Research Directions in Genetically-Mediated Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis
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Recognizing recent breakthroughs in identifying genetic causes of SJS/TEN and the relative dearth of U.S. funded research in this area, the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) sponsored a workshop entitled, *"Research Directions in Genetically-Mediated Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN)."* The meeting was organized as a series of talks and discussions covering the state of the science, international experiences, challenges in case-findings and surveillance, and special topics. There were break-out sessions focused on gaps and opportunities in basic research, clinical implementation and pharmacosurveillance. The agenda, slides, and video are available at www.genome.gov/27560487.

Session 1: State of the Science
Welcome, Introduction and Goals
Teri Manolio of the National Human Genome Research Institute (NHGRI) welcomed participants. This workshop arose from discussions at the NHGRI Genomic Medicine VI: Global Leaders in Genomic Medicine meeting in January 2014 (www.genome.gov/27555775), where a novel method of screening and notifying at-risk participants in Thailand was discussed as a potential model for a global implementation effort. Subsequent discussion within NIH revealed only a handful of ongoing grants related to this condition despite considerable gaps in understanding. The workshop was initiated by ten participating NIH Institutes/Centers and the pharmacosurveillance group of the FDA with three objectives: to review the state of knowledge of surveillance, pathogenesis, and treatment of SJS/TEN; to examine the role of genomics and pharmacogenomics in the etiology, treatment, and eradication of preventable causes of drug-induced SJS/TEN; and to identify gaps, unmet needs, and priorities for research to eliminate genetically mediated SJS/TEN globally.

Clinical syndromes, epidemiology, genomics, diagnosis and treatment
Neil Shear from the University of Toronto reviewed clinical syndromes, epidemiology, genomics, diagnosis and treatment of SJS/TEN, including the high mortality and frequent severe sequelae. FDA guidelines recommend screening for human leukocyte antigen (HLA)-B*1502 for patients with ancestry in genetically at-risk populations prior to initiation of carbamazepine. Detection of a known HLA risk allele can support diagnosis, suggest the offending drug, and aid familial consultation; however, the majority of risk allele carriers do not have an adverse drug reaction (ADR) after drug exposure. Studying drug-tolerant risk allele carriers may provide important information about co-factors that moderate or mediate the impact of HLA alleles. The group discussed the histopathology of SJS/TEN, including how inflammatory markers evolve and how HLA and other metabolites contribute to reactions, and the need to understand why the disease shows specificity for stratified squamous epithelial cells or sun-exposed skin or at other times involves other organs (e.g. liver). Due to difficulty of diagnosis, identifying biomarkers in early stages of disease holds considerable value. Molecular characterization may inform diagnosis, prognosis and treatment. Questions were raised about the cost and turn-around-time for HLA allele testing. Further economic analysis needs to be done to evaluate large-scale testing. The role of SJS/TEN reactions in abandoning the development of promising drugs should also be considered.

Basic science of pathogenesis, functional genomics and mechanisms
Dr. Wen-Hung Chung from Chang Hung University and Memorial Hospital presented on pathogenesis, functional genomics and mechanisms in SJS/TEN. He reviewed multi-ethnic meta-analysis results for the association of HLA-B*1502 with carbamazepine-induced SJS/TEN and HLA-B*5801 with allopurinol-

induced adverse skin reactions. The frequency and severity of drug hypersensitivity is impacted by environmental factors, genetic factors and other host specific factors. Patients with renal dysfunction have higher mortality rates, particularly with allopurinol. Granulysin is expressed in SJS/TEN blister cells; animal models show granulysin binds to the epidermis and granulysin levels are higher in SJS/TEN cases compared to controls, suggesting its potential as an SJS/TEN biomarker. The group discussed detecting protective major histocompatibility complex (MHC) molecules, which could inform understanding of mechanisms underlying causality of disease. Protective HLA alleles may have a stronger metabolite affinity and do not need to bind directly to the drug. The rate of carbamazepine-induced SJS/TEN declined after routine HLA-B*1502 testing was mandated in Taiwan; however there was also a decrease in the years immediately prior to mandatory testing. As awareness of SJS/TEN increased alternate medications were more likely to be prescribed, often including phenytoin which also causes SJS/TEN in HLA-B*1502 carriers. A more comprehensive policy will be needed to fully combat SJS/TEN.

