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The Professionals' Resource on Sjögren's

Sjögren's Syndrome Foundation

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Burden of Illness High in Sjögren's – SSF National Patient Survey Results are in!

The 2016 major Sjögren's Syndrome Foundation (SSF) National Patient Survey on Sjögren's reveals the most prominent and severe symptoms patients face with their disease, assesses quality of life issues, and points to a significant need for therapies to treat and manage the disease. Almost 3,000 patients shared their experiences with living with Sjögren's from day-to-day through the survey.

The SSF partnered with Harris Interactive to design and execute the survey to elucidate the burden of illness for Sjögren's patients; patients and healthcare providers provided input on the questions to be asked as well. Fully understanding the difficulties patients face is critical to everything those of us connected to Sjögren's do and especially to how the SSF determines and prioritizes its initiatives, from awareness and education to support and from determining the topics covered under its Clinical Practice Guidelines to ensuring barriers are lifted to developing new therapies for Sjögren's.

"Living with Sjögren's: Summary of Major Findings" follows and is also available on the SSF website at www.sjogrens.org.

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Biomarkers in Sjögren's: A Key to Implementing Precision Medicine

by Kathy L. Sivils, PhD, Director, the Oklahoma Sjögren's Center of Research Translation
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Introduction

Kathy L. Sivils, PhD

Sjögren's is a heterogeneous autoimmune disease with significant clinical challenges. Implementing precision medicine approaches in clinical care of Sjögren's patients is a major goal that will require development of biomarkers to serve a variety of purposes. Important advances in biomarker discovery have enhanced our molecular understanding of Sjögren's and revealed new opportunities for transitioning from a "one size fits all" approach to diagnosis and treatment towards tailored approaches that best meet individual patients' clinical needs.

By definition, a biomarker is a characteristic that objectively measures or indicates normal biologic processes, pathogenic processes, or pharmacologic responses to therapeutic intervention. Categories of biomarkers include those that indicate

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susceptibility or risk of developing Sjögren's and or those that serve as predictive or prognostic indicators. Biomarkers may also provide tools to monitor disease activity, toxicity, or pharmacodynamics. Biomarkers that have been described over the years in Sjögren's include a variety of autoantibodies, serological and hematological markers, and salivary gland histological markers that have served to define disease subsets, predict specific complications, and reveal disease pathogenesis.

Technological advances in biomarker discovery have significantly expanded the pool of potential candidates in Sjögren's. New methods that enable large scale testing of numerous biomarkers in a single assay have resulted in thousands of new potential biomarkers. Recently identified novel biomarkers for Sjögren's include immune cell profiles, RNA transcripts or proteins that are aberrantly expressed in patients, and genetic risk variants. Most of these candidate biomarkers have been derived from blood-based studies; however, saliva and tears have also been utilized as an alternative biomarker discovery matrix. Here, we highlight examples of recent advances in biomarker discovery with potential for clinical utility in Sjögren's.

Cellular signatures of Sjögren's

Dysregulated cellular profiles have been identified in Sjögren's patients and provide insight into patient subsets. In a study by Mingueneau *et al.*, a cytometric technology based on the detection of cells labeled with metal-conjugated antibodies in a time-of-flight mass spectrometry (CyTOF) was used for highly multiplex immunophenotyping.[1] A blood signature based on six cell subsets was defined based on decreased numbers of CD4 T cells, memory B cells, and plasmacytoid dendritic cells, with increased numbers of activated CD4 and CD8 T cells and plasmablasts. In addition to distinguishing patients from controls, this signature also stratified patients into five groups with distinct clinical and biological features. They also observed increased activated CD8 T cells, plasma cells, and activated epithelial cells in salivary glands from the same patients, with correlations in the blood signature that could potentially be used as a dynamic proxy of glandular changes in clinical trials.

Transcriptional profiling

Methods to measure the expression levels of RNA transcripts across the genome have undergone significant advances in recent years. Microarrays, which primarily measure thousands of messenger RNA (mRNA) transcript levels, have been important tools for identifying molecular signatures based on gene expression. Numerous studies comparing Sjögren's patients and controls have identified a prominent disease signature defined by increased expression of genes inducible by interferons (IFNs) in both peripheral blood and salivary glands. James *et al.* have focused on comparing gene expression profiles among patient subsets stratified by presence of fatigue, one of the most common and disabling extraglandular manifestations in Sjögren's.[2] They successfully identified a 55 gene signature associated with fatigue. Pathways that were enriched in the high fatigue patients included actin-related proteins involved in cell shape and motility, G-protein signaling linked to cytoskeleton and actin fiber function, and the incretin pathway potentially involved in regulation of energy balance. The fatigue patient groups did not show association with the IFN signature, thus suggesting complex underlying processes are independent in these subsets of patients.

Developments in RNA sequencing methods have allowed more extensive interrogation of additional types of RNA. While only about 3% of the human genome is transcribed into protein-coding mRNA, nearly all of the remaining DNA is actively transcribed into non-coding RNA (ncRNA) that fall into other classes, including microRNAs and long non-coding RNAs (lncRNAs). Non-coding RNAs play diverse roles in regulating expression of coding genes. Associations of ncRNAs with disease are rapidly being defined and provide a critical link to how genes and pathways are dysregulated. Use of this approach to characterize expression profiles in labial salivary glands identified 1,243 lncRNAs that were differentially expressed in patients versus controls (Shi *et al.*), thus providing another set of potential biomarkers and therapeutic targets in Sjögren's.[3]

Proteomic Approaches to Novel Biomarker Discovery

Proteomics generally refers to the characterization of numerous proteins in a single assay. Innovative proteomic approaches in Sjögren's have been employed that include evaluation of saliva and tears as non-invasive

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sources for biomarker discovery (Reviewed by Katsiougianni and Wong).[4] A recent study by Delaleu *et al.* screened unstimulated whole saliva using a 187-plex capture antibody-based assay and found two saliva signatures that reflected important clinical manifestations of Sjögren's. In patients with hyposalivation, they identified a 4-plex biomarker panel that reflected activation of IL1 pathways. A 3-plex signature was defined that was associated with germinal-center-like structures and characterized by chemotactic and apoptotic processes.

Proteomic analyses coupled by separation of extracellular vesicles (EV) from saliva and tears were applied by Agrawi *et al.*[5] EVs are comprised of exosomes and/or microvesicles that are released by cells and carry mediators of intracellular communication such as cytokines and complement components. In whole saliva, proteins involved in adaptive immune responses, including antigen binding, calcium ion binding and neutrophin signaling pathways were upregulated in Sjögren's patients. EVs from saliva were enriched for proteins involved in cell adhesion, membrane fusion, and cytoskeleton organization. Upregulated protein signatures in tears reflected increased metabolism and protein folding, while EVS from tears contained proteins involved in TNF-alpha signaling and B cell survival.

Large-scale proteomics approaches using DNA-based aptamers capable of measuring over 1,300 proteins (and growing to over 10,000, www.somalogic.com) provide another important opportunity for biomarker discovery. Applying this method to serum, Nishikawa *et al.* identified 82 serum proteins that were differentially expressed in Sjögren's patients when compared to healthy controls.[6] They further defined five proteins that were correlated to disease activity as measured by ESSDAI scores. Some biomarkers were correlated with specific components of the ESSDAI or specific clinical manifestations, such as CXCL13, which was correlated with lymphadenopathy plus glandular, biological and pulmonary domains.

Autoantibodies

Autoantibody production is a hallmark of almost all autoimmune diseases, and the specificities for antigen targets often are used to aid in differential diagnosis. Novel autoantibody discoveries using high-density antigen arrays have been successful and are currently undergoing validation studies in multiple autoimmune diseases. These novel autoantibodies may fill diagnostic gaps in Sjögren's patients classically defined as "seronegative" and offer significant potential for development of patient stratification approaches.

