Penn Medicine

Implementing HLA testing to prevent Stevens Johnson Syndrome: A view through an implementation science lens

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Acronyms

SJS / TEN	Stevens-Johnson Syndrome / toxic epidermal necrolysis
SCAR	Severe cutaneous adverse reactions
DRESS	Drug reaction with eosinophilia and systemic symptoms
HSR	Hypersensitivity reaction

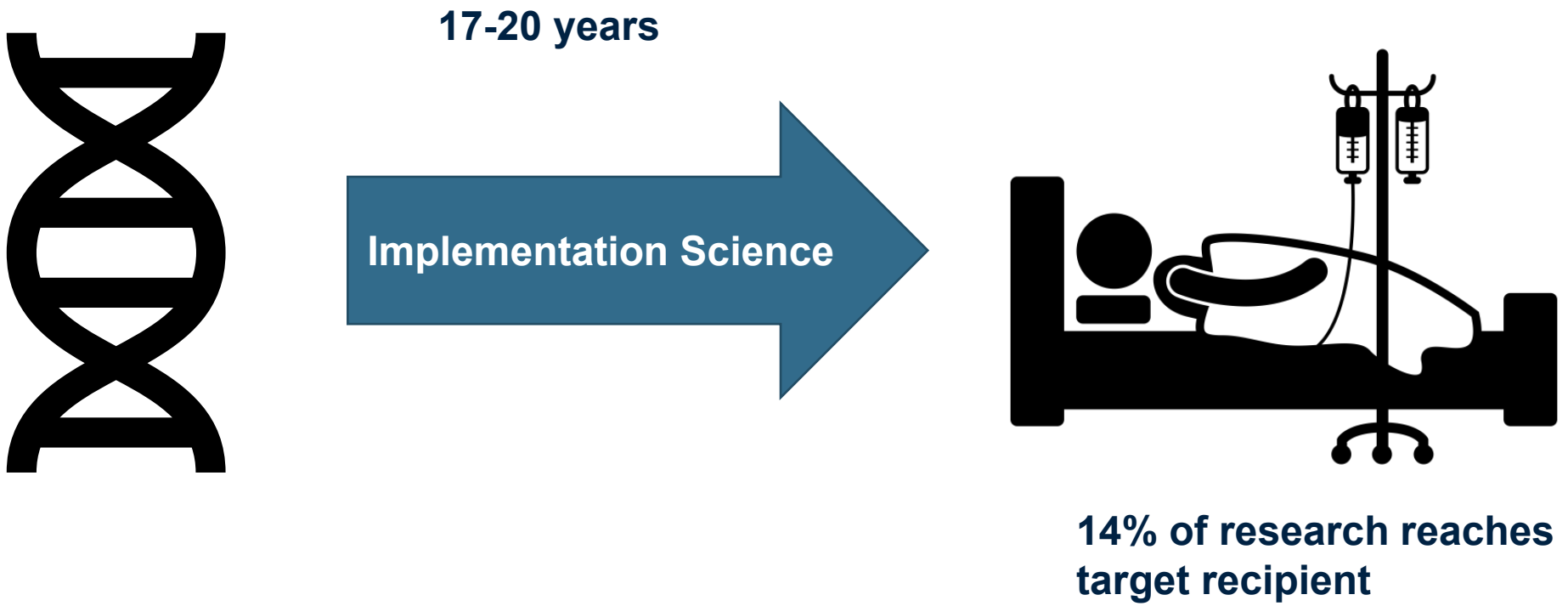
The problem: Stevens-Johnson Syndrome / toxic epidermal necrolysis

- Life threatening, immunologically mediated severe cutaneous adverse drug reaction
- Mortality rate of 15-20% (>50% in elderly and immunocompromised)
- Incidence of 1-2 per million persons per year in the US, higher globally
- Medications implicated in 8 of 10 cases
  - Allopurinol
  - Antiepileptic medications (carbamazepine, phenytoin, phenobarbital, lamotrigine)
- Prescreening for HLA markers can prevent SJS/TEN and other SCAR for some drugs
- But testing is not performed universally (with the exception of HLA-B*57:01 and abacavir)

- WHY?

