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SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation*

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*This article represents a summary of a meeting SJS/TEN 2017 that was held March 2, 2017 preceding the American Academy of Dermatology meeting in Orlando, Florida.

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Web Resources and support services for SJS/TEN patients: General SJS Foundation (http://www.sjsupport.org/sjsupport_group_facilitators.shtml); Canadians against Stevens Johns Syndrome & Toxic Epidermal Necrolysis (CAST); Amalyste (France) http://www.amalyste.fr/; https://www.sjsawareness.org.uk/ (United Kingdom).

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Abstract

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a life-threatening, immunologically-mediated and usually drug-induced disease with a high burden to individuals, their families and society with an annual incidence of 1–5/1,000,000. To effect significant reduction in short- and long-term morbidity and mortality, and advance clinical care and research, coordination of multiple medical, surgical, behavioral, and basic scientific disciplines is required. On March 2, 2017 an investigator-driven meeting was held immediately prior to the American Academy of Dermatology Annual meeting for the central purpose of assembling, for the first time in the United States, clinicians and scientists from multiple disciplines involved in SJS/TEN clinical care and basic science research. As a product of this meeting, this article summarizes the current state of knowledge and expert opinion related to SJS/TEN covering a broad spectrum of topics including epidemiology and pharmacogenomic networks; clinical management and complications; special populations such as pediatrics, the elderly, and pregnant women; regulatory issues and the electronic health record; new agents that cause SJS/TEN; pharmacogenomics and immunopathogenesis; and the patient perspective. Goals include the maintenance of a durable and productive multidisciplinary network that will significantly further scientific progress and translation into prevention, early diagnosis, and management of SJS/TEN. ©2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:38–69)

Keywords

Stevens-Johnson; toxic epidermal necrolysis; HLA; networks; pharmacogenomics; pharmacovigilance; electronic health record; T cells; granulysin

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are the severest in the spectrum of immunologically-mediated adverse drug reactions (IM-ADR) that are considered to be primarily T-cell mediated. SJS/TEN is characterized by a painful blistering skin rash that is often associated with multi-organ involvement, commonly fever, hematologic abnormalities, ophthalmologic and genitourinary involvement. Early dermatologic findings may include erythematous or dusky colored macules that evolve to become fluid-filled bullae and/or denuded skin. Involved non-blistered skin often sloughs with direct lateral pressure (Nikolsky sign) and demonstrates interface dermatitis with necrotic keratinocytes and epidermal separation on histopathologic examination (Table 1). SJS and TEN are thought to be the same disease across a spectrum of severity defined by the percentage of skin detachment related to the body surface area (BSA) comprising SJS (<10%), SJS/TEN overlap (10–30%) and TEN (>30%) (Table 1). The mortality associated with TEN in the setting of aggressive supportive care at experienced centers is approximately 30%; however in the elderly and immunocompromised populations this can exceed 50%. The short-term morbidity associated with SJS/TEN is well recognized and includes sepsis, respiratory complications, gastrointestinal and genital tract mucositis and eye disease. However long-term morbidity is also considerable and includes vision loss, urogynecological complications, chronic respiratory disease, depression and post-traumatic stress, disfigured painful skin, restricted therapeutic choices, and shortened life-span. Over the last 10–15 years there have been significant advances in our understanding of the immunogenomics of IM-ADRs.(1) For SJS/TEN this has included several strong associations from Southeast Asia between HLA Class I alleles and drug-associated SJS/TEN including HLA-B*15:02 and carbamazepine SJS/TEN and HLA-B*58:01 and allopurinol SJS/TEN. This has led not only to successful HLA-B*15:02 screening programs in Taiwan, Singapore, and other parts of Southeast Asia that have almost eliminated carbamazepine associated SJS/TEN, but also furthered our understanding of the immunopathogenesis of SJS/TEN. Despite this progress there are still a large number of clinical and research gaps. A few highlights of these gaps include the lack of 1) an evidence-based approach to guide therapeutic interventions above aggressive supportive care in acute SJS/TEN, 2) predictive biomarkers for early diagnosis and prognosis, 3) genetic predictors for most drugs that cause SJS/TEN, and 4) an explanation for why only a small proportion (<10%) of those carrying an HLA risk allele will develop SJS/TEN following drug exposure.(1)

To explore gaps and unmet needs for further research into the epidemiology, pathogenesis, treatment, and prevention of SJS/TEN, the National Human Genome Research Institute (NHGRI), along with the Food and Drug Administration and 5 other National Institutes of Health institutes and Centers (National Center for Advancing Translational Sciences (NCAT), National Institute on Drug Abuse (NIDA), National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS) and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)) brought together 30 international experts in severe cutaneous adverse reactions, pharmacogenomics, and related fields for a 2015 workshop entitled “Research directions in genetic predispositions to SJS/TEN” (https://www.genome.gov/27560487/research-

directions-in-geneticallymediated-stevensjohnson-syndrometoxic-epidermal-necrolysis/).(2) This two-day workshop reviewed the current state of knowledge of surveillance, pathogenesis, and treatment of SJS/TEN, examined the role of genomics in the etiology, treatment, and eradication of preventable cases of SJS/TEN, and identified gaps, unmet needs, and priorities for future research to work toward the global elimination of genetically-mediated SJS/TEN. A primary conclusion of this meeting was that, although there have been great research strides in SJS/TEN with compelling examples of implementation of personalized medicine, there is continued need to broaden these discoveries for translation and implementation across diverse populations and causative drugs. Overarching and facilitative research goals were set and three high priority areas were identified and targeted: clinical care, pharmacovigilance and epidemiology, and basic research. An important outcome of the meeting was recognition of the need, because of the overall rarity and diverse epidemiology of SJS/TEN, to develop a large global collaborative network and a supportive funding infrastructure to further all aspects of SJS/TEN research.

An ongoing dialogue among an SJS/TEN working group comprising members from academia and government followed this meeting and has led to new initiatives that have included the establishment of an SJS/TEN phenotyping group that published a standardized case report form for SJS/TEN, a subgroup evaluating SJS/TEN causality assessment tools, and a national survey of dermatologists, burn surgeons, and ophthalmologists who care for patients with SJS/TEN that identified knowledge gaps, priorities, unmet needs, and unresolved controversies in SJS/TEN clinical care and research. More than 50% of survey respondents were interested in the opportunity for further engagement in all aspects of SJS/TEN research.

The fundamental clinical, epidemiological, and basic research questions identified in the 2015 National Institutes of Health workshop served as a catalyst for further efforts toward organized collaboration. To engage a broad constituency of stakeholders in this effort, a meeting **“Stevens-Johnson-syndrome/Toxic epidermal necrolysis 2017: Building Multidisciplinary Networks to Drive Science and Translation”** was held March 2, 2017. This meeting had representation across allergy-immunology, dermatology, ophthalmology, burns surgery, gynecology, clinical pharmacology, basic science (immunobiology, genetics), epidemiology, informatics, regulatory science, patients and their families, and government and included 142 participants from six continents (Figure 1). A major goal of this meeting was to bring together established and new investigators to create a durable network of SJS/TEN clinicians and scientists to discuss and prioritize achievable short and long-term research objectives. This meeting was charged with presentation of the most current and cutting-edge research relevant to SJS/TEN, provision of mentorship for new investigators of disparate backgrounds to become future leaders in SJS/TEN, and, importantly, to provide a multidisciplinary and interactive forum where the most controversial areas of SJS/TEN clinical care and research could be discussed. The meeting highlighted key areas amenable to network building and clinical translation. Representatives from three National Institutes of Health institutes: National Human Genome Research Institute, the National Institute of Allergy and Infectious Diseases, and the National Institute of Arthritis, Musculoskeletal and Skin Diseases provided updates on funding mechanisms relevant to SJS/TEN with a focus

on newerR01/R21 fundingrelated toserious IM-ADRs (https://grants.nih.gov/grants/guide/pa-files/PAR-16-274.html; https://grants.nih.gov/grants/guide/pa-files/PAR-16-275.html).

This article is a summary of the proceedings of the meeting that includes the new and evolving science, key controversies, outputs of the meeting, and proposed future directions.

I. Global Epidemiology and Pharmacogenomics Networks[1]

Key Points:

- SJS/TEN is a life-threatening mainly drug-induced disease with considerable short and long-term morbidity and mortality that poses a burden to healthcare systems and families disproportionate to its prevalence.
- The rarity of SJS/TEN has created challenges for the generation of evidence-based treatment.
- Collaborative pharmacogenomics studies have been successful in determining HLA associations in SJS/TEN and provide the promise for more associations to be delineated in the future.
- The development of networks that include an SJS/TEN phenotype adjudication committee as well as centralized biological sample collection and repositories would provide a platform to study pathogenesis and predictors.

A number of collaborative networks exist that study the epidemiology and pharmacogenomics of SJS/TEN across genetically diverse populations, seek to discover pathogenic mechanisms and other mediators of disease risk, and allow for the development of clinical trials to evaluate therapeutic interventions. Session one of *SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation* featured representatives from some of these international collaborative networks. The strength of these networks lies in the rigorous definitions for clinical diagnosis, causality assessment at the individual case level, estimation of risk factors for each severe cutaneous adverse reaction (SCAR)-entity, and centralized collection of samples to facilitate investigation of the mechanisms and search for new therapeutic options.

A. The Society of Dermatology Hospitalists SJS/TEN Study Group (United States)—

The Society of Dermatology Hospitalists (SDH) is a US-based organization dedicated to the care of complex dermatological patients in the inpatient setting. In an effort to describe the SJS/TEN experience of dermatology hospitalists in the United States and explore ongoing management controversies in SJS/TEN, the SDH retrospectively collected information on the disease course, management, and outcomes of patients treated for SJS/TEN at member institutions. As a collaborative research effort of 18 tertiary care centers, the SDH has compiled a database of 405 US SJS/TEN cases between 2000 and 2015, with most patients treated from 2010 onwards. Medications were the most common

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cause of SJS/TEN in this cohort, accounting for 91.3% of cases and trimethoprim/sulfamethoxazole was most often implicated (26.0%). Sixty-six percent of patients met criteria for TEN (>30% body surface area (BSA) denuded) or SJS/TEN overlap (10–30% BSA denuded) at the time of admission. The severity of illness score for TEN (SCORTEN) (5) predicted mortality for the cohort at the time of admission to be 20.0%. Sixty-seven percent of patients were managed in a specialized burn or intensive care unit and 70% received pharmacotherapeutic intervention in addition to supportive care, most commonly corticosteroids, intravenous immunoglobulin (IVIG), or both steroids and IVIG. Only four patients in this cohort received cyclosporine and one patient received the TNF-alpha inhibitor etanercept. Actual mortality of patients in the cohort was 13.7%, for a standardized mortality ratio of 0.69 (95% confidence intervals 0.57, 0.78). The improved survival of patients in this cohort compared to SCORTEN-predicted mortality is notable and likely multifactorial. Preliminary analyses showed an overall lack of consensus regarding management of SJS/TEN and no clear evidence of benefit from any particular pharmacotherapeutic intervention compared to supportive care alone. Additional work to account for relevant confounding factors and choice of pharmacotherapy is ongoing. Future work of the SDH will include evaluation of the updated SCORTEN algorithm to predict SJS/TEN mortality, longitudinal analyses of SJS/TEN survivors to determine sequelae and quality of life following recovery, and a prospective SJS/TEN cohort study and, ultimately, randomized controlled trial.

B. The North American Therapeutics in Epidermal Necrolysis Syndrome Trial Network (North America)—Comprised of 24 academic institutions and burn centers in the US and Canada, the North American Therapeutics in Epidermal Necrolysis Syndrome (NATIENS) Trial Network brings together expertise in burn surgery, dermatology, eye and mucosal complications, and leaders in immunogenetic science to create the feasibility for a multi-center, translational clinical trial comparing cyclosporine, etanercept, and supportive care.(4) The NATIENS Trial Network's mission is to enhance the quality and standardization of care for patients with SJS/TEN through accelerating scientific discovery. NATIENS also includes three scientific centers with expertise in immunogenetics, next-generation genomic sequencing, cellular immunology, and pharmacokinetics. A double blind randomized controlled trial assessing standardized supportive care and immunomodulatory therapeutics in SJS/TEN is planned to begin in 2019 and will be the first to rigorously study SJS/TEN in a multi-center setting. Its members have developed tools for standardized assessment of skin involvement and re-epithelialization to measure response to therapy, a comprehensive supportive care protocol, and immunogenetic and cellular analyses to study the underlying pathophysiology. Outcomes from the NATIENS clinical trial will include a rigorous and objective assessment of a standardized supportive care model and immunomodulatory therapies in acute SJS/TEN, longitudinal patient follow-up for standardized assessment of short- and long-term sequelae, systemic and tissue-specific genetic and immunologic analyses to define pathogenic mechanisms and provide mechanistic support for immunomodulatory therapies in acute disease, as well as the infrastructure and clinical and scientific partnerships for the future study of unexplored therapeutic targets and markers of SJS/TEN risk in North American populations.

C. The Canadian Pharmacogenomics Network for Drug Safety—The Canadian Pharmacogenomics Network for Drug Safety (CPNDS) consists of over 65 multi-disciplinary expert collaborators from 26 pediatric and adult academic health centers in Canada that recruit patients via active surveillance and collect genomic samples and clinical information on drug outcomes. Currently, the CPNDS active surveillance clinical database includes detailed clinical information for various drugs from more than 9,313 adverse drug reaction cases and 84,082 drug-exposure matched controls. More patients are recruited Network-wide each day. The CPNDS has used this methodology to study the pharmacogenomics of several severe ADRs and was the first to confirm the role of *HLA* markers for carbamazepine related skin reactions in children.(6) The CPNDS is actively addressing the problem of these severe reactions by using diverse approaches such as: 1) *Discovery/replication through collaboration.* This approach is used to confirm previously identified pharmacogenomic biomarkers as well as identify novel genomic variation associated with these reactions, which given the rarity of SJS/TEN, requires collaboration between international consortia. Further collaboration with the EpiPGX Consortium (Europe) has led to identification of over 80 cases of severe cutaneous adverse drug reactions associated with anticonvulsants. A genome-wide assessment of these cases employing both genotyping arrays and exome sequencing is in process. Collaborations with additional international consortia are underway. 2) *Knowledge translation and commercialization.* A key outcome is translation of pharmacogenomics into clinical practice. The CPNDS has published clinical practice guidelines for carbamazepine-related ADRs(7) and is currently working with the Clinical Pharmacogenetics Implementation Consortium (CPIC) (https://cpicpgx.org/) to update relevant guidelines and develop commercial pediatric pharmacogenomic panels that will include ADR pharmacogenomic markers.

D. The International Consortium on Drug Hypersensitivity Network—The International Consortium on Drug Hypersensitivity (ITCH) network, coordinated in Liverpool, UK, and funded by the International Serious Adverse Event Consortium (iSAEC), was established for the recruitment of patients with SCAR and now includes 1,500 precisely phenotyped cases from 12 countries with associated genetic data.(8) Analyses using the ITCH cohort have concentrated on identifying drug-specific genetic predisposing factors and genetic factors predisposing to SJS/TEN irrespective of drug etiology. Genome-wide association studies from 1,260 SCAR cases in the ITCH cohort rely on careful quality control procedures that include controlling for population stratification, imputation using the latest releases of genomic data, and validation of imputed genetic variants, where appropriate.

The ITCH database includes 177 SJS/TEN cases that are derived from Caucasian patients from three ethnic groups: Spanish, Italian, and Northern European. Analysis of all 177 SJS/TEN cases identified an HLA-B allele that is associated with SJS/TEN irrespective of drug. This HLA-B allele is present at 0.02% of the general Caucasian population (n = 9,237 not exposed to drug) but is found at 100-fold higher frequency among SJS/TEN cases (M. Pirmohamed, MBChB, PhD, unpublished data, March 2017). Interestingly, this association seems to be largely limited to Italian patients. Replication in Italian patients will be

challenging given the rarity of SJS/TEN and new patients will need to be recruited for this analysis.

Drug-specific analysis in the ITCH cohort has also led to replication of HLA allele associations that have been previously identified in other populations. For instance, in 13 European patients with allopurinol-induced SCAR of whom 9 had SJS, HLA-B*58:01 was identified at a genome-wide significance level with an odds ratio of 36. While the association of HLA-B*58:01 with SJS was just below genome-wide significance in this population, the odds ratio was higher at 45 (M. Pirmohamed, MBChB, PhD, unpublished data, March 2017). This is consistent with previous data that suggest that HLA-B*58:01 is present in approximately 60% of allopurinol SJS/TEN patients of European ancestry.

The ITCH network also includes African recruitment sites. Work in this cohort has identified the association of HLA-C*04:01 carriage and SJS/TEN secondary to the antiretroviral drug nevirapine. Further analysis of the interaction of HLA-C*04:01 with the endoplasmic reticulum aminopeptidase genes that influence peptide processing showed that endoplasmic reticulum aminopeptidase 2 may have a potentially protective effect.(9)

E. The RegiSCAR Network and Sample Repository—The RegiSCAR project was born out of experience with multiple epidemiological studies on SCAR that have been undertaken in Europe during the past three decades. Early studies included large retrospective case compilations performed in the 1980's and published in the early 1990's, followed by a large case-control study that provided the best available evidence for drug causality at the time (SCAR-study).(10–12) In parallel, a population-based registry on SJS/TEN was started in Germany to assess disease incidence and demography, using the same criteria for case validation and ascertaining medication history.(13) Later, a second case-control surveillance (EuroSCAR-study, 1997–2001) was undertaken that could confirm results on drug risk of the previous study and provide new data on recently marketed drugs.(14–17) These studies were followed by a multinational registry (RegiSCAR-study) that was founded to systematically collect biological samples of patients with SCAR and patients were followed longitudinally after hospital discharge.(17–20) These studies required that investigators establish and maintain a network of hospitals and departments likely to treat SCAR, determine precise definitions of clinical entities (phenotypes), and methods for systematic case ascertainment, standardized case validation and data management and statistical analysis. Case ascertainment was done by trained investigators (health care professionals) using a standardized questionnaire in direct conversation with the patient and in cases of severe illness, the patient's relatives, treating physicians, family physician and medical records.