Defining and prioritizing unmet research needs for a rare but deadly disease
Elizabeth Phillips from Vanderbilt University discussed unmet research needs, including: defining the phenotype, improving pharmacosurveillance, acquiring appropriate tissue specific samples, understanding immunopathogenesis, improving management, and building a translational roadmap for prediction and prevention. HLA-B*5701 screening to prevent abacavir hypersensitivity provides a model for successful translation of a pharmacogenetic finding. The group discussed the need for better health care provider education. Suggestions included increased education in medical schools and residency programs and implementation of real-time education through decision support systems.

Discussion
SJS/TEN is a rare disease, which poses challenges in studies of screening and diagnosis. HLA risk alleles identified to date have large effect sizes, so they could be detected in small to moderate sized studies; larger studies will be needed for populations where effect sizes are not constant, and for identifying co-factors that modify or interact with risk alleles. Some SJS/TEN risk alleles are population specific while others are more generalizable. Massively parallel sequencing to define HLA types at the population level will be of potential value, as will adding this information to electronic health records (EHR) to facilitate association studies and clinical implementation, not only for SJS/TEN, but also for other diseases and health outcomes that show associations with HLA alleles. Patients might be willing to pay for testing out-of-pocket particularly if they're aware of risk in a family member. Better informatics, reporting and uptake strategies are needed to fully implement HLA testing.

Directions for mechanistic studies of SJS/TEN include looking for variants that drive immunodominance since alleles involved in hypersensitivity also seem to be involved in viral protection. Better *in vitro* tests are needed for risk assessment and drug development, and may include assessment of T-cell receptor (TCR) clonotypes. Researchers are also examining models to help elucidate the timing of disease, and to better understand the low positive predictive value across alleles. The possibility of shifting to new, safer drugs should also be explored, as should *in vitro* models to screen drugs in the pre-clinical phase.

<u>**Session 2: International Experience Part 1**</u>
Europe
Maja Mockenhaupt from the University of Freiburg gave an overview of RegiSCAR, an international scientific network focused on severe cutaneous adverse drug reactions (SCAR). RegiSCAR maintains an ongoing multinational registry of cases, including the collection of biological samples for genetic and mechanistic studies, and for studies examining SJS/TEN sequelae and the impact of treatments. She noted that patients with the highest incidence are 65 or older and have used certain drugs for 1-4 weeks continuously. RegiSCAR uses an algorithm of drug causality for epidermal necrolysis (ALDEN) for

causality assessment. Preliminary results of 979 cases identified a probable or very probable drug for the majority of cases (~68%); the idiopathic cases include 2-5% that have no report of any drug intake.

Taiwan
Shuen-Iu Hung from the National Yang-Ming University described the Taiwan SCAR consortium of 10+ medical centers and the Taiwan Drug Relief Fund for compensation for drug injuries raised from the pharmaceutical industry. Taiwan's National Health insurance covers the expense of HLA-B*1502 testing before prescription of carbamazepine, and HLA-B*5801 is also routinely assayed when allopurinol is prescribed. Phenytoin SCAR were strongly associated with the CYP2C locus in several Southeast Asian populations; the CYP2C9*3 allele also common in European populations showed a 12-fold risk of SJS/TEN as well as delayed clearance of the drug. SJS/TEN cases even without this allele showed delayed clearance, perhaps due to liver or kidney disease. Research is needed to determine which metabolite is binding to the MHC, and to examine granulysin and TCRs as potential diagnostic tests.

iSAEC
Munir Pirmohamed from the University of Liverpool discussed the international Serious Adverse Event Consortium (iSAEC), whose mission is to identify DNA variants associated with risk of drug-induced serious adverse events. They've conducted several genome-wide association studies (GWAS) focused on specific drugs and outcomes, particularly severe cutaneous adverse reactions and liver and renal injury. Population-specific findings were noted even within Europe, with a specific HLA-B SJS/TEN risk allele in the Italian population driving the overall European association and showing no association in northern European or Spanish populations. To date iSAEC has performed manual investigation of records, rather than structured queries of EHR data. Ethnicity is self-reported and inclusive of grandparental birthplace, and principal components analysis is used to account for population substructure. The group discussed whether there are alleles or markers that cross over from SJS/TEN to more common skin reactions and reactions in other organs, noting that further work is needed in this area.