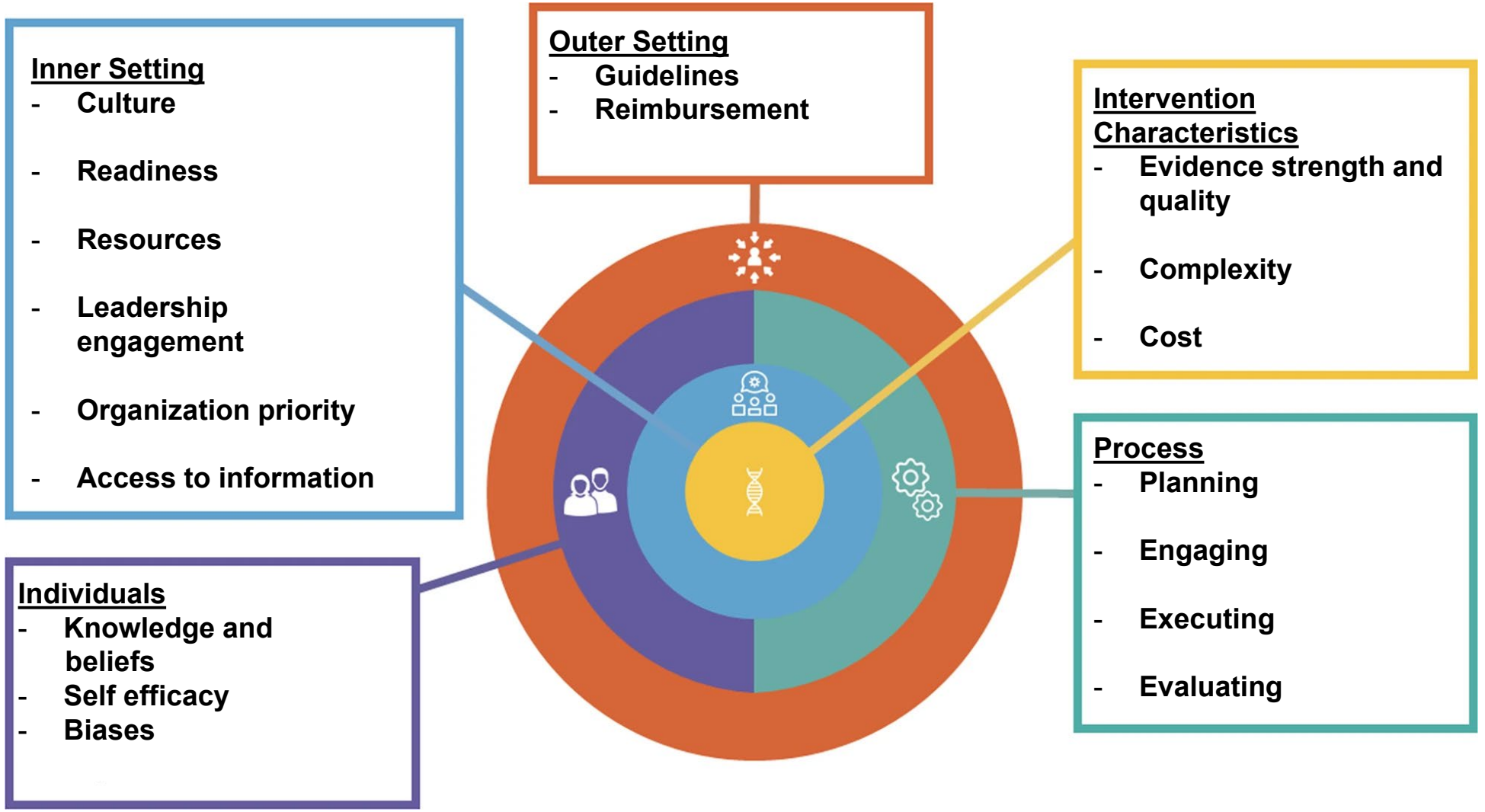
Implementation science bridges the evidence-to-practice gap

The study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine clinical practice



Eccles and Mittman. Implementation Science 2006
Morris Z. J of Royal Society of Medicine. 2011

More than efficacy / effectiveness



CFIR framework. Damschroder 2022; Implementation Science 17: 75.
Best S. et al. npj Genomic Medicine 2021; 6: 5.

Applying an implementation science framework

- Describe the evidence base for HLA testing
- Identify evidence- to- practice gaps
- Review barriers and facilitators to implementation
- Selecting implementation strategies
- Systems to monitor, evaluate, and sustain implementation

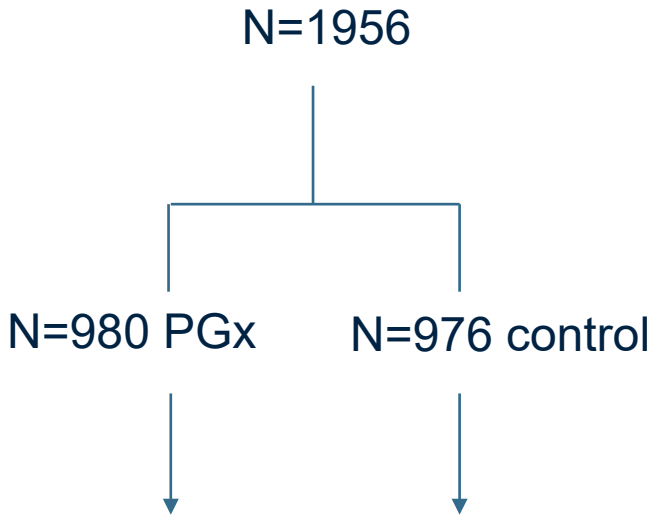
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

HLA-B*5701 Screening for Hypersensitivity to Abacavir

Simon Mallal, M.B., B.S., Elizabeth Phillips, M.D., Giampiero Carosi, M.D., Jean-Michel Molina, M.D., Cassy Workman, M.B., B.S., Janez Tomažič, M.D., Eva Jägel-Guedes, M.D., Sorin Rugina, M.D., Oleg Kozyrev, M.D., Juan Flores Cid, M.D., Phillip Hay, M.B., B.S., David Nolan, M.B., B.S., Sara Hughes, M.Sc., Arlene Hughes, Ph.D., Susanna Ryan, Ph.D., Nicholas Fitch, Ph.D., Daren Thorborn, Ph.D., and Alastair Benbow, M.B., B.S., for the PREDICT-1 Study Team*

N ENGL J MED 358;6 WWW.NEJM.ORG FEBRUARY 7, 2008



HSR			
Immunologically confirmed	0%	2.7%	P<0.001
Clinically diagnosed	3.4%	7.8%	P<0.001