The RegiSCAR project is a registry of SCAR cases in several European and non-European countries that combines a protocol for systematic blood sampling and centralized biobanking of peripheral blood mononuclear cells (PBMCs), plasma and DNA and cohort studies investigating outcome, sequelae, and treatment.(17, 18) Earlier studies focused on SJS/TEN, whereas RegiSCAR includes a broader spectrum of reactions including drug reaction with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, and generalized bullous fixed drug eruption (GBFDE). Continuous surveillance of SJS/TEN in

this cohort shows that approximately 67% of strictly validated cases had a probable or very probable drug cause as determined by the algorithm for causality of epidermal necrolysis (ALDEN) score (Table 2; M. Mockenhaupt, MD, unpublished data, March 2017), 20% were secondary to a possible drug cause, and 13% were unlikely or not at all drug-induced. Genetic studies of SJS/TEN in European cases in the RegiSCAR cohort has led to the identification of risk alleles differing from other ethnic groups and genome wide association study (GWAS) analysis demonstrated that the HLA-region on chromosome 6 is of major importance.(19, 20) A RegiSCAR cohort study of several hundred patients with SJS/TEN revealed that the vast majority of survivors are left with sequelae persisting over months and years.

F. Thai-SCAR and the Southeast Asian Pharmacogenomics Research Network —In Thailand and other parts of Southeast Asia drugs that commonly cause SCAR have been marketed since 1980, an era of less socioeconomic development and limited clinical research capacity in the region, and this resulted in a lack of pharmacovigilance and an increase in SCAR incidence during this timeframe. In 1984 Thailand developed Thai Vigibase, a database and spontaneous reporting system for SJS/TEN and other serious ADRs administered by the Thailand Food and Drug Administration. Thai Vigibase receives approximately 50,000 reports each year of which approximately 20% are serious immune-mediated ADRs and 70.4% of these cases are SJS/TEN. Using this resource, multiple predictive genomic markers that may be used to identify patients at elevated risk for the most common drug-specific SJS/TEN in the Thai population were discovered by the international collaborative research team. For example, HLA-B*15:02 and HLA-B*58:01 are common alleles among Southeast Asian populations and are strongly associated with carbamazepine- and allopurinol-induced SJS/TEN, respectively.(21–25) In Thailand, the Ramathibodi Hospital in Bangkok has effectively incorporated pharmacogenomics practice into health care settings through the use of preprescription genetic testing that has been reimbursed by the Thai universal health coverage scheme since 2014 (cost per test equates to 985.7 THB or approximately US $30 per patient). As a result of the proactive approach, the incidence of SJS/TEN has decreased sharply and the country is now working to eradicate SJS/TEN and the associated morbidity and mortality (Figure 2). Thailand and other Southeast Asian countries have further organized a collaborative approach to overcoming genetically mediated SJS/TEN by forming the Southeast Asian Pharmacogenomic Network (SEAPHARM) that includes 10 nations and approximately 560 million Southeast Asians. The mission of this network is for these countries to work together to collaborate on sustainable pharmacogenomic research amongst regions with similar genetic backgrounds that will lead to further discovery and clinical translation. There is a critical need to identify and determine the population frequencies of genetic variants and implement knowledge of genetic variation in pharmacogenomics in Thailand and other Southeast Asian populations to construct prescribing guidelines that will further facilitate SJS/TEN prevention.

G. The Japanese Research Committee on Severe Cutaneous Adverse Reactions—To date, no epidemiologic data of SJS/TEN has been reported in Japan, a population of 120 million. In Japan, drug-related adverse events are adjudicated by the Ministry of Health, Labor, and Welfare and patient medical costs are partially covered

without revealing the localization of legal responsibility by the Japanese Post Marketing Adverse Event Relief System.(26) To investigate the epidemiology of SJS/TEN, the Japanese Research Committee on Severe Cutaneous Adverse Reactions (J-SCAR) collected a total of 370 cases (258 cases of SJS and 112 cases of TEN) using registration forms obtained from 2005 to 2007. The incidence of SJS/TEN per million per year is similar to other countries (3.1 for SJS, 1.3 for TEN, and 4.4 for SJS/TEN combined) with a relative SJS-to-TEN ratio of 2.3:1. Incidence was highest among Japanese individuals in the seventh decade of life (23.3% of all SJS cases, 19.8% of all TEN cases occurring among persons ages 60–69) and there was no obvious sex bias observed. The mortality rates for SJS and TEN were 3% and 19%, respectively. The rates of mortality and short- or long-term sequelae were significantly higher for TEN than for SJS (mortality $p = 4.39 \times 10^{-7}$; sequelae $p = 1.04 \times 10^{-8}$, Chi-square test). The most frequently suspected agents were antibiotics (16.3% for SJS and 19.5% for TEN), non-steroidal anti-inflammatory drugs (NSAIDs; 14.6% for SJS and 16.8% for TEN), and anticonvulsants (14% for SJS and 9.9% for TEN). The period from the start of anticonvulsant treatment to the onset of the rash was significantly longer than that of antibiotics or NSAIDs (onset of 70–80% of cases was 4 weeks for anticonvulsants, 2 weeks for antibiotics and NSAIDs). Eye involvement was documented in 26% of SJS cases and 77% of TEN patients and mucous membrane involvement was significantly more frequent in TEN than in SJS.(27)

Variants in pharmacogenes associated with carbamazepine and allopurinol SJS/TEN in the Japanese population were also examined in this study. HLA-B*15:02, the risk allele most commonly associated with carbamazepine-SCAR in South East Asians, was not identified among 61 patients with SCAR, whereas, HLA-B*15:11, which along with HLA-B*15:02, belongs to the B75 serotype, was recognized in 4 of 14 patients with carbamazepine-SCAR. (28) In contrast and in keeping with previous published data from Japanese and Europeans, HLA-A*31:01was present in 45 of 77 patients with carbamazepine-induced SCAR, including 21 of 36 patients with DRESS and 5 of 6 patients with SJS/TEN, relative to 54 of 420 carbamazepine tolerant controls (OR 10.8, $p = 3.64 \times 10^{-15}$).(29) Regarding allopurinol, HLA-B*58:01 was found in 10 of 18 patients with SCAR (OR 62.8, $p = 5.39 \times 10^{-12}$).

II. Special Populations and Considerations[2]

Key Points:

- SJS/TEN survivors frequently suffer from psychological complications and decreased health-related quality of life. Prompt recognition and treatment is needed to address the psychological sequelae of SJS/TEN.
- Drugs that are commonly suspected to cause SJS/TEN in children are similar to causative drugs in adults although non-drug related diseases that mimic SJS/TEN such as erythema multiforme majus are common making diagnosis challenging. SJS/TEN mortality is low in children compared to adults.

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- The risk of developing SJS/TEN and particularly drug-related SJS/TEN is significantly higher among the elderly and short and long-term morbidity and mortality are higher as compared to younger adults.
- Pregnant women and especially HIV and or HIV-TB co-infected pregnant women are at risk to receive drugs that more commonly cause SJS/TEN. Available data demonstrate that maternal SJS/TEN does not transmit to the fetus. However, maternal SJS/TEN is associated with higher than expected intrauterine death and sequelae may affect future reproductive capacity.

Session two of *SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation* focused on SJS/TEN in special populations including survivors, the young, the elderly, pregnant females, and individuals with infectious comorbidities.

A. Psychological Complications and Quality of Life in SJS/TEN—Long-term psychological sequelae, post-traumatic stress disorder (PTSD) and fear of taking drugs in the future are important morbidities associated with SJS/TEN.(30–32) Two studies that explored patients' perspectives of surviving SJS/TEN found that adverse drug reactions had a persisting impact on survivors' lives physically and psychologically long after the event.(33, 34) Survivors of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) were found to suffer from psychological symptoms of anxiety, depression, and PTSD.(35)

A recent study characterized the psychological complications and health-related quality of life of SJS/TEN survivors treated at a tertiary care burn center.(32) The Toronto study was conducted between 1995 and 2015 and included 17 adults (≥18 years of age) with biopsy proven SJS/TEN at a mean of 51.6 ± 74.7 months (median = 9, range = 1 – 228) following acute disease who were capable of participating in follow-up and answering questionnaires. Participants were assessed by validated emotional and health-related quality of life questionnaires.(36–41) Participants were also evaluated by a health-related quality of life questionnaire specially designed for this study and by a medical interview conducted with a structured detailed questionnaire. Eleven out of 17 (65%) were found to have symptoms of PTSD (Impact of Events Scale-Revised, mean = 22.4 ± 19.9) and 5 (29%) met the criteria for PTSD. Twelve (71%) had psychological distress (General Health Questionnaire, mean total score = 4.6 ± 4.2) and 11 (65%) had symptoms of a psychiatric clinical disorder (Hospital Anxiety and Depression Scale, mean total score = 14.5 ± 8.4). History of past psychiatric disorder was not significantly associated with scores in the psychological assessment questionnaires. The dermatology quality of life index (DLQI)indicated a moderate to extremely large effect on the lives of 9 (53%) participants (mean total score = 6.9 ± 7.6). Skindex-29 indicated a mild-severe effect on health-related quality of life in 10 (59%) participants (mean = 24.6 ± 21.5). Participants rated their general health at a mean of 66.2/100 ± 18.1 (EQ-5D VAS).(32) Fourteen out of 17 (82%) participants reported that SJS/TEN decreased their current quality of life, 12 (71%) reported that SJS/TEN influenced their current emotional status, and only 29% were employed following SJS/TEN. Participants wrote statements in the open text area, expressing their perspectives: "I have difficulty coping with stress and anxiety", "My emotions are out of whack. It is so easy to be introverted but that makes me depressed, so I keep a journal to record my thoughts and

emotions", "The first years of my recovery were very agonizing and very depressing". Despite most survivors having psychological complications, only four were assessed by a mental health professional during the period following SJS/TEN.(32)

The high burden of psychological sequelae and impact of SJS/TEN on health-related quality of life suggest that all patients and their families should be offered psychological support during hospitalization, prior to discharge and throughout follow-up, and should be offered contact with a support group. Several support groups have been established in different countries (see Box SJS Foundation and patient perspectives).

Box

The SJS Foundation and Patient Perspectives

Jean and Julie McCawley, Katie Niemeyer, and the family of Angela Anderson attended **SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation** on behalf of patients and families around the world who have been affected by SJS/TEN.

Julie McCawley, now aged 23, developed SJS/TEN at age 11 months and as a result suffers from severe sight impairment. In March of 1995, her mother, Jean, founded the Stevens-Johnson Syndrome Foundation (http://sjsupport.org), a grassroots non-profit patient support and advocacy group that aims to bring public awareness to this devastating and life-threatening illness. In 1997, the SJS Foundation launched their first website that included an online chat room for patients and families affected by SJS. Their network quickly brought together numerous patients and families affected by SJS/TEN from around the world. In 1999, the SJS Foundation collaborated with physicians at Johns-Hopkins to create an SJS fact sheet that has now been distributed to >100,000 hospitals and pharmacies and to the general public through awareness campaigns. The SJS Foundation now supports a voluntary case registry, has championed the establishment of August as SJS Awareness month, actively supports SJS/TEN research, and maintains a Facebook page with over 5,000 followers. Julie McCawley is now an elementary school teacher and creator of SJS Kids Support (www.freewebs.com/sjskidssupport), a website for children affected by SJS/TEN that explains the disease and its complications in accessible terminology with content focused on the concerns of young victims and of children with loved ones affected by SJS/TEN.

"Angela was unique. She was a trendsetter…one in a million. The disease that took her was one in a million. Even in death, she stood out from the crowd." –Eulogy for Angela Anderson. Paul Anderson shared the story of his daughter Angela's vibrant 22-year life and tragic 4-day hospitalization with SJS/TEN that ended in her death on December 28, 2015. In memory of Angela, he and his wife, Wanpen, and son, Tim, established the Angela Anderson SJS Research Fund to promote SJS/TEN research. The Anderson family recruited support from family, friends, and the general public through awareness events, media communications, and a GoFundMe campaign to raise $22,000 for SJS/TEN research. This is an especially significant contribution as it represents $1,000 in research funding for each year of Angela's life. Angela's story has been reported in numerous media outlets further raising community awareness of SJS/TEN. The Angela

Anderson SJS Research Fund continues to receive donations to further research efforts and her family and friends continue to work tirelessly to disseminate her story as education for the public and medical communities.

Katie Niemeyer is a survivor of SJS/TEN as a teenager and now works as a certified nurse anesthetist, entrepreneur, mother, and philanthropist to promote SJS/TEN awareness and research. Left with chronic eye irritation that hindered her training as a distance runner, Katie created a high-performance wrist band, Handana, to keep sweat from burning her already sensitive eyes. Handana was the first runner up in the 2015 Under Armour Future Show. Katie has donated proceeds from her business endeavors to supporting research in the treatment of acute and chronic SJS/TEN eye disease and established the Katie Niemeyer Research Fund at the Massachusetts Eye and Ear clinic. Katie is also the founding member of the SJ Syndrome of Texas (www.sjsyndrome.com) and frequently shares her story with healthcare and general audiences around the country to educate and inspire hope within and outside the SJS/TEN community.

These stories underscore major threats associated with SJS/TEN, a disease that 1) affects previously healthy individuals in an unpredictable manner in the absence of validated screening mechanisms, 2) is characterized by sequelae that are numerous, severe, and lifelong, 3) lacks highly specific diagnostic modalities that often results in delayed recognition of acute disease, and 4) in its severest form, moves quickly and with high mortality.

B. SJS/TEN in Children—Estimating the true incidence of SJS/TEN is hampered by the fact that non-drug related diseases such as erythema multiforme majus (EMM) may be confused with SJS/TEN particularly in children. The skin lesions in EMM are often targetoid in appearance with central dusky or blistering skin surrounded by erythematous inflammation and an outer ring of pale edematous skin (Table 1).(42) In children a high percentage of SJS/TEN may be non-drug related and infectious causes are associated in up to 30%. *Mycoplasma pneumoniae* and herpes simplex virus have been associated with EMM in children. In the case of *Mycoplasma pneumoniae* a distinct syndrome has recently been defined called *Mycoplasma* induced rash and mucositis (MIRM).(43–45) MIRM, which may represent an atypical form of EMM, can result in severe mucosal involvement. MIRM differs from typical SJS/TEN due to sparse cutaneous involvement. Additionally, Mycoplasma-associated disease tends to affect younger patients and is not commonly associated with long-term complications. However, recurrence of mucosal and skin lesions has been observed.

Drugs that are commonly suspected to cause SJS/TEN in children are similar to drugs in adults and include sulfa antimicrobials and aromatic anticonvulsants (phenobarbital, carbamazepine, phenytoin, and lamotrigine).(46, 47) Overall mortality is lower in children with SJS/TEN compared with adults (48) suggesting algorithms used in adults to predict SJS/TEN mortality are not applicable to children and the existing models that predict outcomes need to be modified or redesigned for pediatric patients.(49)

Children with SJS/TEN require high acuity hospital care, and up to 50% have long term sequelae including blindness which can occur many years after the initial acute SJS/TEN episode. Ophthalmologic disease may impact children less frequently and preferentially affect those children with more severe disease: 100% of children with TEN had evidence of ocular involvement.(50) Ophthalmologic conditions were more common among children with concurrent infectious diseases than among children with non-infectious diseases, with the highest proportion seen among those with Mycoplasma induced rash and mucositis.(51) As both short and long term ophthalmologic complications can occur in children with SJS/TEN, involvement of a pediatric ophthalmologist should occur early upon diagnosis. In children, recurrence of SJS is well reported occurring in up to 20% of cases.(46)

In summary, compared to adults, children have lower rates of mortality, but their survival comes with high rates of long-term complications. Further work is needed to define SJS/TEN in children and determine the most optimal treatment strategies.

C. SJS/TEN in the Elderly—The incidence of drug associated SJS/TEN in patients greater than 64 years of age is twice as high when compared to patients 20–64 years of age (9.4 per 10^6 versus 4.6 per 10^6 person-years).(52) Whether this is due to polypharmacy or other age-associated factors is unclear. Older adults also appear to be at greater risk of a cutaneous disease similar to SJS or TEN, referred to as generalized bullous fixed drug eruption (GBFDE). The skin lesions seen in GBFDE appear very similar to those of SJS/TEN, consisting of large erythematous, often violaceous patches with overlying fluid-filled bullae, but GBFDE is typically considered less severe than SJS/TEN because constitutional symptoms are absent and lesions are well-demarcated and usually limited to the skin without mucosal involvement (Table 1).(53) Despite its more benign presentation, GBFDE whenassociated with BSA involvement >20% can be associated with mortality rates >20%, which highlights the significance of cutaneous reactions in older adults.(53)

Advanced age is also a predictor of SJS/TEN mortality. Age >40 years is an independent risk factor for death in adults with SJS/TEN and mortality rates as high as 70% have been described in those over 65.(5) Underlying diseases (e.g., severe kidney or liver disease, malignancy) are also associated with higher rates of mortality from 90 days to 1 year following the SJS/TEN presentation.(18) Complications such as multiorgan failure, nosocomial infections, and septicemia may lead to death, even following inital healing of skin lesions. Sekula *et al.* found that 25% of patients with a serious comorbidity or who were over age 70 who survived the first 3 months following a SJS/TEN diagnosis died during the subsequent 9 months.(18)

As the older population continues to grow globally, the number of geriatric patients who develop SJS/TEN will also likely continue to increase. Given the paucity of data on therapeutic approaches to treat SJS/TEN in the geriatric population and the high rate of associated mortality among this group, further studies are needed to determine optimal treatment strategies and decrease risk of death both in the short and long term following a SJS/TEN diagnosis.