Thailand
Wasun Chantratita from Mahidol University reported that screening for HLA-B*1502 has been widely implemented in Thailand, and patients are given pharmacogenomics (PGx) cards with their carrier status as well as counseling during prescription of related drugs. Unfortunately these are not fool-proof methods to prevent at-risk patients from receiving culprit drugs so they are developing EHR linkages to alert doctors and pharmacists, and educational games/apps that patients can use on mobile devices. The group discussed that SJS/TEN has not been observed in children born to women who received nevirapine and developed SJS/TEN during pregnancy, even when the child received the drug post-birth. If reactions are T-cell mediated, some level of protection would be expected, and this is an area that potentially merits further study.

Discussion
International collaborations will be critical for increasing sample size and replicating findings. RegiSCAR is open for other teams to join, and network representatives can help with start-up; however each team needs to provide their own funding and manage jurisdiction-specific legal and policy issues. iSAEC has reached their funding target for patient recruitment but they are interested in collaborations for replication and follow-up studies. NIH funds numerous large patient cohorts that could be queried to determine the number of participants on medications of interest (e.g. carbamazepine), and to gauge willingness to collaborate. The Stevens-Johnson Syndrome Foundation could help to refer patients for research studies as the foundation website serves as a first point of contact for many patients.

Case identification and recruitment remain challenging as SJS is often only recognized in late stages of the disease, and currently phenotyping and case identification requires labor intensive manual review. In the U.K., iSAEC has started work on unifying phenotypes and cases using EHRs and hopes to develop a diagnostic algorithm for SJS/TEN. The group also discussed factors that enabled clinical implementation of HLA screening. Thailand's implementation of SJS/TEN allele screening was possible due to the relatively high prevalence of risk alleles, inexpensive testing (~$30) that can be done immediately in university hospitals, and interest from politicians. In Singapore, the chairman of the Health Science Authority was also the executive director of the Genomics Institute, and they pushed for improved genomics and regulatory research due to the high incidence of SJS/TEN. Overarching key factors that facilitate successful implementation include vocal proponents, political interest, local clinical trials, increased awareness of physicians and pharmacists, and nation-wide infrastructure building.

Session 3: Challenges in Case Finding and Surveillance
Pharmacosurveillance for SJS/TEN in the United States (US)
Lois La Grenade of the FDA reviewed tools used by the FDA to monitor ADRs, including the FDA Adverse Event Recording System (FAERS), the National Electronic Injury Surveillance System-Cooperative Adverse Drug Events Surveillance System (NEISS-CADES), the Sentinel and mini-Sentinel active surveillance programs, and the Molecular Analysis of Side Effects (MASE) project under development. She discussed challenges to SJS studies, including sample size and accurate case definition. The rarity of SJS/TEN makes prospective data collection challenging; SJS is also poorly captured by administrative codes, which is a challenge for retrospective studies, though admission to burn units is a good indicator. Reporting in NEISS-CADES lags up to two years and non-drug related cases are not captured, so more targeted active reporting and case follow-up are needed. The group discussed the potential value of a mandatory reporting system; it would need to have a regulatory justification to be implemented by FDA, so the Centers for Disease Control and Prevention (CDC) may be the more appropriate U.S. agency. Involving burn units or the American Burn Association for targeted active surveillance could improve case capture.

