Physician's View: Stevens Johnson Syndrome

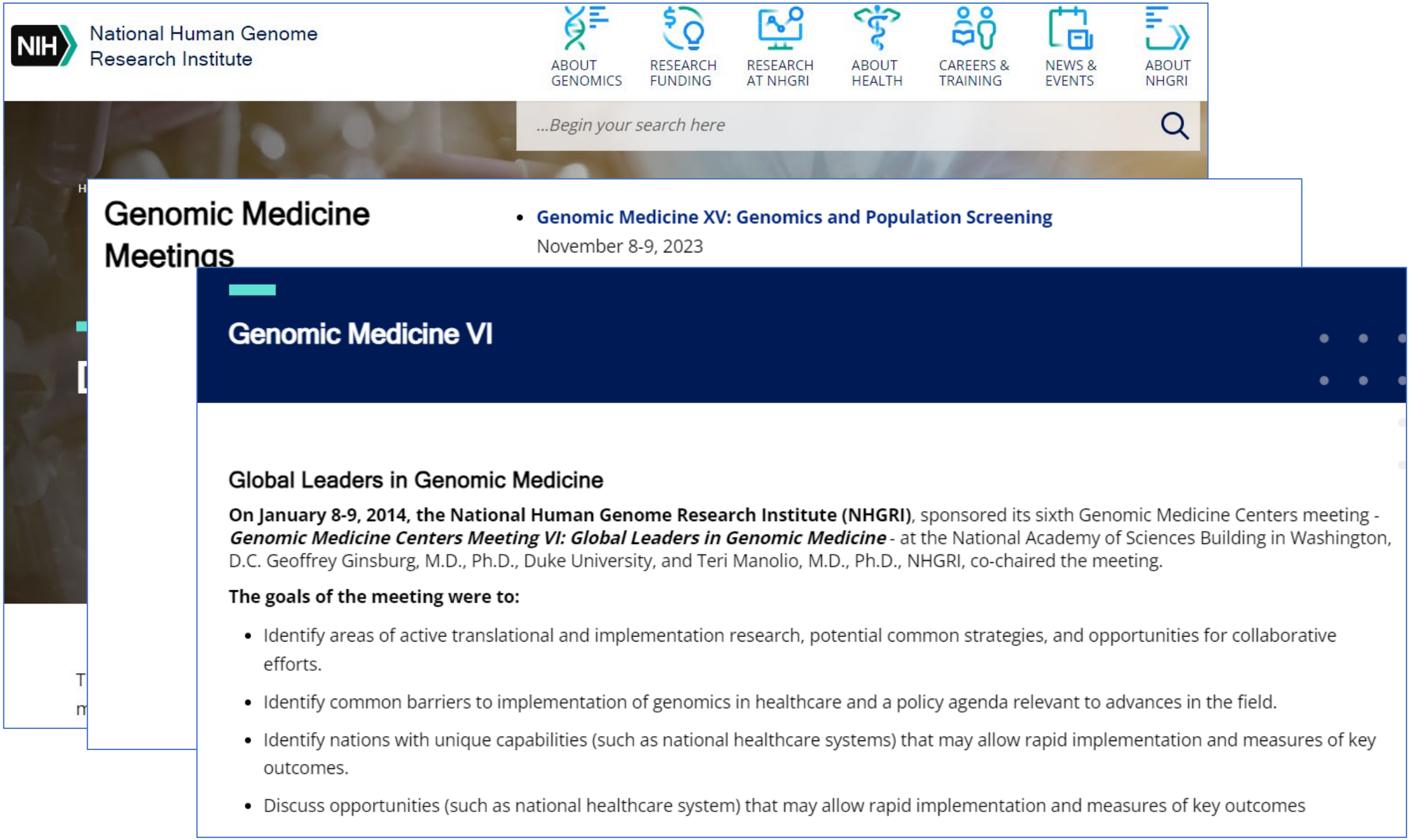
Teri Manolio, M.D., Ph.D.

ClinPGx 2024: Knowledge, Implementation & Education

June 20, 2024

National Human Genome Research Institute

The **Forefront** of **Genomics**®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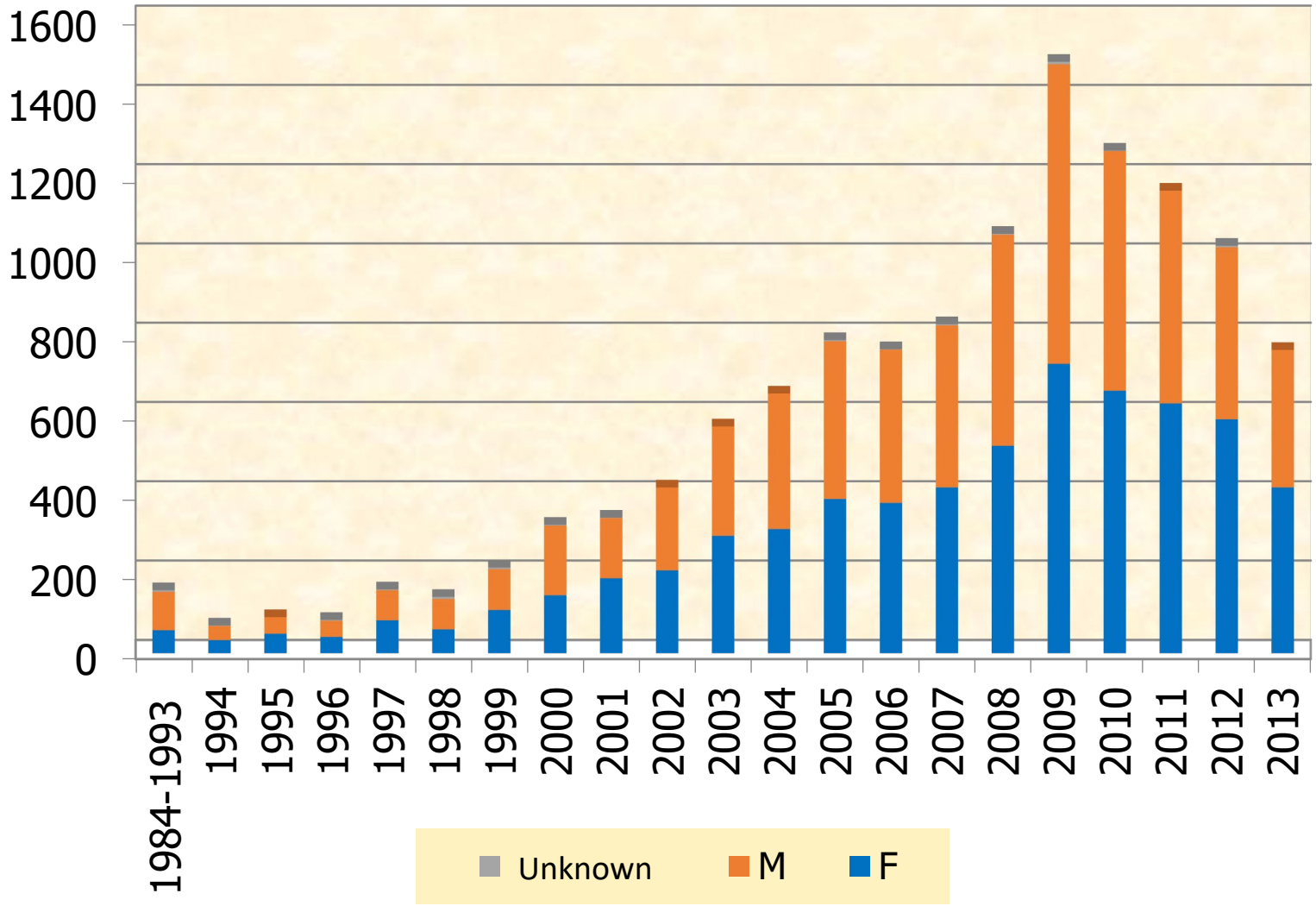
Genomic Medicine Meetings
Genomic Medicine XV: Genomics and Population Screening
November 8-9, 2023
Genomic Medicine VI
Global Leaders in Genomic Medicine
On January 8-9, 2014, the National Human Genome Research Institute (NHGRI), sponsored its sixth Genomic Medicine Centers meeting - Genomic Medicine Centers Meeting VI: Global Leaders in Genomic Medicine - at the National Academy of Sciences Building in Washington, D.C. Geoffrey Ginsburg, M.D., Ph.D., Duke University, and Teri Manolio, M.D., Ph.D., NHGRI, co-chaired the meeting.
The goals of the meeting were to:
Identify areas of active translational and implementation research, potential common strategies, and opportunities for collaborative efforts.
Identify common barriers to implementation of genomics in healthcare and a policy agenda relevant to advances in the field.
Identify nations with unique capabilities (such as national healthcare systems) that may allow rapid implementation and measures of key outcomes.
Discuss opportunities (such as national healthcare system) that may allow rapid implementation and measures of key outcomes