Anti-Ro/SSA and anti-La/SSB antibodies are hallmark biomarkers of Sjögren's. Other specificities that have been described in Sjögren's include rheumatoid factor, anti-citrullinated cyclic peptide (CCP), anti-centromere (ADA), anti-mitochondrial (AMA), and anti-muscarinic 3 receptor (M3R) (reviewed by Fayyaz *et al.*)[7] Other autoantibodies that are important indicators of severe disease include anti-Ro/SSA (60 kD and 52 kD), anti-centromere (ACA), anti-TRIM38, anti-IFI16, and anti-carbamylated proteins. In a recent study by Baer *et al.*, ACA-positive patients had more severe salivary and lacrimal gland dysfunction, increased labial salivary gland focus scores, and lower tear and saliva flow rates.[8] They also had higher frequencies of clinical features associated with limited cutaneous systemic sclerosis. These authors also demonstrated that anti-IFI16 antibodies were associated with germinal-center like structures in labial salivary glands and higher focus scores.

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Genetic determinants of Sjögren's

Genetic factors are known to contribute to the etiology of Sjögren's. Advances in gene mapping have led to the identification of multiples regions in the human genome that harbor genetic variants that increase risk of susceptibility to Sjögren's (reviewed by Reksten *et al.*)[9] Genes in these regions are involved in antigen presentation, anti-viral responses, T and B cell activation, and immune cell trafficking. Ongoing studies continue to identify new genetic associations and reveal mechanisms for how the affected genes contribute to pathogenesis of Sjögren's.

The utility of including genetic risk variants as biomarkers for clinical application remains to be determined; however, several applications are possible. Genetic risk profiles could be informative for diagnosis and classification. Current approaches either for diagnostics in clinical practice or for classification in research settings remains reliant on a battery of tests including salivary and tear flow measures, salivary gland biopsies, and laboratory testing for anti-Ro/SSA autoantibodies. All of these measures are dynamic and are thus subject to environmental influences, may vary among patient subsets, or fluctuate over time. Alternatively, genetic risk factors, detected through genotyping, are based on static determination of presence or absence of defined risk alleles. Thus, as a biomarker property, genetic risk factors could indeed be identified prior to expression of disease manifestations or early in disease onset.

Variants that indicate potential risk for specific clinical manifestations, such as lymphoma, could also be incorporated into clinical assessments. Recent work by Nocturne *et al.* has shown association of a specific variant (rs2230926) in TNFAIP3 is associated with increased risk of lymphoma in Sjögren's.[10] Genetic profiling for the purposes of predicting response to therapy, or pharmacogenomics, is another area of active investigation in autoimmune diseases. Development of genotyping arrays that include specific variants that are highly associated with therapeutic responses have been recently marketed by Illumina, thus supporting the notion that clinical assessment of potential responses based on genetic makeup are potentially feasible.

Collaboration to translate biomarker discoveries into the clinic

In September 2016, the "Biomarkers and Targeted Therapeutics in Sjögren's" (BATTS) conference was held in Oklahoma City, Oklahoma. The BATTS conference was designed to bring together academic and industry investigators to facilitate clinical translation efforts in diagnostics and therapeutics. Overall, 11 companies and 40 academic institutions from 18 countries were present. The program included 36 invited presentations, 9 oral abstract talks, and 74 posters. Abstract and invited presentation summaries are available at omrf.org/batts.

Company representatives expressed a need for academic researchers to help with identifying diagnostic and therapeutic targets, while academic researchers expressed a need for industry to help influence the kind of research that will result in tangible products. A spirit of working together to design stronger, smarter studies was evident and should pave the way towards more efficient progress in improving diagnostics and therapeutics for Sjögren's patients.

In summary, the growth of potential biomarkers for Sjögren's has been extraordinary. Large validation studies in expanded cohorts are urgently needed to validate these candidates, determine their specificity and sensitivity through expanded studies of related phenotypes, and develop feasible testing approaches for translation into clinical practice. ■

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Medical, Science & Industry News

Immunology/Rheumatology

New Preclinical Study on Sjögren's

Servier will soon launch preclinical trials in Sjögren's for an interleukin-7 (IL-7) antagonist. OSE Immunotherapeutics recently licensed the rights to develop and commercialize the therapy to Servier. Effi-7 is a monoclonal antibody that inhibits the IL-7 receptor and leads to an antagonistic effect on T cells. The therapy is already in preclinical trials for ulcertative colitis.

Celgene Expands Autoimmune Portfolio

Celgene is in the process of purchasing a biotechnology company's autoimmune disease-targeted therapies that are in the pipeline. A key therapy developed by Delinia is DEL106 which targets regulatory T cells (Tregs).

Celgene also is buying rights for autoimmune disease therapies produced by Anokion, a Swiss biotech. Anakion is known for engineering proteins in immune tolerance and regulation.

Cancer Risk Study in Sjögren's

Cancer development was studied and characterized in 1300 primary Sjögren's patients fulfilling the 2002 American European Consensus Criteria by the Autoimmune Diseases Study Group (GEAS) of the Spanish Society of Internal Medicine (SEMI).[1] After a median 66 month follow-up, 9.8% of patients developed 133 cancers. The most frequent cancer was B cell MALT lymphoma (20%), other B cell lymphomas (14%), breast cancer (11%), colorectal (7%), myeloid neoplasia/leukemia (6%), lung cancer (5%) and stomach cancer (4%). Overall, an 11-fold higher risk of Sjögren's patients developing hematological cancers was found. Prognostic factors for B cell lymphomas identified at diagnosis included systemic activity, cytopenias and cryoglobulin-related factors, with the weight of these differing according to the lymphoma subtype.

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Burden of Disease Severe in Sjögren's – High Risk of Developing Multiple Extraglandular Manifestations and Additional Autoimmune Diseases

A Dutch cohort of 140 patients were studied retrospectively to determine the development of new extraglandular manifestations and additional autoimmune diseases after diagnosis of primary Sjögren's.[1] Examining records at 10 years after diagnosis, the risk of developing new manifestations or related diseases was found to be 30.7%. Polyneuropathy, interstitial lung disease, polyarthritis, discoid lupus and Hashimoto's thyroid disease were most frequently seen. Those with cryglobulinemia had the highest risk. Investigators did not see a statistically significant difference for risk patients who were auto-antibody positive or had hypergammaglobulinaemia or decreased levels of C3 or C4.

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Incidence and Mortality in Sjögren's

A Mayo Clinic study examined medical records of primary Sjögren's patients diagnosed between 2006 and 2015 that were added to a previous cohort diagnosed between 1975 and 2005.[1] The annual incidence increased over the 40-year period, with a finding for the later period at 5.9 per 100,000 population compared to the earlier period of 5.8 per 100,000. Only primary Sjögren's patients were included. The study did not find a difference in mortality rates compared to normal citizens of the Olmsted County area of Minnesota.

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PD-L1-PD-1 Pathway Implications in Sjögren's

Programmed death ligand[1] (PD-L1) and PD1 have been show to accelerate the development of Sjögren's by

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LIVING WITH SJÖGREN'S

Sjögren's Syndrome Foundation

Summary of Major Findings

Living with Sjögren's was conducted by Harris Poll on behalf of the Sjögren's Syndrome Foundation (SSF), the only non-profit organization focused on increasing research, education and awareness for Sjögren's, an autoimmune disease that affects the entire body. The purpose of the survey was to gain an understanding from adults ages 18 and older who have been diagnosed with Sjögren's about the physical, emotional and financial impact of the disease on their lives.