Potential for electronic phenotyping
Josh Denny from Vanderbilt University presented examples from the NHGRI Electronic Medical Records and Genomics (eMERGE) network highlighting the potential for accurate ADR phenotype identification from EHR data and discovering genome-phenome associations. Manual review of 100K subjects in the Vanderbilt BioVU system in 2012 identified 72 cases of SJS/TEN/erythema multiforme (EM) thought to be drug-related, about half with a drug identified, and many with photos available. Positive predictive values from the HMO Research Network have ranged from 57-92%. The group discussed how key data such as pathology reports are difficult to access electronically when stored in Portable Document Formats (PDFs) or as images. It may be more informative to look at encounters with ophthalmologists, including billing codes, to identify a pattern of recurrence for treatment. Algorithms need to incorporate the timing of exposures (particularly drug prescriptions), and outcomes. Another challenge is the fragmentation that occurs since patients often visit multiple specialists. Health maintenance organizations (HMOs) or other research-oriented networks that share standardized data for a combined patient population may be well-suited to address this challenge.

Pharmacovigilance in Thailand
Wimon Suwankesawong from the Thai Food and Drug Administration presented an overview of the Thai VigiBase showing a drop in SJS/TEN cases reported in Thailand after 2009, which correlates with implementation of the PGx card. The number of reported SJS/TEN cases linked with co-trimoxazole exceeds that of carbamazepine in Thailand, due to its use for in human immunodeficiency virus and acquired immune deficiency syndrome (HIV/AIDS) prophylaxis. The group discussed potential

interactions between SJS/TEN and HIV/AIDS due to altered CD4 counts; however, another study showed that patients with undetectable viral loads are not at higher risk for SJS/TEN. HIV patients with other comorbid conditions, such as tuberculosis, often take many drugs, making it difficult to identify the culprit drug(s). Research in Malawi has followed 1,000 patients on nevirapine, and the Malawian ministry has changed its drug of choice due to the high risk of SJS/TEN. The HLA-B*1501 allele has a north-south gradation in Thailand (6% in the north vs. 10% in the south); future research could examine if there is a corresponding gradation in rates of SJS/TEN.

Discussion
Collaborative possibilities include encouraging the HMO Research Network to make SJS/TEN case-finding a priority since they are part of the FDA Sentinel system. A standardized phenotyping algorithm for SJS/TEN is urgently needed. Prospective collection of phenotype data would be ideal but retrospective assessment is also necessary to not miss cases. Careful case adjudication is typically needed and data on when the drug was started or actual pathology reports often necessitate going back to the physician or patient.   Although it will be important to have standards, exact diagnostic criteria may vary in populations based on prior probabilities. Longitudinal photographs are immensely helpful in diagnosis of SJS/TEN, even more helpful than histopathology, but are often missing. Relatives often take pictures and obtaining those photographs to add to the medical record would be very useful.

Verifying the causal drug is another challenge, especially since multiple drugs are often started concurrently and details about the time of drug initiation may be lacking. Biological samples could help inform causality assessments. *In vitro* cytotoxicity assays are not often used because of high variability and low positive predictive value. New classes of testing including lymphocyte transformation testing and antibody testing but none are highly sensitive. More sensitive *in vitro* testing for diagnosis and causality assessment and screening assays for small molecule testing would be important next steps.

Session 4: Working Groups
Day 1 ended with break-out sessions for the three working groups, summarized in session 7 (see below).

Session 5: International Experience Part 2
Day 1 Recap
Neil Shear recapped challenges in SJS/TEN research, including lack of ownership by a specific discipline, inadequate measurement of the burden of disease and cost to healthcare, poor provider education, and translational hurdles. Areas for opportunity include: assessing cost-effectiveness on a population level; improving understanding of drug development pathways and drug safety; providing insights into mechanisms of other hypersensitivity syndromes; capacity building for laboratory innovation; using evidence-based approaches to mine EHRs; and creating multidisciplinary research teams.

Singapore
Cynthia Sung from Duke-NUS Graduate Medical School described a pharmacogenomics initiative of the Health Sciences Authority that has developed the regulatory expertise and built the infrastructure to implement HLA testing prior to carbamazepine initiation. Recommendations from this initiative included: genotyping the HLA-B*1502 allele prior to the initiation of carbamazepine in patients of Asian ancestry as the standard of care; use of treatment alternatives for HLA-B*1502 positive patients; and further study of other factors such as drug dose, compliance, concomitant medications, co-morbidities and dermatologic monitoring. No carbamazepine-related cases have been identified since initiation of testing while previously there were ~15/year. The importance of engaging multiple stakeholders, especially clinicians, and of lowering the cost and turnaround time of genetic testing were emphasized.