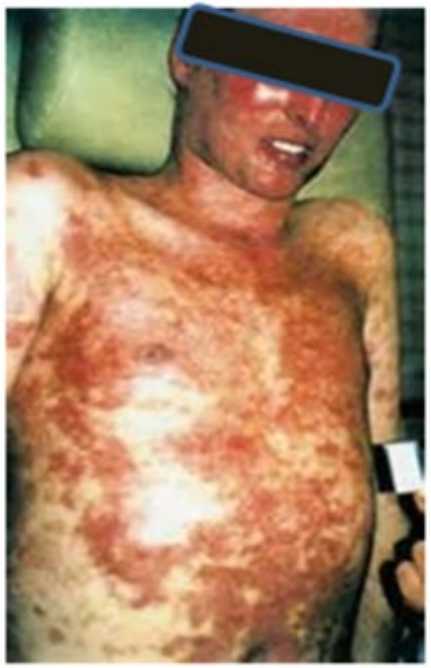
Courtesy W Chantratita, Ramathibodi Hospital

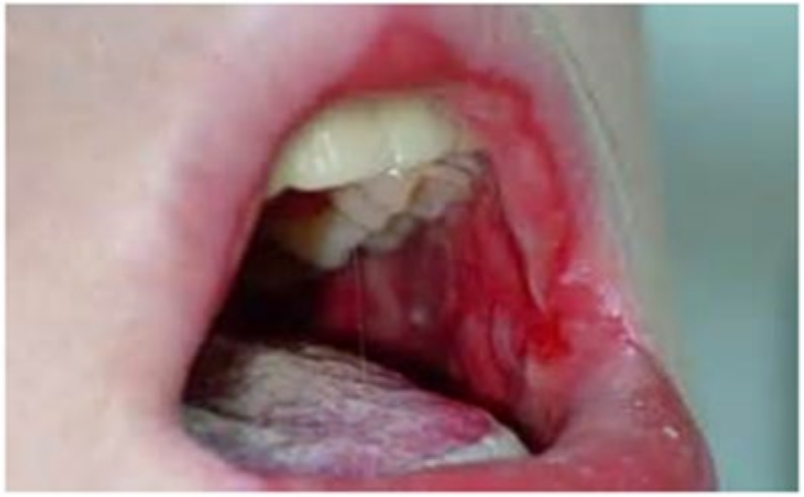
Incidence of SJS/TEN in Thailand, 1984-2013

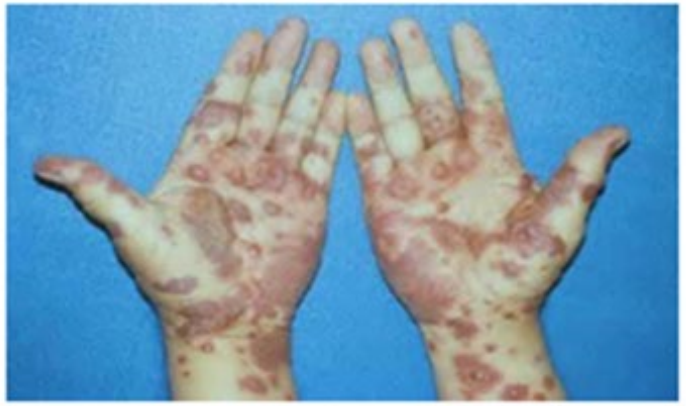


Courtesy Wasun Chantratita, Ramathibodi Hospital

“A Fate Worse Than Death”







In Thailand, we had interviewed many who survived SJS/TEN, they said that their bodies spitted rotting flesh and blood from their mouth. They felt that their bodies were burning and that someone had poured acid into their eyes. The pain was so extreme that they wish to die, but they could not.

Severe or life-threatening skin rash,Steven-Johnson syndrome (SJS) and Toxic epidermal necrosis syndrome (TENS)

