Update on Progress in SJS/TEN Research 2016/2017– Phillips Lab – Vanderbilt University Medical Center (VUMC)

The mission of the SJS/TEN research program at VUMC is to 1) improve preventive efforts and facilitate translation of genetic screening into the clinical and pre-clinical setting to prevent SJS/TEN through excluding patients at risk from high risk drugs and facilitating the development of safer drugs less likely to cause SJS/TEN. 2) Identify biomarkers associated with SJS/TEN that could lead to earlier diagnosis and specific and sensitive measures for point of care diagnosis in communities without access to specialty care (to expedite transition into specialty care such as Burns centers 3) Identify the mechanisms driving SJS/TEN that will lead to an understanding of the molecular and cellular signals that will lead to discovery of targeted therapies to prevent morbidity and mortality associated with SJS/TEN.

Currently our team has accomplished the following:

A. Development of an electronic phenotype and genetic typing

1) Out of >250,000 records (see BioVu, Figure 1 October 2017) we have reviewed over 3000 electronic health records with ICD9 and 10 codes potentially compatible with SJS/TEN. From this we have been able to identify an electronic phenotype that is able to accurately identify patients with true drug-induced SJS/TEN using a combination of coding, word searches and involvement of sub-specialty services such as dermatology (Figure 2)

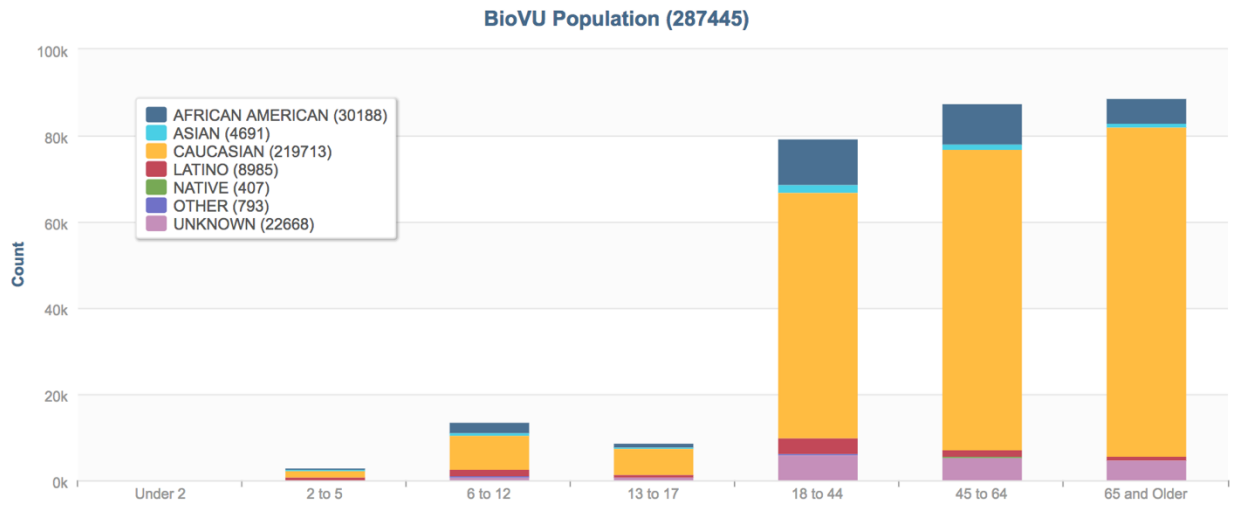