D. SJS/TEN in Pregnancy and in HIV-Infected Pregnant Women—SJS/TEN during pregnancy has potential consequences for both mother and the fetus. There is limited epidemiological data on SJS/TEN in pregnant women and existing evidence is derived mainly from case reports. A review of published literature up to 2010 identified only 36 cases of SJS/TEN in pregnant women. The authors concluded that SJS/TEN mortality in pregnant women is lower than expected and this finding was likely attributable to younger age and lower SCORTEN amongst pregnant patients compared to other SJS/TEN cohorts.(54) Certain antiretroviral drugs are strongly associated with SJS/TEN and other IM-ADRs in certain genetic backgrounds (i.e., nevirapine/HLA-C*04:01 SJS/TEN and abacavir/HLA-B*57:01 hypersensitivity syndrome).(55–59)

In the developing world, nevirapine is used to treat HIV-infected pregnant women. Studies that have examined mother-to-child transmission of HIV have documented cases of maternal SJS/TEN(54, 60, 61) and nevirapine has been identified as a causative drug in multiple cases (Figure 3).(62–64) However, since 2012, nevirapine has been replaced with efavirenz as the NNRTI of choice for prevention of mother-to-child HIV transmission (PMTCT) in South Africa. Between January 2013 and December 2015, the incidence rate of SJS/TEN in the same population dropped to 0 cases per year compared to 3.4 cases per year for the preceding seven years.(63, 64) Although an earlier case-control study of antiretroviral associated SCAR suggested that pregnancy was independently associated with SCAR after controlling for nevirapine exposure,(63) this new data suggests that nevirapine might be associated with a higher incidence of SJS/TEN in pregnancy but that pregnancy does not itself seem to predispose to SJS/TEN.(64) In a case series of HIV infected women, no maternal deaths from SJS/TEN were seen during pregnancy, a finding which supports the findings by Struck *et al.* that SJS/TEN mortality in pregnant women is lower than expected.(5, 54, 63–66)

Despite the observation that pregnant women with SJS/TEN have lower than expected mortality, fetal outcomes are worse, with higher than expected intrauterine death. Five of the 36 cases (14%) published by Struck *et al.* delivered stillbirths and in a separate series of HIV-infected pregnant women this was 11%, higher than expected.(54, 63, 66) It remains uncertain if maternal TEN, the more severe form of the disease, is associated with poorer fetal outcomes. Rarely, SJS/TEN can affect the fetus and there are two published cases of fetal SJS/TEN, one concurrently affecting the mother and the fetus and the other the fetus alone.(67, 68) It may be difficult to differentiate between SJS/TEN and fetal maceration as maceration-associated desquamation starts within six hours of intrauterine death.(69) However, the finding of irregular purpuric macules in the case presented by Rodriguez *et al.* supported a diagnosis of SJS/TEN.(67) The case published by Sweetnam *et al.* healed with keloidal scarring, an unusual feature in SJS/TEN in the absence of secondary infection, immobility, sustained pressure or delayed re-epithelialization.(68, 70) Despite extensive use of nevirapine in PMTCT, there are disproportionately few cases, if any, of neonatal SJS/TEN.(60) We can safely conclude that SJS/TEN rarely, if at all, affects newborns. In the context of PMTCT in HIV-infected mothers with SJS/TEN, concerns regarding the interruption of an antiretroviral causative drug and the potential risk of neonatal HIV infection have been evaluated in only a few instances. Most published reports on SJS/TEN in

pregnant women, including those designed for PMTCT, do not address the risk of maternal HIV transmission to the fetus.(60, 61) Reassuringly, in 12 children who had received PMTCT and were born to mothers with SJS/TEN during pregnancy, all were found to be HIV uninfected at 6 weeks following delivery.(63)

Consideration for the method of delivery in the current and subsequent pregnancies is important as long-term sequelae of genital mucositis in SJS/TEN, including structural changes secondary to adhesions, stenosis, hematocolpos, adenosis and endometriosis, may impact future reproductive health and modes of delivery.(70) Both vaginal and caesarian section deliveries have been reported in the setting of past and current SJS/TEN.(54, 63) The extent to which vaginal delivery is contraindicated is difficult to establish due to the rarity of SJS/TEN in pregnancy, the lack of a standardized case definition for genital disease, incomplete reporting of vaginal complications, and breadth and variability of indication for cesarian section based on hospital practice.(54, 63) Awareness of sequelae and preventative strategies in acute SJS/TEN should reduce the incidence of vaginal fibrosis and consequently number of cesarian section performed.(63)

III. Clinical Management[3]

Key Points:

- Cessation of the implicated drug and intensive supportive care with early multidisciplinary involvement is key to the management of SJS/TEN.
- Up to 77% of patients with SJS/TEN patients have genitourinary involvement in the acute phase and of these up to 25% go on to have some form of chronic complications. Early genitourinary exam and acute management are likely to be key in avoiding chronic complications.
- Ocular disease often precedes skin involvement and patients should be evaluated by an ophthalmologist if there is suspicion of SJS/TEN. Early interventions such as amniotic membrane transplantation have been key to preventing long-term ocular morbidity. For patients who survive the acute phase, ocular complications are the most common and debilitating chronic sequelae and blindness can occur decades after the acute episode which necessitates life-long follow-up.
- Although IVIG has been widely applied there is no evidence base to support its use.
- Improved evidence-based data to support specific clinical management and therapeutic intervention remains a priority need for SJS/TEN.

While characterized by predominant epidermal and mucous membrane involvement, SJS/TEN is a multisystem disease. Session three of *SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation* featured discussion and expert recommendations from clinicians in Dermatology, Burn Surgery and Critical Care Medicine,

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Ophthalmology, and Gynecology. The state of current practices in clinical management of SJS/TEN, unmet clinical research needs, and future directions were discussed (Figure 4).

A. Management and Clinical Guidelines—SJS/TEN causes both acute and chronic complications across a diverse group of patient populations.(71) Although early intervention is considered key to minimizing short and long-term sequelae, international consensus and treatment guidelines for the management of SJS/TEN are lacking. A comprehensive, systematic review of the management of SJS/TEN in adults was undertaken in the UK in 2016 and included accreditation from the British Association of Dermatologists, the British Association of Plastic, Reconstructive and Aesthetic Surgeons and the National Institutes for Health and Care Excellence (NICE).(72, 73) The most important initial step in the management of SJS/TEN is to immediately discontinue any potential culprit drug (Figure 4). In many cases the culprit drug is obvious from the exposure timeline, but in some cases, several or no culprits may be apparent. Where many possible culprits exist, all suspected drugs need to be stopped and if needed, a structurally disparate alternative therapy with low risk for cross-reactivity with the culprit drug should be initiated. Any drug that has been tolerated for more than 3 months can safely be continued. The ALDEN causality score (Table 2), particularly designed and validated for SJS/TEN, is an important tool to help aid in the causality assessment of potential culprit drugs.(74) Other drug causality assessments have also recently been developed.(75) In the cases where no drug is suspected, then infection may be implicated and screening tests are indicated (e.g., Mycoplasma PCR, Herpes simplex swab PCR, Enterovirus PCR). Furthermore, it is important to consider that other dermatoses such as linear IgA disease, staphylococcal scalded skin syndrome, GBFDE, pemphigus vulgaris and other autoimmune bullous diseases, and graft versus host disease can sometimes be difficult to distinguish from SJS/TEN by clinical appearance. Therefore, skin biopsy for routine histology and direct immunofluorescence is an important tool. Despite the urgency of the acute care for SJS/TEN, immediate consideration of post-recovery morbidities such as those involving the eyes and genitourinary mucosa is critical. This requires early input from the relevant specialties (Figure 4).

Optimal therapeutic intervention in SJS/TEN is controversial. Since the first report of a small case series showing response to IVIG, interest in the role of this therapy has been maintained. Recent surveys confirm that many physicians who treat SJS/TEN continue to support its use.(4, 76, 77) One systematic analysis of the published literature of IVIG in SJS/TEN included 17 case series from different countries where comparison with supportive care alone could be made. Although the number of publications showing benefit was greater than those showing no benefit, comparison of the total number of patients reported demonstrated no benefit of IVIG.(16, 76, 78–92) In addition, methodological concerns exist due to evidence of duplicated cases, variable dosing and combined treatment with corticosteroids in many of the published case series. Thus the benefit of treatment of SJS/TEN with IVIG is uncertain. Although review of the literature shows no evidence of harm, overall, there is no convincing evidence of benefit.(72, 73)

Treatment of SJS/TEN with corticosteroids (e.g., prednisolone, methylprednisolone, dexamethasone) versus supportive care was also examined systematically. Only 3 studies out of 10 showed benefit of this treatment and the number of cases treated in studies where no

benefit was seen was again higher than in those showing benefit (273 versus 78).(16, 85, 93–100) One small case series not included in this review suggested that pulsed dexamethasone given at a dose of 1.5 mg/kg for three days was helpful when given near the time of disease onset.(96) The weight of this evidence is small in comparison to the larger systematic review. However, methodological criticisms highlighting poor case validation and variable dosing suggests that some caution in data interpretation is required. A separate recent meta-analysis of observational studies for immunomodulating therapies of SJSTEN (including IVIG, pulsed dose corticosteroids, and cyclosporine) showed that corticosteroids were associated with a survival benefit in three different analyses (aggregated study data: OR 0.5; 95% CI 0.3–1.01; indivudual patient data (IPD) unstratified: OR 0.7; 95% CI 0.5–0.97; IPD stratified: OR 0.8; 95% CI 0.4–1.3). Despite low patient numbers, cyclosporine was associated with a promising significant result in the feasible unstratified IPD analysis (OR 0.1; 95% CI 0.0–0.4). IVIG was not beneficial in this meta-analysis.(101)

The published evidence of cyclosporine treatment of SJS/TEN showed evidence of a therapeutic benefit in case series and an open-label Phase II trial.(102–107) No deaths were reported in the trial and the arrest of disease progression as well as re-epithelialization was hastened. The meta-analysis above(101) also showed both study and patient-level benefit. However, the overall sample sizes reported are low, represent single center experiences or lack control groups. Lack of case validation in the reported case series should create caution against over-interpreting the data. G-CSF and anti-tumor necrosis factor (TNF) receptor antagonists also have some reasonable evidence to suggest further examination of these therapies for SJS/TEN but as yet, experience remains limited with these treatments.(108–111) A recent Phase II randomized control trial showed benefit in mortality of the anti-TNF agent etanercept over steroids (relative risk reduction 50% vs. 20%) and reduction of time to re-epithelialization in the etanercept group.(111) Thalidomide, which was trialed in the late 1990's because of its anti-TNF activity, is the only treatment to have undergone a placebo-controlled randomized controlled trial. This study, however, was stopped early because thalidomide was associated with higher day 2 plasma TNF concentrations and increased mortality.(112)

For all therapeutic interventions to date, the inevitable delay between the onset of the rash and interventional treatment caused by the time taken for transfer to specialist centers means that early intervention has yet to be thoroughly examined. Cyclosporine and etanercept have shown benefit in their respective trials when initiated up to approximately 5 days after the onset of skin signs of disease.

B. Ocular Involvement and Management—Acute ocular involvement in SJS/TEN occurs in up to 100% of patients and ranges from conjunctival hyperemia to near total sloughing of the ocular surface and eyelid margins.(113–116) Acute pathology can result in chronic complications including corneal epithelial stem cell deficiency and eyelid margin keratinization which in turn lead to corneal neovascularization and opacity, persistent corneal epithelial defects, severe dry eye, and ultimately blindness. Blindness can also occur in the acute phase as a result of corneal perforation, largely a result of inadequate care. There is incomplete correlation between the severity of SJS/TEN illness and ocular complications and the degree of ocular involvement in SJS/TEN is highly variable.(114, 115, 117–119)

Furthermore, the immunopathogenesis of how SJS/TEN affects the eye which is an immune-privileged site is also largely unknown. Literature from specific populations has supported potential associations between specific HLA class I alleles and ocular involvement.(120–124)

The single best predictor of chronic corneal complications is acute eyelid margin involvement. Acute eyelid margin de-epithelialization and ulceration leads to eventual eyelid margin keratinization which causes corneal disease through various mechanisms and a window of opportunity exists in the acute phase to mitigate the severity of eyelid margin disease through the use of amniotic membrane transplantation (AMT).(125–128) Early treatment is the key to management and this reduces the risk of blindness. Dissemination of this message is urgently needed as in the United States alone, only 66% of burn intensive care units routinely consult ophthalmology on patients with SJS/TEN during their hospital stay.(4)

The critical period for ophthalmological care is within 7 days of disease onset, beyond which a crucial window of opportunity for ocular intervention is lost, and irreversible damage can occur. Further challenges and constraints on this time window exist due to delays in diagnosis and hence delayed transfer of patients to an appropriate care environment. Further delays may be incurred by aspects of clinical management such as waiting for skin biopsy results or for clinical signs to fully manifest. Importantly, ocular disease often precedes skin involvement and patients should be evaluated by an ophthalmologist even if there is any suspicion of SJS/TEN, while awaiting confirmation.

The ocular exam consists of examining the eyelid skin, eyelid margin, conjunctiva, and cornea, assessing for epithelial sloughing, defects, ulceration, and inflammation. The acute care involves the use of lubrication with artificial tears and ointments, topical antibiotics for infection prophylaxis, topical corticosteroids to control inflammation, and AMT in moderate to severe ocular disease to decrease inflammation, speed healing, and prevent keratinization.(116) The exact mechanism by which AMT improves outcomes is unknown. Treatment regimens depend on the severity of disease and can be found in Figure 4a. Adjunct therapies are used on a case-by-case basis and include the use of bandage and scleral contact lenses for persistent epithelial defects of the cornea. Follow up in the acute phase depends on the severity of ocular involvement, but at the very least, patients should be seen 24–48 hours after initial ophthalmologic exam as ocular involvement can progress quickly over time. Once acute disease has stabilized, follow up can be tailored to the individual.

There is no defined protocol for management of chronic ocular disease after hospital discharge, with few prospective studies and no randomized clinical studies. The consensus from experts in the field is that patients should be maintained on topical corticosteroids for several months, tapering slowly while monitoring the intraocular pressure. Close follow-up by an ophthalmologist is essential as new ocular signs can manifest over time, which also have limited windows during which interventions can be sight saving. These interventions include punctal occlusion, retinoic acid ointment to the eyelid margin, specialized scleral contact lenses, and oral mucous membrane grafting to the eyelids. End-stage disease may require a keratoprosthesis/artificial cornea for visual rehabilitation. A role for topical

cyclosporine for the treatment of chronic dry eye following SJS/TEN may be limited by patient intolerance for the drug formulation.(129) Patients with SJS/TEN should be followed by an ophthalmologist for life, as worsening symptoms and vision loss and can occur decades after disease onset.

C. Genitourinary Disease—The acute genitourinary manifestations of SJS/TEN in females include erosions and ulcerations of the vulva and vagina. These acute manifestations occur in up to 77% of patients and can lead to chronic complications in the form of vulvar adhesions and vaginal stenosis, resulting in hematocolpos, dyspareunia, chronic pain and bleeding, and difficulty conceiving.(63, 130) Data are limited, but it is thought that urogynecological complications are common, and that they occur in up to 77% of female SJS/TEN patients of which 9–25% of survivors go onto have chronic complications..(131, 132) An additional complication is vaginal adenosis, where stratified squamous epithelium is replaced with columnar glandular epithelium.(133) Adenosis can increase the risk of vaginal malignancy. To prevent the complications above, all female patients should have a gynecologic exam at the time of admission for suspected SJS/TEN and should be followed closely in the early stages of SJS/TEN as mucosal disease can develop and spread rapidly. Any vulvar pathology should prompt an evaluation by a gynecologist for possible vaginal involvement.

Special patient categories in this respect include pediatric and pregnant patients. For the former, cooperation with examinations and treatments can be difficult and they may be deemed invasive. For the latter, decisions about mode and timing of delivery can be complicated by the presence of vaginal or vulvar erosions, abdominal skin pathology, or vaginal stenosis. In younger patients, evaluation may need to be done under sedation or anesthesia. General anesthesia may be difficult to accomplish in the acute phase when the patient is too unstable to be taken to the operating room. These determinations should be made on a case-by-case basis, taking patient cooperation and hospital resources into account. The goal of treatment in the acute phase is to decrease inflammation and prevent the development of adhesions. The following treatment recommendations are not all-inclusive and have not been proven through clinical trials but serve as a foundation for treatment as our understanding and study of gynecologic pathology in SJS/TEN grows.

Vulvar skin involvement can be treated with a bland petrolatum-type emollient. A high potency steroid ointment, such as 0.05% clobetasol, can also be used to decrease inflammation and discomfort. If increased irritation occurs with such products, emollients alone should be used. Consider decreasing the frequency of steroid use after initial treatment.(134) Vaginal disease should be treated with twice daily use of a soft, small vaginal mold/dilator or a tampon/roll of gauze covered with a non-lubricated condom. The device should be coated in high-potency steroid ointment before it is applied. This intervention is to provide anti-inflammatory treatment to the mucosa and to physically separate the mucosa to prevent adhesions, rather than to dilate the vagina, and the device should just be large enough to accomplish these ends. The vaginal mold can be left in place for 12–24 hours at a time, but should be removed at least once daily for cleaning of the device with soap and water and for application of additional anti-inflammatory medication.

Even for those patients without visible disease, prophylactic treatment as above should be considered for several hours a day.