N=4855

4483 negative

372 (7.7%) positive

4120 took CBZ

367 did not take CBZ
215 alternative meds

0 SJS / TEN
6 Severe cutaneous events
252 Mild cutaneous events

0 SJS / TEN
1 Severe cutaneous event
5 Mild cutaneous events

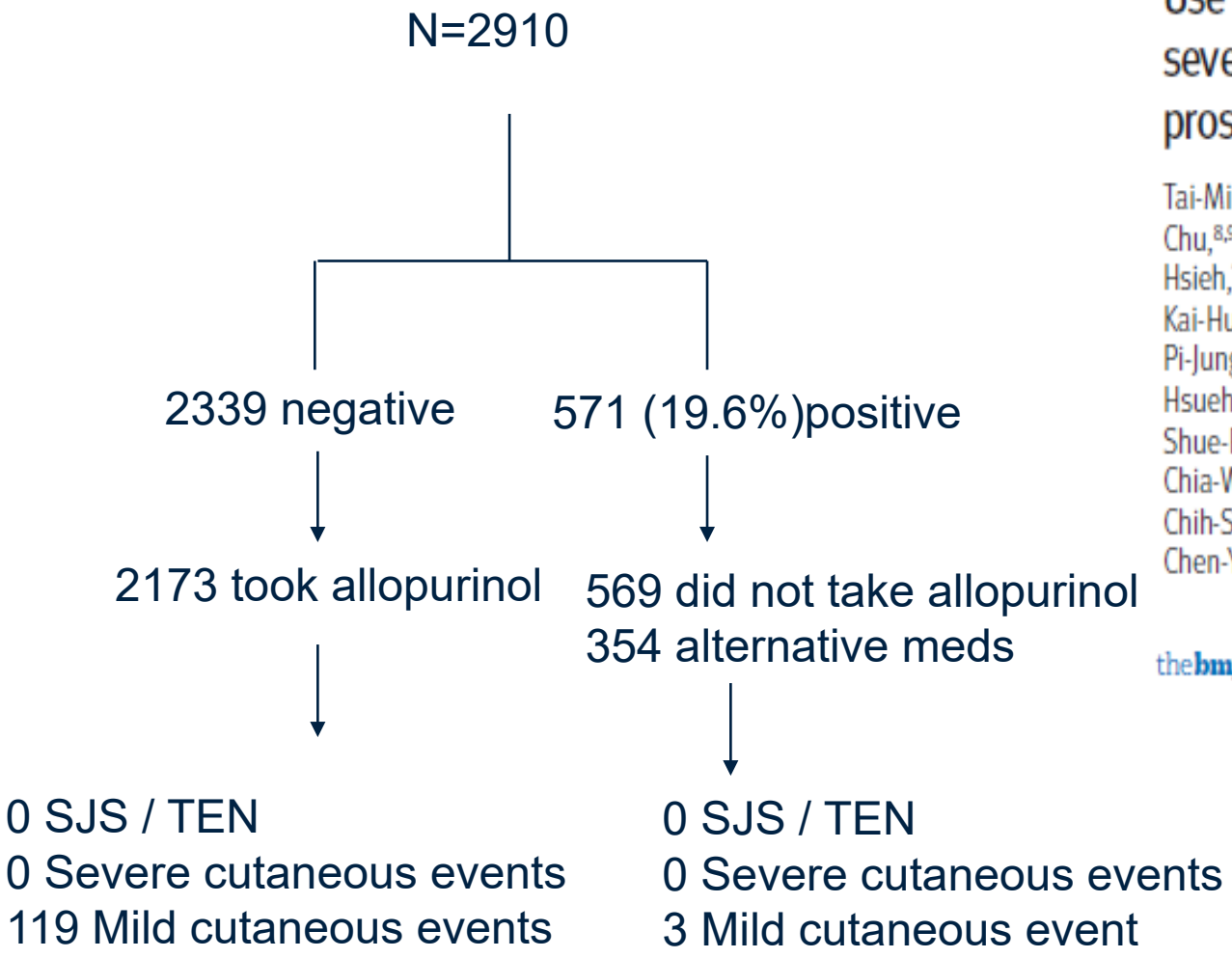
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Carbamazepine-Induced Toxic Effects and HLA-B*1502 Screening in Taiwan

Pei Chen, Ph.D., Juei-Jueng Lin, M.D., Chin-Song Lu, M.D., Cheung-Ter Ong, M.D., Peiyuan F. Hsieh, M.D., Chih-Chao Yang, M.D., Chih-Ta Tai, M.D., Shey-Lin Wu, M.D., Cheng-Hsien Lu, M.D., Yung-Chu Hsu, M.D., Hsiang-Yu Yu, M.D., Long-Sun Ro, M.D., Chung-Ta Lu, M.D., Chun-Che Chu, M.D., Jing-Jane Tsai, M.D., Yu-Hsiang Su, M.D., Sheng-Hsing Lan, M.D., Sheng-Feng Sung, M.D., Shu-Yi Lin, M.S., Hui-Ping Chuang, B.S., Li-Chen Huang, B.S., Ying-Ju Chen, M.S., Pei-Joung Tsai, M.S., Hung-Ting Liao, M.S., Yu-Hsuan Lin, M.S., Chien-Hsiun Chen, Ph.D., Wen-Hung Chung, M.D., Ph.D., Shuen-Iu Hung, Ph.D., Jer-Yuarn Wu, Ph.D., Chi-Feng Chang, Ph.D., Luke Chen, Ph.D., Yuan-Tsong Chen, M.D., Ph.D., and Chen-Yang Shen, Ph.D., for the Taiwan SJS Consortium*

N ENGL J MED 364;12 NEJM.ORG MARCH 24, 2011



Use of HLA-B*58:01 genotyping to prevent allopurinol induced severe cutaneous adverse reactions in Taiwan: national prospective cohort study

Tai-Ming Ko,[1,2] Chang-Youh Tsai,[3,4] Shih-Yang Chen,[5] Kuo-Shu Chen,[6] Kuang-Hui Yu,[7] Chih-Sheng Chu,[8,9,10] Chung-Ming Huang,[2,11] Chrong-Reen Wang,[12] Chia-Tse Weng,[12] Chia-Li Yu,[13] Song-Chou Hsieh,[13] Jer-Chia Tsai,[8,9,10] Wen-Ter Lai,[8,9,10] Wen-Chan Tsai,[8,9,10] Guang-Dar Yin,[14] Tsan-Teng Ou,[8,9,10] Kai-Hung Cheng,[8,9,10] Jeng-Hsien Yen,[8,9,10] Teh-Ling Liou,[3] Tsung-Hsien Lin,[8] Der-Yuan Chen,[4,15,16] Pi-Jung Hsiao,[8,9,10] Meng-Yu Weng,[12] Yi-Ming Chen,[4,15,16] Chen-Hung Chen,[17] Ming-Fei Liu,[12] Hsueh-Wei Yen,[8,9,10] Jia-Jung Lee,[8] Mei-Chuan Kuo,[18] Chen-Ching Wu,[8,9,10] Shih-Yuan Hung,[19,20] Shue-Fen Luo,[7,21] Ya-Hui Yang,[22,23] Hui-Ping Chuang,[1] Yi-Chun Chou,[1] Hung-Ting Liao,[1] Chia-Wen Wang,[1] Chun-Lin Huang,[1] Chia-Shuo Chang,[1] Ming-Ta Michael Lee,[1,24] Pei Chen,[1] Chih-Shung Wong,[25,26] Chien-Hsiun Chen,[1,27] Jer-Yuarn Wu,[1,27] Yuan-Tsong Chen,[1,28] Chen-Yang Shen[1,29,30] For the Taiwan Allopurinol-SCAR Consortium