Figure 1: Consensus of the BioVu Vanderbilt DNA Bank as of October 2017

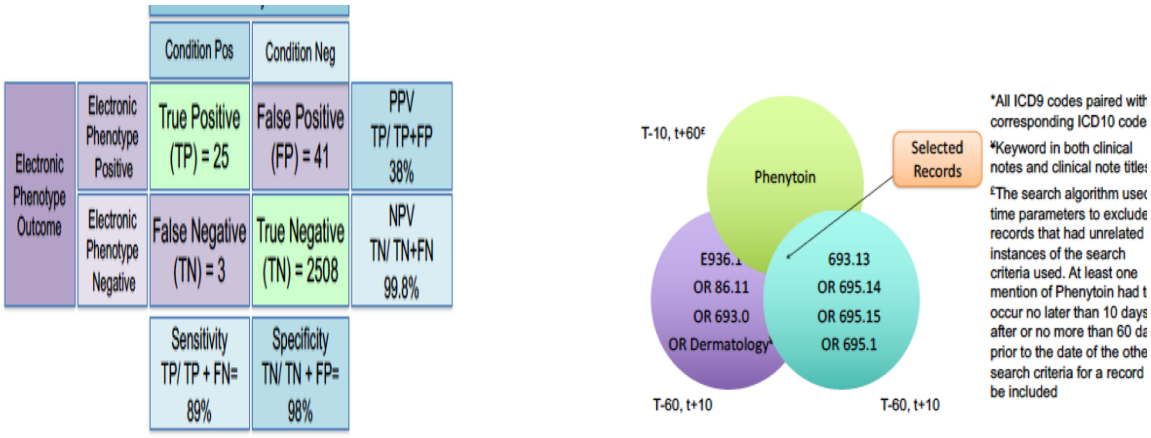


Figure 2: drug-induced SJS/TEN in BioVu

2) 162 cases have had high resolution genotyping including HLA A B C DR DQ DP typing.
3) This typing has shown that in the United States different trends exist in the HLA alleles that drive risk for SJS/TEN and this could be due to the differing populations (European American, African American) and the fact that this represents new discovery (Figure 3). These HLA alleles seem to cluster around certain HLA alleles that share peptide binding specificities indicating that the way they interact with high risk drugs could be similar and that the study of these high risk clusters will be important.

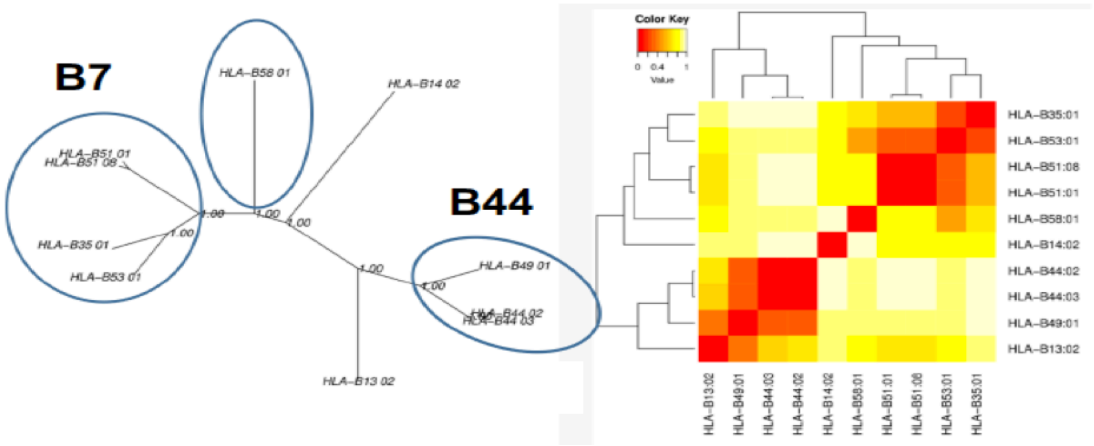


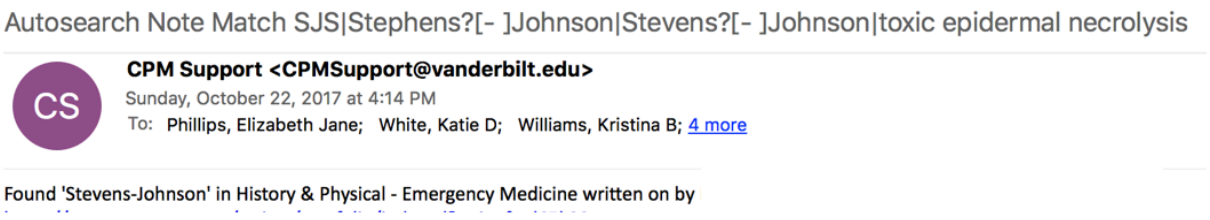
Figure 3: Diagram summarizing the distribution of the Genetics of SJS/TEN seen from the BioVu database. Across all patients typed and all drugs 90% are sharing HLA alleles that conform to one of two super-types identifying that the main HLA risk alleles that are associated with SJS/TEN are associated with HLA super-types that have shared peptide binding specificities. This is likely do to a combination of different types of drugs being associated with SJS/TEN in populations represented in the Vanderbilt BioVu Databank (see racial distribution figure 1) and this impacts on the high risk drugs in this population (antibiotics & anticonvulsants).