Indonesia
Rika Yuliwulandari from Yarsi University reported that 10-17% of Indonesians carry the HLA-B*1502 allele, depending on ethnicity. However, to date there has not been sufficient epidemiological and clinical research on SJS/TEN in Indonesia. Additional training and education of health workers to disseminate knowledge of drug side effects is recommended. Patterns of drug use in Indonesia were discussed, and Rika noted that valproic acid and phenytoin are often preferred by clinicians due to the high risk of carbamazepine side effects. The most common adjunct medication is haloperidol, and when combined this increases the serum level of carbamazepine.

United States
Steven Leeder from Children's Mercy Hospital described the lack of U.S. drug safety research networks analogous to the Canadian Pharmacogenomics Network for Drug Safety, which includes a focus on SJS/TEN. Various hospitals in the United States have participated in international initiatives to monitor ADRs; however, data entry and reporting of these ADRs are still sporadic. The Pharmacogenomics of Pediatric Drug Safety (PPeDS) research program was implemented at Children's Mercy to improve data entry and reporting of ADRs, increase the usability of the data for research analysis, and inform drugs and dosages for pediatric patients. Pediatric patients tend to be more sensitive to ADRs. Development of a national ADR surveillance program will require infrastructure building, but will increase the research potential and will be crucial for decreasing the prevalence of ADRs. The group noted that institutions are more willing to invest in infrastructure if a high clinical value is demonstrated. Ideally, we would create a research database and reporting structure to automatically send ADR reports to FDA's FAERS.

Discussion
Many U.S. hospitals including the NIH Clinical Center require HLA genotyping for abacavir and offer HLA testing prior to prescribing carbamazepine, phenytoin, and allopurinol. The PPeDS system could be used as a model for other systems locally and internationally. A network for rare events could be built, with information in EHRs including a system of common data elements and clinical decision support to investigate causality at the bedside.   Challenges include developing standardized phenotypes and creating interoperable systems. One strategy to engage the larger community would be to take advantage of the momentum from the Genomic Medicine VII meeting and the Institute of Medicine's Electronic Heath Record (EHR) Action Collaborative, and to engage with ongoing patient safety initiatives within the Agency for Healthcare Research and Quality (AHRQ), the CDC, the Office of the National Coordinator for Health Information Technology (ONC), the Patient-Centered Outcomes Research Institute (PCORI), the FDA, and other US and international institutions. Developing and disseminating new standard of care guidelines has proven to be effective in Singapore and can have a major impact on clinical implementation. In the U.S., the Clinical Pharmacogenetics Implementation Consortium (CPIC) is developing guidelines that assume existing pharmacogenomics test results rather than proposing who should be tested. Professional societies for specialties that prescribe associated drugs (e.g. epilepsy, neurology) could be targeted for education and guideline development. Clinical decision support tools might also be effective for educating providers and improving implementation.

<u>Session 6: Special Topics</u>
Regulatory consideration of pharmacogenomics data in labeling
Mike Pacanowski from the FDA reported that FDA mandates updating of drug labels when ADRs are found with language commensurate with the severity of the reaction. To date there are well over 150 gene-drug pairs in FDA labels, about half of which are actionable rather than descriptive. Most of the important data for ADRs arise in post-market settings that are external of the sponsor's original development plan. Drug labels are often silent on specific testing recommendations to acknowledge clinical judgment and potential uncertainty. The warning on the label of carbamazepine includes which

populations are high risk, the allele distribution, management recommendations, and considerations with respect to timing of the adverse event. FDA has identified four major focus areas to mitigate the potential for ADRs: 1) establishing infrastructure for capturing cases and specimens, interoperable repositories, dynamic clinical decision support, and evaluating post-SJS/TEN treatments/outcomes; 2) promoting consistency and quality in research methods; 3) strengthening experimental models; and 4) developing reliable biomarkers.