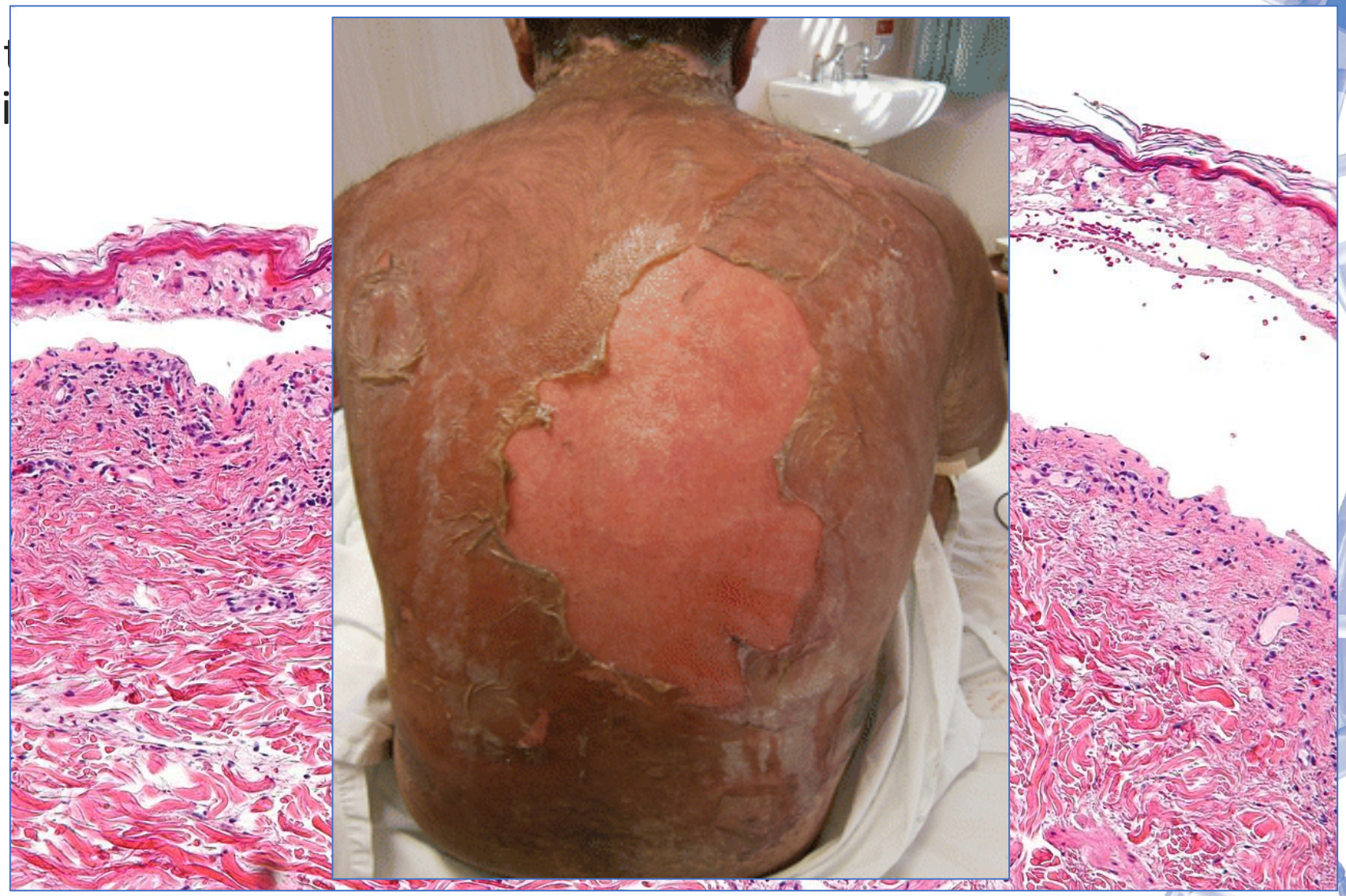
Courtesy Wasun Chantratita, Mahidol U

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

40 US Genomic Leaders and NHGRI Staff

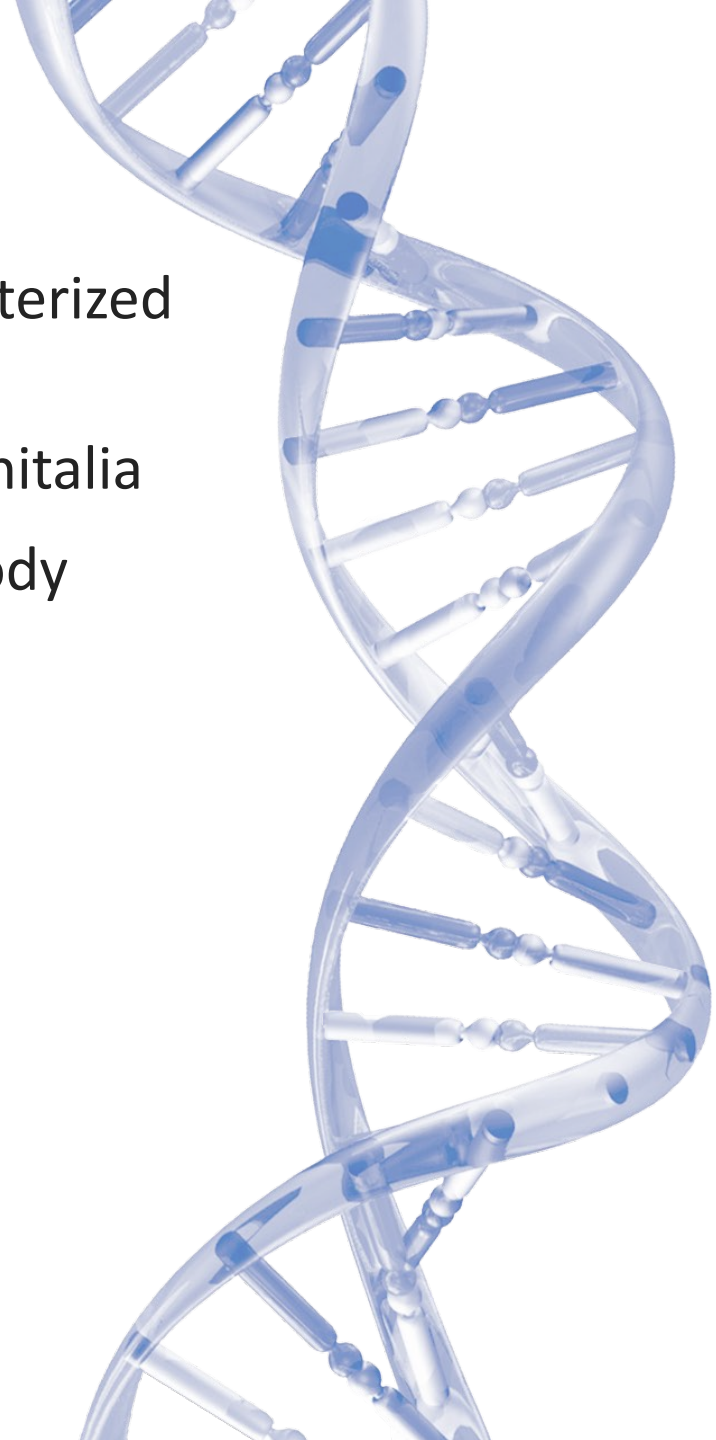
Stevens Johnson Syndrome - Primer

- Severe cut
  by extensi



Stevens Johnson Syndrome - Primer

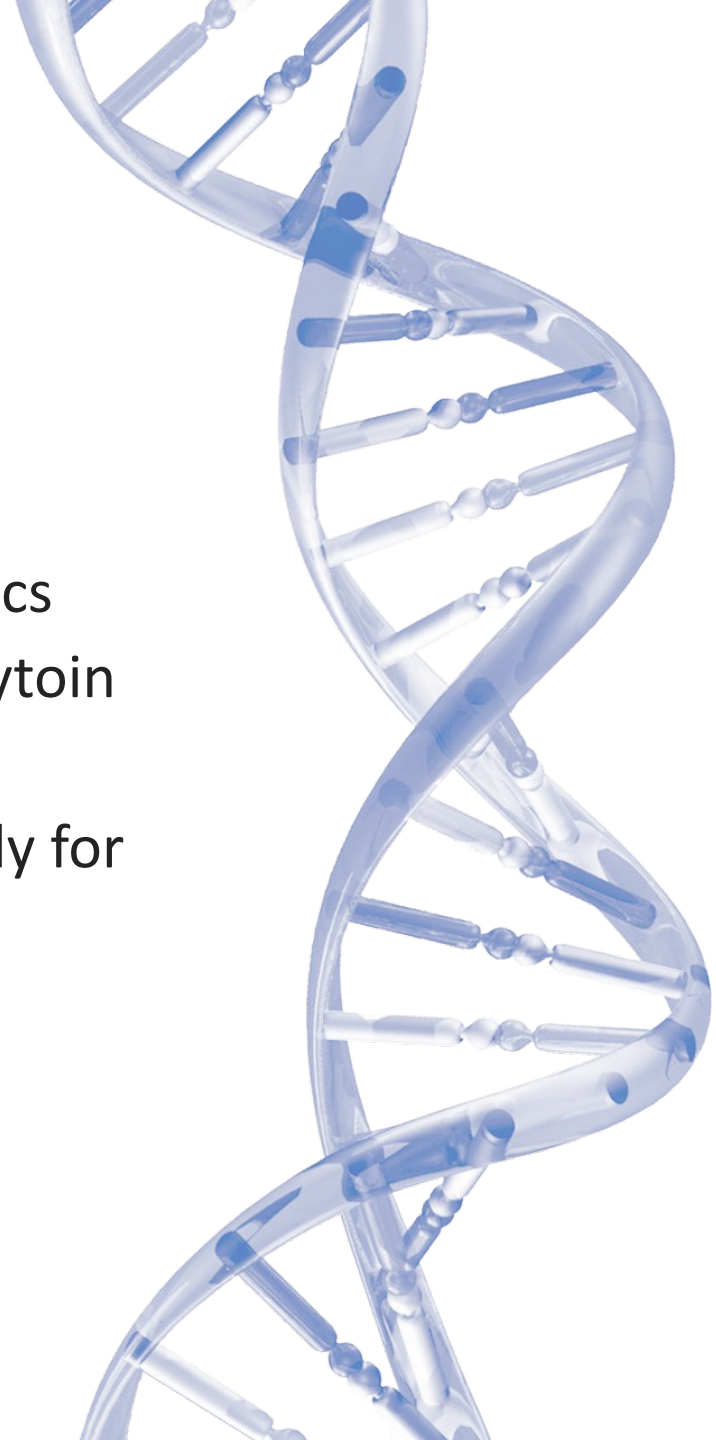
- Severe cutaneous adverse reactions to viruses or drugs characterized by extensive necrosis and detachment of the epidermis
- Mucous membranes are affected > 90% including eyes and genitalia
- SJS and TEN are continuum, classified by percentage of skin body surface area detached:
  - < 10% detached – SJS
  - 10 to 30 % detached – SJS/TEN overlap
  - > 30 % detached – TEN
- Incidence: 5-6 cases/million/year with SJS most common
- Multinational studies estimate median age 50-52 years
- More common in girls/women by ratio 2:1 vs. boys/men



Adapted from *UpToDate*

SJS/TEN – Risk Factors

- Risk factors
  - Human immunodeficiency virus (HIV): 12-fold risk
    - Contributing factors: high risk drugs (nevirapine), opportunistic infections (co-trimoxazole, anti-TB meds)
  - Connective tissue disease: 2-fold risk, though may be mimics
  - Malignancy: 30-60-fold, common triggers TMP-SMX, phenytoin
  - Older age, Black and Asian ethnicity
  - Increased drug doses and impaired renal function especially for allopurinol-induced SJS/TEN
- Mortality:
  - Acute episode: overall 23%, range 12-49% increasing with increased severity
  - One-year: increased to 34%