Patients uncomfortable with using a vaginal dilator/mold, particularly pediatric patients, can apply medication twice daily with a vaginal applicator. Even for virginal and/or pediatric patients, use of a small mold or a condom-covered tampon should be encouraged if the patient in emotionally and physically comfortable with the regimen. Other general considerations include menstrual suppression to reduce discomfort and to possibly decrease the risk of vaginal adenosis. Systemic and/or topical antifungal medication may be considered to decrease the risk of vaginal candidiasis in the setting of vaginal steroid use. The medication on the dilator can be changed to, or alternated with, estrogen cream to help promote healing of the vaginal mucosa. Lidocaine 5% ointment can also be used at the vaginal introitus, once open sores have healed, to reduce discomfort with use of the vaginal dilators. In pregnant women, usual obstetric care should continue and decisions about delivery made in consultation with the obstetrical team.

As with complications associated with SJS/TEN, outpatient follow up after discharge from the hospital is essential. All patients should be scheduled for follow up with a gynecologist within 3 months of discharge. Patients who had active vaginal disease in the acute phase should continue to use a dilator at least 2 times a week for 2–3 months after discharge.

Additional acute and recovery management of respiratory and gastrointestinal complications in SJS/TEN may be required as outlined in Figure 4. Although limited data suggest that urologic manifestations are common in SJS/TEN, aside from acute supportive measures and catheterization, there is limited research in this area and currently no clear guidelines or expert consensus on the management of acute urethral involvement or long-term urethral complications.(135) This represents an important area of future work in the field.

D. Clinical Management Summary—Rapid withdrawal of the culprit drug and intensive supportive care from a multidisciplinary team is the central priority in management of acute SJS/TEN. There is no conclusive evidence that IVIG or corticosteroids are harmful or beneficial in the context of SJS/TEN. Smaller studies have shown some benefit but the weight of evidence does not currently support their use. It may be that initiation of therapy close to the time of skin signs is needed with loss of efficacy within a few days. Although accumulating evidence exists for the use of cyclosporine and other immunomodulatory therapies such as etanercept from small studies and now Phase II trials, sufficient experience with these treatments to recommend their use is lacking. In addition, it is currently unknown if patients would present early enough at most centers for these treatments to be beneficial. Regardless of therapeutic intervention, there should be efforts to move towards a harmonized strategy of aggressive supportive care. Multidisciplinary collaboration is required in the acute care setting and in follow-up to identify and manage potential chronic sequelae early.

IV. Pharmacovigilance and the Electronic Health Record[4]

Key Points:

- The FDA Adverse Event Reporting System (FAERS), a database of spontaneous adverse event reports, is the primary tool used by the FDA to detect safety signals of SJS/TEN in the post-marketing setting.
- The Singapore Health Sciences Authority has evaluated two common (~15–20% carriage) HLA allele-drug pairs associated with SJS/TEN:
  - Genotyping for HLA-B*15:02 for new users of carbamazepine in patients of Southeast Asian descent/ethnicity became a diagnostic standard in 2013 and widespread screening has reduced the number of associated cases of SJS/TEN from ~18 per year to 1 case in the 4 years since implementation.
  - Genotyping for HLA-B*58:01 for new users of allopurinol was not mandated due to lower efficacy or higher costs of alternative gout medications. However, clinicians were notified of a laboratory where testing was available.
- Mining Electronic Health Records (EHR) can reliably identify common disease phenotypes for genomic studies. Rare drug adverse events have also been successfully studied using this technique.
  - 12% of general medicine patients in a large EHR were exposed to one of five SJS/TEN-associated drugs. Combining this information with genetic data could be used to prevent SJS/TEN in persons at high risk.

Session four of *SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation* centered on pharmacosurveillance mechanisms and sources of large datasets and bioinformatic methods for the detection and validation of SJS/TEN cases and predictors of risk.

A. Regulatory Science and Pharmacosurveillance: US Food and Drug Administration—The FDA's Division of Pharmacovigilance (DPV) uses a number of tools and processes for the detection and evaluation of safety signals for SJS/TEN.(136) The FDA Adverse Event Reporting System (FAERS) is the primary tool used in the post-marketing setting (Figure 5). FAERS is a database of spontaneous adverse event reports that supports FDA's post-marketing surveillance program for drugs and therapeutic biologics. The data files, which are updated quarterly, can be downloaded from the FDA's website (https://www.fda.gov/drugs/informationondrugs/ucm135151.htm), and individual case safety reports can be requested by submitting a Freedom of Information Act request. Adverse event reports can be submitted to the FDA from the website, or through MedWatcher, a free mobile application. Case reports for SJS/TEN should include patient characteristics such as age, sex, medical history, and all descriptors of the event including diagnostic information and the time to onset of symptoms from initiation of drug therapy to onset of disease should also be included. A comprehensive list of drugs including concomitant and recently discontinued products, including over-the-counter products and supplements, and time of

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initiation should also be included. The specific action taken for the suspect and concomitant products (continuation, discontinuation) should be reported. The reporter contact information should be included and if significant additional information becomes available after a report has been submitted, a follow-up report should be considered.

Adverse events that are reported to a drug manufacturer are required to be submitted to the FDA within 15 days of receipt if they are serious and unexpected by regulatory definition. Relevant to SJS/TEN, serious adverse events are defined as those that result in death, are life-threatening, result in initial or prolonged hospitalization, are associated with persistent or significant disability or incapacity, congenital anomalies, or other serious events. Expectedness is based on what currently appears in the FDA-approved labeling for that product. Events that are serious and expected as well as non-serious events, can be submitted to the FDA on a quarterly basis for the first three years after product approval, and then annually.

Healthcare professionals review incoming FAERS reports. These safety reviewers receive a list of incoming reports for SJS, TEN, and other selected serious adverse events to ensure that those reports are prioritized. They use case definitions and causality assessment tailored to spontaneous reports to evaluate potential safety signals. Examples of regulatory actions that may be taken when a safety signal is identified include 1) updating the product labeling, 2) issuing a Drug Safety Communication, 3) post-marketing requirements or commitments to evaluate the event, 4) implementing Risk Evaluation and Mitigation Strategies to manage serious risks while enabling patients to have continued access to the product, or 5) market withdrawal (Figure 5).

In addition to FAERS, safety reviewers use VigiBase®, a global database of adverse event reports maintained by the World Health Organization-Uppsala Monitoring Centre. Data mining in FAERS and Vigibase® can be used to identify events that are disproportionately reported for a drug. Reports for the event are then reviewed to determine if there is a potential safety signal. The medical literature is another important data stream because some published cases may not have been previously reported to regulatory authorities or manufacturers. The National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES) database is another useful resource. It uses trained abstractors to collect data on adverse drug events diagnosed and treated in a nationally representative sample of Emergency Departments.

Post-marketing pharmacoepidemiology studies using prospective data collection, such as registries, can be useful in providing specific patient information, such as genetic information and ethnicity. Important limitations include under-ascertainment of cases and the need for large numbers of enrolled patients to identify rare events. Pharmacoepidemiology studies involving retrospective data collection, for example from large administrative databases, have the advantage of providing large numbers of patients with longitudinal follow-up in “real-world” settings, but cases may not be captured by billing codes alone and there may be incomplete capture of certain information such as ethnicity.

Finally, Sentinel is an active surveillance system sponsored by FDA that uses administrative and claims data. The Active Risk Identification and Analysis (ARIA) System is a component of Sentinel comprising predefined analytic tools that enables rapid querying of the database.(137) Although evaluating SJS/TEN in Sentinel would be challenging at this time, research is ongoing.

In summary, FAERS is the primary tool used by DPV for the detection of safety signals for SJS/TEN and submission of high quality reports by healthcare providers is essential. Supplementary tools include Vigibase®, data mining, the medical literature, NEISS-CADES, pharmacoepidemiologic studies, and Sentinel/Active Risk Identification and Analysis.

B. Finding rare diseases such as SJS/TEN in the Electronic Health Record— Electronic Health Record (EHR) data have proven to be an effective and efficient resource for studying common diseases and drug response phenotypes (e.g., drug efficacy or adverse drug responses). The genetic basis for hundreds of diseases have been uncovered, including replicating many known, expected genetic associations.(138, 139) However, finding these diseases in the EHR is not a trivial effort. EHRs represent a longitudinal record of diseases with records generated for a variety of purposes along the course of illness.(140, 141) Thus, they can contain inaccurate data.(142) Accurate disease phenotypes typically require some combination of multiple types of EHR data including billing codes, laboratory data, medications prescribed to the patient, and narrative data such as in clinical reports (Figure 6).(140) Algorithms leveraging scores, Boolean logic, natural language processing, and machine learning approaches typically produce reliable algorithms.(143) These algorithms typically are usually developed with clinical experts working in concert with biomedical informaticians. Several example algorithms were presented, including autoimmune hypothyroidism(144) (as an example of one of many disease phenotypes) and two drug adverse events phenotypes, angiotensin converting enzyme inhibitor associated cough(145) and heparin induced thrombocytopenia,(146) for which significant novel genetic associations were discovered using EHR data. The latter example demonstrates the potential for using EHRs for rare drug adverse events, such as SJS/TEN.

In a recent study of twelve research units and managed care organizations in the United States covering almost 60 million lives, electronic medical record databases were used to identify potential cases of SJS/TEN using ICD-9 codes. Medical records were abstracted and standardized criteria applied by board-certified dermatologists to adjudicate diagnoses. Multivariate models were developed to identify factors independently associated with validated SJS/TEN case status. The likelihood of case status increased with the length of hospitalization and with the use of new ICD codes specific to SJS/TEN. The positive predictive value (PPV) of International Classification of Diseases, Ninth Revision codes 695.12–695.15 was 50% among hospitalized cases. Among patients hospitalized for three or more days, the PPV of these codes was even higher, and ranged from 57% to 92%. These results suggest that case finding using electronic health record data can be carried out using a combination of search codes and search terms.(147)

At Vanderbilt, manual chart reviews were used to investigate the potential identification of SJS/TEN in the EHR (Figure 6) including before 2008 when specific SJS/TEN billing codes, an important part of most algorithms, did not exist. Preliminary data suggest SJS/TEN specific ICD codes have a positive predictive value (PPV) around 29%. Use of drug-specific ICD codes in combination with SJS/TEN or the more general erythema multiforme codes improve performance, increasing the PPV to 38% and maintaining a 99.8% negative predictive value for phenytoin-related SJS/TEN. Given the rarity and severity of SJS/TEN, EHR-based algorithms designed to find SJS should focus on being able to identify most cases (that is, with a high senisitivity and high NPV) with reasonable PPV. Another challenge in finding SJS/TEN cases in the EHR is confirming the phenotype since it can be difficult to verify the true diagnosis and clinical details of the cases if clinical details such as body surface area involved, presence of mucosal involvement, pathology results, pictures and other materials that are faxed into the EHR in a pdf format and are not accessible by automated search methods. Many cases called “SJS” or “TEN” by treating physicians may not be SJS/TEN. The presence of a high-risk drug given in the appropriate time frame significantly increases the probability of a cases identified through the EHR being SJS/TEN. In addition to difficulties finding true cases of SJS/TEN in the EHR it is challenging to ascertain drug causality particularly if multiple drugs were started in a short time frame.

To estimate the potential number of individuals at risk, prescribing records of nearly one hundred thousand individuals at Vanderbilt University Medical Center “medical home” patients were analyzed for exposure to five drugs associated with severe delayed hypersensitivity syndromes including but not limited to SJS/TEN with known genomic predictors (allopurinol, lamotrigine, phenytoin, carbamazepine, and abacavir). Twelve percent of patients took at least one of these five medications, all of which except abacavir are known to associated with SJS/TEN, and 6% took more than one. These numbers demonstrate the potential for prospective genotyping programs to potentially avert SJS/TEN events for these medications.

C. Regulatory Perspective on Pharmacogenomic Screening for SJS/TEN in Singapore: Experience with Implementation and Cost-effectiveness—The experience of the drug regulatory authority of Singapore, the Health Sciences Authority (HSA), illustrates some of the benefits and challenges of implementing genetic screening to reduce the incidence of SJS/TEN. Two genetic associations with drug-induced SJS/TEN are relevant to this experience: HLA-B*15:02 with carbamazepine and HLA-B*58:01 with allopurinol. DNA collection of SJS/ TEN cases and drug-tolerant controls confirmed strong genetic associations in the Singapore population (for carbamazepine: OR, 181; 95% CI, 8.7-3785; for allopurinol: OR, 100; 95% CI, 3.5-2820). Given the population frequency of these alleles (14.9% for HLA-B*15:02 and 18.5% for HLA-B*58:01), specificity and sensitivity of the tests,(148, 149) and incidence of the reaction, the PPV of the genetic tests in Singapore is ~6% for HLA-B*15:02 and ~2% for HLA-B*58:01. Both tests have nearly a 100% negative predictive value across Southeast Asian populations.

Patients testing positive for HLA-B*15:02 have a number of alternative drugs to treat epilepsy or neuropathic pain. Cost-effectiveness analyses conducted from a health-systems perspective showed that genotyping for HLA-B*15:02 for new users of carbamazepine falls

below a commonly used incremental cost-effectiveness ratio of US $50,000 per quality adjusted life year.(150) Prior to implementation, discussion sessions with clinicians and stakeholders highlighted two key concerns: genotyping test costs and turnaround time. Centralization of testing achieved a 40–50% cost reduction to US $146 and a turnaround time of three days. In April 2013, the Singapore Ministry of Health and HSA issued a joint Dear Health Care Professional Letter (DHCPL) stating that genotyping for HLA-B*15:02 would be the standard of care prior to prescribing carbamazepine to new users with a 75% subsidy to low-income patients for the HLA-B*15:02 test.(151) Orders for the HLA-B*15:02 test have since reached a steady rate of 250 tests per quarter. In the three years after the DHCPL, there were no reported cases of carbamazepine-induced SJS/TEN in genotyped patients in Singapore. In the fourth year, HSA received one report of SJS in a HLA-B*15:02 negative patient. Overall, genotyping has led to a significant reduction of carbamazepine-SJS/TEN from the historical incidence of 18 cases per year obtained from voluntary reporting. Similar national health policy programs for genotype reimbursement have been in place in Taiwan since 2010 and in Hong Kong since 2008 and have successfully reduced HLA-B*15:02 associated carbamazepine SJS/TEN in both settings.(152, 153)

The case for HLA-B*58:01 genotyping for allopurinol has been more challenging because of limited options for treatment of chronic gout. At 2% PPV, many HLA-B*58:01 positive patients would be given second-line or more expensive gout drugs. A similar cost-effectiveness analysis as done for carbamazepine was done for HLA-B*58:01 in the setting of new users of allopurinol and included an option for an enhanced safety monitoring program. At a test cost below US $90, genotyping would become cost-effective if test positive patients are given probenecid and non-responders are switched to allopurinol with an enhanced safety program. An enhanced safety program for all patients with gout without genotyping would become cost effective at a program cost of <US $39 per patient.(154) In March 2016, the Singapore Ministry of Health and HSA issued another DHCPL stating that routine genotyping for HLA-B*58:01 was not required as standard of care but could be considered for patients who have other pre-existing risk factors such as renal impairment. (155) Information on availability of an HLA-B*58:01 genotyping test at a similar price as the HLA-B*15:02 test was communicated. Additional measures to mitigate the risk are publication of clinician and consumer guides for earlier recognition of different types of severe cutaneous adverse reactions, design of a low-cost safety program, and targeted genotyping for a higher risk subgroup of patients with gout.

In summary, systems-wide implementation of genotyping requires weighing a multiplicity of factors: from the strength of the genetic association and prevalence of the allele in the population to the PPV and availability of alternative drugs or treatment plans for test-positive patients.(156)

V. SJS/TEN Prevention, Prediction, and Pathogenesis: What's New and What's Next[5]

Key Points:

[5]Riichiro Abe, MD, PhD; Wen-Hung Chung, MD, PhD; Shuen-Iu Hung, PhD; Mario E. Lacouture, MD; David A. Ostrov, PhD; Rebecca Pavlos, PhD; Alec Redwood, PhD; Michael D. Rosenblum, MD, PhD; Katie D. White, MD, PhD

- HLA associated SCARs including SJS/TEN have provided models for T-cell mediated ADRs and a roadmap for assessment and implementation of pharmacogenomic screening that can be applied in clinical use for the prevention of drug hypersensitivity. Despite strong HLA associations, positive predictive values (PPVs) remain relatively low and many other factors contribute to the development of disease and present opportunities for further research into mechanism and pathogenesis.
- SJS/TEN and other cutaneous reactions secondary to immune checkpoint inhibitors (ICI) of cytotoxic T-lymphocyte -- associated protein 4 and programmed cell death protein 1 (PD-1)/programmed cell death protein ligand 1 during treatment of cancer are increasing as use of these agents rises. The severity of adverse cutaneous reactions to immunotherapies correlates with improved cancer outcomes and survival suggesting that patients most likely to benefit are also those most likely to develop toxicity. This provides potentially important clues to the immunopathogenesis of these reactions and underscores the need to manage these toxicities so that patients can benefit from anticancer therapies. In addition, gene expression analyses have shown similarities between lichenoid rash associated with immune checkpoint inhibitors and SJS/TEN to non-cancer agents.
- In SJS/TEN there is currently much focus on effector memory $CD8^+$ T cell responses. However suppressor immune responses, such as those conferred by regulatory T cells, play a key role in the maintenance of immune homeostasis in the skin and are notably diminished early in the course of SJS/TEN. Augmenting regulatory immune responses might provide alternative or complementary treatment modalities for SJS/TEN.
- Blisters fluid cells from the skin lesions in SJS/TEN patients are characterized by the infiltration of $CD8^+$ T cells, NK cells and NKT cells. A public TCR$\alpha\beta$ clonotype has been found in blister fluid and peripheral blood mononuclear cells (PBMCs) from Taiwanese patients with HLA-B*15:02 restrictedcarbamazepine-SJS/TEN. Binding assays with this TCR recombinant protein support a P-I (pharmacological interaction with immune proteins) model for carbamazepine-SJS/TEN. The applicability of this model to other class I HLA restricted drug-induced SJS/TEN is currently being explored.
- Virtual modeling predicts that carbamazepine binds to HLA-B*15:02 at higher affinity in the absence of peptide and contacts both HLA and TCR.
- T cell, NK cell, and NKT cell derived granulysin is a key mediator of tissue damage and disease in SJS/TEN. Serum granulysin levels, as well as IL-15, may prove useful as prognostic markers during acute SJS/TEN. Targeting granulysin as well as pathogenic T cells may provide additional therapeutic interventional strategies to join other biologics such as anti-TNF (etanercept) therapy.
- In some patients, a generalized exanthema develops following antibiotic treatment for gastrointestinal infection. It is hypothesized that risk for cutaneous

ADRs may be influenced by the gut microbiome or potentially other bacterial pathogens.

