Following Autoimmune Diseases Through Patient Interactive Diaries: **Continuous Quality Improvement**

BY KATELYN M. UPDYKE, BS; BRITTANY URSO, BS; HAIDER ALI, BS; IAN BROOKS, PHD; VERNON BURTON, PHD; ROBERT P. DELLAVALLE, MD, PHD, MSPH; AND JAMES A. SOLOMON, MD, PHD

Autoimmune diseases (AID) usually generate autoantibodies that can cause immune complex driven tissue inflammation and end-organ damage. For example, antinuclear autoantibodies (ANA) are often present in various AID and can form immune complexes that lead to disease. Furthermore, there are other autoantibodies capable of causing immune complex disease, including anti-Smith, anti-dsDNA, anti-SSA, etc. These diseases often have unpredictable flares in symptoms that can be difficult to manage and are associated with treatment regimens that are not without serious side effects.[1,2] However, some studies have shown that different exogenous exposures are capable of triggering flares in certain AID. For example, cigarette smoke, photosensitizing drugs, and ultraviolet exposure can all lead to a decline of self-tolerance and induction of autoimmunity in patients with systemic lupus erythematosus.[3] Additionally, dietary risk factors have been associated with several AID. A diet rich in animal protein has a predisposing role in Crohn's disease, while the consumption of milk, animal fat, and meat may have a positive incidence in both Multiple Sclerosis and Rheumatoid Arthritis.[4] The reagents used to identify ANA and other "autoantibodies" fail to include individualized self-DNA nor pooled human DNA, but rather DNA from animal sources or human-viral malignant cell lines.[5] Reactions to the non-self-antigens correlate with true autoantibodies. Nonetheless, these reactions also identify antibodies against the exogenous DNA from the reagent source. Because people believed that ingested DNA will not pass through the gut/blood barrier, this cross reactivity has not been considered clinically relevant. Now, however, this assumption that DNA cannot pass the gut/blood barrier has been shown to be inaccurate; Several published studies show that ingested animal DNA can access peripheral circulation in humans, as well as in animal models.[6]

Previous studies have linked vegan diets with protection against AID. Vegan diets have been shown to decrease disease activity in rheumatoid arthritis patients and lower the risk of hypothyroid disease.[7] Thus, we hypothesize that certain subpopulations of patients with AID are not only generating immune complex disease against self-antigen, but also are sensitive to exogenous antigens with similar, if not identical, antigenic epitopes (Figure 1). This model is known as molecular mimicry, as seen in Rheumatic Heart Disease (RHD), where immune complex disease is formed against cardiolipin after exposure to Group A *Streptococcus* that produce antigenic proteins that are similar to human cardiolipin.[8] After bacterial exposure, the susceptible human makes antibodies that react to both these bacte-

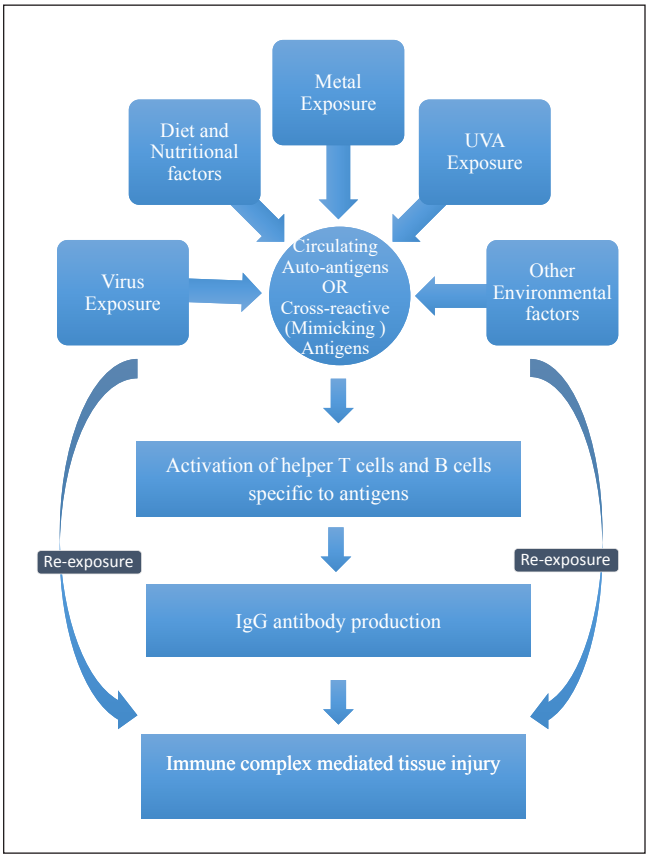

Figure 1

rial proteins as well as to "self" cardiolipin. Exacerbations of RHD occur with *Streptococcal* reinfection. Treating the *Streptococcal* infection, as well as reinfection, early enough prevents formation of these antibodies in titers high enough to attack the heart.