Adapted from *UpToDate*

SJS/TEN – Etiology

- High-risk medications
  - Allopurinol, lamotrigine, aromatic anticonvulsants, antibacterial sulfonamides, and "oxicam" or cyclooxygenase-2 (COX-2) inhibitor nonsteroidal anti-inflammatory drugs (NSAIDs)
  - Novel anticancer therapies, such as immune checkpoint inhibitors (ipilimumab, pembrolizumab, nivolumab, atezolizumab)
  - Timing: causative medication typically started one week to one month prior to symptom onset
- Other causes: 15% no clear causal drug
  - Infection: Mycoplasma, other bacterial or viral infections
  - Controversial attributions: chemical exposures, complementary/ traditional medications, vaccinations, foods
  - Idiopathic SJS/TEN
- Predisposing HLA haplotypes in certain ethnicities for specific drugs, have been basis for pharmacogenetic guidelines

Adapted from *UpToDate*

SJS/TEN – Clinical Presentation

- Prodro
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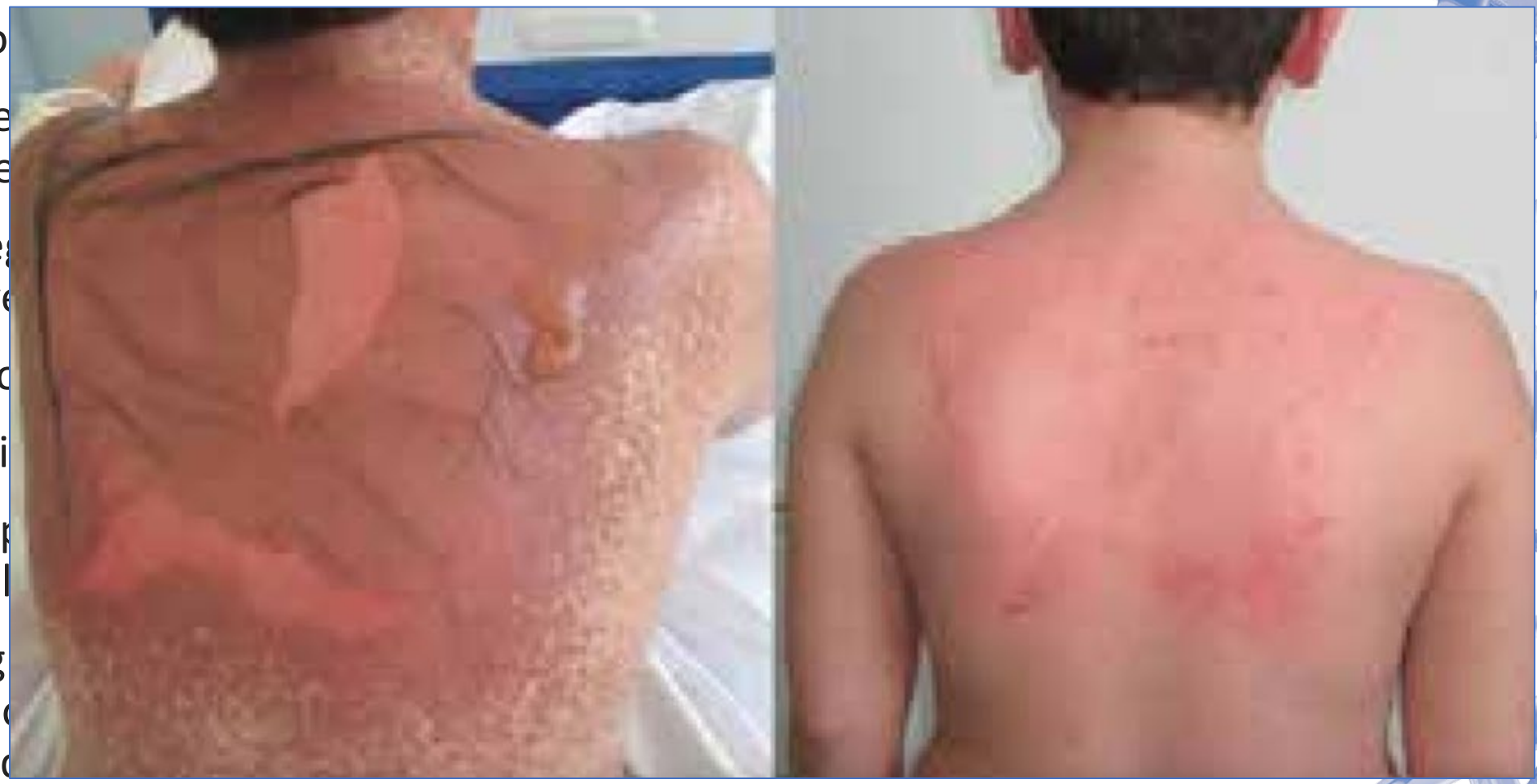


Adapted from *UpToDate*

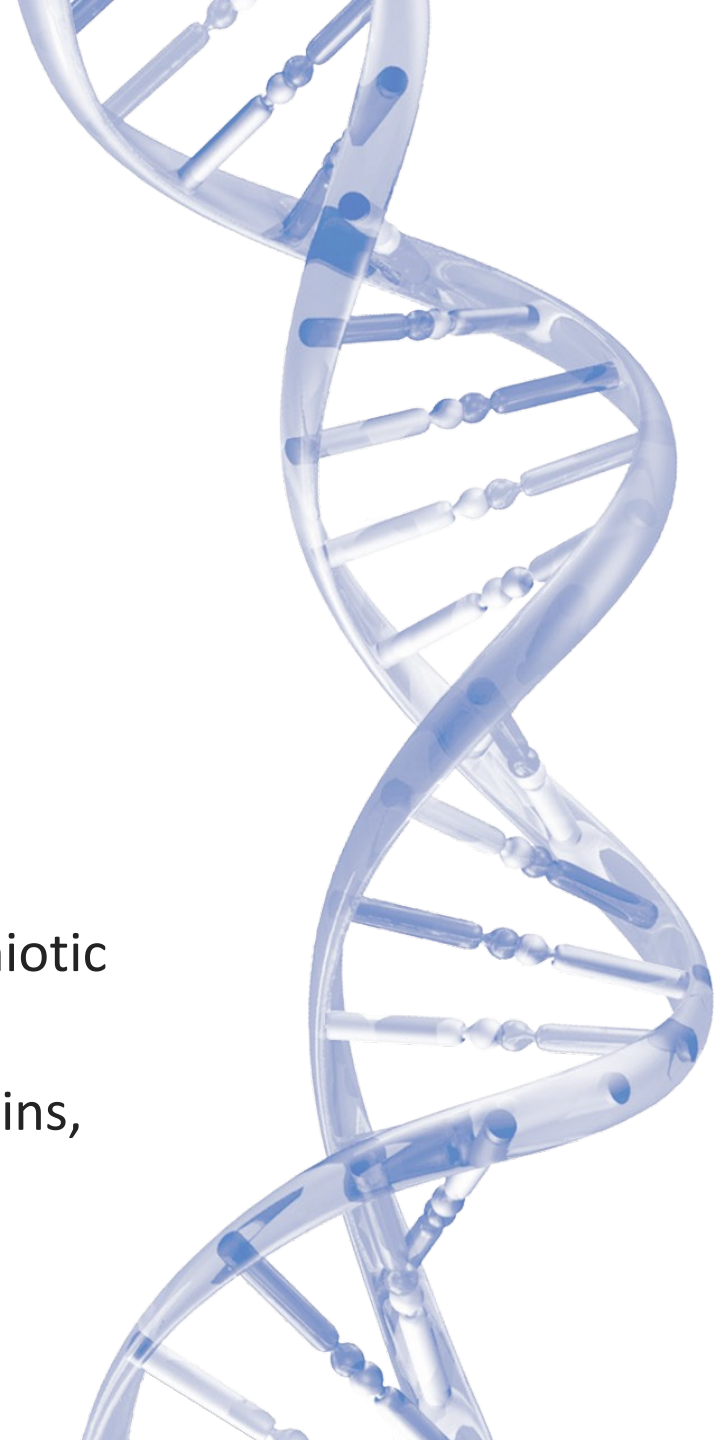
SJS/TEN – Extracutaneous Involvement and Complications