Understanding the immunopathogenesis of SJS/TEN is central to the development of pre-therapy screening strategies and effective SJS/TEN treatment regimens. Critical to this is deciphering and linking the influences of host genetics and structural, biochemical, and functional interactions between drugs and/or pathogens and the immune system. Session five of *SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation* reviewed seminal advances in our understanding of the pharmacogenomics and immunology of SJS/TEN and other T-cell mediated severe adverse drug reactions and ongoing basic and translational science research in this field.

SJS/TEN is an IM-ADR influenced by genes that affect pharmacokinetics, pharmacodynamics, and immune responses. Additional influences include comorbid disease, such as renal impairment and external factors such as environmental exposures and viral infection.(157) Class I associations that have also provided key insights to IM-ADR pathogenesis include carbamazepine and HLA-B*15:02 in SJS/TEN and allopurinol and HLA-B*58:01 in severe cutaneous adverse reactions (SCAR).(158–160) Many other HLA associations with drugs that cause SCAR including SJS/TEN are documented and incidence varies across ADR phenotypes and across populations, reflecting risk allele carriage (Figure 7). However, for most drugs that are implicated in SJS/TEN there remains no known HLA association, and for up to 20% of SJS/TEN cases no causative drug is identified.

Carriage of a given risk HLA allele is permissive but insufficient for development of drug hypersensitivity as evidenced by the small percentage of individuals carrying the risk alleles that develop an adverse drug reaction when exposed to drug (Table 3). Identifying additional factors that contribute to development of ADRs will be important in understanding mechanisms of pathogenesis and also help guide pharmacogenomic screening in the future. Drug dose, metabolism, and clearance rate are known to be independent pharmacological factors in the development of SJS in some settings and may account for part of the PPV gap. For example, variants in the allele coding for the metabolic enzyme *CYP2C9*3* are significantly associated with phenytoin SCAR in Taiwan, Japan, Malaysia and Thailand.(161, 162) In addition to HLA and metabolic based genetic factors, potential roles for risk enhancing T-cell receptor (TCR) clonotypes, tissue specific memory T cells subsets, NK cells, and NKT cells are under investigation. Finally, the nature of HLA and peptide alterations following drug exposure as determined by genetic factors within the proteasome pathway and peptide processing machinery may potentially contribute to disease pathogenesis and are under study.

Studies showing a strong association between HLA class I alleles and drug-induced SJS/TEN disease support the concept that class I restricted antigen driven $CD8^+$ T cells are of fundamental importance in immunopathogenesis (Figure 8). Hung *et al.* have shown that cells recruited to the blisters in SJS/TEN are predominantly T cells, NK cells, and NKT cells, and that the percentage of each cell subset varies between patients (Table 4). Using blister fluid as a source of potentially pathogenic effector cells, T cells identified in blister fluid from individuals with SJS/TEN are characterized by one or a few dominant clonotypes,

defined as a population of $CD8^+$ T cells that express the same TCR sequence. These data, suggest the authors, indicate that T cells bearing this TCR are able to bind and be stimulated by peptides from the eliciting drug. These T cells also express granulysin and granzyme-B consistent with a cytotoxic T lymphocyte phenotype. Similar shared TCRs were not found in patients with allopurinol SCAR, although some evidence of clonal expansion within individual patients was seen in blister fluid.(163)

Surface plasmon resonance experiments have demonstrated that carbamazepine (and carbamazepine metabolites) are capable of binding directly to HLA-B*15:02 and residues important in the HLA-carbamazepine interaction have been mapped to the HLA peptide binding groove using site directed mutagenesis studies.(164, 165) Ostrov *et al.* and Illing *et al.* previously solved the crystal structure of abacavir bound to HLA-B*57:01 that defined the altered peptide repertoire model for drug-HLA interaction.(166, 167) More recent work by Ostrov *et al.* has focused on determining if known HLA and drug structures can be used to predict which drug will bind a particular HLA protein. Modeling algorithms of drug binding affinities predicted that abacavir would bind to HLA-B*57:01 with higher affinity in the presence of a self-peptide. This is consistent with known crystollagraphy data and represents proof-of-concept for this type of *in silico* approach to predicting drug-HLA interactions. Using this approach, carbamazepine binding was not predicted to bind a site within the antigen binding cleft (under the peptide, as abacavir interacted with the F pocket of HLA-B*57:01). Based on the crystal structures of HLA-B*15:02, TCR complexes with HLA-B molecules and atomic models of HLA-B*15:02 complexed with peptides corresponding to HLA-B*15:02 elution studies and TCRαβ sequences of the shared TCR discovered in Taiwanese patients mentioned above, carbamazepine was predicted to bind complexes of peptide and HLA-B*15:02 in a TCR contact site located at interface of the trimolecular HLA-B*15:02-peptide-TCR complex (D. Ostrov, PhD, unpublished data, March 2017).

Cytotoxic protein and cytokine mediators are important in SJS/TEN pathogenesis and have potentially important applications as diagnostic and predictive markers and therapeutic targets. Chung *et al.* discovered that the cytolytic protein granulysin, produced by $CD8^+$ T cells, NK cells and NKT cells is a primary mediator of keratinocyte cell death in SJS/TEN.(168) Granulysin is found at high concentration in serum and blister fluid from patients with SJS/TEN and plasma levels correlate with disease severity and prognosis.(168, 169) Chung *et al.* have developed a rapid immunochromographic test to measure blister fluid granulysin concentration and this assay measured over multiple time points appears to distinguish SJS/TEN and bullous fixed drug eruption from other blistering skin diseases such as bullous erythema multiforme, bullous pemphigus, and viral infection (Table 5).(169) His group has also identified that systemic IL-15, a cytokine that activates NK cells and cytotoxic T cells, is also correlated with SJS/TEN severity and both IL-15 and granulysin may be used as prognostic markers during acute SJS/TEN.(169)

Chung *et al.* have also conducted an open, prospective, randomized trial evaluating the efficacy of immunomodulatory therapies for the treatment of SJS/TEN. This study included 48 patients randomized to receive the TNFα inhibitor etanercept and 45 patients to receive corticosteroid therapy. This study demonstrated that etanercept reduced time to re-

epithelialization and reduced mortality. This work and other early studies suggest potential efficacy of etanercept as a therapeutic option for SJS/TEN and provide a mechanism to explain therapeutic responses with this drug.(108, 111, 170, 171) Future work that may translate into targeted therapy is focused on developing and testing novel inhibitors to pathogenic mediators in SJS/TEN including a monoclonal antibody targeting granulysin and a monoclonal antibody targeting the TCRαβ subunits to disrupt TCR signaling.(172, 173) Another insight into the immunopathogenesis of SJS/TEN has come from studies demonstrating that interaction of annexin A1 with the formyl peptide receptor 1, expressed on the surface of keratinocytes obtained from patients with SJS/TEN but not present on control keratinocytes, is a key mediator of keratinocyte necroptosis in SJS/TEN.(174)

More recently Abe *et al.* (R. Abe, MD, PhD, unpublished data, March 2017) have examined the role of the microbiome in the development of severe cutaneous ADRs. Using PBMC obtained from patients who developed a generalized exanthema within 1–3 days after completing treatment for gastrointestinal bacterial infection, they have shown that $CD4^+$ cells express the activation marker CD154 following exposure to whole, killed bacteria. Cell culture supernatants from these experiments contain elevated levels of inflammatory cytokines compared to cultures derived from PBMC obtained from normal donors. Abe *et al.* are investigating the hypothesis that treatment of bacterial gastrointestinal infection generates bacterial products that stimulate an immune response. This raises the interesting possibility that risk for cutaneous ADRs may be influence by the microbiome and in particular bacterial pathogens in the gut.

Severe cutaneous syndromes associated with novel cancer immunotherapeutics have provided significant insights into the potential immunopathogenesis of SJS/TEN. First approved for clinical use in 2011, the immune checkpoint inhibitors are a class of drugs that block inhibitory receptors such as PD-1 (nivolumab) and CTLA-4 (ipilimumab) on the surface of T cells promoting T-cell activation and effector functions.(175) This class of therapy has shown tremendous efficacy in the treatment of certain cancers including stage IV melanoma, lymphoma, and cancers of the head and neck, lung, bladder, and kidney. Cutaneous eruptions occur in approximately one-third of patients treated with checkpoint blockade (Table 6). Most often these eruptions are clinically benign, do not limit treatment and respond to topical corticosteroids. A small proportion of patients receiving checkpoint inhibitor blockade develop SJS/TEN.(176–178) Importantly, the severity of the cutaneous ADR related to checkpoint inhibitor therapy correlates with improved tumor response and patient survival.(179, 180) Similarities in gene expression profiling amongst the various phenotypes of cutaneous reactions associated with anti-PD1/PDL-1 therapy that resemble those associated with SJS/TEN suggest that PD-1 may be important in specifically regulating epidermal integrity.(181) Lacouture *et al.* have shown that serum IL-6 is elevated in patients with early maculopapular rash secondary to checkpoint inhibitor therapy. Further, they are investigating whether therapeutics that target T-cell activation pathways and inflammation, such as JAK kinase inhibitors and/or IL-6 inhibition, might provide benefit for treatment of checkpoint inhibitor blockade associated cutaneous reactions.

Another key in the immunopathogenesis of many immunologically-mediated diseases including SJS/TEN is thought to be an imbalance of effector/autoreactive and regulatory

immune responses. Extensive research supports the scientific premise that autoimmune disease reflects a disruption of this balance. Regulatory T cells (Tregs) are defined as $CD4^+$ T cells that express the transcription factor FoxP3 that drives the suppressor phenotype. Tissue resident Tregs are highly abundant in the skin and gut tissues of mice and humans. Individuals who lack functional Treg responses succumb at an early age to fulminant systemic autoimmune disease highlighting the critical role these cells play in immune regulation.(182, 183) Treg suppressor function is mediated via a variety of mechanisms including IL-10 secretion, surface expression of the inhibitory receptor CTLA-4, and through IL-2 consumption by the high affinity IL-2 receptor CD25. Rosenblum *et al.* have developed a murine model of cutaneous autoimmune disease that demonstrated that mice spontaneously suppress skin inflammatory responses over time despite ongoing antigen exposure but that depletion of Tregs in these mice leads to prolonged disease and death.(184) These data support a mechanistic role for Treg cells in maintaining immune homeostasis in the skin. Further, it has been shown that 1) Tregs are less abundant in skin from patients with SJS/TEN compared to erythema multiforme,(185) 2) that circulating Tregs obtained from patients with SJS/TEN display impaired suppressor function,(186) 3) that Tregs can prevent epidermal injury in animal TEN model systems,(187) and 4) that Treg-mediated suppression decreases cytotoxic T-cell responses to drug in *in vitro* systems.(188) Data from human trials have shown that therapies that augment Treg function (including adoptive transfer of expanded autologous Tregs and low-dose systemic IL-2) ameliorate alopecia areata, chronic graft-versus-host disease, and systemic lupus erythematosus.(189–192) As noted above, immunohistochemistry experiments have shown that Tregs are present at significantly reduced numbers in skin from patients with SJS/TEN compared to EMM and this can be used to differentiate these two disease phenotypes.(185) The use of strategies to boost regulatory immune responses in acute SJS/TEN is intriguing and warrants further study.

Discussion and Future Directions

SJS/TEN is a life-threatening disease that in adults is usually drug related and in children in particular, both SJS/TEN and its mimickers (Table 1) can create unique diagnostic challenges in the absence of an apparent causative agent. The low incidence of SJS/TEN of 1–5/1,000,000 and high mortality rate have highlighted the need for research and clinical networks to drive research, translation, consensus guidelines, and evidence-based approaches. This one-day meeting highlighted that there has been significant progress to strengthen SJS/TEN research efforts over the last decade. Harnessing strengths and opportunities and proactively addressing weaknesses and threats will be crucial to these research efforts moving forward (Figure 9). Key strengths have included the establishment of epidemiological and pharmacogenomic networks, the ability to use informatics tools to find SJS/TEN cases in the electronic health record, and access to genetic tools to analyze the data. With these research strengths has come the opportunity to establish and access DNA and cellular biobanks to facilitate further genetic and mechanistic discovery science. The pre-existing networks also create a unique platform for establishment of larger multidisciplinary networks where clinical protocols can be harmonized and therapeutic approaches studied. Addressing weaknesses and threats will be equally important. Lack of

evidence-based treatment guidelines and consensus on standardized clinical care has been a hurdle to the creation of very large global networks to study treatment interventions. In addition, many studies have been strictly epidemiologically based and have not had the resources or infrastructure to collect and cryopreserve valuable research samples. Ultimately creative strategies will be needed to maximize and coordinate research efforts and may require creative funding mechanisms from multiple governments and other sources. It is also predicted that the patient-centered integrated -omics approaches that are part of the personalized medicine of the future will be key to not only understanding the mechanistic basis of SJS/TEN but also furthering preventive efforts and facilitating earlier diagnosis and treatment (Figure 10).

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Acronyms and abbreviations

AGEP	acute generalized exanthematous pustulosis
ALDEN	Algorithm for assessment of drug causality in epidermal necrolysis
AMT	Amniotic membrane transplantation
ARIA	Active Risk Identification and Analysis
BSA	Body surface area
CPIC	Clinical Pharmacogenetics Implementation Consortium
CPNDS	Canadian Pharmacogenomics Network for Drug Safety
DHCPL	Dear Health Care Professional Letter
DPV	Division of Pharmacovigilance
DRESS	Drug reaction and eosinophilia and systemic symptoms
DSC	Drug Safety Communication
DQLI	Dermatology quality of life index
EMM	Erythema multiforme majus
EHR	Electronic Health Records

ERAP	endoplasmic reticulum aminopeptidase
FAERS	FDA Adverse Event Reporting System
GBFDE	Generalized bullous fixed drug eruption
GWAS	Genome Wide Association Study
HAS	Health Sciences Authority
HCP	Health Care Professional
ICI	Immune checkpoint inhibitors
IM-ADR	Immunologically-mediated adverse drug reactions
iSAEC	International Serious Adverse Event Consortium
ITCH	International Consortium on Drug Hypersensitivity
IVIG	Intravenous immunoglobulin
J-SCAR	Japanese Research Committee on Severe Cutaneous Adverse Reactions
MIRM	Mycoplasma induced rash and mucositis
NATIENS	North American Therapeutics in Epidermal Necrolysis Syndrome
NCAT	National Center for Advancing Translational Sciences
NEISS-CADES	National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance
NHGRI	National Human Genome Research Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis, Musculoskeletal and Skin Diseases
NICE	National Institutes for Health and Care Excellence
NIDA	National Institute on Drug Abuse
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NSAIDS	Non-steroidal anti-inflammatory drugs
PBMCs	peripheral blood mononuclear cells
PMC	post-marketing commitments
PMR	post-marketing requirements

PMTCT	prevention of mother-to-child HIV transmission
PPV	positive predictive value
PTSD	Post-traumatic stress disorder
REMS	risk evaluation and mitigation strategies
SCAR	Severe cutaneous adverse reaction
SJS/TEN	Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis
SDH	Society of Dermatology Hospitalists
SCORTEN	Severity of illness score for TEN
SEAPHARM	Southeast Asian Pharmacogenomic Network (SEAPHARM)
TCR	T-cell receptor
TEN	Toxic Epidermal Necrolysis
TNF	Tumor Necrosis Factor