In order to identify which subpopulations may be reacting to which of a large number of molecular mimickers of autoantigens, one must obtain highly detailed prospective information from thousands of individuals. This process is called continuous quality improvement (CQI). Until recently researchers could not interact with this number of individuals, nor analyze large amounts of data to identify these subpopulations. This challenge can be met through the rapidly growing use of social media worldwide as well as the advancements in supercomputer technology and programing with complex adaptive systems assessment software.

The global use of social media has grown exponentially in recent years. Currently, 3.5 billion people, >49 percent of the world's population, use the Internet. Social media use now comprises 2.7 billion people with more than 1.5 billion users per day on Facebook alone. Once thought to be a media exclusively used by teenagers and young adults, social media now involves all ages with >40 percent of those 65 years and older participating. Similarly, social media use does not favor demographics such as education, job status, income, geographical location, and more.[9-11]

Social media now allows physicians and patients to connect with one another and share important medical information.[12] Health information sharing through different social media platforms has provided patients with an outlet to share personal experiences of their disease progression and treatment outcomes.[13] Patients may use social media as a resource to seek advice from other patients with similar health-related issues, access medical advice from medical professionals, or connect with various support groups.[14] Moreover, there are several million posts per month by dermatology patients on social media, wherein they freely and openly share in the public domain pictures and videos of rashes,[15-19] provide their opinions about price and value of cosmetic procedures,[20] and their concerns and desires related to disease severity, as well as what they believe is needed from the treatments to promote acceptable outcomes. Thus, social media is potentially a valuable resource to gain insights from patients with AID who utilize the Internet and social media to guide the process of establishing patient-oriented clinical outcomes.

An extensive literature review of AID revealed multiple exogenous factors that may be involved in AID relapses and remissions. Our group has used social media, with restricted time frames and work effort, to contact more than a thousand participants from around the globe who completed detailed questionnaires containing dozens of pages of numerous questions related to factors affecting outcomes (FAO) and patient reported outcomes (PRO). Thus, we propose that with a focused effort our group can

ABBREVIATIONS

AID: Autoimmune diseases
ANA: Antinuclear antibodies
DNA: Deoxyribonucleic acid
dsDNA: Double-stranded deoxyribonucleic acid
RHD: Rheumatic heart disease
PRO: Patient reported outcomes
FAO: Factors affecting outcomes
HIPAA: Health Insurance Portability and Accountability Act
CAS: Complex adaptive systems
UV: Ultraviolet
CQI: Continuous quality improvement
PID: Patient interactive diary
IT: Information technology