- Mucosal involvement: all mucosal surfaces can be involved, most often include buccal, oro/nasopharyngeal, anogenital mucosa
  - Can include epiglottis and laryngeal involvement threatening airway
  - Genital erosions and pain can cause urinary retention, labial and vaginal adhesions
- Eye involvement: common (60-100%), can be simple conjunctival hyperemia or pseudomembrane formation or corneal perforation
- Acute ocular involvement strongest predictor for long-term ocular complications; 20-75 % of survivors have chronic eye sequelae including lid and eyelash adhesions, corneal scarring, reduced visual acuity, blindness
- Other organs: acute kidney injury, lung injury (sloughing of bronchial epithelia), GI involvement and ulceration, liver injury, hematologic abnl, bacteremia and sepsis

Adapted from *UpToDate*

SJS/TEN – Management

- Discontinue potentially causal drugs
- Largely supportive, often in burn units
- Fluid and temperature management
- Nutrition
- Pain control
- Prevention and treatment of infections
- Advanced prevention and treatment of urogenital lesions
- Advanced treatment of ocular lesions including corticosteroids, amniotic membrane transplantation
- No advantages to systemic therapy with intravenous immune globulins, corticosteroids, cyclosporine
- ? Tumor necrosis factor inhibitors (infliximab, etanercept)



Adapted from *UpToDate*

Stevens-Johnson Syndrome, *HLA-B*15:02*, and Carbamazepine

Chung et al., *Nature* 2004;428:486.

*Cw*0801, A*1101* and *DRB1*1202* within the HLA region occurred at increased frequency

The Pharmacogenomics Journal (2014), 1–8
© 2014 Macmillan Publishers Limited All rights reserved 1470-269X/14
www.nature.com/tpj

ORIGINAL ARTICLE

Ances
carba

PW Payne[1,2]

CAUTION: This patient carries the *HLA-B*15:02* allele, a known risk factor for carbamazepine-induced SJS in persons of Asian ancestry…

In an effo ssued an alert in 2 -induced skin reac t these people a evidence relied upon by the FDA and finds that the alert does not accurately reflect the medical evidence relied upon in 2007 or evidence that has been generated over the last 5 years since the label was created. The FDA drug labeling should be modified to reflect current medical evidence.

The Pharmacogenomics Journal advance online publication, 22 April 2014; doi:10.1038/tpj.2014.14

HLA-A*3101
More Likely

Stevens-Johnson Syndrome, *HLA-B*15:02*, and Carbamazepine

WARNINGS

SERIOUS DERMATOLOGIC REACTIONS AND HLA-B*1502 ALLELE

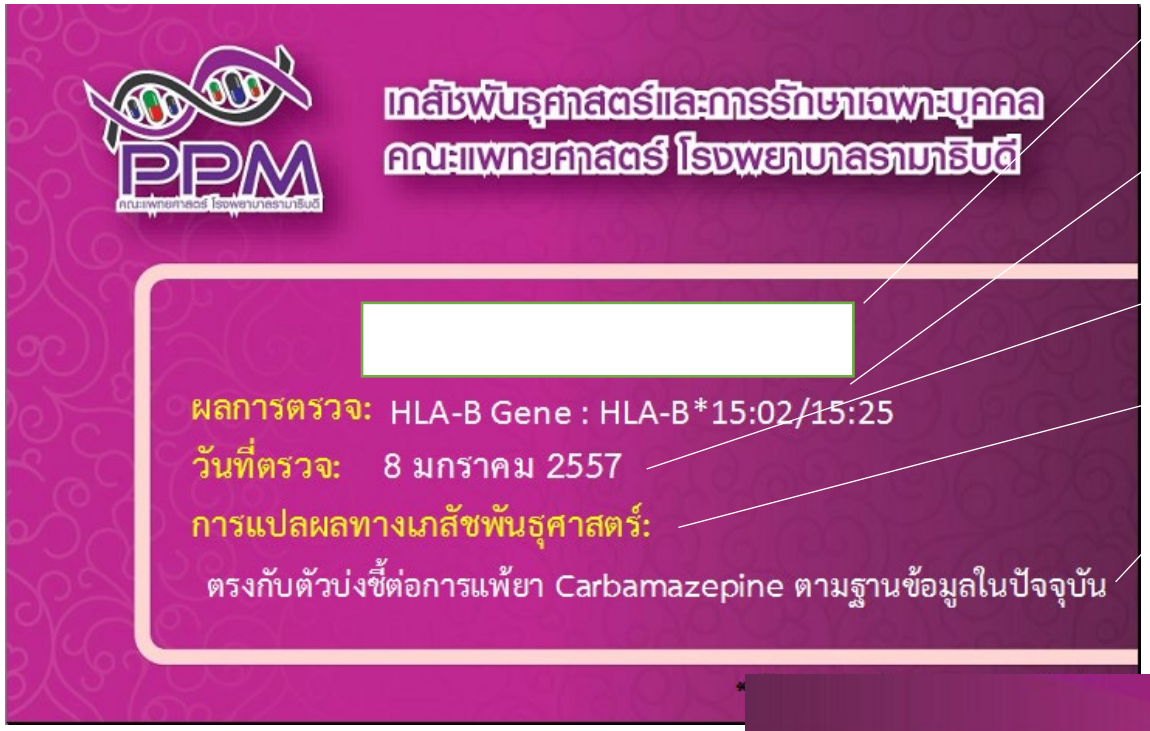
SERIOUS AND SOMETIMES FATAL DERMATOLOGIC REACTIONS, INCLUDING TOXIC EPIDERMAL NECROLYSIS (TEN) AND STEVENS-JOHNSON SYNDROME (SJS), HAVE BEEN REPORTED DURING TREATMENT WITH TEGRETOL. THESE REACTIONS ARE ESTIMATED TO OCCUR IN 1 TO 6 PER 10,000 NEW USERS IN COUNTRIES WITH MAINLY CAUCASIAN POPULATIONS, BUT THE RISK IN SOME ASIAN COUNTRIES IS ESTIMATED TO BE ABOUT 10 TIMES HIGHER. STUDIES IN PATIENTS OF CHINESE ANCESTRY HAVE FOUND A STRONG ASSOCIATION BETWEEN THE RISK OF DEVELOPING SJS/TEN AND THE PRESENCE OF HLA-B*1502, AN INHERITED ALLELIC VARIANT OF THE HLA-B GENE. HLA-B*1502 IS FOUND ALMOST EXCLUSIVELY IN PATIENTS WITH ANCESTRY ACROSS BROAD AREAS OF ASIA. PATIENTS WITH ANCESTRY IN GENETICALLY AT-RISK POPULATIONS SHOULD BE SCREENED FOR THE PRESENCE OF HLA-B*1502 PRIOR TO INITIATING TREATMENT WITH TEGRETOL. PATIENTS TESTING POSITIVE FOR THE ALLELE SHOULD NOT BE TREATED WITH TEGRETOL UNLESS THE BENEFIT CLEARLY OUTWEIGHS THE RISK (SEE WARNINGS AND PRECAUTIONS, LABORATORY TESTS).

Clinical Pharmacogenetics Implementation

Table 2 Recommendations for carbamazepine therapy based on *HLA-B* and *HLA-A* genotypes

Genotype[a]	Implication	Therapeutic recommendation	Classification of recommendation	Considerations for other aromatic anticonvulsants
*HLA-B*15:02* positive[c] and any *HLA-A*31:01* genotype (or *HLA-A*31:01* genotype unknown)	Greater risk of carbamazepine-induced SJS/TEN	If patient is carbamazepine-naïve, do not use carbamazepine.	Strong	Other aromatic anticonvulsants[d] have weaker evidence linking SJS/TEN with the *HLA-B*15:02* allele; however, caution should still be used in choosing an alternative agent.
		The latency period for drug-induced SJS/TEN is short with continuous dosing and adherence to therapy (~4-28 days), and cases usually occur within three months of dosing; therefore, if the patient has previously used carbamazepine consistently for longer than three months without incidence of cutaneous adverse reactions, cautiously consider use of carbamazepine in the future.	Optional	Previous tolerance of carbamazepine is not indicative of tolerance to other aromatic anticonvulsants.[d]

Phillps E *et al., Clin Pharmacol Ther* 2018;103:574-81.