4) We have validated the imputation of HLA data from Exome chip and GWAS platforms that will be used to generate HLA data from >120,000 samples typed by MegaChip by the end of 2018.

B. Development of Information Technology to facilitate earlier identification and study of SJS/TEN

Dr. Josh Denny who is part of our PGRN NIH funded program has developed natural language processing skills and written code that sends alerts to our emails when individuals specific symptoms, signs and words in their medical note that indicate that they could have SJS/TEN or be evolving into SJS/TEN. This has allowed us to identify cases at the earliest possible point and has in cases facilitated diagnosis when the diagnosis was not yet entertained and has facilitate collection of samples into our studies. This type of program can be transferred to different facilities to raise awareness for earlier diagnosis and recognition for SJS/TEN.

Example of search string with e-mail alert


Autosearch Note Match SJS|Stephens?[-]Johnson|Stevens?[-]Johnson|toxic epidermal necrolysis

CS

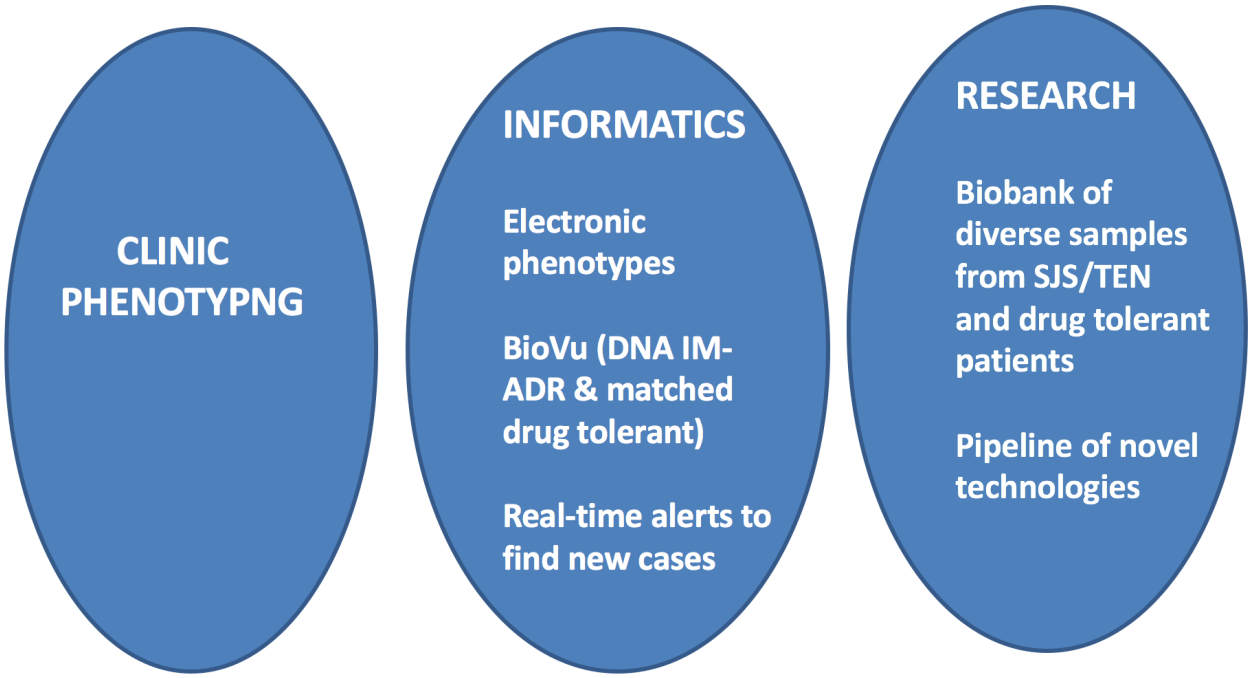
CPM Support <CPMSupport@vanderbilt.edu>

Sunday, October 22, 2017 at 4:14 PM

To: Phillips, Elizabeth Jane; White, Katie D; Williams, Kristina B; 4 more

Found 'Stevens-Johnson' in History & Physical - Emergency Medicine written on by

This has also facilitated integrated approaches to boost our ability to identify and genotype SJS/TEN cases



