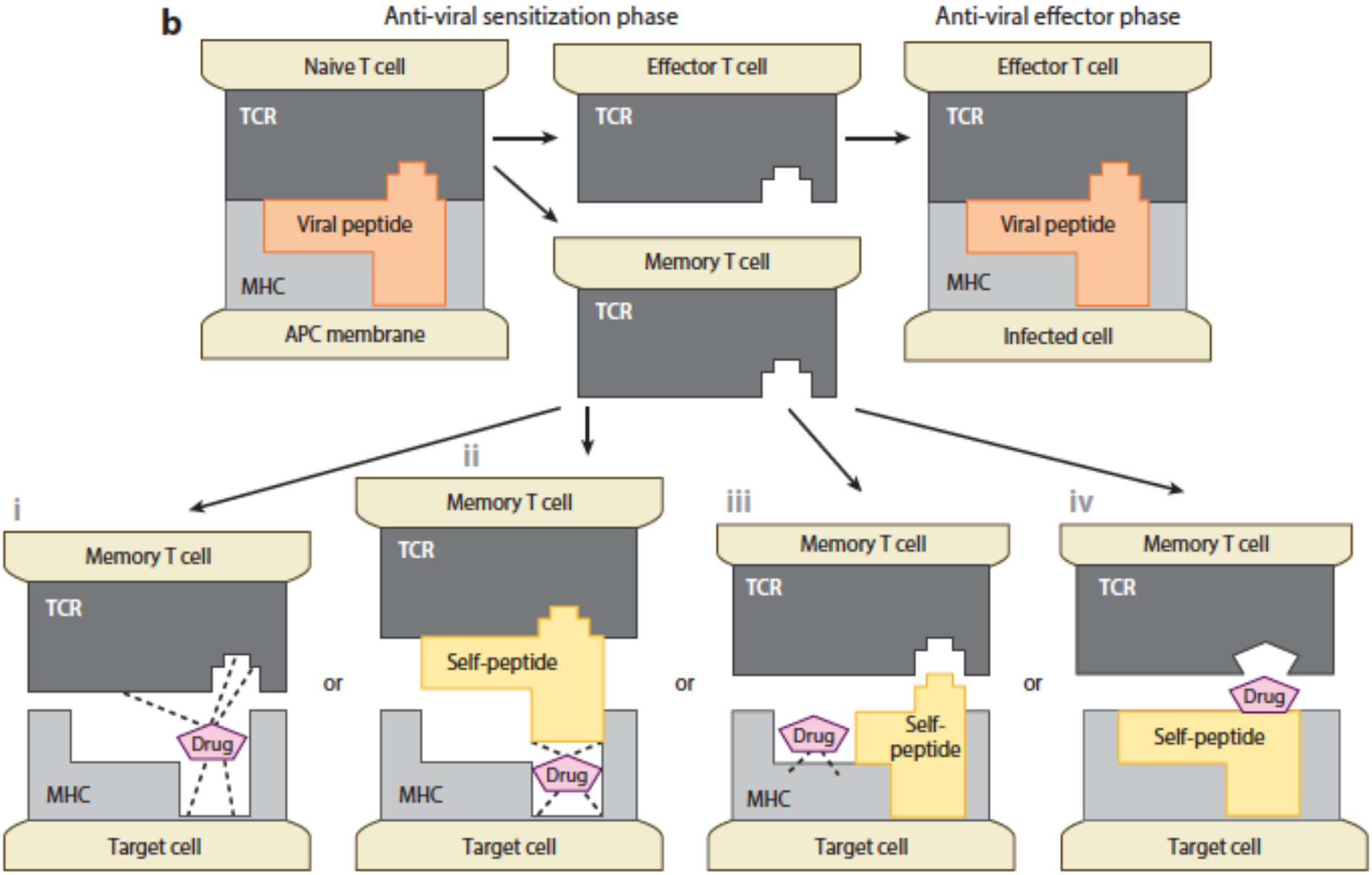
Pavlos et al JACI IP 2014; 2(1):21-33

New Models Consider Role of Cross-Reactive Memory T-cell Responses



Heterologous immunity model of drug hypersensitivity

Pavlos et al Annual Review of Medicine 2015;66:439-54

Challenge#5: Management

- Early recognition and diagnosis
- Diagnostic markers, *in vivo/in vitro/ex vivo* assessment to guide causality
- Lack of targeted approaches
- Lack of evidence base
- Identification and management of short and long-term complications