Name & Family Name

Outcome of the PGX assay

8 Jan 2014

PGx Interpretation

High Risk of SJS/TEN from Carbamazepine, according to update information

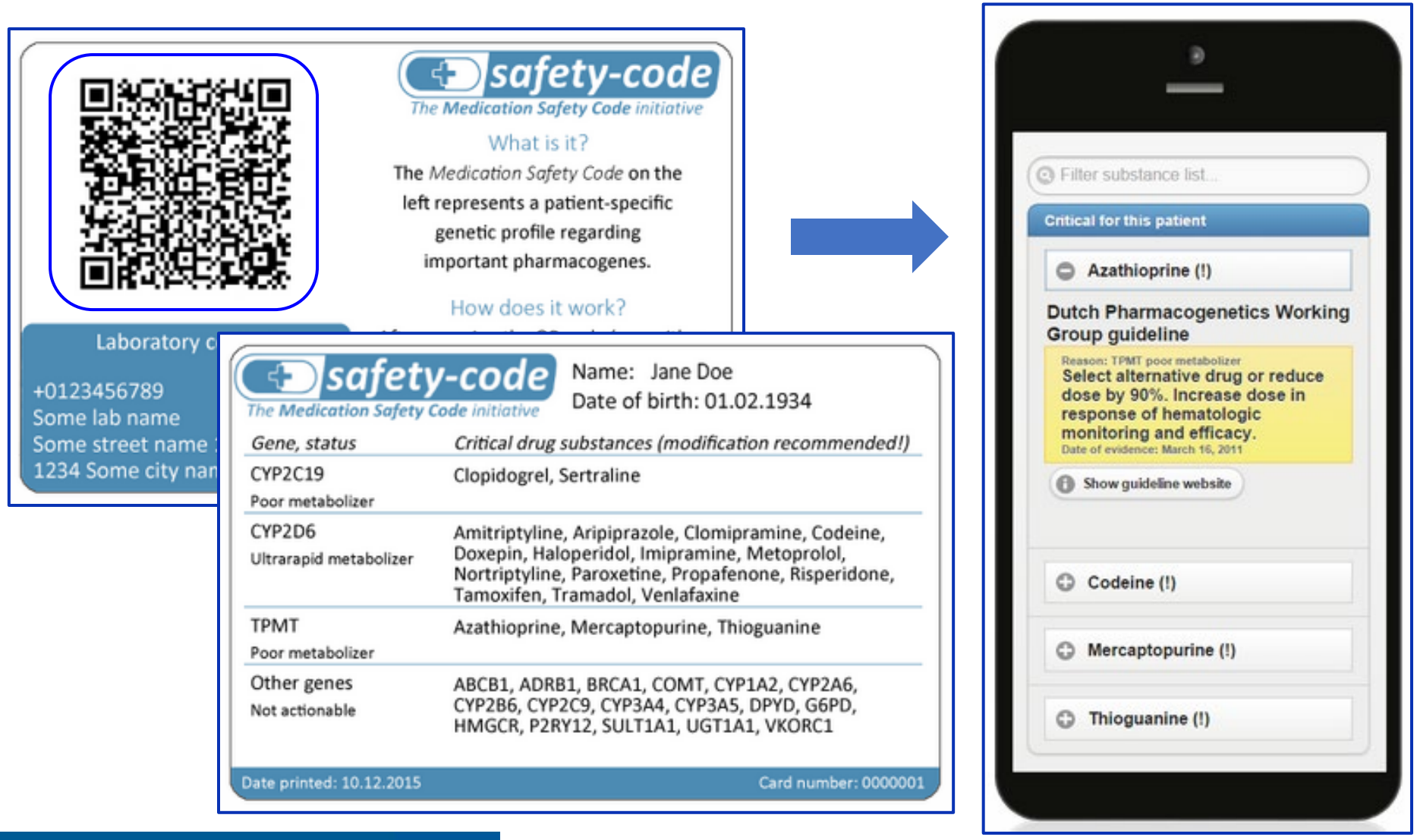
Suggestion: According to update information, this person has HLA-B*1502 which has a high risk to develop a severe skin disorder (SJS/TEN), if he takes carbamazepine or drug structurally similar.

Need more information: please contact our PGx laboratory. Tel 02-200-4330-3…

Signature of molecular clinical pharmacist.

Point of Care PGx Information

http://safety-code.org/



Cost Effectiveness Analysis

Epilepsia, **(*):1–11, 2013
doi: 10.1111/epi.12325

FULL-LENGTH ORIGINAL RESEARCH

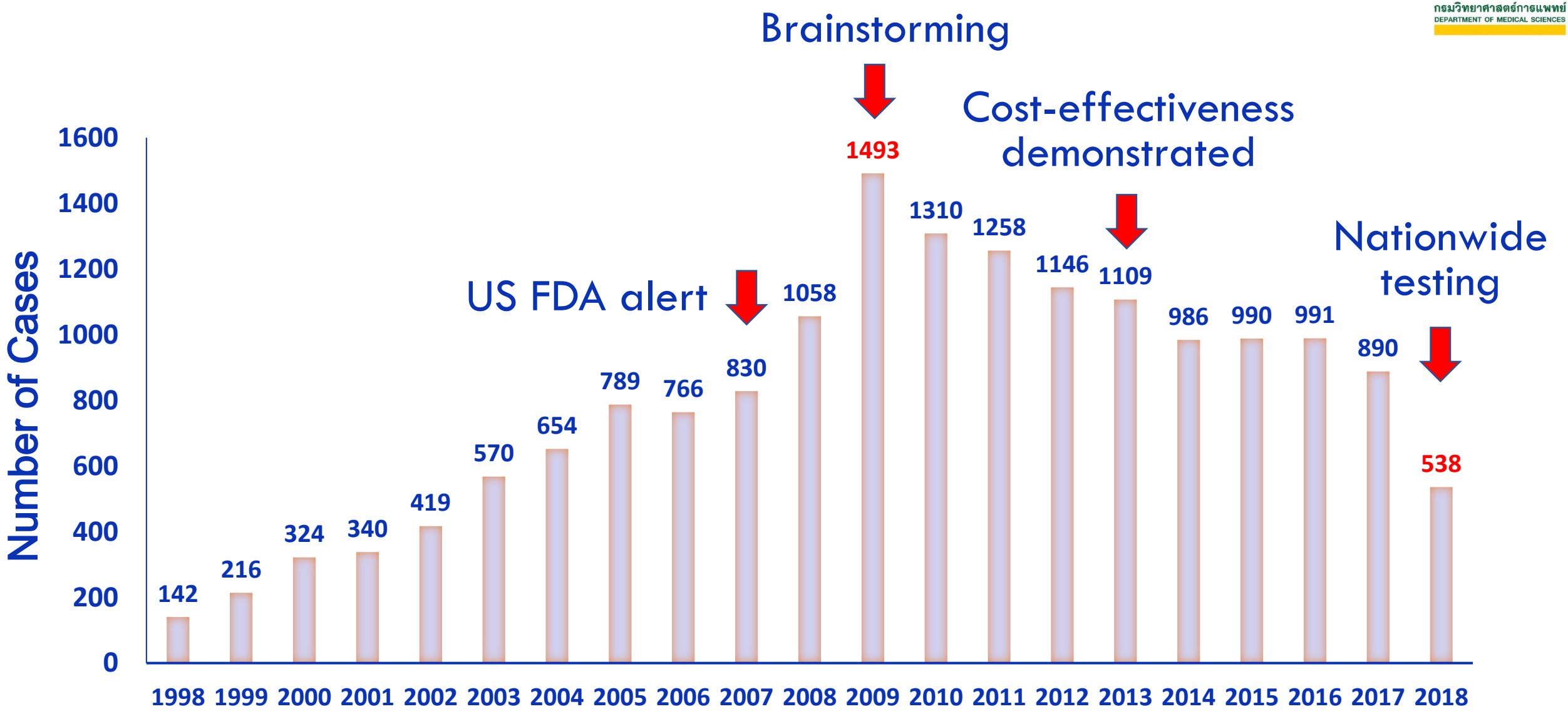
Economic evaluation of HLA-B*15:02 screening for carbamazepine-induced severe adverse drug reactions in Thailand