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C. Development of a North American Network to Prospectively Study SJS/TEN

The NATIENS network was developed to study new treatment interventions in SJS/TEN. Vanderbilt will be the study coordinating and sample coordinating site for this study. The NATIENS study will be a multi-center double-blind randomized controlled study that will enroll from 24 sites across North America with a planned enrollment of almost 300 SJS/TEN patients over 4 years. The study has three major aims: 1) To establish the most effective therapy for SJS/TEN: the study will examine which of supportive care, cyclosporine or etanercept causes the greatest outcome in re-epithelialization; 2) Define the genetic and biomarker predictors of SJS/TEN. This study will utilize HLA typing as well as whole genome analysis both on the subset of patients with HLA risk compared to drug tolerant controls as well as the populations as a whole. It is anticipated that new genetic associations will be identified through this study. In addition, cytokine and

protein analyses will be done at different time points through SJS/TEN with the important outcome of identifying a point of care biomarker (real time blood test) that can be used to facilitate earlier diagnosis of SJS/TEN in the community. This will ensure that patients get triaged into appropriate care. 3) To determine the basic mechanisms driving SJS/TEN. We will identify the specific immune cells driving SJS/TEN and define their specific signatures. This will ensure that the most targeted and effective therapies can be developed for SJS/TEN.