Sjögren's Survey Patient Demographic Profile

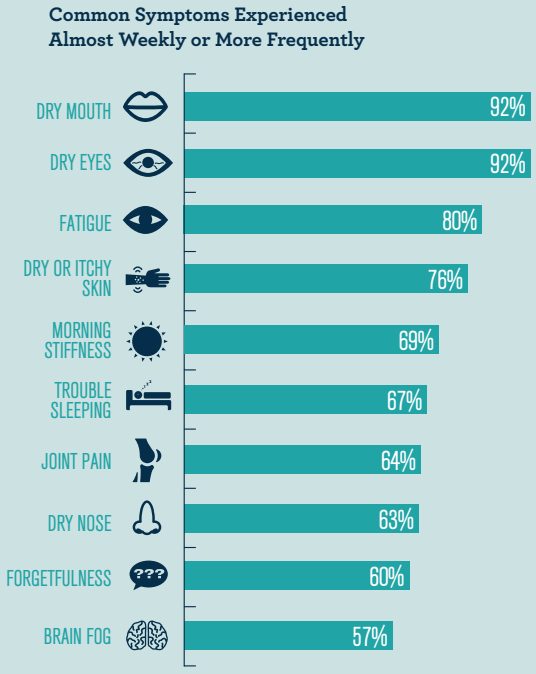
The vast majority (96%) of Sjögren's patients who completed the survey were female. About one-third (32%) of respondents were 60 years of age or younger. On average, respondents said they were diagnosed with Sjögren's over a decade ago (12.3 years mean).

Most Common Symptoms Experienced

The vast majority of Sjögren's patients reported having experienced dry eyes (97%), dry mouth (97%), fatigue (94%), dry or itchy skin (93%), trouble sleeping (91%) and forgetfulness (90%) over the last year. Most said that their dry mouth (92%), dry eyes (92%), and fatigue (80%) symptoms occurred almost weekly or more frequently.

Patients 60 years of age and under said they were more likely than patients over age 60 to experience brain fog (i.e., confusion, forgetfulness, and lack of focus and mental clarity) (66% vs. 53%) and joint pain (67% vs. 62%) almost weekly or more frequently. Patients over 60 years of age reported that they were more likely than patients 60 years of age and under to experience dry nose (65% vs. 59%) and photosensitivity (sunlight) (64% vs. 56%) almost weekly or more frequently.

Half of Sjögren's patients with severe dryness (53%) also have severe fatigue.



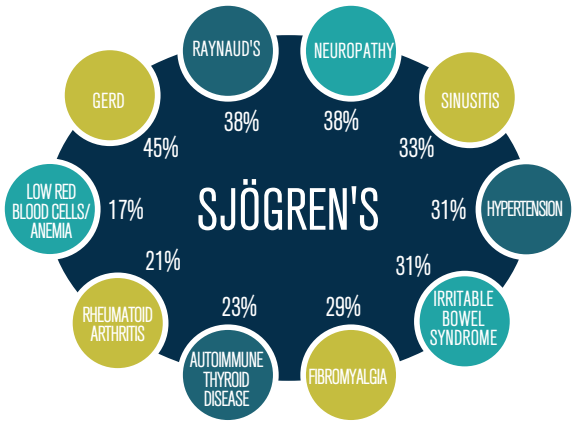
How Sjögren's Affects Daily Activities

Over 7 in 10 Sjögren's patients (71%) agreed that their Sjögren's gets in the way of the things they need to do each day. Most commonly, nearly half (49%) of patients reported Sjögren's having a great deal or a lot of negative impact on participating in hobbies, social activities, and extracurricular activities. Around a third say it negatively impacts making diet adjustments (35%), performing activities of daily life (34%), traveling or taking a vacation (34%), and overall mood (33%).

Nearly 7 in 10 people living with Sjögren's (67%) agreed that they struggle to cope with their Sjögren's. Even more agreed that living with Sjögren's makes every day a challenge (86%).

Other Diagnosed Health Conditions for Sjögren's Patients

There are many known comorbidities or manifestations of Sjögren's that can occur in conjunction with the disease. Survey respondents reported having been diagnosed by a health care provider with an average of five other health conditions, including Gastroesophageal Reflux Disease (GERD) (45%), Raynaud's (38%), Neuropathy (38%), Sinusitis (33%), Hypertension (31%), and Irritable Bowel Syndrome (31%).



Visits to a Healthcare Professional

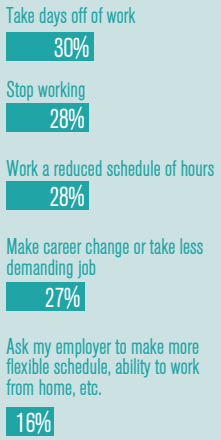
Sjögren's patients, on average, said they see almost five different healthcare professionals (4.6 mean) at least once a year to help manage their disease. Nearly 7 in 10 (68%) of patients surveyed said they see between two and five healthcare providers.

Changes at Home Due to Sjögren's

The majority (79%) of Sjögren's patients surveyed say their disease has led them to make at least one day-to-day change around the house, such as stopping or cutting back on housework (74%) or hiring additional service providers to help with housecleaning or child care (38%).

Changes at Work Due to Sjögren's

More than half (54%) of Sjögren's patients surveyed say they have made at least one change regarding work, including having to stop working (28%), reduce their schedule of hours (28%), and make a career change or take a less demanding job (27%) due to their Sjögren's.



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Treatments and Medications Used

Today, there is no cure for Sjögren's, so patients must resort to using a multitude of treatments to help them cope with various symptoms. On average, Sjögren's patients said they use nearly nine (8.8 mean) medications and treatments to help with their Sjögren's symptoms, with an average of over four prescription medications or treatments. Patients living with Sjögren's for a longer period of time (5-9 years) reported using slightly more treatments than patients living with Sjögren's for a shorter period of time (0-4 years) (8.7 vs. 8.2 mean).

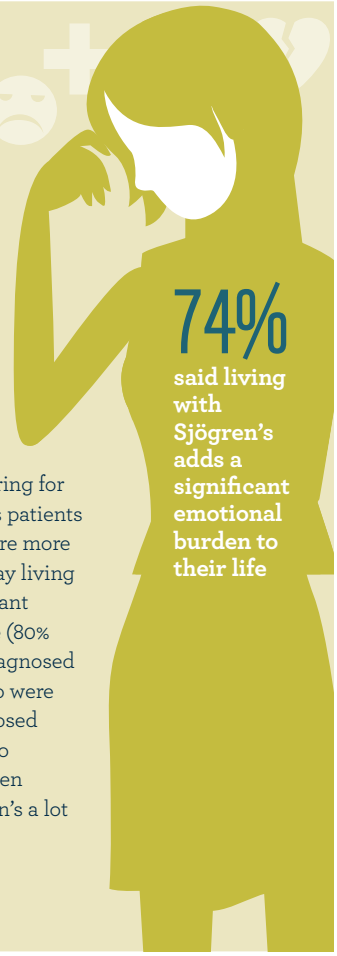
Virtually all patients (97%) reported using eye drops, artificial tears, or non-prescription eye ointments for treatment at some time, while a majority said they have used ibuprofen or other anti-inflammatory agents (81%), disease-modifying anti-rheumatic drugs (DMARDs) (67%) and OTC or prescription fluoride (67%), or corticosteroids (62%) for treatment. Younger patients (60 and under) were significantly more likely than patients over 60 to have used health food supplements/ remedies (90% vs. 87%), exercise (88% vs. 83%), and alternative therapies (70% vs. 58%) to treat their Sjögren's.

Sjögren's Impact on Speech and Concentration

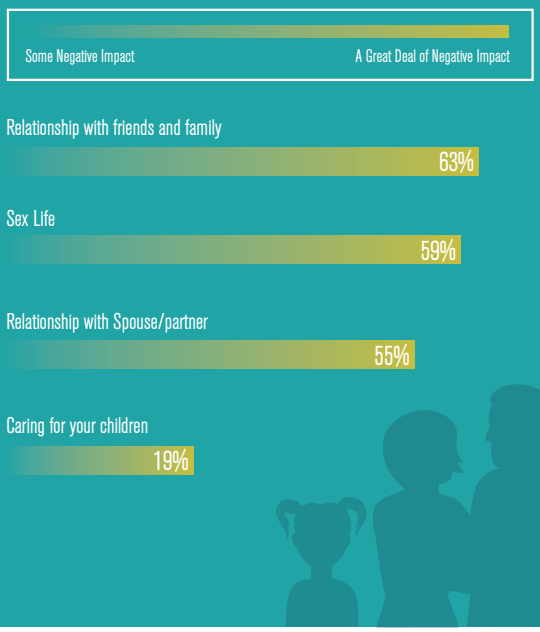
More than two in five (44%) patients said that Sjögren's has had a great deal or a lot of negative impact on finding the correct word during conversation. Slightly fewer said Sjögren's has had a great deal or a lot of negative impact on concentrating on more than one task at a time (38%) or remembering details at home or work (32%). Brain fog (55%) and forgetfulness (49%) were among symptoms that patients said have had a moderate to major impact on their lives in the last year.