*Waranya Rattanavipapong, *Tanunya Koopitakkajorn, *†Naiyana Praditsitthikorn, ‡Surakameth Mahasirimongkol, and *Yot Teerawattananon

*Health Intervention and Technology Assessment Program (HITAP), Nonthaburi, Thailand; †Bureau of AIDS TB and STIs, Department of Disease Control, Ministry of Public Health, Nonthaburi, Thailand; and ‡The National Institute of Health, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand

- Incremental cost-effectiveness ratio of universal *HLA-B*15:02* screening estimated at 222,000 THB ($6,660)/QALY gained for epilepsy pts; 130,000 THB/QALY for neuropathic pain pts
- Test 343 patients to prevent one case of SJS/TEN

SJS/TEN is Declining in Thailand (1998-2018)



Courtesy S. Mahasirimongkol; Data source: Health Product Vigilance Center, Thai FDA, 2018.

Effectiveness of Screening in Taiwan

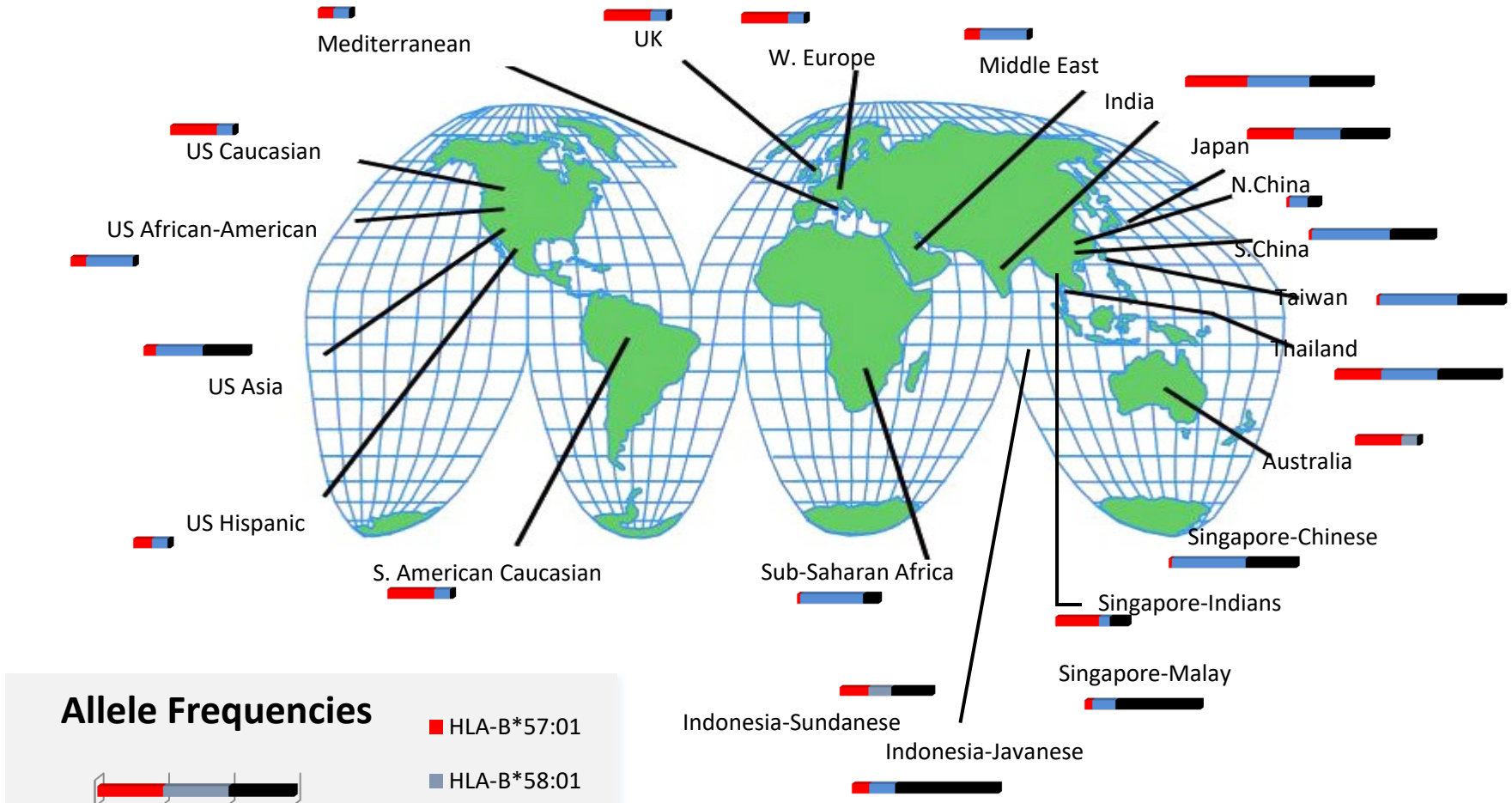
ORIGINAL ARTICLE

Carbamazepine-Induced Toxic Effects and HLA-B*1502 Screening in T...n

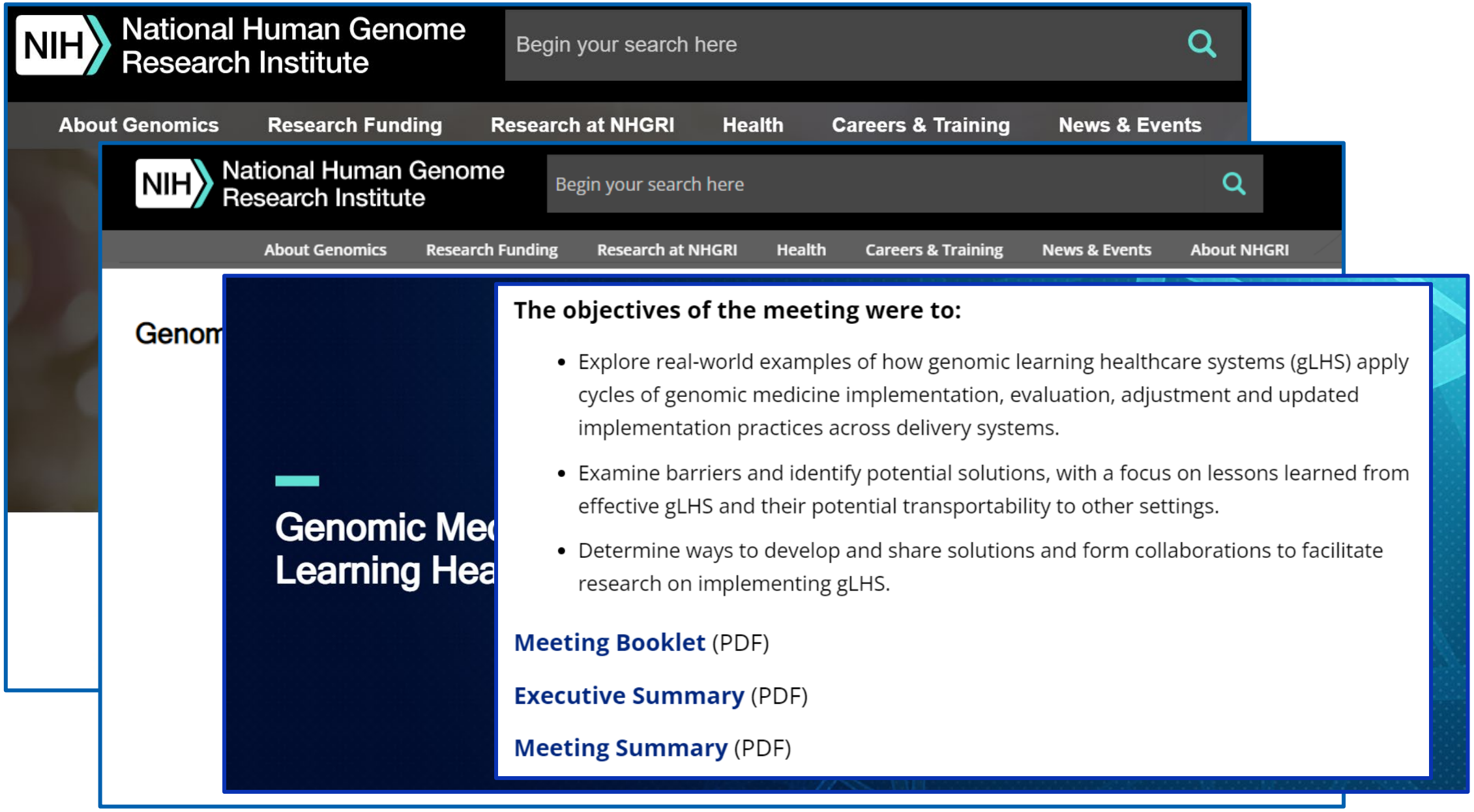
Pei Chen, Ph.D., Juei ...
Cheung-Ter ...g, M.D.,
Chih-Ta ... M.D., Yung-Chu Hsu, M.D.,
Hsiang... Chung-Ta Lu, M.D., Chun-Che Chu, M.D.,
...u-Hsiang Su, M.D., Sheng-Hsing Lan, M.D.,
...ng Sung, M.D., Shu-Yi Lin, M.S., Hui-Ping Chuang, B.S.,
Li-Chen Huang, B.S., Ying-Ju Chen, M.S., Pei-Joung Tsai, M.S.,
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*