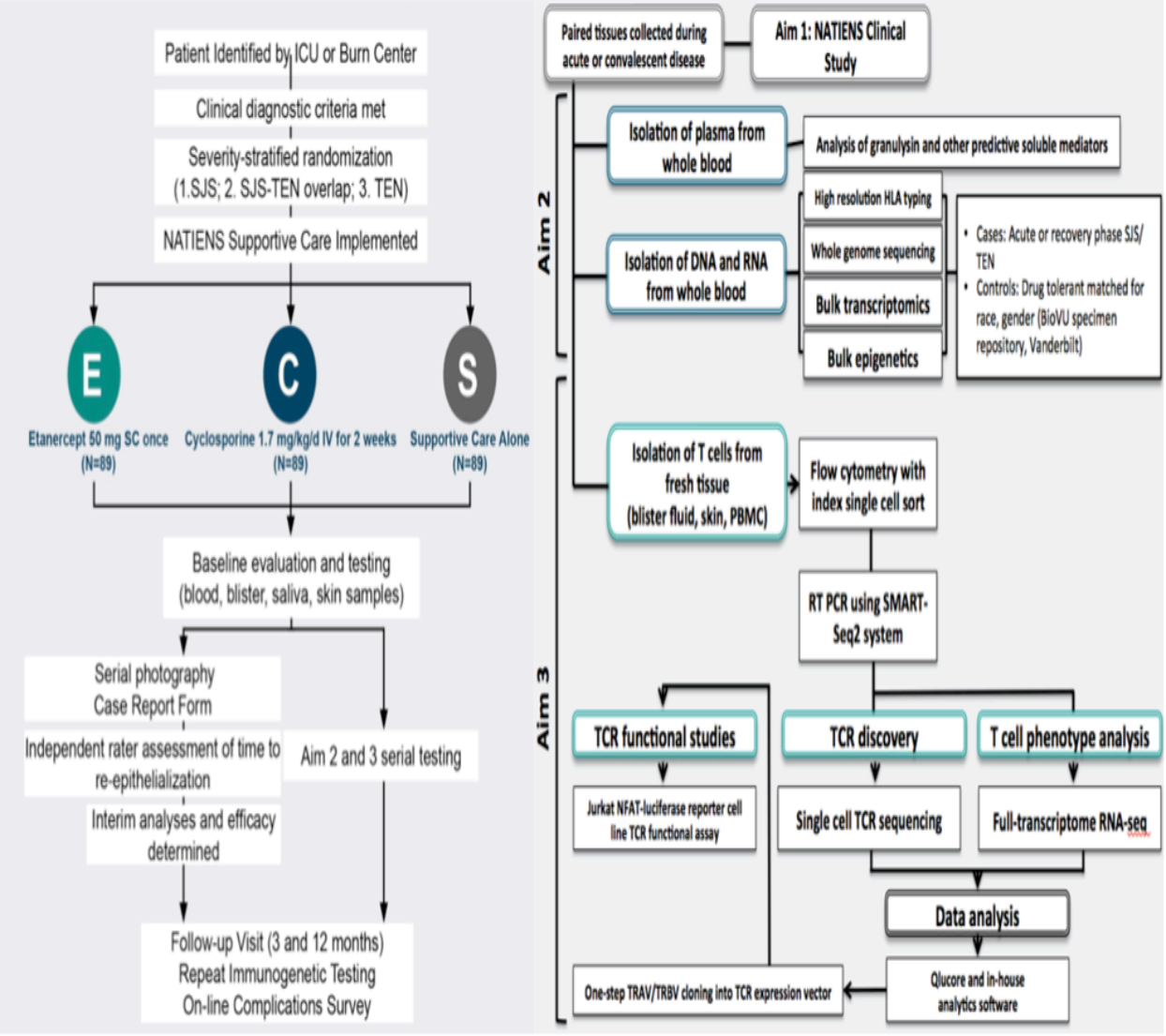

Figure 4: Planned Multicenter study to examine the efficacy and safety of new treatments for SJS/TEN. A pilot study of this study is underway that will be examining measures to standardize and optimize the best supportive care

across sites. As part of this study the inter-individual variability of handling drugs used to treat SJS/TEN will be examined.

D. Examining the Mechanisms of SJS/TEN Disease

An important aspect of advancing prevention, early detection and treatment of SJS/TEN is understanding the biological and cellular processes that drive disease. Significant advances have been made in understanding the genetic basis for this disease but we still do not understand what why some drugs interact the way they do with some patients and why this results in epidermal (skin) necrosis. Our lab is taking tissue specific approaches to examine the cells doing the heavy lifting in the blister fluid and skin. By taking these approaches we can identify 1) the cellular and genetic signatures of SJS/TEN in essence creating an atlas or library of what is driving the tissue damage 2) Identify a targeted approach to SJS/TEN (identify the drugs most likely to be effective in abolishing the processes that lead to short and long-term morbidity and mortality in SJS/TEN 3) Understand why some drugs specifically lead to SJS/TEN which will lead to better pre-clinical screening strategies in drug development and development of safer drugs. We will be specifically using selected populations of blister fluid and skin cells from patients with SJS/TEN using their affected and unaffected skin and blister fluid cells as well as skin cells from individuals of matched genetics tolerating the drug.

Currently our lab has defined the following 1) The cellular and molecular signatures defining SJS/TEN are very different at the skin and blister fluid level than peripheral blood 2) That dominant clonotypes exist that define the signatures of drug specific SJS/TEN 3) The definition of family members who develop SJS/TEN versus tolerating the drugs in the same family will give great insight into the mechanisms driving SJS/TEN and why only 5% of those carrying a specific HLA risk allele will develop drug-induced SJS/TEN. In addition, in whole transcriptome single cell RNA seq data we have defined the specific phenotype of the activated T cells from the blister fluid and skin implicated in SJS/TEN that affirms that these T cells bearing the same T cell receptor clonotype are granulysin producing. This suggests that granulysin could be developed as a point of care biomarker to identify patients early in SJS/TEN disease for earlier diagnosis and treatment.

We have also defined mechanisms to store and cryopreserve cells from skin. This is allowing us to act as the sample coordinating site for the NATIENS study and to receive skin samples from across North America.

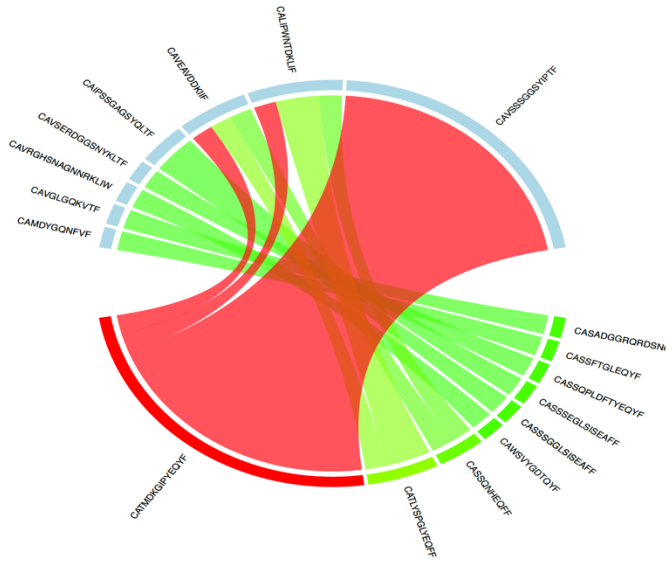

Figure 5: T-cell receptor sequencing of SJS/TEN blister fluid: Expression of a dominant T-cell receptor clonotype in the blister fluid of SJS/TEN shown in Red.