Emotional Burden of Sjögren's

Three-in-four patients (74%) said living with Sjögren's adds a significant emotional burden to their life, having at least some negative impact on relationships with friends and family (63%), sex life (59%), relationships with spouse/partner (55%), and caring for their children (19%). Sjögren's patients 60 years of age and under were more likely than those over 60 to say living with Sjögren's adds a significant emotional burden to their life (80% vs. 71%). Sjögren's patients diagnosed with the disease 0-4 years ago were more likely than those diagnosed with Sjögren's 5-9 years ago to say their overall mood has been negatively affected by Sjögren's a lot or a great deal (42% vs. 36%).



Impact on Relationships



Financial Impact of Sjögren's

Two in three (66%) Sjögren's patients said living with Sjögren's adds a significant financial burden to their life. Sjögren's patients 60 years of age and under reported spending more money, on average, on treatments and were more likely than those over 60 to say living with Sjögren's adds a significant financial burden to their life (72% vs. 63%). When asked how much money they spent on different types of medical expenses in the past 12 months, patients said they spent the most, on average, on dental care followed by prescription medications, and healthcare appointments/ co-payments.

Hope for New Treatments

The vast majority (96%) of Sjögren's patients reported they wish there were additional treatments available. Four-in-five (82%) said that it is extremely important/absolutely essential that new systemic therapies addresses dryness symptoms throughout their body (eyes, mouth, skin, vagina). Respondents also identified the importance of the need for new treatments for fatigue (63%), brain fog/forgetfulness (53%), sleep problems (51%), joint pain or swelling (48%) and muscle pain (43%).

"The Sjögren's Syndrome Foundation is committed to accelerating the development of better diagnostic, management and therapeutics that will have the greatest potential impact on improving the quality of life for Sjögren's patients."

- Steven Taylor, CEO, Sjögren's Syndrome Foundation

About the Survey

Living with Sjögren's was conducted in the United States using a paper instrument by Harris Poll on behalf of the Sjögren's Syndrome Foundation between May 11 and July 11, 2016. The research, conducted among 2,962 adults aged 18+ who reported having been diagnosed with Sjögren's by a medical professional or doctor, examined the variety and severity of experiences Sjögren's patients have with Sjögren's and the impact it has on their quality of life. Data was not weighted and therefore represents only the individuals surveyed. Because the sample was based on the individuals from SSF's database who agreed to participate, it is not possible to estimate a theoretical sampling error.

About the Sjögren's Syndrome Foundation

The Sjögren's Syndrome Foundation is the only non-profit organization focused on increasing research, education and awareness for Sjögren's, one of the most prevalent autoimmune disorders, affecting as many as four million Americans, with an estimated 2.5 million patients currently undiagnosed. For more information, visit www.sjogrens.org or call 1-800-475-6473.

Sjögren's Syndrome Foundation

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investigators at the Forsyth Institute and Harvard Dental School of Medicine. Zhou *et al* found that PD-L1 and PD1 work together to interfere with normal protective immunity and worsen autoimmune responses. Their findings point to a potential therapeutic target in the PD-L1-PD1 pathway.

1. Zhou J, Jin JO, Kawai T, Yu Q. Endogenous programmed death ligand-1 restrains the development and onset of Sjögren's syndrome in non-obese diabetic mice. *Sci Rep*. 2016 Dec 14;6:39105. PMID: 27966604.

Gene Expression Profile Changes Lead to Salivary Gland Inflammation and Dysfunction

Investigators at the NIDCR, NIH in Bethesda and Jefferson College of Biomedical Sciences, Thomas Jefferson University in Philadelphia have identified a role for two chemokines in salivary gland inflammation and loss of salivary function.[1] After using laser microdissection to access salivary gland tissue from subjects with and without Sjögren's, RNA-seq analysis was performed on acinar, ductal and infiltrating cells.

A major difference was found in gene expression changes in ductal and infiltrating cells compared to acinar cells. Activity of two chemokines associated with immune cell trafficking, CCR7 and CCL21, was markedly increased in Sjögren's patients and could contribute to inflammation and loss of salivary function.

1. Tandon M, Perez P, Burbelo PD, Calkins C, Alevizos I. Laser microdissection coupled with RNA-seq reveal cell-type and disease-specific markers in the salivary gland of Sjögren's syndrome patients. *Clin Exp Rheumatol*. 2017 Apr 18. [Epub ahead of print] PMID: 28421997

Ocular

Restasis® Offered in Multi-Dose Bottle

Restasis®, cyclosporine ophthalmic emulsion 0.05%, is now available in a multi-dose bottle. Similar to traditional individual vials of the therapy, Restasis® Multidose™ offers sterile delivery and contains no preservatives. The new delivery system uses a patented unidirectional valve and air filter technology that eliminates the need for a preservative.

Restasis® was the first prescription therapy to hit the market for dry eye. Produced by Allergan, it reduces inflammation to help increase tear production in chronic dry eye. The product will continue to be offered in the traditional individual single-dose vials, with the cost being similar for either delivery system.

Two Potential Dry Eye Therapies Make Progress

Clinical Trials Begin for one Potential Therapy

Human trials are just being launched for a dry eye therapy that differs from other such therapies in that it attempts to treat the cause of dry eye. Phase I/II trials at 27 U.S. sites are underway using Lacripep™ in Sjögren's patients with dry eye. The tear protein lacritin (discovered by Gordon Laurie and his lab at the University of Virginia) and Lacripep™ (which naturally exists in tears as a lacritin fragment) are dramatically deficient in the tears of Sjögren's patients compared to healthy subjects. Lacripep restores the natural basal tearing mechanism, including the corneal nerves that trigger the production of tears.[1]

Laurie formed the company, Tear Solutions, Inc., to produce Lacripep, which then contracted with Lexitas Pharma Services in Durham, North Carolina to oversee the clinical trials.

1. McNamara NA, Ge S, Lee SM, Enghauser AM, Kuehl L, Chen FY, Gallup M, McKown RL. Reduced Levels of Tear Lacritin Are Associated With Corneal Neuropathy in Patients With the Ocular Component of Sjögren's Syndrome. *Invest Ophthalmol Vis Sci*. 2016 Oct 1;57(13):5237-43. PMID: 27711909.

Another Potential Therapy is Licensed

Novartis will license a potential new ocular therapy everywhere but Europe subject to regulatory approval and other standard closing conditions. The therapy already is licensed for Europe to Dompe, an Italian pharmaceutical company.

Lubricin is a natural lubricant that is deficient in dry eye patients. A small Phase II study demonstrated the efficacy of ECG843, a recombinant human lubricin protein, in improving signs and symptoms of dry eye. The protein was discovered by David Sullivan, PhD and colleagues at Schepens Eye Research Institute, Harvard Medical School, who then formed Lubris BioPharma, LLC which made the deal with Novartis. Lubris compares the protein to Teflon on non-stick pans. Earlier, lubricin was shown to improve dry eye signs and symptoms compared to sodium hyaluronate (HA).[1]

1. Lambiase A, Sullivan BD, Schmidt TA, Sullivan DA, Jay GD, Truitt ER 3rd, Bruscolini A, Sacchetti M, Mantelli F. A Two-Week, Randomized, Double-masked Study to Evaluate Safety and Efficacy of Lubricin (150 µg/mL) Eye Drops Versus Sodium Hyaluronate (HA) 0.18% Eye Drops (Vismed®) in Patients with Moderate Dry Eye Disease. *Ocul Surf*. 2017 Jan;15(1):77-87. PMID: 27614318.