Challenge#6: Prediction & Prevention

- Translational roadmap
- Safety issues (100% negative predictive value, laboratory standards)
- More than high odds ratios ("number needed to test" to prevent one case)
- Characteristics of drug are important (are alternatives available)
- Population (ethnicity) specific
- Economic arguments
- Common drug structures, common HLA associations
- Sensitive and specific *in vitro* pre-clinical approaches needed

Prerequisites	Drug/*HLA* association			
	ABC	CBZ	ALL	NEV
Test				
• *HLA* allele is strongly associated with the toxicity, and the negative predictive value of the test is high*	+++	+++	++	++
• The number of patients needed for testing to prevent a case of toxicity is low*	++	++	++	++
• *HLA* allele is prevalent in a large, non-disenfranchised population*	++	+	+	++
Drug				
• Drug exhibits favorable attributes, such as good efficacy, convenience in dosing and administration, tolerability and pill burden*	++	+	++	+
• Alternative drug(s) that do not require pharmacogenetic testing are either absent or have negative attributes*	++	+	+++	+
Drug toxicity				
• Toxicity is severe and persistent* (ie, not isolated mild rash)	++	++	++	++
• Toxicity is readily and accurately phenotyped*	+	++	++	–
• An adjunctive diagnostic test, such as skin patch testing, can improve phenotypic precision	++	–	–	–
Environment				
• Champions available (eg, clinical academics, industry [if drug not off patent*], professional bodies, regulatory agencies, guideline committees, patient advocacy groups, laboratory providers and the media), willing and able to drive pharmacogenetic test development and implementation	+++	–	–	–
Generation of high-level evidence				
• Case-control studies with estimated predictive values based on the assumed prevalence of the *HLA* allele	++	++	++	–
• Population-based cohort studies with directly calculated predictive values of the test	++	–	–	++
• Open screening studies	++	–	–	–
• Supportive experimental data	++	–	–	–
• Blinded randomized controlled trials	+++	–	–	–
• Evidence across ethnic groups and geographical areas to determine the clinical settings that the test may be applied to	+++	–	–	–
• Cost-effectiveness data	++	–	–	–
Development and availability of appropriate laboratory support				
• No patent restriction on use of the test	++	–	–	–
• Development of simple, inexpensive, robust, unambiguous laboratory tests	+	+	+	+
• Rapid and simple report and interpretation	++	–	–	–
• Development of reagents (eg, mAbs, PCR-based kits)	++	–	–	–
• Global distribution and commercialization of allele-specific test	+	–	–	–
• Allele-specific quality assurance targeted to avoid false-negative results and consequent morbidity or mortality	+	–	–	–
• Reimbursement of test	+	–	–	–
Design and implementation of appropriate clinical systems				
• Education of clinicians, nurses, pharmacists, phlebotomists and patients	++	–	–	–
• Systems to ensure appropriate and routine triggering of ordering of the test	+	–	–	–
• Systems in the clinic to ensure the correct blood samples are sent to the correct laboratory for analysis	+	–	–	–
• Systems to ensure test results and correct interpretation is rapidly transmitted to, retained by and acted on by the healthcare team and patient	+	–	–	–