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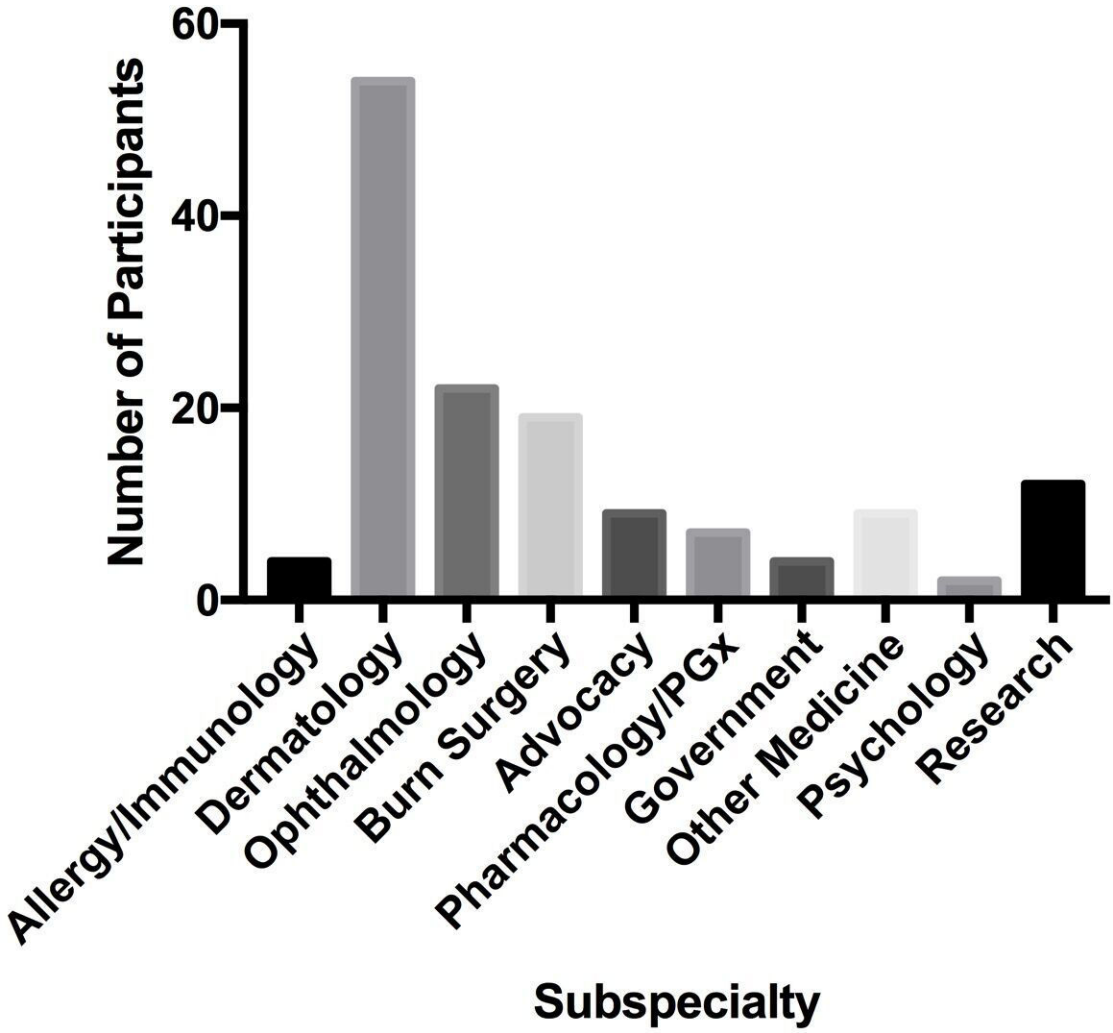
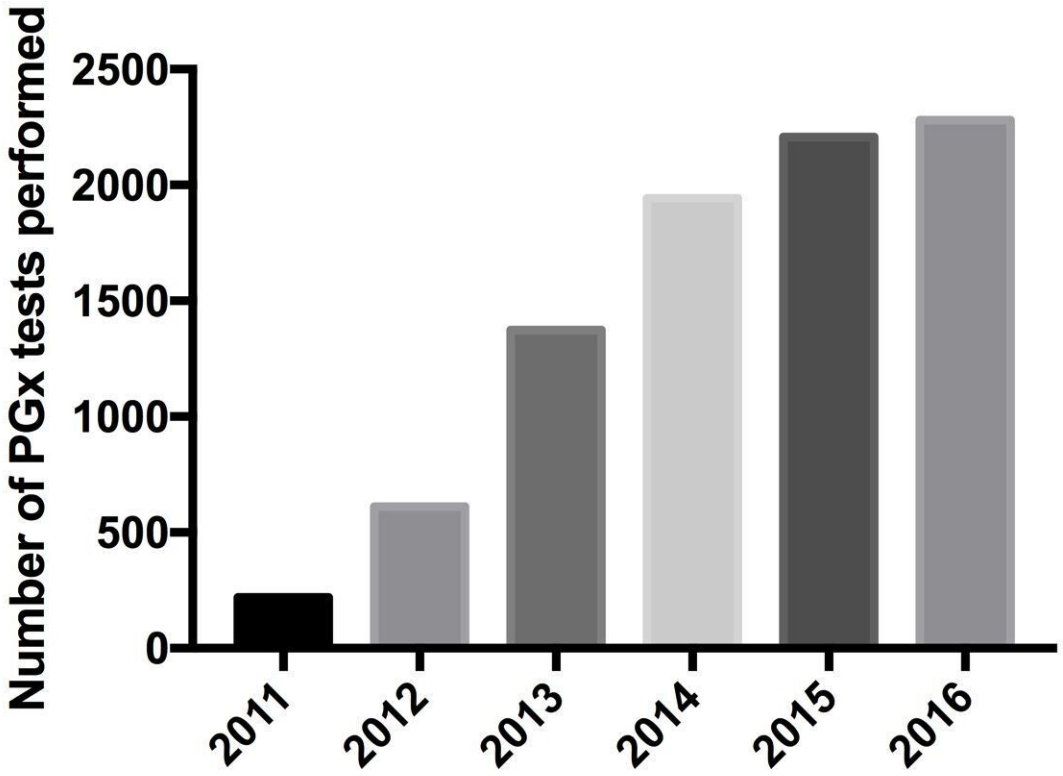
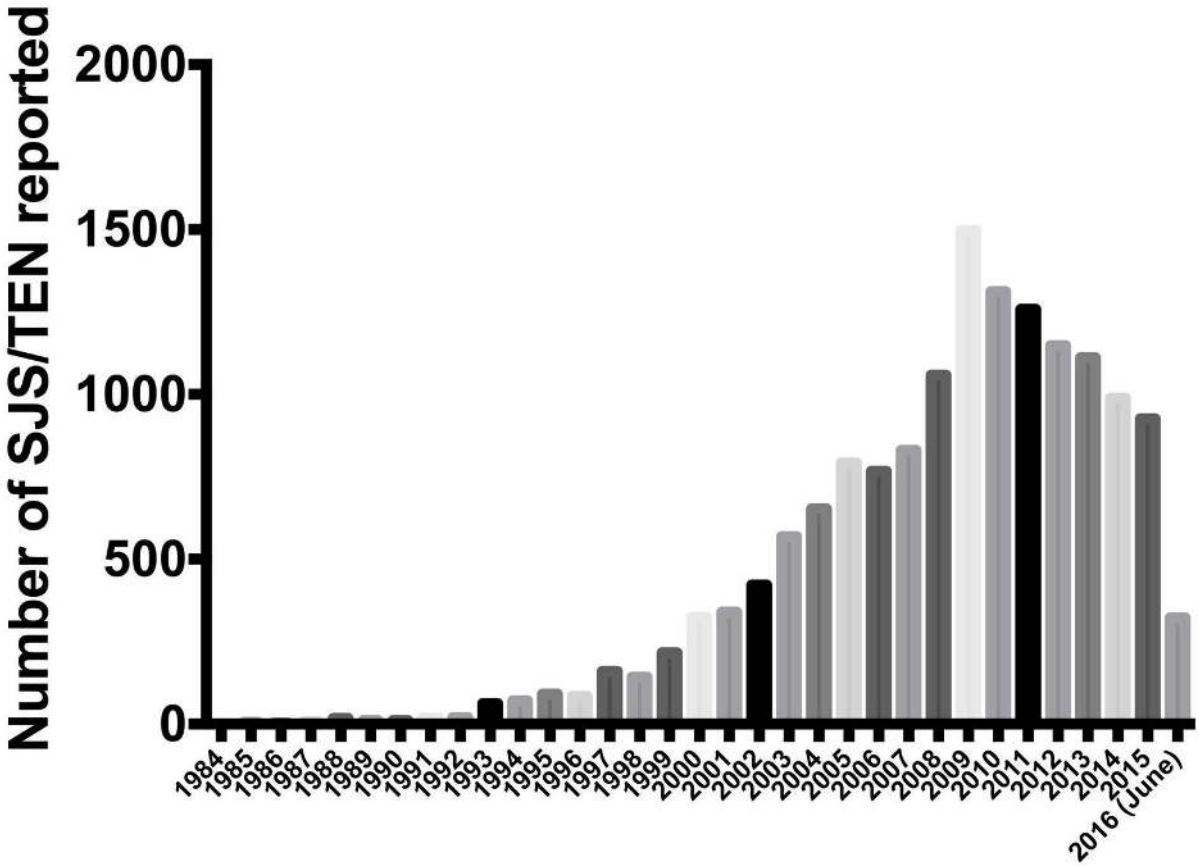


Figure 1. Distribution of participants at SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation

Participants representing 14 countries from six medical subspecialties, SJS/TEN advocacy groups, the US government, and the SJS/TEN research community gathered in Orlando, Florida, on March 2, 2017, for the inaugural *SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation meeting*. Thirty pre- and post-doctoral trainees attended and presented original research at this meeting.





	Carbamazepine and HLA-B*15:02	Allopurinol and HLA-B*58:01
Subsidy for genotyping	75% (for subsidized class of patients)	Not available
Drug label update	Genotyping is highly recommended	Pharmacogenomic association is reported
Genotyping facilities	Laboratories with validated assays identified and cost and turn-around times shared with healthcare professionals	
Outcome	1 case of carbamazepine-SJS/TEN in genotyped patients in 4 years following implementation of pre-prescription screening Compared to 18 per year prior to 2013 implementation ~1000 cases typed per year	Annual number of SCAR cases unchanged (1 year data)

Figure 2. Pharmacogenomic testing to prevent SJS/TEN in Thailand and Singapore

A. Thai Vigibase and implementation. A. Following the incorporation of pharmacogenomics testing at Ramathibodi Hospital in Bangkok, Thailand, the number of pharmacogenomics tests performed rose from <500 in 2011 to >2,000 in 2015. Concurrently, with financial reimbursement supplied by the Thai universal health coverage scheme from 2014 onward, the number of reported cases of SJS/TEN collected through Thai-Vigibase fell demonstrating the efficacy of genetic testing to prevent SJS/TEN in this population. **B. Pharmacovigilance in Singapore.** Carbamazepine and allopurinol are two of

the most common causes of SCAR in Singapore and the risk alleles associated with carbamazepine- and allopurinol-SCAR (HLA-B*15:02 and HLA-B*58:01, respectively) occur at high frequency in the Singapore population. In 2013, the primary regulatory body in Singapore, the Health Sciences Authority (HSA), in conjunction with the Ministry of Health recommended HLA-B*15:02 genotyping prior to initiation of carbamazepine as standard of care for new patients of Asian ancestry. Following this recommendation, only 1 case of carbamazepine-associated SJS/TEN in 4 years has been reported, a marked reduction in incidence from the pre-testing baseline of ~18 cases per year. For allopurinol, due to the low (2%) PPV of HLA-B*58:01 testing and lower efficacy or higher cost of alternative medications, genotyping was not recommended for routine standard of care for chronic gout patients initiating drug therapy, although testing facilities were identified so that physicians have the option to conduct genotyping for high-risk patients such as those with renal impairment.

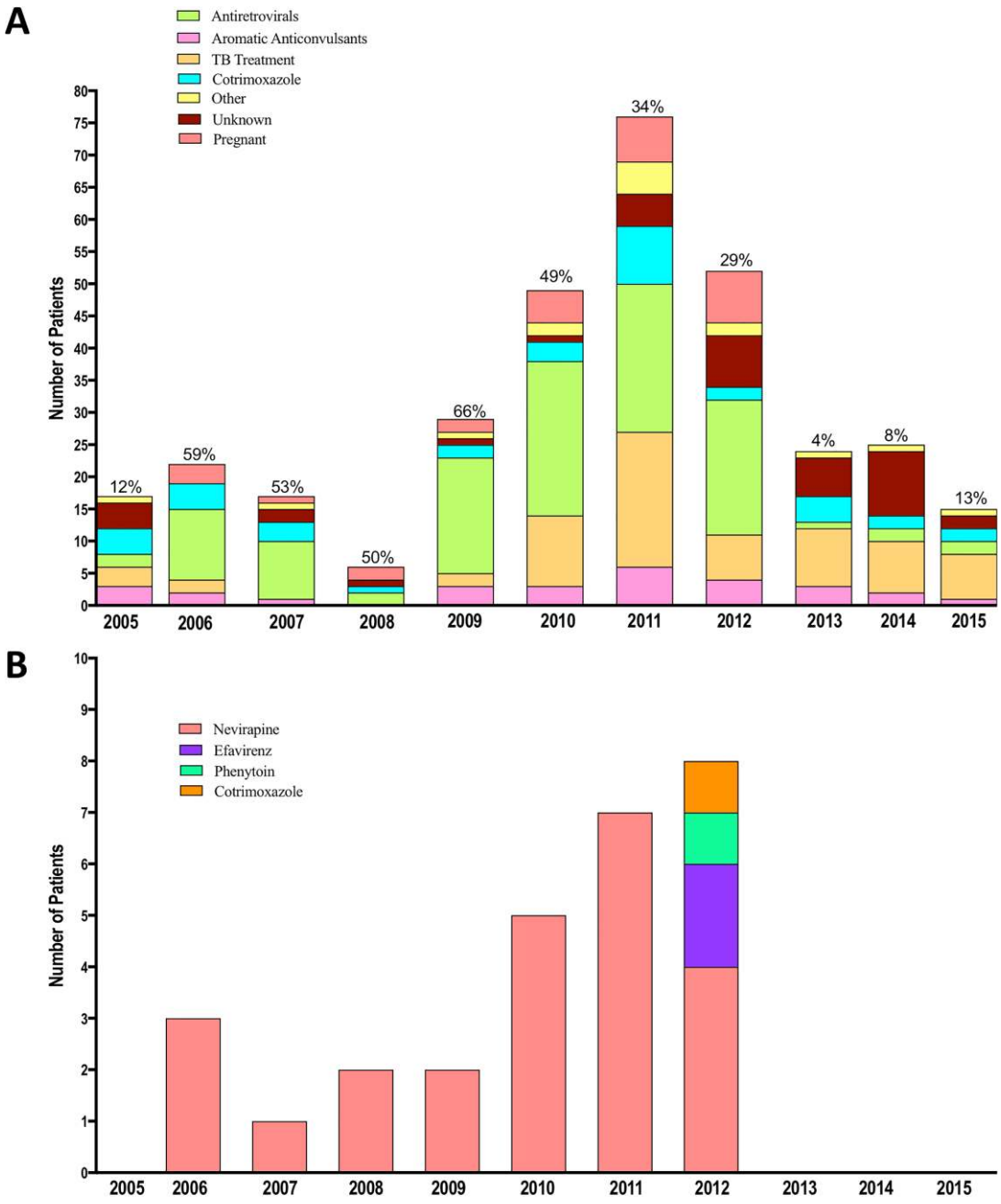


Figure 3. Epidemiology of SJS/TEN in special populations

A. All cases of SJS/TEN seen at Groote Schuur Hospital in South Africa between 2005 and 2015 showing the proportion of offending drugs. The proportion attributable to nevirapine for that year is shown as a percentage. **B.** All cases of pregnant women with SJS/TEN seen at Groote Schuur Hospital between 2005 and 2015 showing the proportion of offending drugs.

Figure 4a: Multidisciplinary approach to management of acute SJS/TEN

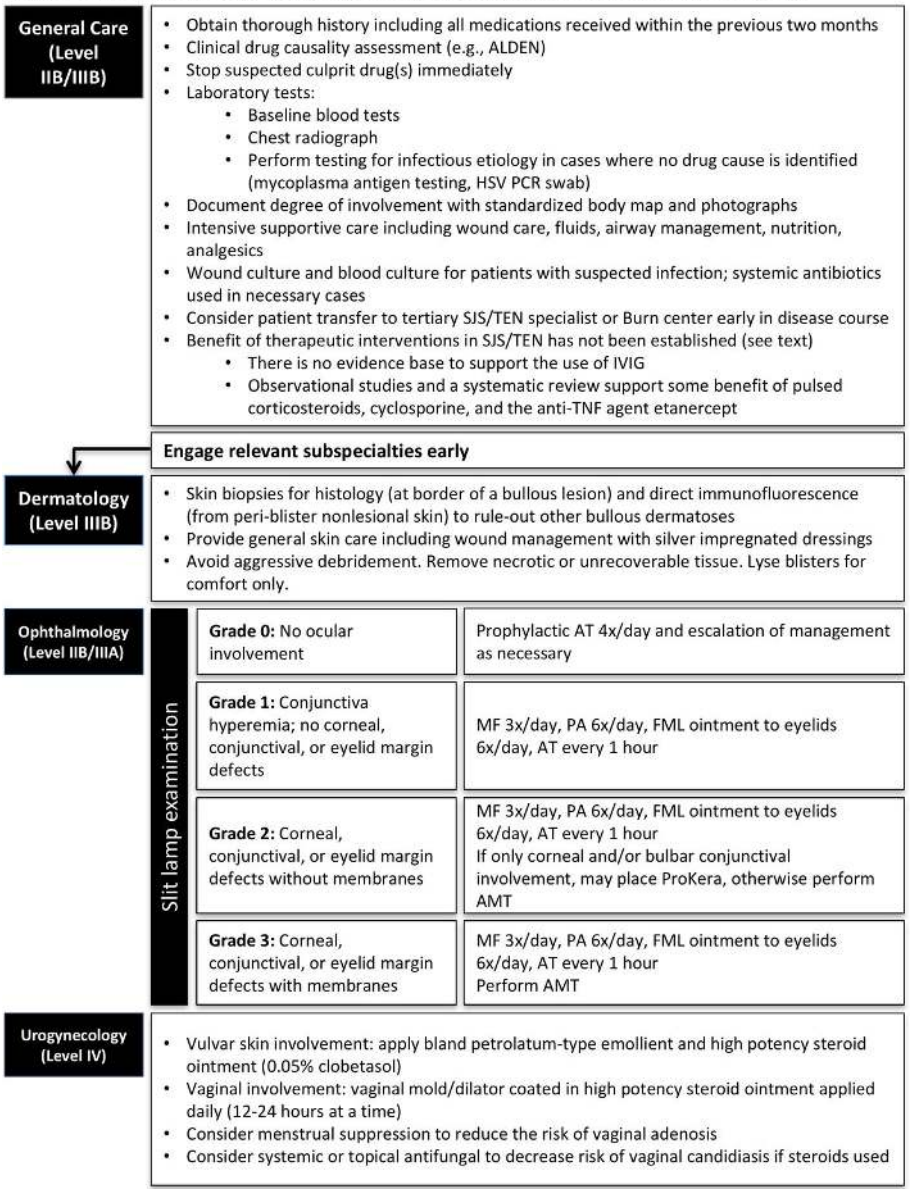


Figure 4b: Multidisciplinary approach to management of recovery SJS/TEN (Level V Evidence)