Shire Gains Rights to New Potential Dry Eye Therapy

Shire, which just launched Xiidra® (lifitigrast) for treatment of Dry Eye Disease (DED) last summer, now has a new potential therapy for DED in its arsenal. Shire has purchased worldwide rights to P-321 ophthalmic solution developed by Parion Sciences, Inc. of Durham, North Carolina. A Phase I/IIa trial of P-321, an epithelial sodium channel inhibitor, demonstrated potential improvement of dry eye symptoms compared to placebo. Plans for a Phase IIb trial are underway.

Allergan Develops Nerve Stimulator to Increase Tears

An intranasal tear stimulator developed by Allergan has received FDA clearance. TrueTear™ is a handheld device that stimulates the trigeminal nerve and temporarily increases tear production.

Functional Recovery of Lacrimal Glands with Progenitor Cell Treatment

Gromova *et al* have established a potential therapeutic approach for aqueous-deficient dry eye. Using endogenous lacrimal gland epithelial cell progenitors (EPCPs), the researchers injected the cells into damaged lacrimal glands of the human Sjögren's mouse model TSP1-/-. This resulted in long term engraftment of the EPCPs and functional recovery of the glands.[1] EPCP-treated mice demonstrated reduction of cell infiltration into the lacrimal glands, differentiation of the donor EPCPs into secretory acini and improvement of structural integrity and function of the lacrimal glands. The Scripps Research Institute scientist and senior author of the work, Helen Makarenkova, PhD, told Drug Discovery and Development, "This is the first step in developing future therapies for the lacrimal gland."

1. Gromova A, Voronov DA, Yoshida M, Thotakura S, Meech R, Dartt DA, Makarenkova HP. Lacrimal gland repair using progenitor cells. Stem Cells *Transl Med*. 2016 Aug 15.

Editors Note: Dr. Makarenkova received an SSF research grant in 2009 and 2010 for her project on Molecular Mechanisms of Lacrimal Gland Development and Regeneration.

Eye Pain and Dry Eye Severity Correlated

Ocular pain is associated with a greater severity of dry eye, according to a longitudinal study of 120 dry eye patients.[1] Nearly half of the dry eye patients, or 44.8%, progressed to more severe dry eye one year later. Ocular pain and neuropathic pain-like ocular symptoms were determined to be risk factors. Sleep disturbance, mental health status, medications and non-ocular pain did not contribute to a risk of greater dry eye severity. Ong *et al* conclude that gauging ocular pain and ocular pain perception is an important tool when evaluating and managing dry eye patients.

1. Ong ES, Alghamdi YA, Levitt RC, McClellan AL, Lewis G, Sarantopoulos CD, Felix ER, Galor A. Longitudinal Examination of Frequency of and Risk Factors for Severe Dry Eye Symptoms in US Veterans. *JAMA Ophthalmol*. 2016 Dec 22. PMID: 28006039.

Dry Eye Affects Reading Speed

Reading speed evaluations may find utility as a measure for functional impairment in dry eye patients. Research from Mathews *et al* of Johns Hopkins University in Baltimore, Maryland, has demonstrated that patients with dry and normal visual acuity read more slowly compared to controls. Director of the Ocular Surface Disease and Dry Eye Clinic at the Wilmer Eye Institute of Johns Hopkins, member of the SSF Board of Directors, and senior author Esen Akpek, MD said "even though [dry eye patients] had normal visual acuity, during a 30-minute reading test, patients with dry eye read out loud and silently and more slowly than normal." Each study participant engaged in three reading tests. They performed two out-loud reading speed tests and a novel 30-minute silent reading speed test. Dry eye patients performed all three reading tests more slowly, but the researchers report that in the sustained silent reading test, dry eye patients were 14% slower than controls.

Mathews PM, Ramulu PY, Swenor BS, Utine CA, Rubin GS, Akpek EK. Functional impairment of reading in patients with dry eye. *Br J Ophthalmol*. 2016 Jul 22.

Understanding of Lacrimal Gland Phenotypes Increases

The number and diversity of lacrimal gland (LG) autoimmune and immune-mediated inflammatory process (IMIP) phenotypes might be higher in number and more diverse than previously recognized, according to a new study published by Mircheff *et al*.[1] Currently, at least 4 IMIP LG phenotypes have been identified in Sjögren's. This study introduces new protocols and demonstrates the usefulness of Principal Component Analysis (PCA) in generating and characterizing LG phenotypes. Ultimately, understanding these multidimensional phenotypes could lead to better diagnostics in Sjögren's, the identification of phenotype-specific therapeutic targets and improve patient classification for clinical trials.

1. Mircheff AK, Wang Y, Schechter JE, Li M, Tong W, Attar M, Chengalvala M, Harmuth J, Prusakiewicz JJ. Multiple Natural and Experimental Inflammatory Rabbit Lacrimal Gland Phenotypes. *Ocul Surf*. 2016 Oct;14(4):460-483.

Oral

Does Calcium Sodium Phosphosilicate Improve Tooth Remineralization?

Calcium sodium phosphosilicate (CSPS) has been found not to hinder nor help the remineralization of caries lesions.[1] A single-center, randomized, placebo-controlled blinded trial involving 77 subjects investigated whether adding the use of CSPS to that of a non-aqueous fluoride-containing toothpaste would affect cariostatic properties. While the CSPS had no effect, the level of fluoride in the five dentifrices used did have an impact, with higher fluoride concentrations leading to a higher degree of remineralization.

1. Parkinson CR, Siddiqi M, Mason S, Lippert F, Hara AT, Zero DT. Anticaries Potential of a Sodium Monofluorophosphate Dentifrice Containing Calcium Sodium Phosphosilicate: Exploratory in situ Randomized Trial. *Caries Res*. 2017 Feb 21;51(2):170-178. PMID: 28219056

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"Medical, Science & Industry News" Continued from page 11 ▼

Do Key Oral Hygiene Regimens Help Decrease Caries?

A longer time spent brushing one's teeth and the quantity of fluoride-containing dentifrice used likely help tooth remineralization. According to a recent study by Creeth *et al*, the benefits of using these tools to prevent caries had a statistically significant impact on remineralization, fluoride uptake and net acid resistance.[1] The study showed that these actions influence fluoride bioactivity and thus have the potential to reduce caries.

1. Creeth JE, Kelly SA, González-Cabezas C, Karwal R, Martinez-Mier EA, Lynch RJ, Bosma ML, Zero DT. Effect of toothbrushing duration and dentifrice quantity on enamel remineralisation: An in situ randomized clinical trial. *J Dent*. 2016 Dec;55:61-67. PMID: 27717756.

Is One Type of Fluoride More Effective Than Another, and is Fluoride Better Than no Fluoride?

Different toothpastes containing fluoride were found to be equally effective when compared to one another and more effective than placebo in a recent study.[1] The single-center, randomized, placebo-controlled trial compared the use of two low- and medium-abrasive gel-to-foam fluoride toothpastes and a standard reference toothpaste – all with 1,450 ppm fluoride as NaF. These were compared to one another and compared to a toothpaste with no fluoride. Percent surface microhardness recovery (%SMHR) and percent relative erosion resistance (%RER) were measured. All dentifrices with fluoride fared equally well and were superior to the non-fluoride dentifrice.

1. Nehme M, Jeffery P, Mason S, Lippert F, Zero DT, Hara AT. Erosion Remineralization Efficacy of Gel-to-Foam Fluoride Toothpastes in situ: A Randomized Clinical Trial. *Caries Res*. 2016;50(1):62-70. PMID: 26862746

A Natural Means for Treating Large Cavities?