Phillips E, Mallal S, Current Opinion in Molecular Therapeutics 2009;11:231-42

Differing Strength of Association

DRUG	HLA ALLELE	HLA CARRIAGE RATE	DISEASE PREV.	OR	Negative Predictive Value	Positive Predictive Value	NNT to prevent "1"
Abacavir **Hypersensitivity Syndrome**	B*57:01	Caucasian (5-8%) African/Asia (<1%) African American (2.5%)	8% (3% true HSR and 2-7% false positive diagnosis)	960	100% for patch test confirmed	55%	13
Allopurinol **SJS/TEN and DRESS/DIHS**	B*58:01	Han Chinese(9-11%) Caucasian (1/6%)	1/250-1/1000	>800	100% in Han Chinese	3%	250
Carbamazepine **SJS/TEN**	B*15:02	Han Chinese (10-15%) Caucasian (<0.1%)	<1-6/100	>1000	100% in Han Chinese (with other B75 serotype)	3%	1000
Dapsone **DRESS/DIHS**	B*13:01	Chinese (2-20%) Papuans/Australian Aboriginals (28%) European/African(0%) Japan (1.5%)	1.4% (Han Chinese)	20	99.8%	7.8%	84
Flucloxacillin **Drug-induced liver disease**	B*57:01	As above for abacavir	8.5/100,000	81	99.99%	0.12%	13819

Differing Implications for Translation

DRUG	HLA ALLELE	HLA CARRIAGE RATE	DISEASE PREV.	OR	Negative Predictive Value	Positive Predictive Value	NNT to prevent "1"
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Flucloxacillin **Drug-induced liver disease**	B*57:01	As above for abacavir	8.5/100,000	81	99.99%	0.12%	13819

Effects of a HLA-B*15:02 screening policy on antiepileptic drug use and severe skin reactions

Neurology 2014;83:1-8

Zhibin Chen, MBiostat
Danny Liew, MD, PhD
Patrick Kwan, MD, PhD

ABSTRACT

Objective: To assess the effects of an active pharmacogenetic screening policy for antiepileptic drug (AED) therapy on everyday clinical practice and clinical outcomes.

-4,196 HLA-B*15:02 tests were performed on 4,149 patients (45 tested twice and 1 x 3).
-67.5% first time users of antiepileptic drugs
-Good turnaround time with 4 day median (2-6)
-Examined post-policy implementation of HLA-B*15:02 screening
-Compared prescription of anti-epileptic drugs between pre and post-screening policy and adherence to the policy

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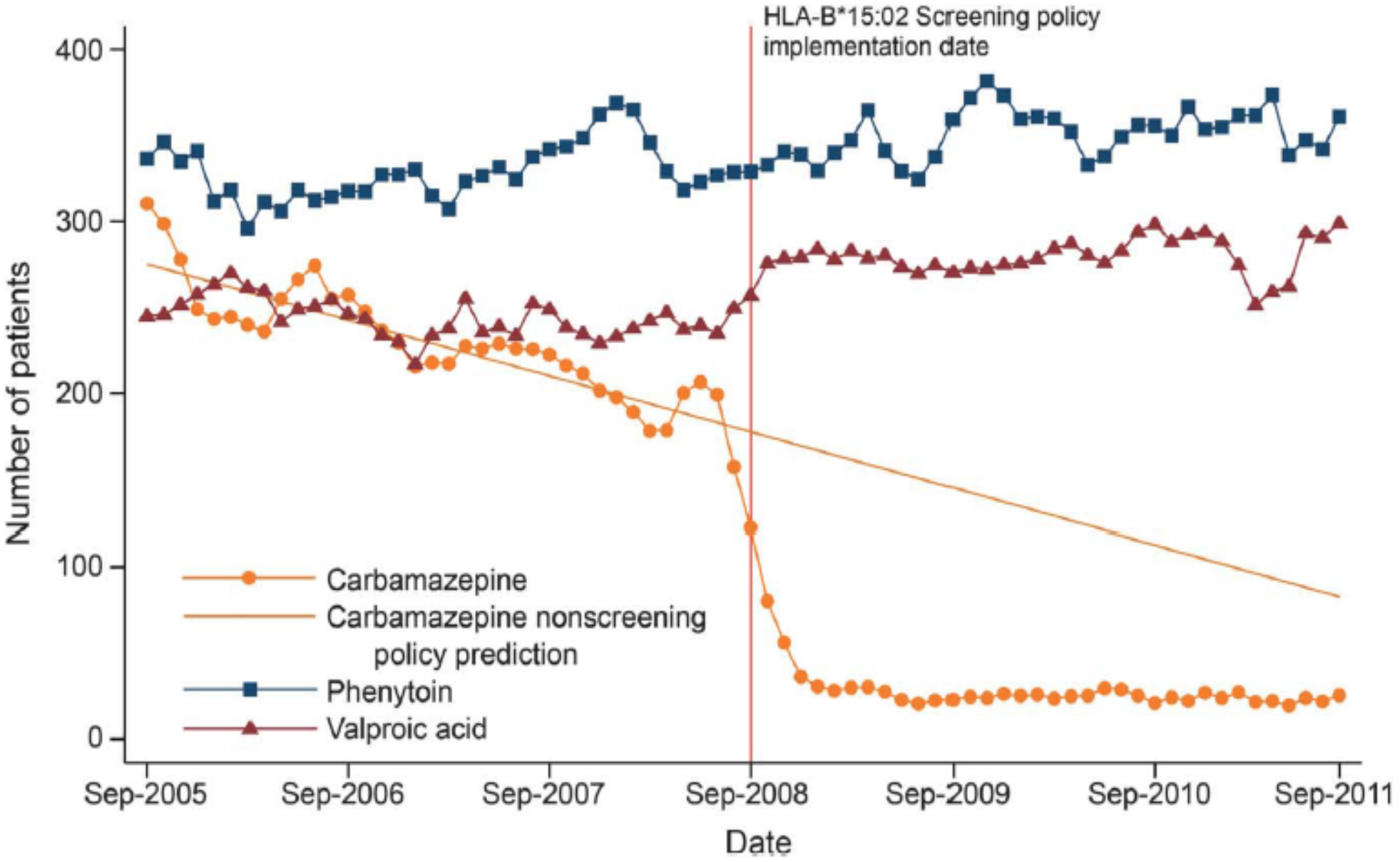
Monthly prescriptions of carbamazepine, phenytoin, and valproic acid in antiepileptic drug-naive patients