	Early Recovery (<6 months)	Late Recovery (6-12 months)	Lifelong
General Care	• Connect with SJS Foundation • MedicAlert Bracelet	• Address ongoing patient needs and concerns as they arise	
Dermatology	• General skin care including emollients for previously involved skin	• Scar care and revision as needed • Treat mottling or dyspigmentation in cosmetically-sensitive areas	
Ophthalmology	• Continue topical steroids for several months with slow taper • Monitor intraocular pressure frequently • Tailor interventions to individual case	• Regular, lifelong follow-up is required for SJS/TEN survivors	
Gynecology Urology	• Follow-up exam within 3 months • If vaginal mucosa involved, continue dilator daily for 2 weeks and then at least twice weekly for 2-3 months • Switch to estrogen cream for vaginal mucosa for use with the dilator • Calcineurin inhibitor for ongoing inflammation of penile skin	• Ongoing follow-up for urological, gynecologic, and/or obstetric complications	
Psychiatry	• Evaluate for psychological sequelae of SJS/TEN including depression, anxiety, post-traumatic stress disorder and fear of taking medications • Offer individual and group support resources		
Other	• Respirology: Consider pulmonary function testing as a baseline within the first 6 months after discharge for those with lung involvement. Ongoing pulmonary rehabilitation may be required depending on severity of involvement. • Gastroenterology: Follow-up dictated by gastrointestinal involvement (e.g., esophageal stricture, GERD, resolved GI bleed)		
Future	• Consider *ex vivo* (peripheral blood ELIspot, flow cytometry) and *in vivo* (patch testing) drug causality assessments • Genetic testing for known risk alleles in patient and family • Expert guidance on safe medications for patient and family		

Figure 4. Suggested multidisciplinary approach to management of acute and recovery phase SJS/TEN

Key points highlighted include the necessity to 1) recognize and stop the offending medication quickly, 2) provide care for SJS/TEN in a tertiary critical care center (most often a Burn Center), 3) consider all organ systems involved in SJS/TEN and consult relevant subspecialists early in the disease course, and 4) provide post-hospital and long-term follow-up for patients to management complications of SJS/TEN. AT: artificial tears; MF: moxifloxacin 0.5% ophthalmic solution; PA: prednisolone acetate 1% ophthalmic solution; FML: fluorometholone 0.1% ophthalmic ointment; AMT: amniotic membrane transplant.

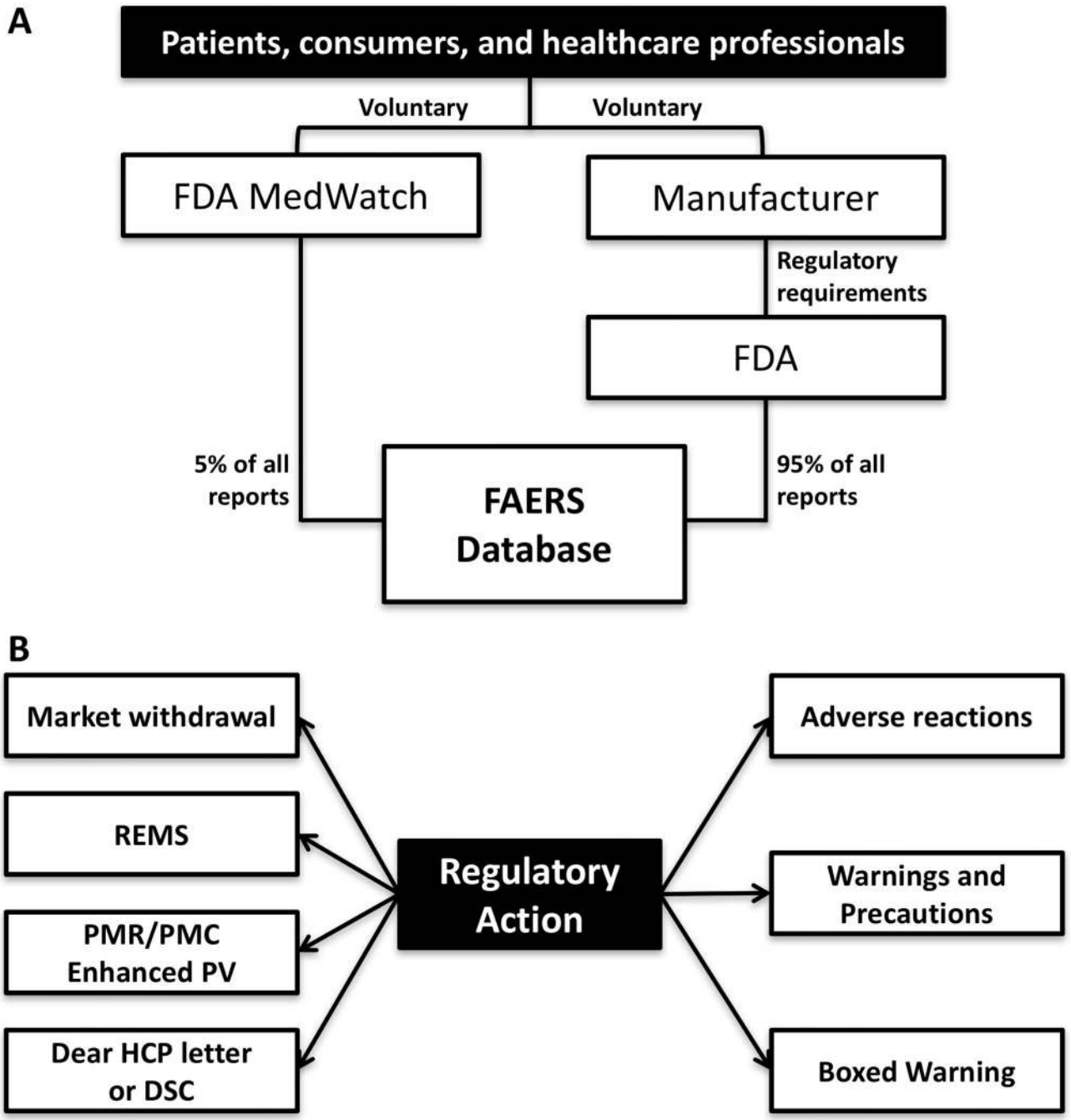


Figure 5. Regulatory mechanisms in the United States

A. The FDA Adverse Event Reporting System (FAERS) is a spontaneous adverse event reporting database that is the primary tool used for the detection of safety signals by the FDA. Reports are generated on a voluntary basis by patients, consumers, and healthcare provider. Reports may be submitted to FAERS either directly by the consumer through the FDA MedWatch event reporting system or by drug manufacturers as determined by regulatory requirements. **B.** When a safety signal is identified there are a number of possible regulatory actions that may be issued by the FDA. Regulatory actions highlighted in blue

represent options for drug label modifications to reflect the adverse event. Drug-associated SJS/TEN is most often reported in the *Warnings and Precautions* section but may also appear as a *Boxed Warning* or in the *Post-Marketing Experience* section of the drug label. Other potential regulatory actions are highlighted in green. These include 1) manufacturer issuance of a Dear Healthcare Professional (HCP) letter or a Drug Safety Communication (DSC), 2) use of post-marketing requirements (PMR) or post-marketing commitments (PMC) to further evaluate the event, 3) use of risk evaluation and mitigation strategies (REMS) to manage risk while enabling continued access to the drug, and 4) drug withdrawal. PV: pharmacovigilance.

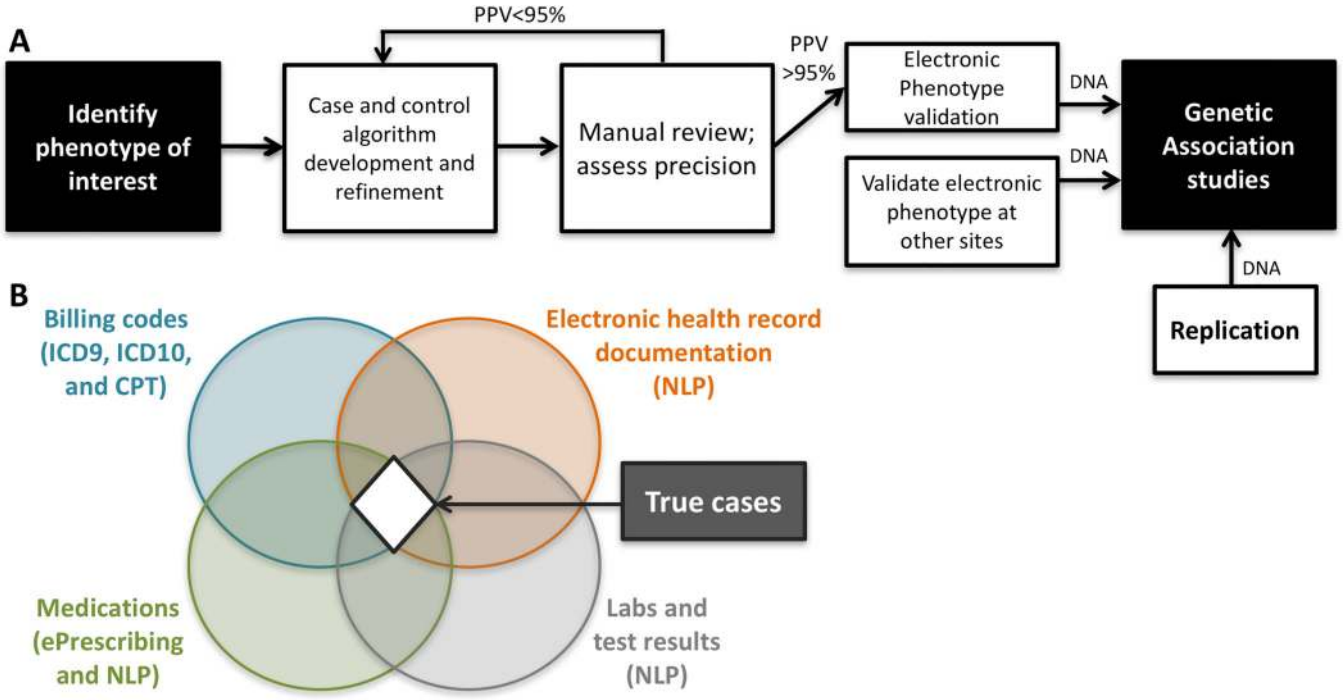


Figure 6. Use of electronic health data to identify rare disease cases and for the discovery of genetic associations

A. For a phenotype of interest, an iterative algorithm incorporating multiple aspects of patient data is developed and validated to identify cases in the medical record. The predictive algorithm is deployed at the test site and replicated across additional sites. Identification of allelic variants associated with the phenotype of interest is achieved using genetic analysis of biobanked DNA linked to the research EHR. **B.** A predictive algorithm with high positive predictive value (PPV) relies on the incorporation of multiple forms of patient data including billing codes, medication history, clinic notes, and lab and test results. NLP: natural language processing.

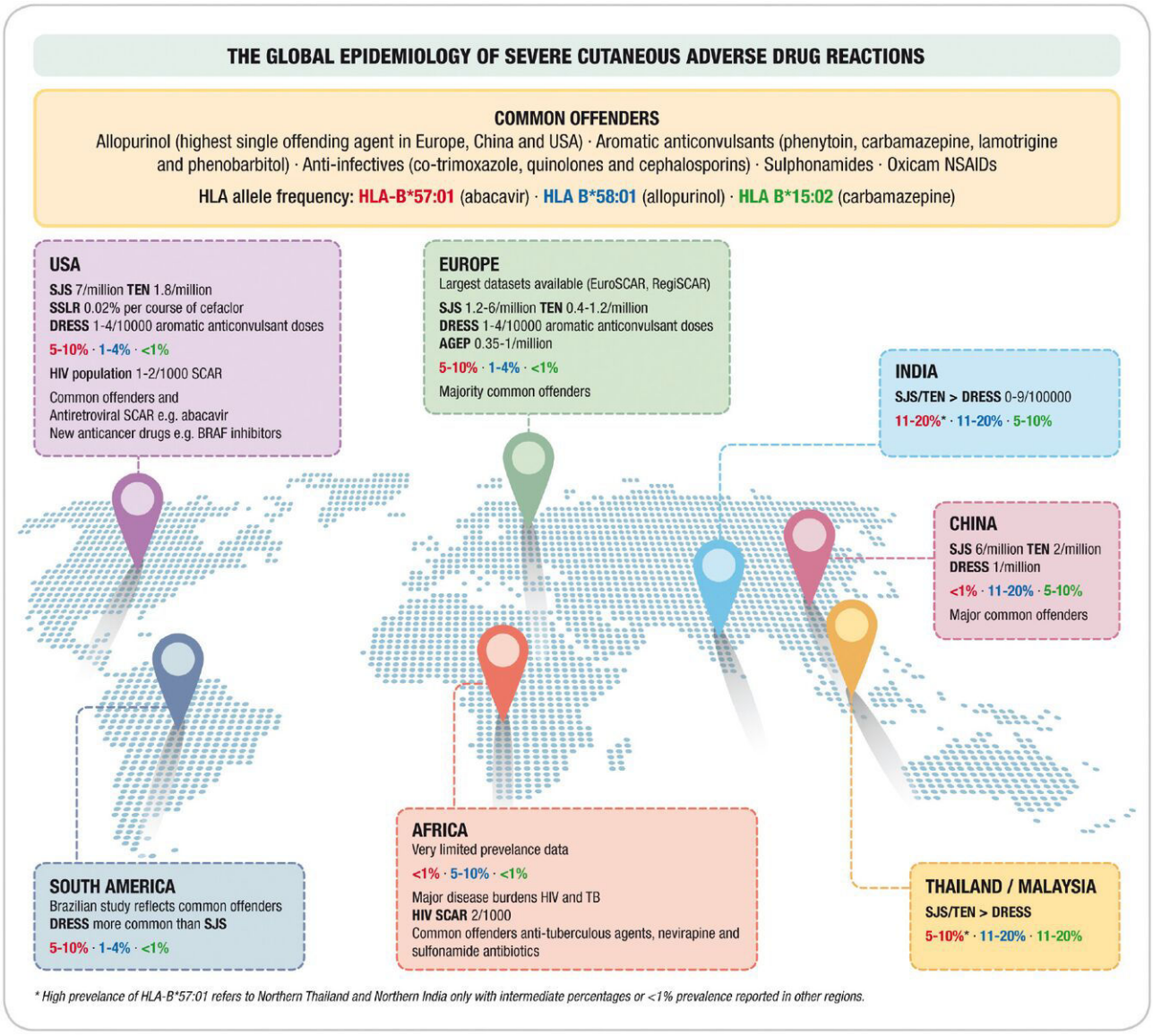


Figure 7. Worldwide risk HLA allele and IM-ADR frequencies

Global epidemiology of SJS/TEN and frequency of known risk HLA alleles. Incidence of SJS/TEN and other SCAR are represented for populations around the globe. Known common HLA risk allele frequencies are shown and color-coded to match the associated drug. NSAIDs: nonsteroidal anti-inflammatory drugs; SSLR: serum-sickness like reaction; DRESS: drug reaction with eosinophilia and systemic symptoms; AGEP: acute generalized exanthematous pustulosis. Reproduced with permission from Peter *et al.*(205)

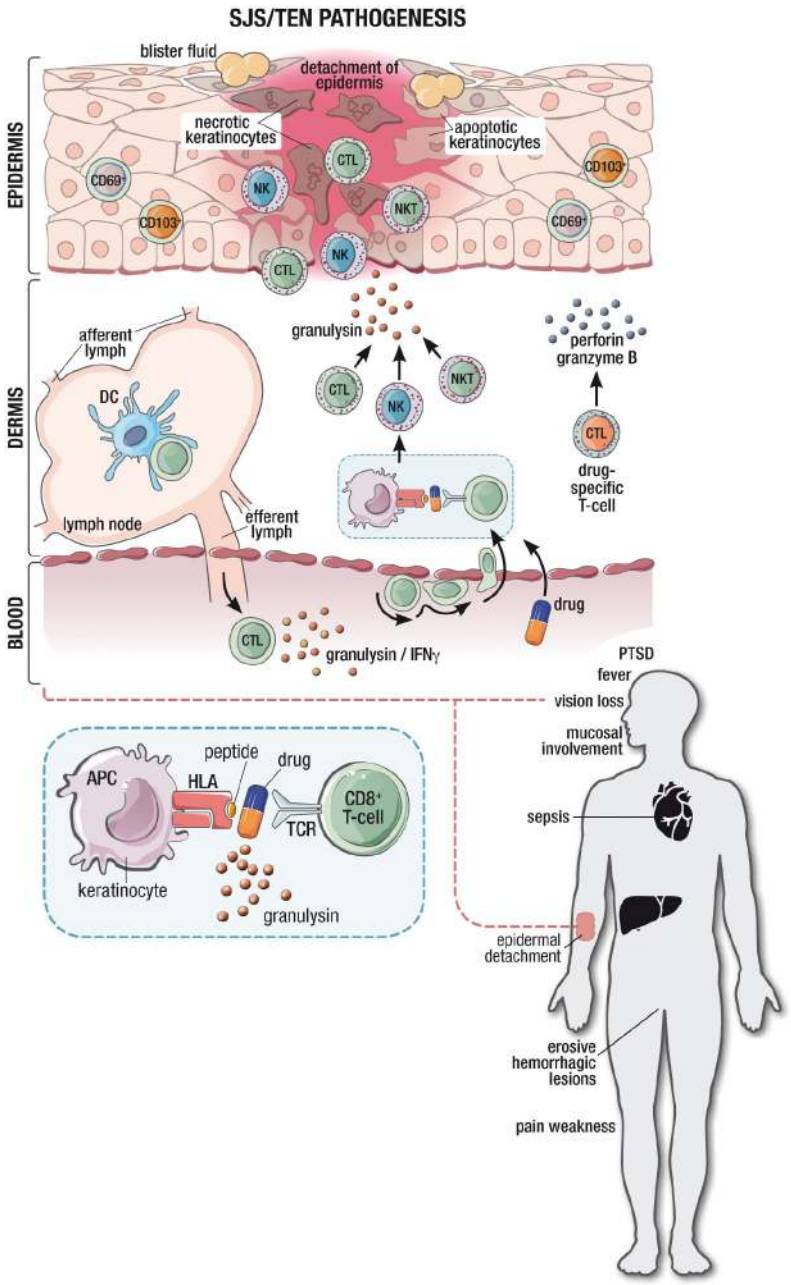


Figure 8. Proposed model of SJS/TEN immunopathogenesis

SJS/TEN affects the epidermis following interaction of pathogenic immune effector cells with drug-modified epitopes presented by HLA on the surface of keratinocytes. Cytotoxic CD8+ T cells, NK cells, and NKT cells that recognize HLA-drug epitopes produce cytolytic proteins such as granulysin and other mediators of inflammation. The result is widespread keratinocyte death, the formation of fluid-filled bullae containing immune cells, and, ultimately, epidermal necrosis and sloughing.