Large cavities could eventually be repaired without using traditional fillings if the findings of researchers at King's College London Dental Institute in the U.K. are proven in human clinical trials.[1] The new method stimulates the renewal of living stem cells in tooth pulp using a biodegradable collagen sponge containing three small-molecule glycogen synthase kinase (GSK-3) antagonists. One of the antagonists, Tideglusib, has already demonstrated safety in much larger doses than would be used in dentistry in clinical trials for Alzheimer's patients. Investigators hypothesize that dentine will replace the sponge over time and the decayed tooth will repair itself naturally, offering a simple and non-invasive approach to treating caries.

1. Neves VC, Babb R, Chandrasekaran D, Sharpe PT. Promotion of natural tooth repair by small molecule GSK3 antagonists. *Sci Rep*. 2017 Jan 9;7:39654. PMID: 28067250.

Topical Solution in the Works Might Stop Caries

Investigators at the University of Pennsylvania School of Dental Medicine have developed an oral topical solution prototype that could potentially stop caries development.[1] The solution uses plant-produced antimicrobial peptides to control oral biofilms and kill *Streptococcus mutans* and could be delivered via an oral rinse or in chewing gum. Traditionally, plant-produced protein drugs have had little usefulness in dentistry because of the need to deliver them via invasive surgery, so their deliverance as a topical solution would be novel, easy to use and much less costly. This concept for decreasing dental caries still must be assessed in a clinical setting.

1. Liu Y, Kamesh AC, Xiao Y, Sun V, Hayes M, Daniell H, Koo H. Topical delivery of low-cost protein drug candidates made in chloroplasts for biofilm disruption and uptake by oral epithelial cells. *Biomaterials*. 2016 Oct;105:156-66. PMID: 27521618

For the range of patients with xerostomia

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References: 1. NeutraSal® [Instructions for Use]. Invado Pharmaceuticals LLC. **2.** Levin EZ. Management of xerostomia and microflora with supersaturated calcium-phosphate rinse. 2013. Available at www.neutrasal.com. Accessed May 13, 2015.

*Eligibility Restrictions and Requirements: The NeutraSal® Direct Access Program is available for US residents only. All prescriptions must be dispensed from a pharmacy qualified by the NeutraSal® Direct Access Program. The program is not valid for prescriptions eligible to be reimbursed, in whole or in part, by Medicare, Medicaid, Tricare, or any other federal- or state-funded healthcare benefit program, or by private plans or other health or pharmacy benefit programs which reimburse the patient for the entire cost of the prescription drugs. The maximum copay coverage is $125 per box. The NeutraSal® Direct Access Program does not represent prescription drug coverage or insurance and is not intended to substitute for such coverage. By using this program, the patient agrees not to make such a claim under such programs and the patient is responsible for reporting to its insurer these copay reimbursements. OraPharma, Inc., and Valeant Pharmaceuticals reserve the right to rescind, revoke, or amend this offer without notice. Offer is void where prohibited or restricted.

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Research UPDATES

How Best To Treat a Filling Gone Bad

Your dentist is part of the National Dental Practice-Based Research Network, a group of dental practices that treat patients and also do dental research. For more information go to **www.nationaldentalpbrn.org.**

As you may have already experienced, fillings in your teeth can get worn out, chipped, or cracked. What's the problem with having some nicks and dents in a tooth? They can create tiny openings where bits of food and bacteria hide and, over time, cause tooth decay.

Dentists have thought that replacing, instead of repairing, fillings gone bad is better for the patient. **But a new study has found that repairing a filling is often a good choice, compared to replacing it.** That's good news for you because repairs under the right circumstances may be quicker and less expensive than replacements.

Why repairing a filling can be a good option

- Compared to replacing fillings, repairing them often lasts about the same amount of time and causes less damage and stress to the rest of the tooth, the study found.
- The study did not show that it's always better to repair a bad filling than replace it, but it did show that dentists should **consider** repairing versus replacing more often than they now do.
- A thorough examination, which may include x-rays of your teeth, helps your dentist find problems before the filling fails or you get that tell-tale toothache.
- *Your dentist will decide on the best treatment for you. Every patient and tooth is different!*

More about the study

Dentists participating in the study repaired one-fourth of the thousands of worn out or damaged fillings they examined as part of the study, and they replaced the rest. After one year, most of the repaired and new fillings were fine. Only 5 percent of the replaced and 7 percent of the repaired ones needed follow-up care—and the new fillings needed more work to fix than the repaired fillings did.

Why do some fillings go bad sooner than others?

Daily activities, like eating or clenching your teeth, gradually wear out your fillings. Here's what else can affect how long your fillings last:

- The material used to fill your cavity
- The type and size of the cavity
- How well you care for your teeth and gums—your oral health
- Your overall risk for cavities.

Reference: Gordan VV, Riley JL, Rindal DB, Qvist V, Fellows JL, Dilbone DA, Brotman SG, Gilbert GH. Repair or replacement of restorations: a prospective cohort study by dentists in The National Dental PBRN. *Journal of the American Dental Association.* 2015;146(12):895-903

Funded by National Institutes of Health grant U19DE22516

To ensure excellent dental care, the Network carries out our studies in real-world settings—like your dentist's office—with regular patients like yourself who volunteer to participate. The studies wouldn't be possible without the involvement of our wonderful patients.

Thanks to everyone who participated in this and all of our studies!

SSF in Action!

Meetings Highlights

SSF Talks Patient Engagement in Clinical Trials

SSF CEO Steven Taylor participated in a panel-discussion at the 2016 Partnerships in Clinical Trials (PCT) conference held as part of Biotech Week Boston in October. Taylor joined other patient engagement experts to discuss "How to Incorporate Patient Insights into a Drug Development Program?" In addition to patient centricity and engagement, the conference explored topics including strategic partnership in the clinical trial space, data/informatics and innovation/disruptive technologies.

Steven Taylor, SSF CEO

SSF Speaks at Tear Film & Ocular Surface (TFOS)

SSF Vice President of Medical and Scientific Affairs Katherine Hammitt presented at the 8th International Conference on the Tear Film & Ocular Surface: Basic Science and Clinical Relevance. The conference took place from September 7-10, 2016, at the Corum in Montpellier, France. This conference allowed top scientists to assess the current knowledge and 'state of the art' research on the structure and function of the tear film and ocular surface in health and disease. Hammitt presented on the work of the TFOS DEWSII Public Awareness and Education Committee, which she chairs. The TFOS DEWSII report will be published in early summer of 2017.

American College of Rheumatology Annual Meeting

SSF Booth at ACR

The SSF was out in force during the annual American College of Rheumatology meeting in November. Members of the SSF Medical & Scientific Advisory Board and friends led numerous educational programs including "Clinical Conundrums in Sjögren's" with Julius Birnbaum, MD, MHS, Alan Baer, MD, and E. William St. Clair, MD; "When to Consider Childhood Sjögren's" with Scott Lieberman, MD, PhD; and "Controversies in Sjögren's" with Frederick Vivino, MD as part of the Meet the Professor series. In addition, two study groups – the annual Sjögren's Study Group led by Athanasios Tzioufas, MD and including Kathy Sivils, PhD and a second Study Group on Childhood Sjögren's led by Lieberman and including Jay Mehta, MD, MS – and two oral abstract sessions on Sjögren's were held. The SSF also hosted its annual luncheon program and an SSF Clinical Trials Consortium meeting, held meetings on the SSF Clinical Practice Guidelines, and met with many colleagues and pharmaceutical companies interested in clinical trials in Sjögren's.

Education

Carteron Delivers Sjögren's Audio Lectures

Medical and Scientific Advisory Board Chair and Member, SSF Board of Directors, Nancy Carteron, MD, FACR, delivered two lectures on Sjögren's for Henry Stewart Talks Ltd (HSTalks).