None of 4,877 CBZ-treated patients developed SJS/TEN vs. 10 expected

Global Frequency of Drug-Specific HLA alleles

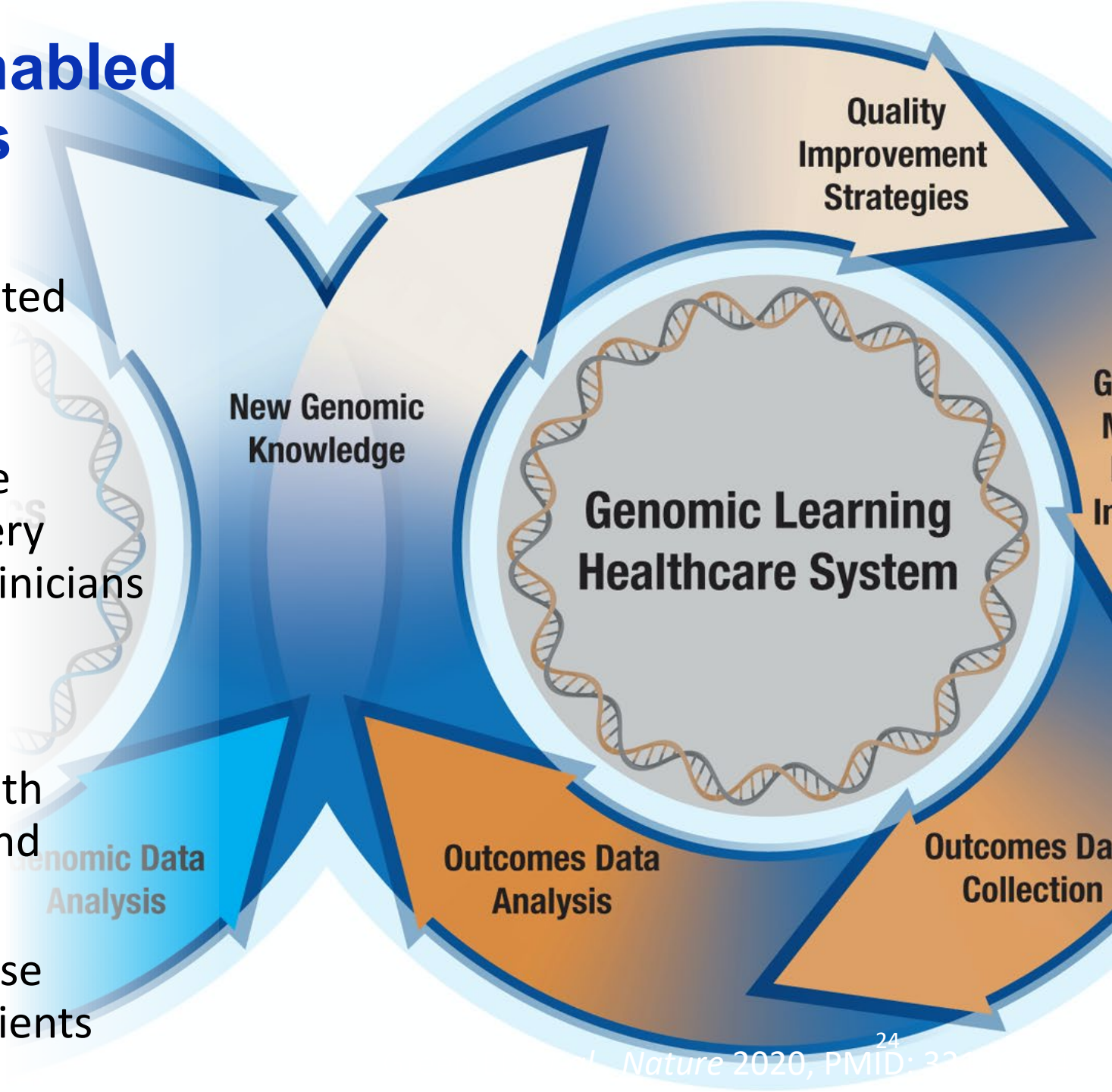


Genomic Medicine Meetings



Network of Genomics-Enabled Learning Health Systems

- Systems in which internal data and experience are systematically integrated with external evidence and resulting knowledge is put into practice
- Fundamental principle: Generalizable knowledge can be captured from every patient encounter and provided to clinicians to improve practice
- Examples:
  - Testing and de-labeling patients with reported penicillin allergy is safe and effective
  - Balanced crystalloids reduce adverse kidney outcomes in critically ill patients



Nature 2020, PMID:

Department of Health and Human Services

Part 1. Overview Information

Funding Opportunity Title	Network of Genomics-Enabled Learning Health Systems (gLHS)
Notice	
Compa	

Objective: Establish network of institutions with track record of using gLHS approaches in their health system, including in resource limited communities

- Refine and develop these practices into implementation resources
- Identify 2-4 Network-wide implementation projects
- Implement the 2-4 implementation projects network-wide
- Use implementation projects to increase system-wide and across health systems interoperability and refine resources for broader sharing
- Establish validated tools and resources for sites implementing a gLHS

Many Thanks…

Veronica Abraham
Zo Bly
Marcus Brown
Christine Chang
Jessica Chong
Heather Colley
Priscilla Crockett
Jyoti Dayal
Carmen Demetriou
Eric Green
Peggy Hall
Sarah Hutchison
Rongling Li
Alanna Kulchak Rahm
Esperes Mfwilwakanda
Iman Martin
Joannella Morales
Jahnavi Narula
Weini Ogbagiorgis
Erin Ramos
Renee Rider
Karyn Roberts
Robb Rowley
Alessandra Serrano-Marroquin
Simona Volpi
Nephi Walton
Riley Wilson

Carol Bult, Rex Chisholm, Pat Deverka, Geoff Ginsburg, Gillian Hooker, Gail Jarvik, George Mensah, Casey Overby Taylor, Dan Roden, Marc Williams

Genomic Medicine Program Investigators and Participants

eMERGE network
ELECTRONIC MEDICAL RECORDS AND GENOMICS

IGNITE Implementing GeNomics In practicE

NSIGHT Newborn Sequencing

cser Clinical Sequencing Evidence-Generating Research

UDN Undiagnosed Diseases Network

ClinGen Clinical Genome Resource

PRIMED consortium

GWAS Catalog
The NHGRI-EBI Catalog of published genome-wide association studies
Search the catalog
Examples: breast carcinoma, rs7329174, Yao, 2q37.1, HBS1L, 6:16000000-25000000