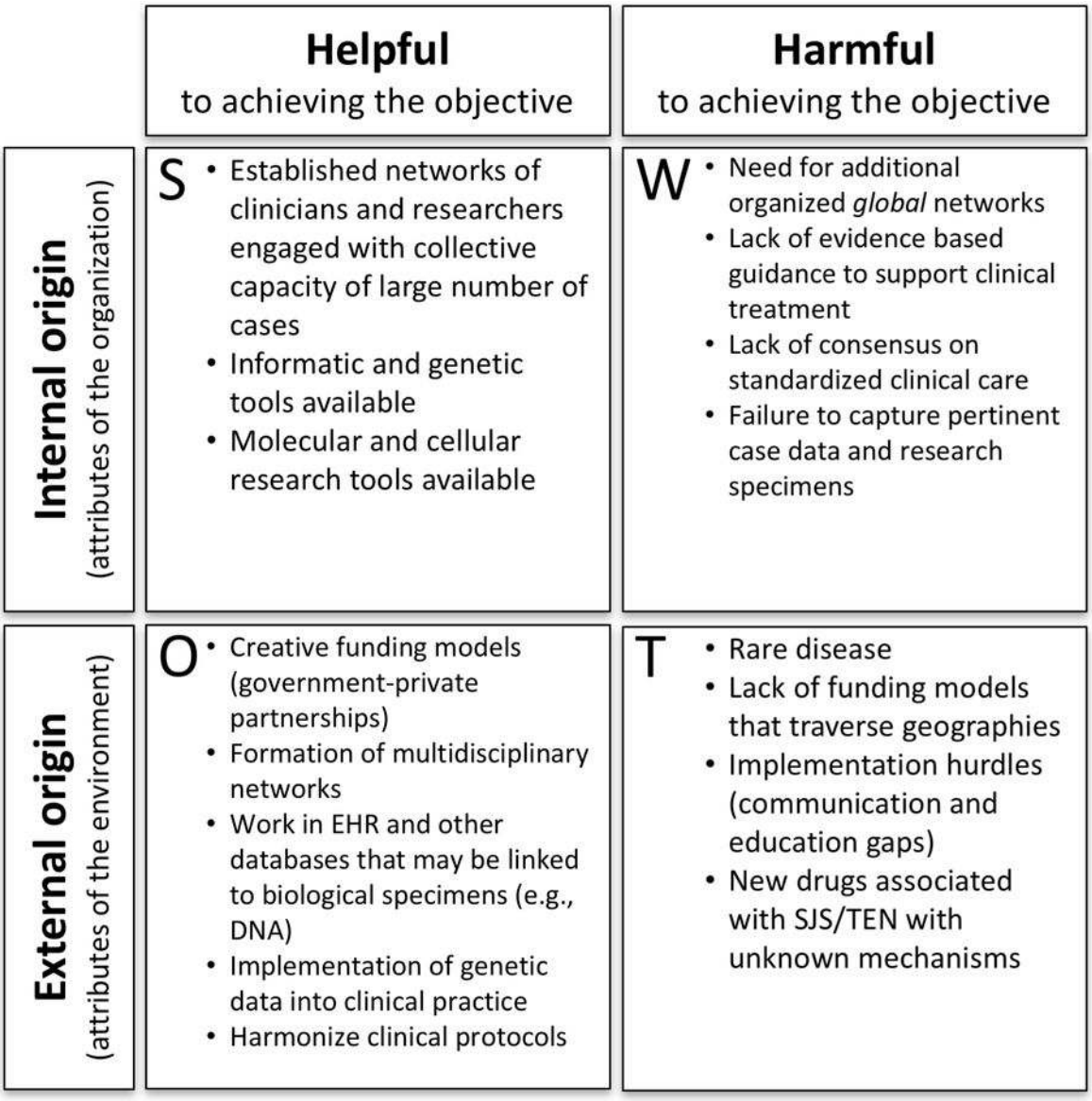


Figure 9. Strengths, Weaknesses, Opportunities, and Threats analysis for SJS/TEN clinical management and research

Participants at SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation contributed to a SWOT analysis to define unmet needs in SJS/TEN clinical care and research and to identify approaches to address these needs.

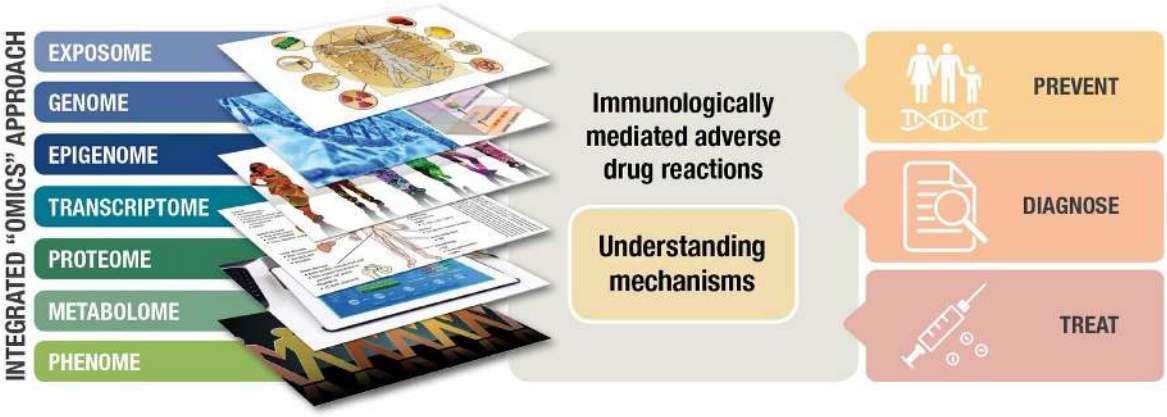


Figure 10. Integrated –omics approaches as part of personalized medicine in SJS/TEN

There exist multiple opportunities to apply personalized medicine approaches for the prevention and treatment of SJS/TEN. Part of these approaches will include integrated –omics platforms that link genetic, immunologic, ecologic, and other data within an individual patient to estimate risk of disease, facilitate precise and rapid diagnosis, inform prognosis and response to therapy, and predict which medications are safe for future use. Aggregation of these data may allow us to define the general principals of immunopathogenesis and genetics that may be applied more broadly to larger populations.

Figure 11. TO INCLUDE IN PATIENT PERSPECTIVES BOX (permission obtained from all participants to include photos)

Photo 1: Julie McCawley

Photo 2: Katie Neimeyer with SJS/TEN survivor and PGA champion Gene Sauers

Photo 3: Angela Anderson

Table 1

Phenotypic characteristics of SJS/TEN and severe cutaneous syndromes.

	SJS/TEN	Erythema multiforme majus	Generalized bullous fixed drug eruption
Target lesions	Flat, atypical target lesions present	Typical or raised atypical target lesions	No
Blisters and erosions	Yes <10%: SJS; 10–30%: SJS/TEN overlap; >30%: TEN	Yes, in the center of targets	Yes
Distribution	Widespread	Mainly limbs or acral	Localized
Well demarcated, erythematous patches (≥5 cm)	No	No	Yes
Erosions of mucosa (eye/lip/genital)	Yes	Yes	Yes or no
Recurrent history	Rare	Occasional	Common
Prognosis	Mortality depends on risk factors (SCORTEN(5))	Favorable	Generally favorable butassociated with higher morality with >20% BSA involvement and in elderly
Etiology	Usually drug-induced	Suspected infection not drug	Usually drug-induced

Severity of illness score for TEN (SCORTEN) – Age <40 years (0), > 40 years +1; Associated malignancy – no (0), yes (+1); Heart rate (beats per min) - <120 (0), >120 (+1); serum BUN (mg/dl) - <28 (0), >28 (+1); detached or compromised body surface - <10% (0), >10% (+1); Serum bicarbonate (mEq/L) - >20 (0), <20 (+1); Serum glucose (mg/dL) - <252 (0), >252 (+1).

Table 2

The algorithm of drug causality for epidermal necrolysis (ALDEN) score

Criterion	Values	Rules to apply	Score
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 index day	
		In case of previous reaction to the same drug, only changes for: Suggestive: +3: from 2 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 fine 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 the 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]	

Criterion	Values	Rules to apply	Score
	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 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 in 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.

This table is reprinted with permission from Sassolas *et al.* (74) The legend has been modified from the original text.

[a]Drug (or active metabolite) elimination half-life from serum and/or tissues (according to pharmacology textbooks and in reference (74)), 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 (anatomical therapeutic chemical) code up to the fourth level (chemical subgroups, http://www.whocc.no/atcddd); see reference (74) for methods.

[d]See Mockenhaupt *et al.* (15) for definitions of "high risk", "lower risk", and "no evidence of association". "High risk" drugs include sulfamethoxazole-trimethoprim, sulfonamide anti-infectives, allopurinol, carbamazepine, phenytoin, phenobarbital, oxicam-NSAIDs. "Lower risk" drugs include acetic acid NSAIDs, macrolides, quinolones, cephalosporins, tetracyclines, aminopenicillins. Drugs with "no evidence of association" with SJS/TEN include beta blockers, ACE inhibitors, calcium channel blockers, thiazide diuretics, furosemide, propionic acid NSAIDs, sulfonylurea antidiabetics, insulin.

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Table 3

Adverse drug reactions with well-defined HLA associations.

Drug ADR	HLA Allele	Allele Frequency and Carriage Rate[#]	Disease Prevalence	OR	NPV	PPV	NNT to prevent "1"	HLA screening
Abacavir Hypersensitivity Syndrome(22, 56– 59)	B *57:01	*Allele frequency (%):* 1.6–7.1 European Caucasoid <3 Sub-Sahara African <3 SoutheastAsian 0.3–2.4 African American 1–4 Thai *Carriage rate (%):* 1.4–11.2 European Caucasoid[#] <1 Sub-Sahara African 0–2 Southeast Asian 0–2 African American	8% (3% true HSR and 2–7% false positive diagnosis	960	100% for patch test confirmed	55%	13	Yes
Allopurinol SJS/TEN and DRESS/ DIHS(20, 22, 23, 159, 193, 194)	B *58:01	*Allele frequency (%):* 0.5–6 European Caucasoid 2–8 Sub-Sahara African 0.5–17 Southeast Asian 2.6–6.4 African American 6–8.4 Thai *Carriage rate (%):*	1/250–1/1000	580	100% (Han Chinese)	3% (Han Chinese) *	250	Not in wide use (see section IV.C.)

Drug ADR	HLA Allele	Allele Frequency and Carriage Rate[#]	Disease Prevalence	OR	NPV	PPV	NNT to prevent "1"	HLA screening
		0–6.7 European Caucasoid 5.5–14 Sub-Sahara African 2–22 Southeast Asian >5.3 African American						
Carbamazepine SJS/TEN(22, 158, 160, 195–197)	B *15:02	*Allele frequency (%):* <1 European Caucasoid <3 Sub-Sahara African 1–36 Southeast Asia <0.2 African American 8 Thai *Carriage Rate (%):* <1.2 European Caucasoid Up to 34 Southeast Asia	<1–6/1000	>1000	100% in Southeast Asian (with other B75 serotype)	2–8 *%	1000	Yes
Oxcarbazepine SJS/TEN(198)	B *15:02	*As above*		27.9	99.9% (Han Chinese)	0.73% (Han Chinese)		No
Carbamazepine DRESS/DIHS(199, 200)	A *31:01	*Allele frequency (%):*						
		1–6 European Caucasoid	0.05%	57.6	99.9%	0.89%	3,334	Not in wide use
		<2 Sub-Sahara African 0.5–6 Southeast Asian <1 African American 7–12% Japanese Up to 9.2% European Caucasoid[#] 5.5% Korean	0.05%	23	99.9%	0.59%	5,000	Not in wide use

Drug ADR	HLA Allele	Allele Frequency and Carriage Rate[#]	Disease Prevalence	OR	NPV	PPV	NNT to prevent "1"	HLA screening
		Carriage rate (%): Up to 6 European Caucasoid <1 Sub-Sahara African						
Dapsone DRESS/DHIS(201)	B*13:01	*Allele frequency (%):* <2 European Caucasoid 1–28 Southeast Asian 0 African American 28 Papuans/Australian Aboriginals 1.5 Japanese 2–4 Thai	1–4% (Han Chinese)	20	99.8%	7.8%	84	Not in wide use
		Carriage rate (%): Up to 3.8 European Caucasoid 2–52 Southeast Asian						
Flucloxacillin DILI (202)	B*57:01	*As above*	8.5/100 000	81	99.99%	0.12%	13819	No

[#]Allele frequencies and carriage rates were obtained from allelefrequencies.net. Allele frequency describes the total number of copies of the allele in the relevant population. Allele carriage rate refers to the percentage of individuals who have the allele in the population including both homozygous and heterozygous carriers. For carbamazepine-induced SJS/TEN and abacavir hypersensitivity, there is no current evidence to suggest a gene-dose effect (i.e., homo- or heterozygosity for an HLA risk allele) appear equally associated with risk of SJS/TEN

[*]Although NPV has been 100% for both HLA-B*15:02 and carbamazepine and HLA-B*58:01 and allopurinol SJS/TEN across Southeast Asian population there has been variability in PPV (2–8% for SE Asians for carbamazepine and 2% - allopurinol SJS/TEN in Singapore).

Table 4

Frequencies of immune subsets in blister fluid obtained from patients with acute SJS/TEN.

Surface CD expression	Case 1	Case 2	Case 3	Case 4	Case 5
CD3+	46%	70%	33%	68%	61%
CD4+	4%	0%	0%	9%	0%
CD8+	42%	70%	33%	59%	61%
CD20+	0%	0%	0%	0%	0%
CD56+	48%	70%	100%	100%	72%
CD3+, CD56- (T cells)	42%	30%	0%	0%	30%
CD3-, CD56+ (NK cells)	44%	30%	66%	32%	41%
CD3+, CD56+ (NKT cells)	4%	44%	33%	68%	31%
CD4+, CD56+	0%	0%	0%	9%	0%
CD8+, CD56+ (NKT cells)	4%	44%	33%	59%	31%

Hung *et al.*, unpublished data and reference (168).

Table 5

Rapid immunochromographic test for granulysin.

Syndrome	Blister fluid granulysin concentration
SJS/TEN	High: 100 ng/ml
Bullous fixed drug eruption	High: 100 ng/ml
Bullous erythema multiforme	Moderate: 50 ng/ml
Hand-foot-and-mouth disease bullae	Low: 10 – 20 ng/ml
Chemotherapy hemorrhagic bullae	Low: 10 – 20 ng/ml
Pemphigus	Negative (<5 ng/ml)
Bullous pemphigoid	Negative (< 5 ng/ml)
Acute generalized exanthematous pustulosis	Negative (< 5 ng/ml)

Chung *et al.*, unpublished data and references(168, 169)

Table 6

Cutaneous adverse events and SJS/TEN associated with immune checkpoint inhibitors

Drug name	Target	Indication	Severe rash (%)	SJS/TEN reported(203, 204)
Ipilimumab	CTLA-4	Melanoma	2.4	Yes
Nivolumab	PD-1	Melanoma, NSCLC, RCC, HL, HNSCC, UC, CRC	1.2	Yes
Ipilimumab+nivolumab	CTLA-4+ PD-1	Melanoma	5.0%	Yes
Pembrolizumab	PD-1	Melanoma, NSCLC, HNSCC, HL, dMMR tumors	1.7%	Yes
Atezolizumab	PD-L1	Bladder cancer, NSCLC	1.3%	No
Avelumab	PD-L1	Merkel cell carcinoma	0%	Yes

CTLA4 or CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-1, Programmed cell death protein 1; PD-L1, Programmed cell death protein ligand 1; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; HNSCC, head and neck squamous cell carcinoma; UC, urothelial carcinoma; HL, Hodgkin lymphoma; CRC, colorectal cancer; dMMR, defective mismatch repair