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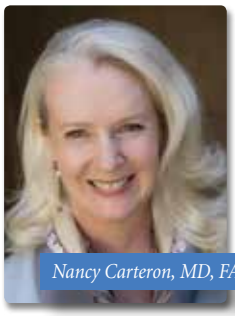
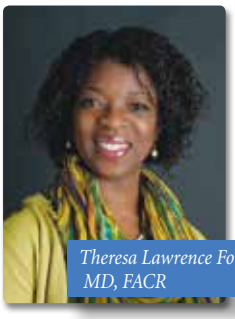
"SSF in Action" Continued from page 15 ▼


Nancy Carteron, MD, FACR

HSTalks is a leading provider of specially prepared, animated, online, audio-visual lectures, seminar-style talks and case studies for medical schools in over 60 countries around the world. Carteron's lectures, "Sjögren's disease – symptoms, clinical signs and treatment & Sjögren's disease – epidemiology, etiology, pathogenesis," are available online at www.hstalks.com.

Ford Talks Sjögren's, Clinical Trials at Rheumatology Meetings


Theresa Lawrence Ford, MD, FACR

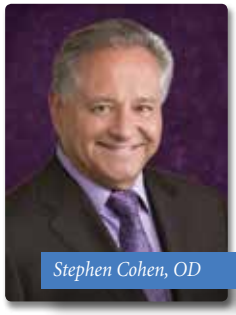
Theresa Lawrence Ford, MD, FACR, was invited to deliver a lecture on Sjögren's at the Ohio Association of Rheumatology's 11th annual meeting. She covered clinical presentation, classification criteria and laboratory findings, the relationship between Sjögren's and other autoimmune diseases, the risk for lymphoma, and current and future therapies.

Ford also presented an educational lecture on clinical trials and performing them for future investigators at the recent Association of Women in Rheumatology (AWIR) meeting. Dr. Ford of North Georgia Rheumatology Group, PC serves on the AWIR Board of Directors as Treasurer, Chairs the SSF Clinical Trials Consortium, and serves on the SSF Board of Directors.

PhRMA Research and Hope Awards

Cynthia Lopynski and Patricia Hurley, MSc of the Sjögren's Syndrome Foundation's Board of Directors and SSF CEO Steven Taylor attended the Pharmaceutical Research and Manufacturers of American (PhRMA) 2016 Research & Hope Awards in Washington, D.C on September 13. This year's program celebrated the progress and promise of Autoimmune Research & Care. PhRMA recognized patient advocates and researchers for their tireless efforts to advance the treatment and care of patients with autoimmune diseases. Among them, SSF Vice President of Medical and Scientific Affairs, Katherine Hammitt, was honored and provided insight into the autoimmune patient experience. The evening featured a keynote address by actress Jamie-Lynn Sigler who was diagnosed with multiple sclerosis in 2002 and is best known for her role in the HBO television series "The Sopranos."

SSF Leaders Interviewed by Tear Film & Ocular Surface


Stephen Cohen, OD

Two SSF members of the TFOS DEWSII (Dry Eye Workshop II) initiative were interviewed by Dominica Drazal, Director of TFOS Global Ambassador Program, for posting on the TFOS blog (tfosblog.org) and Facebook in November. The Chair of the SSF Board of Directors, Stephen Cohen, OD, discussed the rise in dry eye in children due to use of electronic gadgets. According to an American Optometric Association 2015 survey, parents say their children spend more than three hours a day using digital devices. Cohen said, "When parents read that artificial light can provoke obesity or cancer, they are most likely to panic. Why don't they have the same reaction when hearing that artificial light can trigger dry eye?"

Drazal also sat down with Katherine Hammitt, our own SSF Vice President of Medical and Scientific Affairs and Chair of the TFOS Public Awareness & Education Subcommittee. They talked about advocating for change, overseeing SSF key research and medical initiatives to increase knowledge about Sjögren's, improving idea exchange to accelerate research and setting the stage for better Sjögren's management through awareness and fundraising. In the article, Hammitt asked doctors and researchers to "pause for a moment and acknowledge how difficult it is to live with an invisible disease. Even worse, imagine living a normal life, and then, increasingly suffering from an onslaught of ailments, resulting in a diagnosis and the assumption of a new normal - a new normal that is extremely painful and debilitating, ultimately upending families, careers and daily lives, and one that cannot be readily cured."

Dry Eye Awareness Month

A coalition has formed that is excited to reinvigorate and expand July as Dry Eye Awareness Month. The SSF, working with the National Women's Health Resource Center, launched Dry Eye Awareness Month in 2006 after Senator Mark Dayton, D-Minnesota, obtained recognition for it in the Congressional Record. The effort will help draw attention to the TFOS-Dry Eye Workshop II (DEWSII) report which is slated to be published in early summer of this year. Our own Vice President of Scientific and Medical Affairs, Katherine Hammitt, has been instrumental in contributing to the DEWSII report. ■

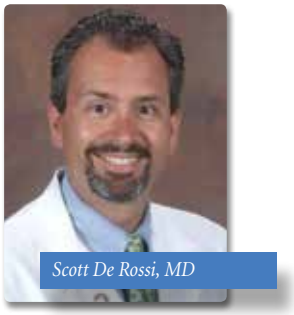
Transitions


Vidya Sankar, DMD, MHS

Former SSF Board of Directors member, Vidya Sankar, DMD, MHS, has moved her practice to Brigham and Women's Hospital, Boston, MA. Before joining Brigham and Women's, she was an Associate Professor with tenure and Director of the Oral Medicine Clinic at the Center for Oral Health and Research at the School of Dentistry, University of Texas Health Science Center, San Antonio, TX.

Dr. Sankar Co-Chaired the Topic Review Group on "Use of Biologics for Sicca Symptoms" for the SSF Clinical Practice Guidelines, which were published online in the summer of 2016 and appeared in hard copy in *Arthritis Care & Research* in April.[1]

1. Carsons SE, Vivino FB, Parke A, Carteron N, Sankar V, Brasington R, Brennan MT, Ehlers W, Fox R, Scofield H, Hammitt KM, Birnbaum J, Kassan S, Mandel S. Treatment Guidelines for Rheumatologic Manifestations of Sjögren's Syndrome: Use of Biologic Agents, Management of Fatigue, and Inflammatory Musculoskeletal Pain. *Arthritis Care Res* (Hoboken). 2017 Apr;69(4):517-527. PMID: 27390247


Scott De Rossi, MD

Friend of the SSF, Scott De Rossi, MD, was named the new dean of the School of Dentistry at The University of North Carolina at Chapel Hill. De Rossi was most recently Chair of the Oral Health and Diagnostic Sciences Department at Augusta University's Dental College of Georgia. ■

Sjögren's Syndrome Foundation

Legacy of Hope

If you would like to receive information on how you can *Leave a Legacy* to support the Sjögren's Syndrome Foundation's critical research initiatives or to support one of our many other programs, please contact Steven Taylor at (800) 475-6473.

Leave A Legacy – Remember Us in Your Will

NIDCR 2030: Envisioning the Future Together

The National Institute of Dental and Craniofacial Research (NIDCR) at the National Institutes of Health (NIH) has developed a program to gather new research ideas for the future called "NIDCR 2030: Envisioning the Future Together." The program website provides an opportunity for everyone from healthcare providers and researchers to patients to submit ideas for research and to vote on ideas that already have been submitted.

The Sjögren's Syndrome Foundation (SSF) urges you to take a look, submit your ideas, and add your vote to those ideas that are relevant for Sjögren's patients. NIDCR Director, Dr. Somerman, asks us to think outside the box and submit ideas based on dreams that we would hope could happen someday and not to worry about the practicality of getting there. Of course, ideas that have a practical basis in what we know now also are welcome.

Here's how to provide input:

- Go to https://nidcr2030.ideascale.com/
- Register
- Add the NIDCR 2030 as a Community
- Click on "Submit New Idea" or click on one of the 5 overarching areas for which ideas have already been submitted

If you have questions, read the information under the "How to Participate" tab.

NIAID Researchers Seek People with Chronic Mucocutaneous Yeast Infections

Yeast is a fungus that lives almost everywhere, including in the human body where the immune system usually keeps it under control. Current treatment options are limited, and resistance to them can develop. Treatment is especially difficult for Sjögren's patients with dry mouth.