Identifying causal variation in studies of disease associations with MHC genes
Mary Carrington of the National Cancer Institute described the multifaceted manner by which HLA variation influences disease through both acquired and innate immunity. HLA-B shows the strongest allelic associations with HIV control, and higher HLA-C expression associates with better HIV control in European and African Americans. The importance of functional data for attributing causation to a genetic association was stressed. Through multivariate analyses using expression as a continuous variable, it is possible to find specific alleles with protective effects; HLA may thus modulate expression of other immune genes. Expression levels of HLA-B*1502 may differ in drug-tolerant patients and could be investigated as a possible modifier of allele-associated risk.

Drug-induced liver injury and cross-reactivity across drugs/organs
Jay Hoofnagle of the National Institute of Diabetes and Digestive and Kidney Diseases reported that drug-induced liver injury accounts for 3-10% of acute liver injury in the U.S., is the largest cause of acute liver failure, and is a common cause for a medication to be abandoned during development. The Drug-Induced Liver Injury Network (DILIN) was created to collect and fully characterize cases of clinically apparent drug induced liver injury. DILIN has created a causality assessment which considers factors similar to those used in the ALDEN score. In terms of cross-organ reactivity, nine patients in the DILN cohort also have SJS/TEN. These patients were also exposed to multiple medications (mean=5), which makes determining causality difficult. DILIN has created a website (livertox.nih.gov) that allows for searching on specific drugs, and allows for patients to submit their own case reports of liver injury.

Health economics, policy implementation, and cost-effectiveness research
Dave Veenstra from the University of Washington presented on economic considerations in SJS/TEN eradication. Economic evaluation of health care is a field that has seen rapid growth. In health care, cost-effectiveness is typically about increasing value and spending money more effectively rather than minimizing costs. A framework for evaluating the cost-effectiveness of pharmacogenomic testing would need information on the severity and frequency of SJS/TEN, the strength of genotype-phenotype association, the prevalence of the variants in question, and direct and induced costs. Multiple studies support the value of HLA testing to prevent SJS/TEN in Asian countries, but evidence of economic value in specific U.S. populations is lacking. Rare diseases such as SJS/TEN may have a higher incremental cost effectiveness ratio (ICER) threshold than used for common diseases. Economic analytic tools, modeling, and sensitivity analysis can help quantify uncertainty and identify which unknowns have the biggest impact on cost-effective estimates. This can then inform priority areas for additional research.

Discussion
A number of SJS/TEN risk alleles are population specific, so studies of SJS/TEN need to account for race/ethnicity and broad categories are often not sufficient; this is especially challenging in populations with high levels of admixture and globalization. The group noted that most SJS/TEN studies to date have been performed in populations of European or Asian ancestry, with less information on individuals of African ancestry. African Americans are overrepresented in liver ADRs from allopurinol, and SJS/TEN tends to have higher mortality and morbidity outcomes in those of African descent, possibly due to lack of early diagnosis or access to health care. The International Conference on Harmonisation of Technical

Requirements for Registration of Pharmaceuticals for Human Use (ICH, http://www.ich.org/home.html) could provide an avenue to discuss standardizing the use of race/ethnicity in drug labeling.

Evidence exists for the efficiency of screening; however, the odds ratio threshold to cross to make affirmative recommendations has not been defined. One major hurdle is the need for inexpensive HLA typing with quick turn-around-times. Testing is more expensive when assessing individuals in a clinical setting, compared to high-throughput research settings. The group debated how much resolution was needed in HLA typing, and how much is gained through deep sequencing vs. other assays for HLA groups. Transplant labs could be a model for getting rapid, cost-effective, and sufficient HLA resolution.

Session 7: Report of Working Groups
Basic Research working group report
Lauren Trepanier from the University of Wisconsin-Madison and Wen-Hung Chung summarized the key gaps in basic knowledge, including: defining the cellular processes that lead to the development of drug neoantigens prior to MHC presentation; characterizing how specific drugs activate immune responses outside of MHC restriction; characterizing co-factors that drive immunogenicity; validating early diagnostic and prognostic markers; and developing reliable and safe *in vitro* challenge test(s). To fill these gaps, a critical mass of well-phenotyped patients is needed, as well as expanded prospective surveillance and biobanking. Areas to explore in the next 5 years include: investigation of differences between maculopapular rash and SJS/TEN; biomarkers in acute phase to facilitate diagnosis, prognosis, and treatment; massively parallel sequencing of HLAs linked to medical records; predictive tests beyond HLA, such as pathway analysis of GWAS data; predictive models based on mechanistic studies of metabolism and plasma drug/tissue concentrations.