thebmj | *BMJ* 2015;351:h4848 | doi: 10.1136/bmj.h4848

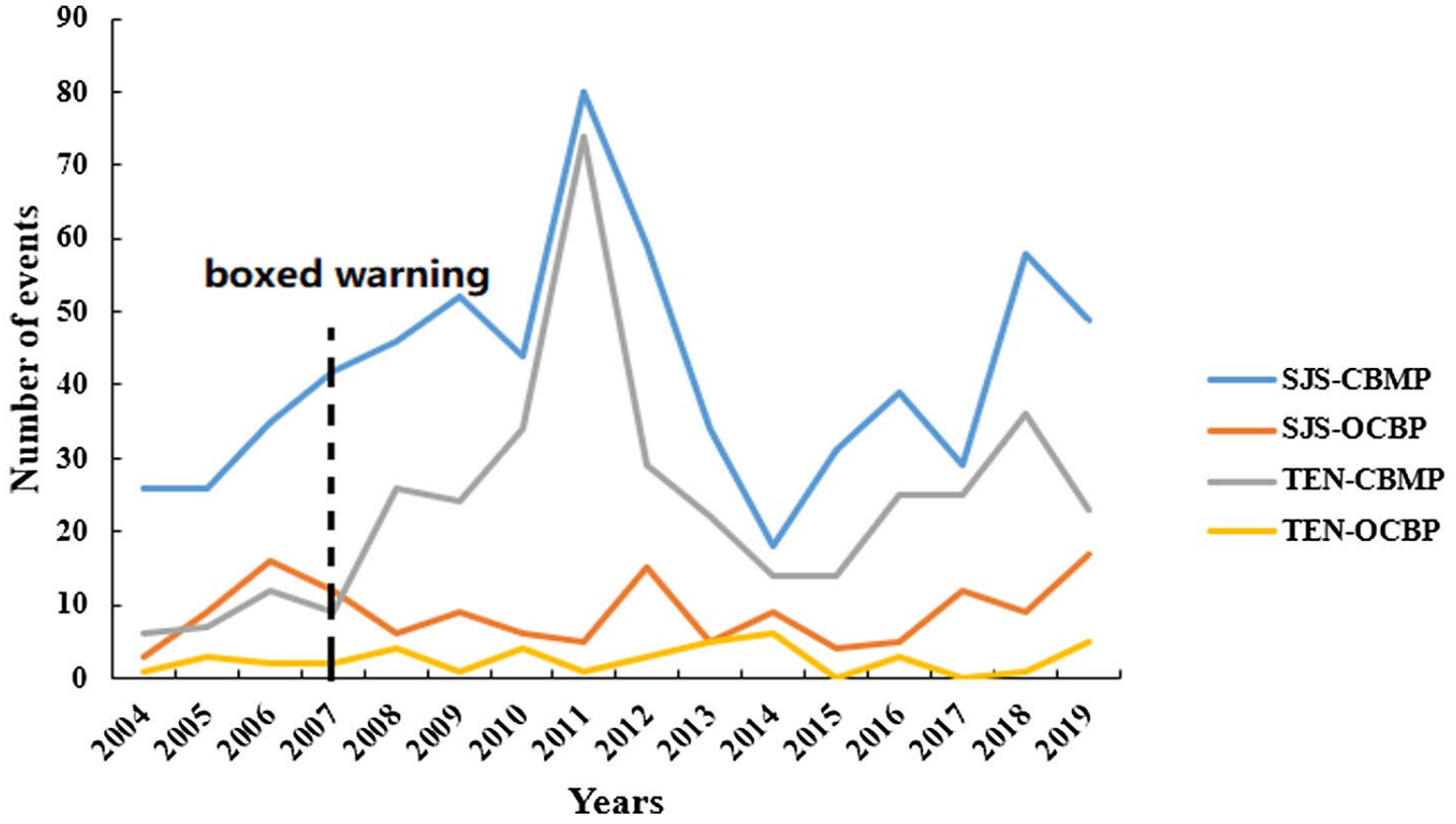
Guidance regarding HLA testing

Drug	Gene / Allele	FDA	CPIC guideline	Other
Abacavir	HLA-B *57:01	**BOXED WARNING-** testing required	Level A	Infectious Disease Society of America
Allopurinol	HLA-B *58:01	Recommended for at risk populations -African, Asian (Han Chinese, Korean, Thai), and Native Hawaiian/Pacific Islander ancestry	Level A	American Society of Rheumatology
Carbamazepine	HLA-B *15:02 HLA-A *31:01	**BOXED WARNING-** required for genetically at risk populations (Asian) HLA-A 31:01 not mentioned	Level A	
Oxcarbazepine	HLA-B *15:02	Should be avoided in patients positive for HLA-B*1502 unless the benefits clearly outweigh the risks.	Level A	
Phenytoin	HLA-B*15:02 CYP2C9	Consider avoiding phenytoin as an alternative to carbamazepine in patients who are positive for HLA-B*1502 or in CYP2C9*3 carriers.	Level A	

Applying an implementation science framework

- Describe the evidence base for HLA testing
  - Do we have evidence that it works? YES
  - What are the benefits of testing? (prevents serious cases SJS)
- Identify evidence- to- practice gaps
- Review barriers and facilitators to implementation
- Select implementation strategies
- Systems to monitor, evaluate, and sustain implementation