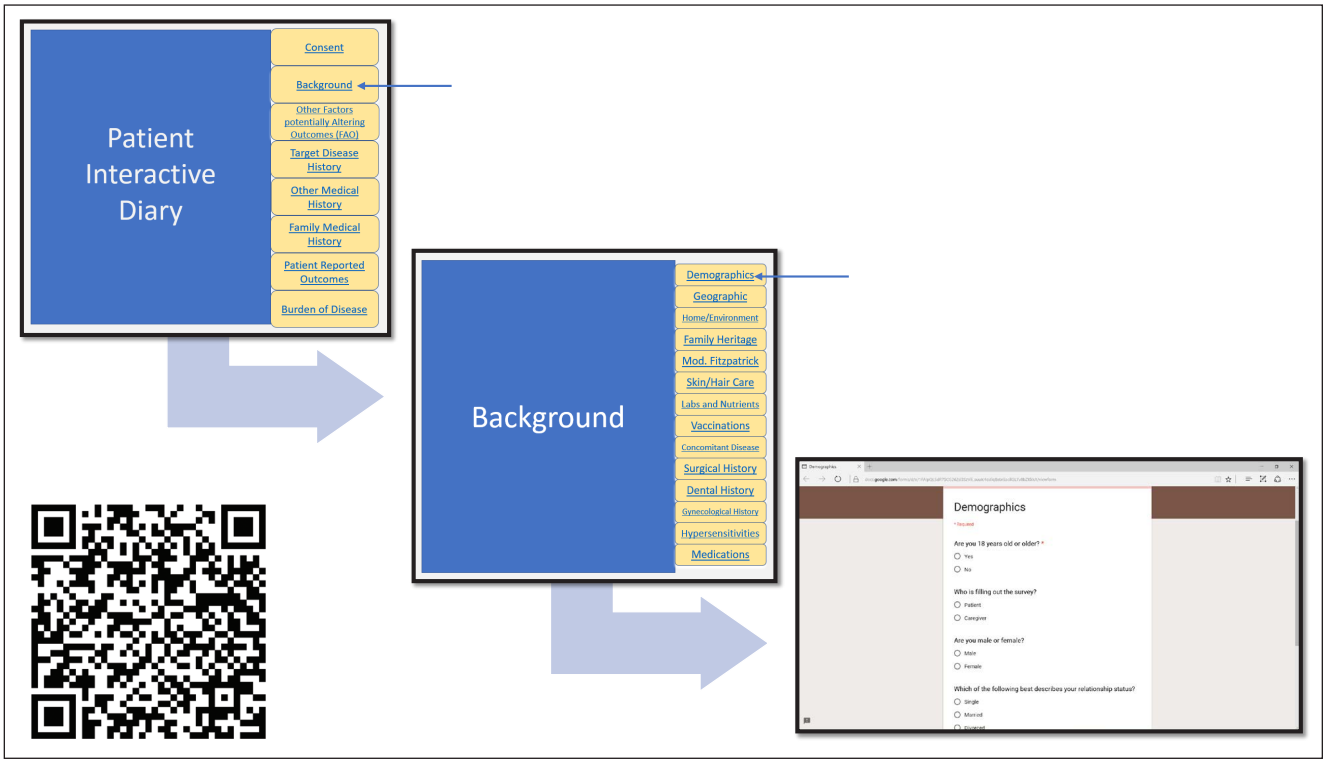

Figure 2. To access a sample of the PID, use the QR code.

utilize social media to interact with tens of thousands of patients who suffer with AID in a comprehensive continuous quality improvement effort.

STUDY DESIGN

Our research goal is to construct a comprehensive longitudinal patient interactive diary (PID) in which thousands to tens of thousands of patients from around the globe who self-report as diagnosed with AID will participate. Participants for this research project will be recruited through social media platforms. Patients will complete an initial highly detailed diary form capturing PRO and exposures to FAO through a newly developed HIPAA compliant Internet platform (Figure 2). These patients then will update their diary when changes occur in PRO and/or FAO or on a once-a-month basis to confirm the lack of changes. Supercomputers and complex adaptive systems methodology (CAS) will be used to analyze the data obtained to identify the subpopulations of AID-diagnosed patients in whom PRO vary similarly in associations with a given set of FAO over various periods of time. CAS performs multi-factorial analysis, recognizing non-linear, non-time dependent relationships.

FAO exposures occur through patient lifestyle, which includes smoking tobacco and alcohol use. Additionally, other FAO include diet (which foods, which source of those foods, which preparation methods of those foods), water sources (with or without filters), cookware, concomitant diseases, medications, nutritional supplements, UV radiation exposures, and other exposures. Although these data may identify solitary FAO with higher risks or lower risks, the focus will be on the interactions of the FAO and the variable time frames involved.

Continuous quality improvement methodology has only recently been utilized in medical care. This process involves identifying which patterns of prior, current, and future factors affect outcomes.[21] Fundamental to CQI methodology is the requirement that all participants are alerted at log on of any patterns that have been confirmed by the investigator group that relate arrays of FAO exposures to improving or worsening PROs. These participants are free to continue as before, or make changes in their exposures to FAO. The continuous monitoring identifies in which group which responses are helpful or harmful. The results as well as participants suggested changes in the information being captured results in a dynamic adaptive interactive system approach.

Participants will be recruited from various social media platforms on the Internet (Facebook, LinkedIn, Twitter, etc.) to include patients with AID in this study throughout the United States. The PID will be first written in English

and eventually translated into other languages, in order to include multiple nationalities of participants in the study. Participation in this study will be strictly voluntary.

Potential participants will receive a unique email address and password for their PID account through a computer server that interacts directly with the participants. This server then assigns a number identifier to that account to a second server wherein all the data is captured and analyzed. This two server system protects the participants' privacy. Each participant has a unique account with login user name and password that allows the participant to complete the initial PID, as well as subsequent monthly updates, in multiple sessions, if required. A consent form will be given prior to patient participation in the PID.

Patients will be assigned an initial baseline PID form to complete using the Internet. This PID questionnaire will capture initial disease status measurements for the individual patient. The patient will enter data in follow-up CAS-PID questionnaires monthly. These PIDs will then be put through a non-linear statistical array analysis to determine if there are any patterns of improvement or exacerbation of the patient's disease state relative to any of the analyzed factors. These patterns are compared to determine if they correlate with a specific time or place setting affecting any subpopulation of patients.[22] There will be no treatments given to patients, but patients will receive feedback in regards to helpful or harmful exposures and are free to adjust their behaviors accordingly. This process will be repeated, improving the ability of the array analysis to detect patterns and subpopulations of patients whose PRO status is related to arrays of specific FAO including times/place of the events. Data points will be added or removed from the questionnaires as their significance is elucidated.