Discussion of basic research opportunities
The group agreed that biobanking, especially of early samples, is a fundamental first step for research into mechanisms and ultimately for finding new therapeutic targets. A global registry with well-phenotyped cases and harmonization of clinical characteristics should be prioritized; information should also be collected on molecular signatures and long-term sequelae. One major challenge is funding these initiatives long-term. Working on rare outcomes is not easily sustainable, and biobanking is expensive. Japan and Taiwan have implemented systems in which pharmaceutical companies contribute funds to patient care; public-private partnerships with shared contributions from pharmaceutical companies could be an effective model. This network would have a synergistic effect on clinical trials. Samples could be collected from clinical trials, and results from mechanistic research would provide new markers, diagnostics and treatments for future clinical trial testing. Infrastructure needs include specialized centers to receive and characterize samples and development of standard consent forms to facilitate sending samples across country borders. The role of infection needs further research; HIV and Epstein Barr Virus (EBV) are cofactors, and SJS/TEN may involve pathogen signaling through innate pathways. Lastly, there's a need to look beyond T cells to NK cells, regulatory T cells, dendritic cells, and checkpoint blockade molecules, as well as cheminformatics of TEN drug culprits. At present, predictive genetic testing appears to be the only thing ready for translation.

Clinical Implementation working group report
Howard McLeod of the Moffitt Cancer Center and Surakameth Mahasirimongkol of the Thai Ministry of Public Health summarized promising opportunities for the next 5 years, including: developing a low cost pharmacogenomic assay that can be included in state/national health programs; incorporating genotypes into the medical record; implementing testing in high-risk populations and studying impact; and piloting pre-emptive testing. The break-out group noted that SJS/TEN is an iatrogenic event, leading to a moral obligation to act. They also discussed the importance of understanding the efficacy, long-

term outcomes, and possible side effects of prescribing alternative medications, particularly since many HLA risk alleles have low positive predictive value. Additionally, some countries observed a drop in carbamazepine prescriptions prior to implementation of screening, which is partially attributed to doctors opting away from SJS associated drugs; this raises concern of the risk associated with not pre-testing and instead universally moving from effective drugs with known, but preventable, ADRs to alternative drugs with lesser known safety profiles. The burden of SJS/TEN is unknown in many populations, particularly ethnic subgroups in the U.S.; studies in Asian-Americans would seem particularly important but have not been conducted to date. Short-term projects in implementation and cost-effectiveness will likely focus on specific gene-drug pairs; however, research should expand beyond one gene-one drug interactions, and ultimately multi-gene tests or genome sequencing will likely be more favorable economically. Organ donors have HLA testing done after death; conceivably doing HLA testing earlier in life could also be useful in maintaining a possible organ donor's own health.

Discussion of clinical implementation research opportunities
The group again discussed the importance of studies and study designs that are applicable to populations with different ethnic diversity, including admixed populations. This discussion echoed that of working group 1 in recommending an international network with a biorepository. The group noted the importance of qualitative and mixed-method studies, and suggested studies surveying patients, their loved ones and the general population in the areas of patient preferences, cost-effectiveness, risk assessment for severe rare outcomes, and communicating uncertainty in implementation. A pilot study conducted in the U.K. suggested many patients would rather take a drug with decreased efficacy in place of one with a higher risk for an ADR.

Pharmacosurveillance working group report
Robert Davis of the University of Tennessee Health Science Center and Simone Pinheiro of the FDA identified accurate and reliable case ascertainment as a key challenge. A standardized case definition focused on a minimum set of variables to differentiate cases from non-cases may be helpful. Tools should be generalizable for use on common data models and health record systems, with the subsequent ability to dig more deeply into medical charts to validate phenotype, drug culprits, timing of exposure, and risk factors. Potential next steps include: evaluating current case definitions (e.g. EuroSCAR, RegiSCAR); undertaking an iterative process among researchers and clinicians to arrive at a common case definition; collaborating on the development and optimization of electronic algorithms; and facilitating active surveillance with real-time data collection for prospective studies.