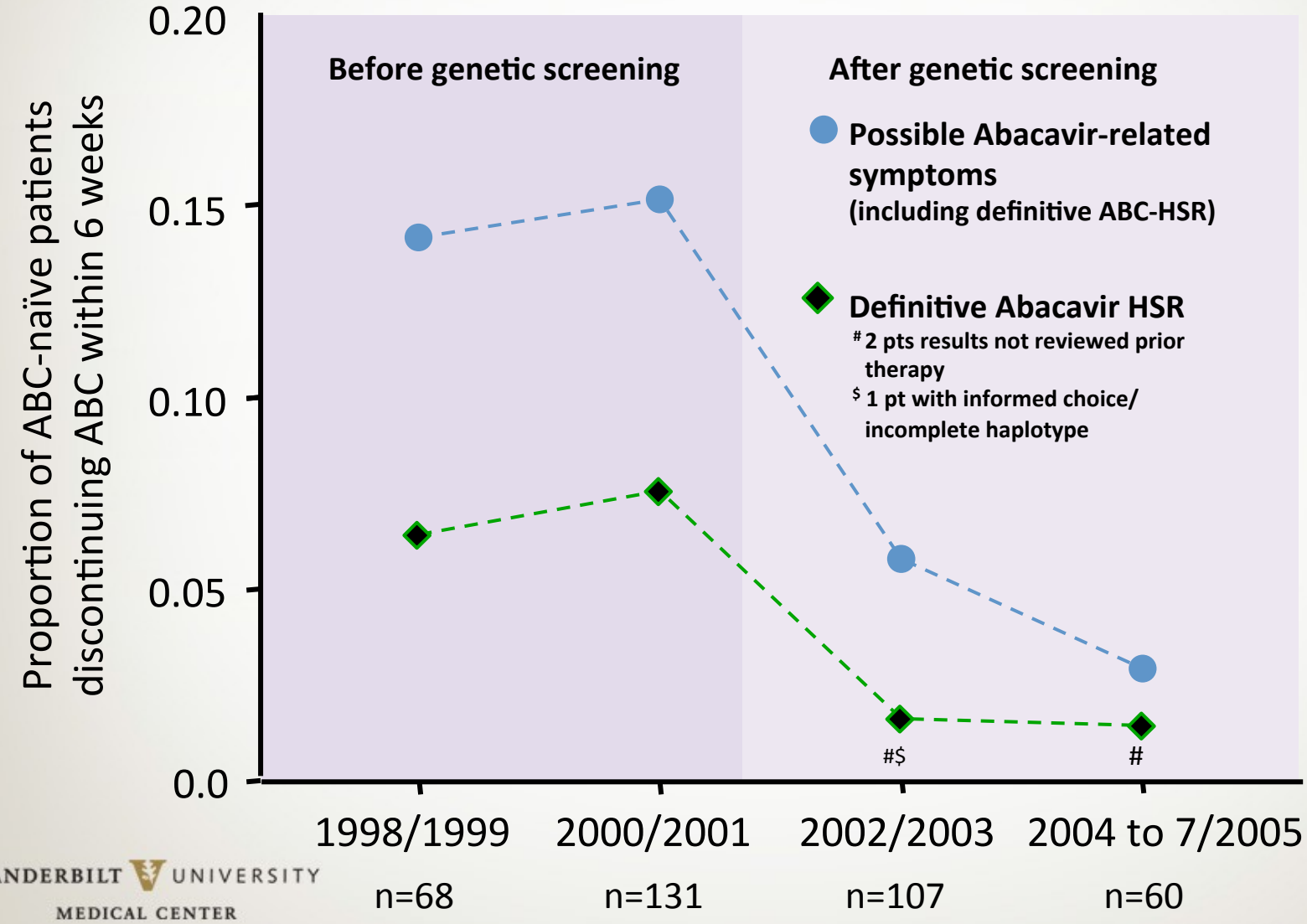


Post HLA-B*15:02 Screening in Hong Kong

- Prescription of carbamazepine declined (16.2% to 2.6%) and SJS/TEN in first time AED users associated with CBZ decreased from 0.24% to 0%
- Prescription of other AEDs increased
- SJS/TEN associated with phenytoin increased! (0.15% to 0.26%) and the overall incidence of AED SJS/TEN was unchanged
- Overall adherence to screening only 26.4%
- CONCLUSIONS:
  - When HLA-B*15:02 screening was performed and CBZ prescribed it worked
  - More than 50% tested did not commence an AED
  - Almost 40% who had testing sent were commenced on a non-CBZ drug before test results became available
  - Physicians reacted to the new HLA-B*15:02 policy by not prescribing CBZ

Neurology 2014;83:1-8

Fall in Early Discontinuation of Abacavir after Introduction of Prospective Genetic Screening



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Rauch, et al. *Clin Infect Dis* 2006;43:99-102.

Is the Objective Achievable?

Strengths

- Relevance to all NIH institutes/research organizations
- Broad global relevance (high risk drugs across all ethnicities and the developing/developed world)
- Paradigm shifting science
- Rapidly evolving technologies
- Multidisciplinary and collaborative research networks evolving

Weaknesses

- Relevant to all but "owned" by none
  - Lack of cohesive patient, provider, or scientific constituency
- Perception as rare and stochastic
- "Fear factor": Industry constraints/litigation environment