We present the strategy of this clinical quality improvement project as a unique method for multidisciplinary collaboration, driven by patient-entered data to improve the value of medical care for patients diagnosed with an AID. PID-CAS will deliver individualized and opportune feedback for each AID patient intended to improve their overall quality of treatment response and cost of care. This model for continuous quality improvement can be additionally applied to other multifaceted and chronic diseases to improve quality of care by adopting an individualized patient-focused approach to treatment.

DISCUSSION

Continuous quality improvement remains in its infancy as applied to medical disorders. To obtain enough factors from enough individuals, one requires a recruiting apparatus with hundreds of millions to billions of participants; i.e. Internet and social media. Additionally, to interpret this large set of data one needs to incorporate supercomputers running CAS software. CAS is an evolving field of science, that recognizes the dynamic interactions between and among all factors, specifically with AID interacting with all organ systems within a patient and the patient's environment. CAS predicts that distinct and seemingly simple relationships become more complex as the number of events increases through a sequence of changes until random-like relationships appear. Nevertheless, it is these complex interactions that permit the human body to function.[23] The field recognizes that patients are likely able to be categorized in many different subgroups that must be tested separately. Subgroups must be identified and clarified, either based on their variable genetics, environments, disease state, age, sex, etc. Furthermore, it is possible for individuals to move from one subgroup to another at any point in time based on changing variables that.

> Combining CAS Science and PID (CAS-PID) recognizes that all events occurring within patient organ systems interact with one another. CAS-PID will capture these events as data points and analyze them en masse.

Use of a global, Internet-based social media promoted PID platform combines CQI with CAS and provides the ability to meet several significant components of high-value health care delivery. These components include considering a patient's medical condition, their geographic region, and measuring costs and outcomes for each patient. PID are designed as an information technology (IT) platform organized around a patient's specific medical condition, that can be integrated across separate facilities, and expanded in geographic reach by being adaptable to Internet based platforms.[24] In this study, the PID will be written as patient questionnaires where responses are arranged as data points. PID analyzed by CAS adds to the process by having the ability to recognize and capture data points that fluctuate in time and place and may only affect subpopulations.

Using CQI-CAS ability to recognize non-linear dynamic adaptive multifactorial relationships follows that the human body's behavior of endless interactions between genetic pathways, subcellular processes, organ responses and overall human health status. Thus, it is important to

recognize that interactions between human physiology and its environment is a complex, multifactorial process which can result in different clinical results in each patient subpopulation. Combining CAS Science and PID (CAS-PID) recognizes that all events occurring within patient organ systems interact with one another. CAS-PID will capture these events as data points and analyze them *en masse*. It is anticipated that this analysis will then reveal the subpopulations for which these events are real.[23] Thus, the PID also contains questions to collect standard data, including patient demographics, disease history (i.e. onset, response to prior treatments, current disease status, etc.), current medication usage, concomitant diseases, medical surgical history, and social behavior (i.e. tobacco or alcohol use).

Over time, CAS-PID captures the way in which a disease state changes (i.e. in a consistent direction or through fluctuations) and its association with any other variations or uniformities with collected standard data. CAS-PID connects this information with patient behavior and exposures. Thus, we hope to identify multifaceted patterns of exacerbation and remission in disease state within subpopulations of patients with AID who respond either negatively or positively to numerous external exposures to improve patient outcomes and quality of care. We propose that this model can then be extrapolated to any other disease process in medicine. ■

Katelyn M. Updyke, BS, University of Central Florida College of Medicine, Orlando, FL.

Brittany Urso, BS, University of Central Florida College of Medicine, Orlando, FL.

Haider Ali, BS, University of Central Florida College of Medicine, Orlando, FL.

Ian Brooks, PhD, University of Illinois School of Information Sciences, Champaign, IL.

Vernon Burton, PhD, Clemson University, Clemson, SC.

Robert P. Dellavalle, MD, PhD, MSPH, Denver Veterans Affairs Medical Center, Denver, CO; University of Colorado at Denver College of Medicine, Denver, CO.

James A. Solomon, MD, PhD, University of Central Florida College of Medicine, Orlando, FL, University of Illinois School of Information Sciences, Champaign, IL; Ameriderm Research, Ormond Beach, FL.

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