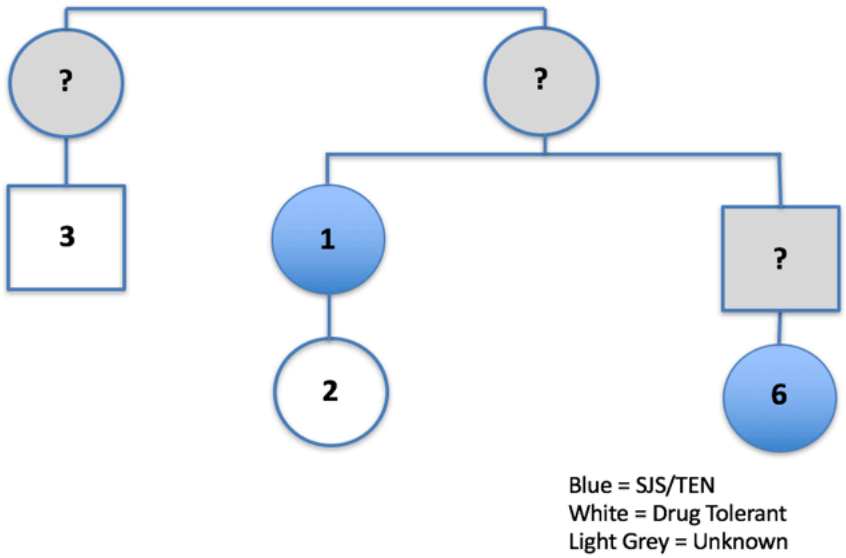

Figure 6: Study of Genetic Pedigree of Family members exposed to the same drug developing versus not developing SJS/TEN

Broadened Efforts for SJS/TEN Research in 2017/2018

1. New collaborations – our collaboration with the department of defense is ongoing and they are independently conducting genome wide studies, whole transcriptome studies in the peripheral blood. Other biobanks exist across North America and are being pursued. Ongoing collaborations exist with Thailand and Taiwan.
2. Using Social Media to identify new cases of SJS/TEN to broaden genetic studies and discovery.
3. Preparation for the next SJS/TEN research meeting: in follow-up to the meeting in Orlando March 2017 a meeting is planned at the American Burns Association meeting in Chicago (April 2018) as well as a larger multi-disciplinary meeting for March 2019 (currently funding applications are being organized for the March 2019 meeting). From the March 2017 meeting a publication has been prepared and reviewed and this is expected to be out in print by late 2017 or early 2018.
4. Improved ways of data-mining SJS/TEN: new tools in development for identification of SJS/TEN in the electronic health record.
5. Outreach to the community.

PUBLICATIONS - Related to SJS/TEN 2016-2017 (from Phillips Lab)

1. Manolio T, Hutter C, Avigan M, Cibotti R, Davis R, Denny J, La Grenade L, Wheatley L, Carrington M, Chantratita W, Chung W, Dalton A, Hung S, Lee M, Leeder S, Lertora J, Mahasirimongkol S, McLeod H, Mockenhaupt M, Pacanowski M, Phillips E, Pinheiro S, Pirmohamed M, Sung C, Suwankesawong W, Trepanier L, Tumminia S, Veenstra D, Yuliwulandari R, Shear N. Research directions in genetic predisposition to Stevens-Johnson Syndrome/Toxic epidermal necrolysis. Clinical Pharmacology and Therapeutics (accepted September 20, 2017).