Researchers at the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH) in Bethesda, Maryland, are seeking people with chronic mucocutaneous candidiasis who are not responding to standard non-intravenous treatment to volunteer in a clinical research trial to evaluate the safety and effectiveness of an oral medication.

Read more about the clinical trial of CAMB/MAT2203 in Patients With Mucocutaneous Candidiasis (study ID NCT02629419) http://clinicaltrials.gov/ct2/show/NCT02629419.

Adapted from an announcement from NIAID, NIH

Save the Date for the next ISSS!

Next year, over 400 clinicians and scientists will meet for 2 ½ days in Washington, DC for the 14th International Symposium on Sjögren's Syndrome (April 18-21). First held in 1986, this important meeting has been hosted in the United States only three times. Drs. Alan Baer (rheumatologist) and Esen Akpek (ophthalmologist) from the Jerome Greene Sjögren's Syndrome Center at Hopkins and Dr. Ilias Alevizos (oral medicine specialist) from the Sjögren's Syndrome Clinic at the National Institutes of Health have the honor of serving as co-chairs. The meeting is being coordinated by the Johns Hopkins Office of Continuing Medical Education.

This symposium is the leading venue for scientists and clinicians from different disciplines to come together and present their latest research on Sjögren's. It is the only such meeting in the world to do this. The meeting serves to foster important collaborations, set the agenda for research in the field, and introduce young investigators to an important area of study.

An important goal of the co-chairs is to support young investigators at the meeting, with the provision of travel funds, reduced registration fees, and awards for best papers. This type of support for young investigators will require elicitation of support for the meeting by various sponsors, including pharmaceutical companies, NIH, and private foundations.

The International Sjögren's Syndrome Symposium (ISSS) is the only international meeting specifically dedicated to Sjögren's. It occurs every 2-3 years and brings together oral medicine specialists, rheumatologists, ophthalmologists, drug developers and basic researchers to present their latest research findings and insights on the topic of Sjögren's. The previous meeting was in Norway in May 2015 and the last meeting in the USA was in 2006. Ilias Alevizos, Tenure Track Investigator, NIDCR (oral medicine), Alan Baer, Associate Professor of Medicine, Johns Hopkins (rheumatology) and Esen Akpek, Professor of Ophthalmology, Johns Hopkins (ophthalmology)] competed successfully before an international committee to host the 14th symposium in the United States in 2018, and opted to do this in Washington, D.C. from April 18-21.

The primary objective of the 14th ISSS will be to foster successful drug development and clinical trial design for Sjögren's.

The title of the symposium will thus be "Sjögren's Syndrome: Paths to Precision Diagnosis and Therapy." The symposium will focus on identifying disease subsets through the use of biomarkers, genetic tests and molecular studies of target tissue, clinical trial design and outcome measures, standardization of salivary gland histopathologic scoring, and identification of pathophysiologic pathways amenable to therapeutic targeting.

The secondary objectives of the 14th ISSS include:

- To develop consensus on a protocol for the histopathologic interpretation of labial and parotid gland biopsies, to be used for SS diagnosis in clinical practice and as an entry criterion and outcome measure for clinical trials.
- To develop consensus on a standardized format for cohort database entries. With the advent of high-throughput sequencing data, we have the opportunity to initiate collaborations and exchange ideas on how to obtain and organize the appropriate clinical information and link them to genetic data to better interpret this plethora of information. We will host a workshop for academic groups with large SS cohorts to reach this consensus.
- To bring together young investigators, clinical fellows and postdoctoral associates in this international, focused conference and provide them with the chance to present their work, exchange ideas and network with more senior investigators in the field.

Watch for more information at http://tinyurl.com/ISSS2018.

Sjögren's Syndrome Foundation

Patient Education Sheet

Understanding Clinical Trials

by Herbert S. Baraf, MD, FACP, MACR
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Clinical Research, Clinical Trials, Clinical Studies, Protocols

These are terms that describe the process by which we advance our understanding of disease and make medical progress in treatment.

Goals of Clinical Research

- Identify causes of disease
- Evaluate treatment options with either new or existing medications or therapies
- Compare treatments

Phases of Drug Development

Before being tested in humans, new treatments are usually evaluated in animals to evaluate basic measures of therapeutic effect and safety. Once certain safety criteria are met and the nature of the effect a drug has in animals is understood, the drug may move on to testing in human volunteers. This testing occurs in four phases:

Phase 1

- The first testing of a drug in humans
- Conducted with a small number of volunteers (20-100 participants)
- Purpose is to determine how the body handles a drug – how it is metabolized and eliminated
- Screens for adverse effects

Phase 2

- Small-scale program in up to a few hundred patients with the targeted disease
- Purpose is to evaluate efficacy and side effects and to determine ideal dosing
- About 33% of drugs studied in phase 2 go on to the next phase

Phase 3

- Larger number of patients with disease studied (from 200 to >3,000); Primary concern is effectiveness and safety
- About 25-30% of new treatments are eventually approved

Phase 4

- These studies are usually performed after a drug has been approved.
- Often mandated by the FDA and agreed to by the sponsor (drug company) as a condition of drug approval
- Large-scale program evaluating several thousand volunteers with focus on safety

Will I always get the new drug if I participate?

Earlier phase trials usually dispense the new medication to all patients.

Later phase trials usually involve randomly receiving a placebo or the medication being tested in one or more doses. This is called a placebo-controlled Randomized Clinical Trial (RCT) and is considered the gold standard for determining whether a medication works or not. Neither the patient or the clinician knows whether the patient is receiving a placebo or the drug.

In some late phase trials, all patients will receive the active drug; the informed consent and the personnel conducting the study will make this clear at the outset of the trial

Please see the Patient Education Sheet on "Clinical Trials – Getting Involved" for more information on clinical trials. This sheet will appear in the summer 2017 issue of the Sjögren's Quarterly and is available on the SSF website at http://www.sjogrens.org/home/about-sjogrens/brochures-and-fact-sheets.

Additional information and a list of specific trials currently available for enrollment can be viewed by visiting http://www.sjogrens.org/news/486-sjogrens-s-clinical-trials.

For more information on Sjögren's, contact the Sjögren's Syndrome Foundation at:
6707 Democracy Blvd, Suite 325, Bethesda, MD 20817 • 800-475-6473 • www.sjogrens.org • ssf@sjogrens.org.

Sjögren's Quarterly
Sjögren's Syndrome Foundation Inc.
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Pipeline Grows for

Potential Therapies in Sjögren's

According to an April 2017 report on therapies in the pipeline, 29 therapies are now in the active stage of development for Sjögren's. The "Sjögren's Syndrome Therapeutics Pipeline Analysis, 2017 – Clinical Trials & Results, Patent, Designation, Collaboration and Other Developments," produced by P&S Market Research, cites three drugs currently in Phase III trials, ten in Phase II trials, seven in Phase I trials, and nine therapies in preclinical stages. In all, 42 candidates for treating Sjögren's are under consideration by pharmaceutical companies. The therapies fall under the following categories:

Approximate %	Type of Therapy
38%	Biologics
35%	Small molecules
10%	Fusion proteins
16%	Includes proteins, peptides, and recombinant proteins

The Sjögren's Syndrome Foundation (SSF) spearheads an international initiative, the SSF Clinical Trials Consortium, to increase the availability and accessibility of therapies for Sjögren's. Chaired by Theresa Lawrence Ford, MD, this SSF consortium works closely with pharmaceutical companies that are implementing or considering potential therapies for treating Sjögren's and identifies and tackles barriers to the development of new therapeutics. This issue of the *Sjögren's Quarterly* includes the first of two Patient Education Sheets that cover understanding and participating in clinical trials. Watch for upcoming articles on conducting clinical trials from the physician's perspective and an in-depth look at what the SSF is doing to ensure new therapies enter clinical trials for Sjögren's. ■