Discussion of pharmacosurveillance research opportunities
Existing large databases such as the HMO Research Network in the U.S. may be a promising tool for surveillance, if cases can be identified reliably and accurately. These databases may not be sufficient for pharmacogenomic studies due to size requirements and potential lack of available specimens on all cases; however they could be complemented by additional prospective data and specimen collection through burn units and other venues. Large-scale collaborations in the U.S., building on the DILIN experience, might be stimulated by efforts to deposit data into ClinVar, dbGaP or others. Estimating rates of SJS/TEN will be important for cost-effectiveness studies to estimate burden of disease and product-specific rates. The ScoreTEN system could be used in future studies to address the range and extent of outcomes and disabilities in SJS/TEN patients. Immediate needs include improved collection of race/ethnic data in databases, standardized case definitions and valid e-algorithms, and a minimum set of criteria useful for both retrospective and prospective studies that balances the tradeoff between sensitivity and specificity. The group again discussed how partnering with major burn units could improve the active accrual of validated cases and noted that the National Institute of General Medical

Studies has a burn research program. However, it was noted that patients in burn units typically have severe late-stage disease and alternative methods will be needed to identify patients in earlier stages of disease.

Session 8: Wrap-up and Next Steps
Discussion of next steps

Several opportunities to move the field forward were suggested, including: comparison and harmonization of case-report forms and databases across studies; working with patient advocates to encourage ADR reporting; providing research case reports directly to the FDA electronically; and performing "pre-emptive" HLA typing linked to the EHR. High priority research areas included: collecting biospecimens early in the disease progression to develop diagnostic and prognostic biomarkers; creating a large-scale international network for collection of biospecimens and harmonized phenotyping; collecting ethnicity information in surveillance data; conducting descriptive and analytical epidemiologic studies in non-European racial-ethnic populations in U.S., including subgroups; developing standardized case definitions and e-phenotypes useful for both prospective and retrospective studies; engaging burn units in research; collecting long-term outcomes including serious morbidity and non-standard sequelae such as arthralgias and myalgias; and developing small pilot projects on patient preferences.

Innovative studies suggested by workshop participants included: looking at genetic variation in drug trials that were halted for SJS/TEN, especially if DNA were stored; including negative predictive value as well as positive predictive value of HLA testing in cost-effectiveness studies; stepping backward from identified risk allele to immunopathogenesis; moving toward *in vitro* preclinical testing of drugs; correlating HLA expression levels with SJS/TEN risk; studying risk allele carriers who don't get disease to identify protective factors; and surveillance and research in burn units. The major challenges include: difficulties in identifying patients at early stages; lack of systemic reporting (and whether it should be mandated); practitioner education and awareness; balancing individual utility versus the societal impact of SJS/TEN; lack of animal models; and defining the burden of SJS/TEN.

Immediate next steps from the workshop include: NIH staff will draft a meeting summary and executive summary; meeting speakers and moderators will write a white paper; funding agencies will consider possible research initiatives; NIH will reach out to federal partners (AHRQ, CDC, FDA, NIH, ONC, PCORI) to identify potential joint efforts in drug safety and SJS/TEN research; workshop participants will facilitate comparison and harmonization of phenotyping and case report efforts; and all will stimulate interest amongst their home agencies in a collaborative effort.

Workshop participants suggested several other research opportunities including: creating a centralized, international IRB consent form for biobanking and biorepositories; integrating existing databases like ClinVar and dbGaP into this initiative; and exchanging data among members of the workshop to stimulate further research and focused conversations. Suggestions for increasing awareness and health provider education included: developing model case studies for various specialties for reference in future diagnostic and prognostic pathways for SJS/TEN; producing short summaries of the clinical problem and research needs for key subspecialty journals; writing a "call for action" that would be published in a major journal highlighting the importance of research and developments of genetic screening for SJS/TEN and various other SCARs and ADRs; and developing slides for promotion of SJS/TEN awareness at various meetings and conferences for related specialties.

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