2. Trubiano J, Strautins K, Redwood A, Pavlos R, Konvinse K, Slavin M, Thursky K, Grayson L, Phillips E. The combined utility of ex vivo enzyme linked immunospot (ELISpot) and In vivo skin testing in patients with antibiotic-associated severe cutaneous adverse reactions. JACI in practice (accepted September 18, 2017).
3. Pavlos R, Mckinnon E, Ostrov D, Peters B, Buus S, Koelle D, Chopra A, Schutte R, Rive C, Redwood A, Restrepo S, Bracey A, Kaever T, Myers P, Speers E, Malaker S, Shabanowitz J, Yuan J, Gaudieri S, Hunt D, Carrington M, Haas D, Mallal S, Phillips E. Shared peptide binding of HLA class I and II alleles associate with cutaneous nevirapine hypersensitivity and identify novel risk alleles. Scientific Reports 2017;7(1)8653[epub August 17].
4. Karnes J, Bastarache L, Shaffer C, Gaudieri S, Xu Y, Glazer A, Mosley J, hao S, Raychaudhuri S, Mallal S, Ye Z, Mayer J, Brillian M, Hebbring S, Roden D, Phillips E, Denny J. Phenome-wide scanning identifies multiple disease and disease severity phenotypes associated with HLA variants. Sci Translat Med 2017;9eaai8708:1-3.
5. Karnes J, Shaffer CM, Bastarache L, Gaudieri S, Glazer AM, Steiner HE, Mosley JD,Mallal S, Jenny JC, Phillips E, Roden D. Comparison of HLA Allelic Imputation Programs. PLoS One 2017; 12(2):e0172444.
6. Thomas M, Hopkins C, Duffy E, Lee D, Loulergue P, Ripamonti D, Ostrov D, Phillips E. Drug specific reaction with eosinophilia and systemic symptoms (DRESS) syndrome during treatment of HIV infection with raltegravir is strongly associated with the HLA-B*53:01 allele. Clin Inf Dis 2017;64(9):1198-1203.
7. Trubiano J, Pavlos R, Redwood A, Phillips E. Drug specific upregulation of CD137 on CD8+ T cells aids in the diagnosis of multiple antibiotic toxic epidermal necrolysyis. JACI Practice 2017;5(3):823-26.
8. Pavlos R, Redwood A, Phillips E. AdDRESSing T-cell responses to anti-tuberculous drugs. British Journal of Dermatology 2017;176(2):292-3.
9. Jing L, Laing K, Dong L, Russell R, Haas J, Ramchandani M, Johnston C, Buus S, Redwood A, White K, Mallal S, Phillips E, Posavad C, Wald A, Koelle D. Extensive CD4 and CD8 T-cell cross-reactivity between alpha herpesviruses. *J Immunology*. 2016; 196(5):2205-18.
10. Phillips E. Classifying ADRs: does dose matter? *British J Clin Pharm*.

2016;81(1):10-2.

11. Pavlos R, White K, Wanjalla C, Mallal S, Phillips E. Severe delayed drug reactions: role of genetics and viral infections. Immunology & Allergy Clinics 2017;37:785-815.
12. Somogyi A, Phillips E. Genomic testing as a tool to optimise drug therapy. Australian Prescriber 2017;40(3):101-4.
13. Garon S, Pavlos R, White KD, Brown NJ, Stone CA Jr, Phillips E. Pharmacogenomics of off-target ADRs. British J Clin Pharm 2017;83(9):1896-1911.
14. Adler NR, Aung AK, Ergen EN, Trubiano J, Goh M, Phillips E. Recent advances in the understanding of severe cutaneous adverse reactions. British J Derm 2017 March 3[epublished ahead of print].
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16. Konvinse K, Phillips E, White K, Trubiano J. Old dog begging for new tricks - Current practices and future directions in the diagnosis of delayed antimicrobial hypersensitivity 2016; 29(6):561-576.
17. Pavlos R, Karnes J, Trubiano J, Peter J, Phillips E. Pharmacogenomics of drug allergy. Chapter 5. Drug Allergy Testing. Elsevier First Edition 2017 (Aleena Banjeri, David Khan Editors).
18. White K, Konvinse K, Lehloenya R, Redwood A, Phillips E. Immune Mechanisms of Drug Allergy. Chapter 4. Drug Allergy Testing. Elsevier First Edition 2017(Aleena Banjeri, David Khan Editors).
19. Aung AK, Phillips EJ, Hulgan T, Haas DW (2015) Implications of Pharmacogenetics for Antimicrobial Prescribing. In: Molecular Microbiology: Diagnostic Principles and Practice 3rd Edition, ASM Press 2017.