Cases of SJS and TEN reported to FDA adverse reporting system (FAERS) database associated with carbamazepine and oxcarbazepine



Int J Clinical Practice, Volume: 75, Issue: 8, 2021, DOI: (10.1111/ijcp.14273)

Cases of SJS and TEN reported to FAERS database associated with antiepileptics medications

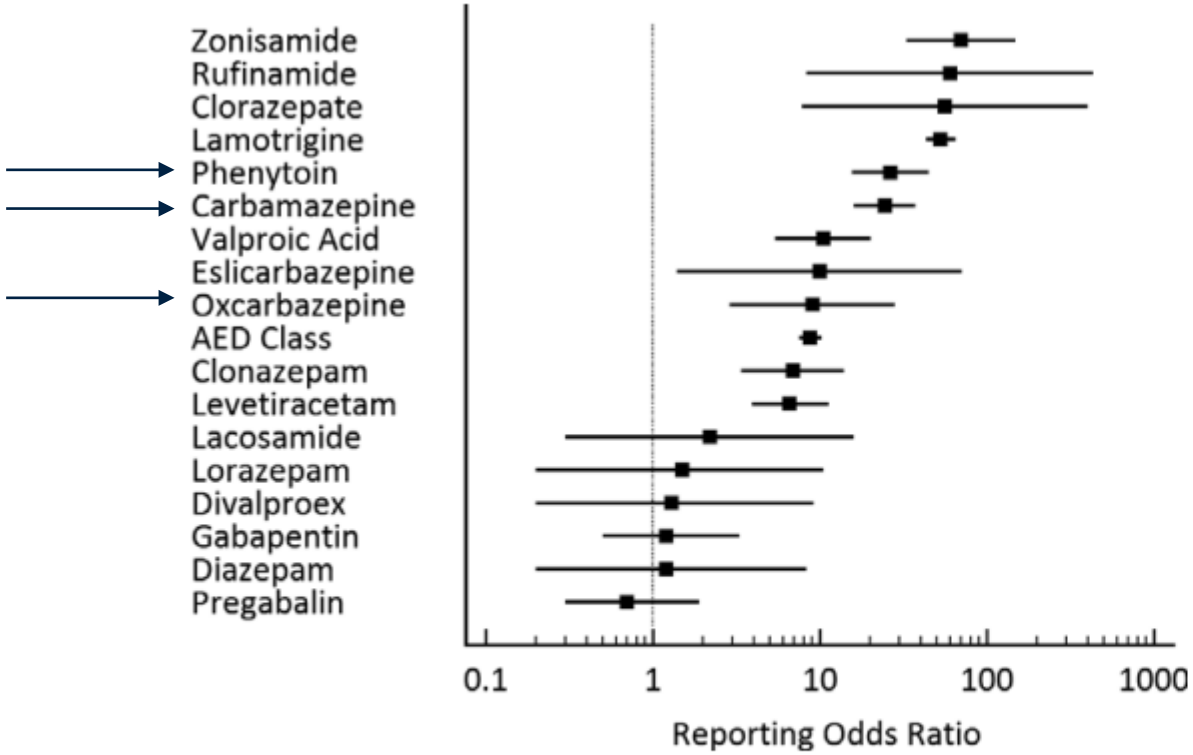


FIGURE 1 Antiepileptic medications and Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), reporting odds ratios

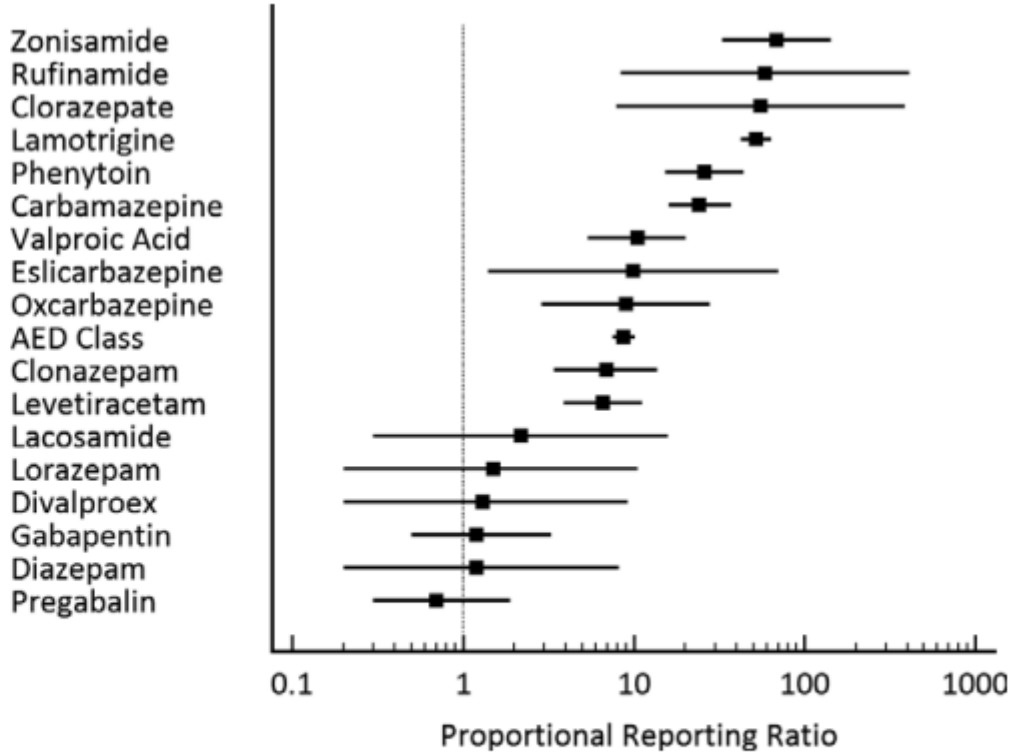


FIGURE 2 Antiepileptic medications and Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), proportional reporting ratios