- Burden of disease and cost to healthcare/industry not adequately measured
- Poor provider education
- Few experts and "succession planning"
- Translational hurdles

Opportunities

- Potential for good global return on investment
  - Cost-effectiveness of treatment on a population level
  - Reduced morbidity and mortality, improved drug development pathway and drug safety
- Insights into mechanisms of other hypersensitivity syndromes (roadmap for study)
  - Capacity building for laboratory innovation
- Electronic health record reform; evidence based approaches to mine data from E.H.R.
- Creation of multidisciplinary research teams and new strategic alliances

Threats

- Lack of leadership/dilution of responsibility
- Lack of disease specific funding initiatives appropriate to lack of current capacity
- Lack of established networks (or collaborations too "new" to be considered competitive for peer-reviewed funding
- Huge infrastructure and capacity building required

What strategies can be generated for SJS/TEN?

- How can we Use each Strength?
- How can we Stop each Weakness?
- How can we Exploit each Opportunity?
- How can we Defend against each threat?

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Michaela Lucas
Campbell Witt
Ar Kar Aung

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Todd Hulgan
Imir Metushi
Simon Mallal
David Ostrov
Bjoern Peters
Imir Metushi
David Haas
Jing Yuan
Pablo Plascenia
Yuri Pomeu
Mariana Castells
Neil Shear
Sandra Knowles
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