Borrelli EP. Epilepsia 2018; 59: 2318-2324

Practice gap: testing is not occurring

- In a large biobank 36,424 with PGx results [1]
  - 2,327 (6.4%) HLA-A *31:01 positive
  - 3,543 (9.7%) HLA-B *15:02 positive
  - 92 of the HLA positive patients received a prescription for carbamazepine or oxcarbazepine
  - 4 (4.3%) experienced a rash that warranted drug discontinuation
  - Ancestry- 1 Asian, 2 White, 1 Black

- EHR records review from one healthcare system [2]
  - 3,063 prescriptions for carbamazepine or oxcarbazepine
  - 302 with race coded as “Asian”, “Other”, “Unknown”
  - 27 treatment naïve with Asian ancestry
  - 0/6 carbamazepine and 1/6 oxcarbazepine were HLA pre-screened

1. Shah S. Drug Safety 2021; 44: 601-607
2. Bui VL. Pharmacogenetics and Genomics 2024; 34: 16-19

Practice gap- an imperfect test

Not all alleles associated with multiple clinical phenotypes of SCAR

Drug	HLA risk allele	HSS	SJS-TEN	DRESS/ DIHS	DILI	MDE
Allopurinol	HLA-B *58:01					
Abacavir	HLA-B *57:01					
Carbamazepine	HLA-B *15:02^					
Carbamazepine	HLA-B *31:01					
Phenytoin	HLA-B *15:02					

^ B75 serotype (15:02 + *15:21, *15:08, *15:11, *15:30, *15:3)

HSS, hypersensitivity syndrome; SJS/TEN, Stevens-Johnson syndrome/ toxic epidermal necrolysis; DRESS/ DIHS, drug reaction with eosinophilia and systemic symptoms / drug-induced hypersensitivity syndrome; DILI, drug induced liver injury; MDE, maculopapular drug eruption

Marks M et al. Frontiers in Medicine 2023;

Practice gap- An imperfect test: low PPV

Drug	Gene/allele	Populations	PPV	NPV	NNT	Onset on HSR
Abacavir	HLA-B *57:01	>10% India 5-10% EUR 5-10% S. America	48-76%	100%	14-42	~6 weeks
Allopurinol	HLA-B *58:01	>10% China, Taiwan >10% India 5-10% Africa	1.5%	100% in Han Chinese	~500	Weeks-months
Carbamazepine	HLA-B *15:02	>10% Thailand 5-10% China, Taiwan <1% Europe	1-2%	100% in Asian	400-3000	4-28 days
Carbamazepine	HLA-A *31:01	5-10% Japan, Korea 1-5% Europe 1-5% Africa	0.2-0.9%	100%	3000-6000	~8 weeks
Phenytoin	HLA-B *15:02	>10% Thailand 5-10% China, Taiwan <1% Europe	0.2-1.4%	100%	400-3000	~8 weeks

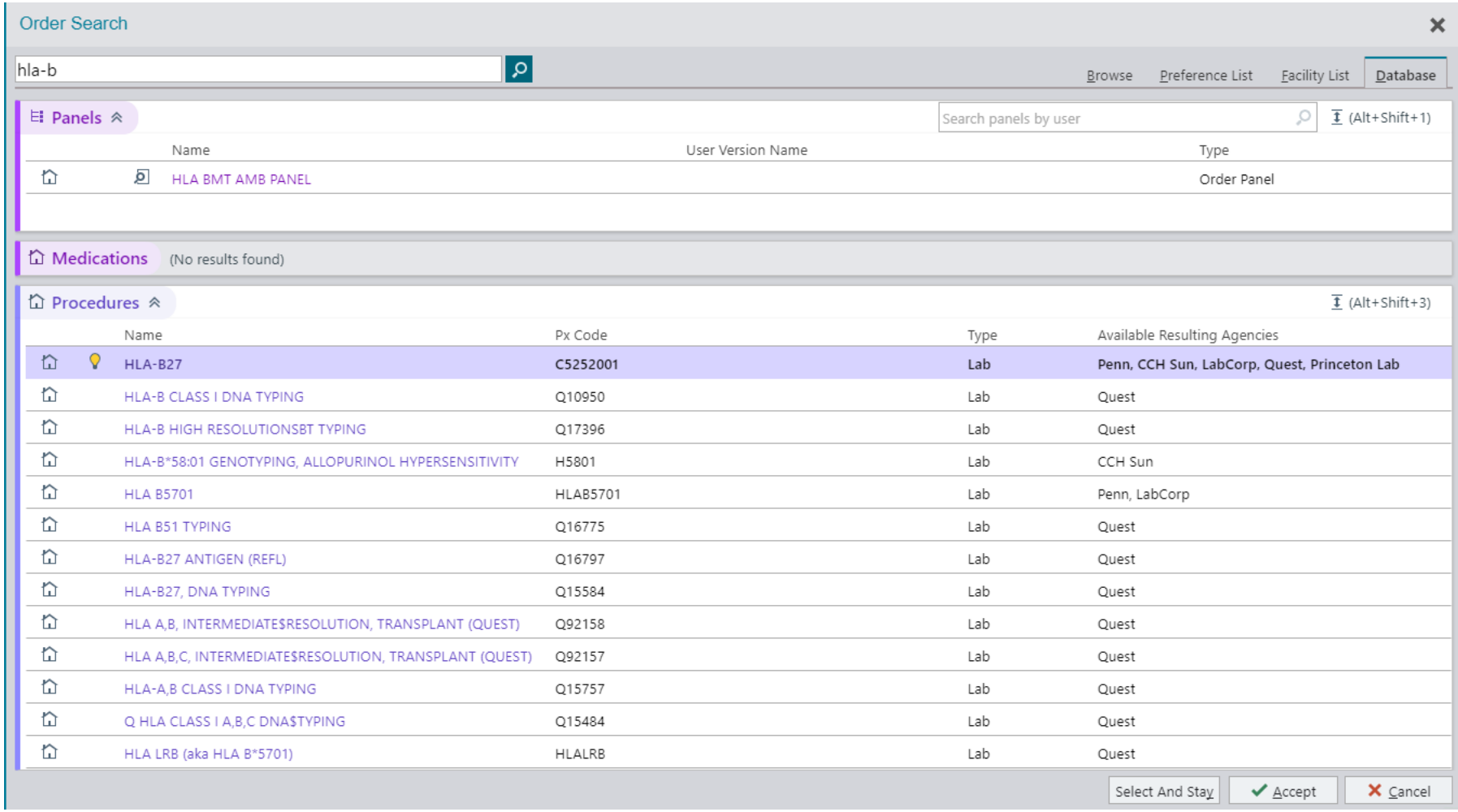
Hung S et al. Nature Reviews disease primers 2024; 10:30

Practice gap- cost-effectiveness studies are mixed

Drugs	Marker	No. Articles	Cost-saving	Cost effective	Not cost effective	Uncertain
Abacavir	HLA-B *57:01	8	2	4	1	1
Allopurinol	HLA-B *58:01	10	1	4	5	-
Carbamazepine Phenytoin	HLA-B*15:02	7	1	2	4	-
	HLA-A*31:01	1	-	1	-	-
Total		26	**4 (15%)**	**11 (42%)**	**10 (38%)**	1

Morris SA. Clinical Pharmacology and Therapeutics 2022; 112: 1318

Practice gap- confusion about the appropriate test



Applying an implementation science framework

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  - What are the benefits of testing? (prevent death, serious cases SJS, healthcare costs)
- Identify evidence- to- practice gaps
  - HLA testing and guidelines are available however, not widely implemented
  - Cases of SJS /TEN continue to occur
  - Optimal screening strategies have not been developed
  - Test characteristics not optimal
  - Lack of awareness among prescribers about testing and how to order testing
- Review barriers and facilitators to implementation
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Barriers and facilitators at each level

Domain	Barriers	Facilitators
Outer setting	- Fragmented healthcare system - Cost of testing - Cost of alternative treatments - Equity gap	- Disease specific guidelines - CPIC guidelines - FDA labels - Implementation working groups - Pharmacovigilance registries
Inner setting	- Lack of institutional support - EHR integration of discrete results	- Early screening program - Identify early adopters
Individuals	- Clinician lack of knowledge - Patient lack of awareness - Impact on family members - Population admixture	- Targeted education - Shared decision making - EHR algorithms suggesting testing
Intervention	- Patients are not offered testing - Testing options unclear - Low PPV of test	- EHR based alerts - Collaborations and patient registries - Quality inexpensive test
Process	- Lack of time for pre-test counselling - Send out test (manual process)	- Precision medicine / PGx teams - Multi-gene panels

Hooker. Am J Med Genet 2021; 187: 95. Sperber. BMC Med Genomics; 2017: 10: 35.
Tuteja. Clinical Translational Science 2021; 15: 371. Hung. Nature reviews disease primers 2024; 10:30.

Implementation strategies

Plan	Gather data, build buy-in, develop relationships, needs assessment
Educate	Inform stakeholders
Finance	Incentives, train and support, new funding
Restructure	Alter staffing, physical structure and data tracking
Quality management	Develop tools, remind clinicians, feedback
Attend to the policy context	Accreditation, legal

Powell BJ. Medical Care Research and Review 2012; 69: 123-157.
Powell BJ. Implementation Science 2015; 10: 21.

Factors influencing HLA testing and potential strategies

CFIR domain	Example factor	Potential strategy
Outer setting	Rheumatology guidelines CPIC guidelines	Disseminate guidelines to primary care providers
Inner setting	Unclear how and which test to order	Streamline the testing options
Characteristics of individuals	Clinician lack of awareness for the need of testing	Provide education in readily accessible format (e.g. UptoDate)
Intervention characteristics	Patients are not offered testing	Create a pre-test alert in EHR
Process	Lack of clinician time for pre-test counselling	Create educational materials for patients Engage PGx pharmacists

Powell BJ. Implementation Science 2015; 10:21

Engaging end-users regarding pharmacogenetic testing

Physician DCE

Question: 'You have decided to prescribe carbamazepine for your patient. You may either select the following pharmacogenetic test prior to the prescription, or select not to test and proceed with the prescription blindly'

Cost	£35
Days to result	2
Positive predictive value (PPV)	2%
Negative predictive value (NPV)	70%
Coverage	Serious ADRs ONLY
Inclusion in British National Formulary (BNF)	Yes

- ☐ I WOULD select the test prior to the prescription of carbamazepine
- ☐ I WOULD NOT select the test and proceed with the prescription of carbamazepine blindly

Patient DCE

Question: 'Which medication would you prefer?'

	MEDICATION A	MEDICATION B
Stop Seizures *One year after starting this medication*	5 in 10 people seizures stop	3 in 10 people seizures stop
Fewer Seizures *One year after starting this medication*	3 in 10 people experience fewer seizures	1 in 10 people experience fewer seizures
Mild skin rash *A blotchy, itchy red rash on your upper body*	1 in 100 people experience a mild skin rash	26 in 100 people experience a mild skin rash
Memory Problems *These are frequent and affect activities of daily life*	1 in 100 people experience memory problems	7 in 100 people experience memory problems
Potentially life-threatening reaction *Severe skin reaction that may cause death*	**UNCOMMON** More than 1 in 1000 people experience a life-threatening reaction	**RARE** More than 1 in 10,000 people experience a life-threatening reaction
Which medication would you prefer to take?	☐	☐

Powell G. BJP 2015; 80: 1149-59.

Engaging end-users regarding pharmacogenetic testing

Clinician discrete choice results

- Odds that respondents selected the test
  - decreased by 1% for every £1 increase in cost of test
  - Increased if the PPV increased, test was contained in the formulary, test predicted both severe and mild ADRs
  - Improvement in PPV from 26% to 70%, increased the probability of requesting the test almost 8-fold, to 88.6%

Patient discrete choice results

- Willing to accept reduction in 12 months chance of remission in seizures in exchange for a reduction in adverse events.
  - 0.58% reduction in remission for 1% reduction in skin rash, 3.2% reduction in memory problems, and 0.001% reduction in risk of severe ADR
  - Overall, probably of test uptake 55%

Powell G. BJP 2015; 80: 1149-59.

Clinician perspectives on HLA testing for allopurinol

"I think it depends on my patients, if they are the type that who are more affluent, good health literacy and they can afford the febuxostat in the future. I would be more willing to offer those types of patients the HLA test for them. But if my patient is from the poorer social economic group and they keep on suffering from gout attack, they need to be on preventive medication. I think those are the patients that I would just counsel, please watch out for the side effect, anything happens come back immediately."

(Doctor 2, female, 7 years of experience, university hospital)

Ng WL. PLoS One 2024; 19: e0296498

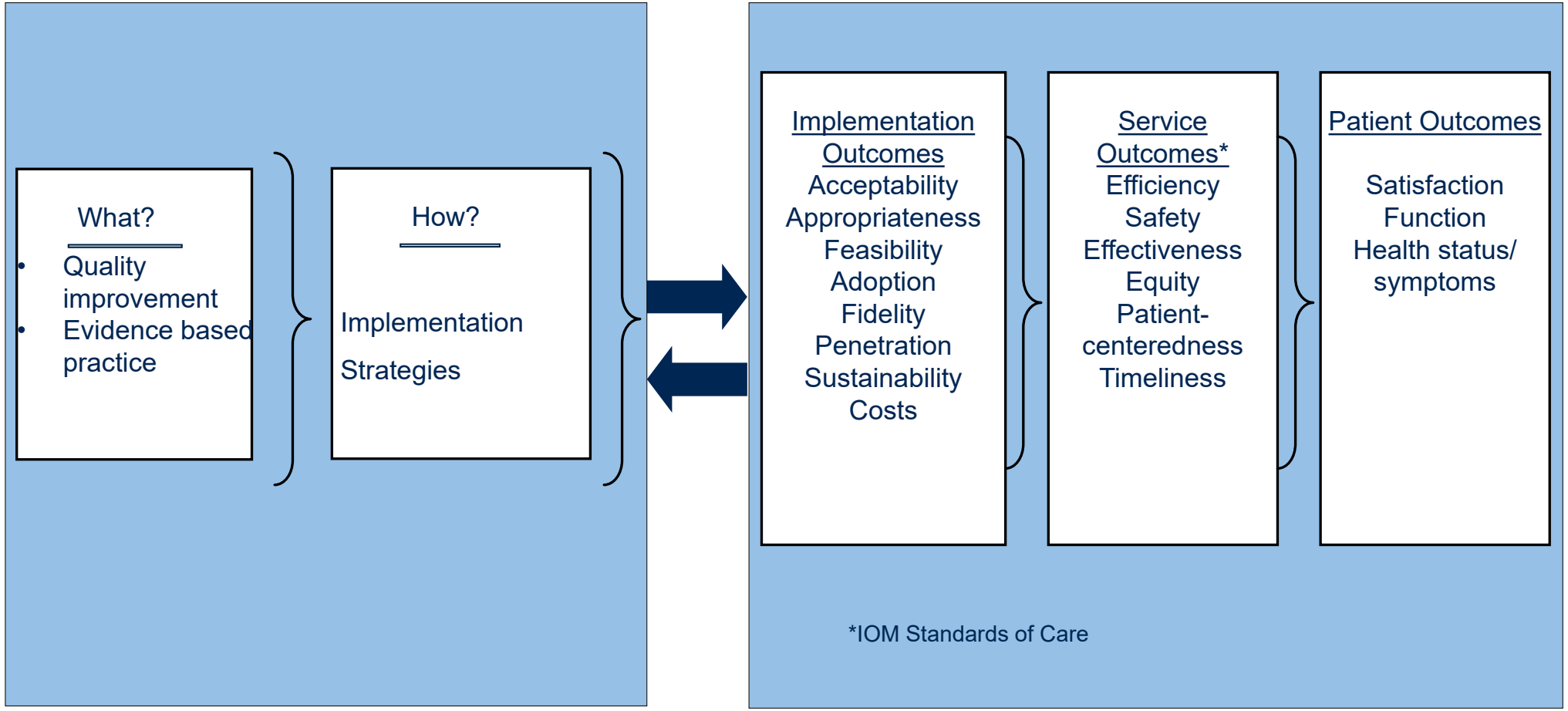
Patient perspectives on HLA testing for allopurinol

"If I see the value of it, I would do it. Because the investment is for your health, and so I will do it. Normally I can claim because I'm still working with a company now. So, to my best ability, I will claim. But if I cannot claim, what to do, you need to pay myself. Well, to answer your question, in short, if I see benefit in it, because there's an appeal, just find money to afford it."

(Patient 11, 52-year-old Malay male, had gout for 12 years, not on allopurinol, follow-up in private GP clinic)

Ng WL. PLoS One 2024; 19: e0296498

Monitor, evaluate, and sustain



Proctor EK. Adm Policy Ment Health 2009; 36(1)

Conclusions

- Describe the evidence base for HLA testing
  - Do we have evidence that it works? YES
  - What are the benefits of testing? (prevent death, serious cases SJS, healthcare costs)
- Identify evidence- to- practice gaps
  - HLA testing and guidelines are available however, not widely implemented
  - Cases of SJS /TEN continue to occur
  - Optimal screening strategies have not been developed
  - Test characteristics not optimal
  - Lack of awareness among prescribers about testing and how to order testing
- Review barriers and facilitators to implementation
- Select implementation strategies
- Systems to monitor, evaluate, and sustain implementation
- Pay particular attention to issues of equity

Future directions

- Conduct studies across diverse population groups (age, race, gender, ethnicity)
- Rigorous evaluation of strategies and contextual modifiers of successful implementation
- Collaborations to increase power and evaluate multiple contexts
- Studies that include genetic and other risk factors
- Bolster pharmacovigilance methods to alert new adverse drug effects
- Research to identify additional genetic susceptibility loci

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