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MACRA: Putting Together the Pieces for Practice

Be careful what you wish for: sustainable growth rate and fee for service (FFS) will be models of the past; the success of the alternative payment model (APM) and merit-based incentive payment systems (MIPS) will rely on compensation, collaboration, and participation; and, to date, much remains to be done in the development of quality-based payment reform under MACRA.

Timothy J. Laing, MD, member of the Rheumatology faculty and the senior associate chair for clinical programs at the University of Michigan, spoke at the American College of Rheumatology's 2016 Annual Meeting about implementation and opportunities under the Medicare Access and CHIP Reauthorization Act (MACRA) and regulation being promulgated to implement MIPS and the APM.

Centers for Medicare & Medicaid Services (CMS) is bound and determined to move providers from a FFS claims-based model to a quality-based, cost-contained, bundled payment methodology. Manage the risk under an APM or manage the penalties under

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Results Show Vectra DA's Ability to Predict Radiographic Progression, Likelihood of Flare

The 12-biomarker test is gaining acceptance among rheumatologists and was recently added to a clinical guideline.

A series of abstracts on the Vectra DA test from Crescendo Bioscience was presented at the 2016 Annual Meeting of the American College of Rheumatology (ACR) in Washington, DC. The company explained that the abstracts add to the growing body of evidence on the test's clinical utility and ease of use.

Vectra DA, a 12-biomarker test, helps evaluate the progression of rheumatoid arthritis (RA), a debilitating autoimmune disease with possible genetic and environmental causes that affects about 1.5 million Americans. RA is characterized by chronic inflammation, pain, and stiffness in the joints, which can progress to disability.

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Supplement to
The American Journal of Managed Care

MACRA: Putting Together the Pieces for Practice (Continued from page 1)

MIPS? Inaction in 2017 will result in a payment penalty felt in 2019.

Calendar year 2017 is a reporting year. Clinicians, at a minimum, must report to CMS on at least 1 process and 1 outcome measure. It may turn out that 2017 becomes a beta test year for CMS as it assesses the quality of its systems, reviews and values the data coming in, and manages, both internally and externally, the change management of payment reform. In 2018, CMS will provide feedback to payers, and in 2019, MIPS and MACRA will likely go into full effect.

To obtain a positive performance adjustment, eligible clinicians—the formal term for participating providers in the APM and MIPS—must meet thresholds for quality, advancing care information, improvement activities, and cost containment. Cost data will be required in 2017, but it will not have an impact on the 2019 adjustment. Eligible clinicians can elect to report as individuals or a group practice. If reporting as a group practice, all providers must report on the same measures, and there is a single payment to the group.

The highest-risk practices are small group practices. An individual opening a practice will receive a pass from CMS for year 1, however. Online tools for practices with a history of using the Physician Quality Reporting System are available now, illustrating how a given provider or practice could fare under MIPS or the APM.

To move the mountain and the providers that rely on Medicare monies will require fundamental shifts in reporting, oversight, and infrastructure for CMS and clinicians, explained Dr Laing. Although there is $20 million in the CMS budget to support individuals' and providers' change management technical assistance, that sum does not appear to provide near enough funding. An electronic health record (EHR) and a patient registry will be critical to successful participation in MIPS or the APM. Clinicians running a practice using an EHR will find the change to MIPS or an APM less demanding. The codes for rheumatology practices follow clinical standards of practice.

Under MIPS and the APM, there remain serious concerns about attribution costs as they relate to hospital stays and drug costs. Deeply troubling is the potential that some providers will abandon high-risk, hard-to-reach, less-compliant patients to their risk or penalty. The APM will likely be limited to a small bubble of eligible clinicians, as the incentivized payment methodology requires eligible clinicians to have higher thresholds of risk to participate. Most providers will be paid under the performance-based payment adjustment that is MIPS. Either way, fundamental changes to payment reform are on the horizon. Anticipate, and plan now for tomorrow. ●

Results Show Vectra DA's Ability to Predict Radiographic Progression (Continued from page 1)

Bernard Tobin, president of Crescendo Bioscience, said the studies presented at ACR build on earlier work, which showed how clinicians and patients benefit from objective information about the course of the disease. Physicians can use the test both at baseline (when a patient is diagnosed) and when patients report symptoms that can't be explained by a physical exam. In some cases, Tobin said, "The Vectra DA test will come back showing there's smoldering disease that they're not able to pick up clinically."

In recent years, a new class of disease-modifying antirheumatic drugs (DMARDs), the so-called biologics, have been developed to target the action of the immune system, thereby interrupting inflammation and disease advancement. When these biologics work, they are game-changing, but they have side effects and do not work for everyone. Vectra DA helps rheumatologists evaluate which patients are experiencing disease progression that warrants use of biologics

and which patients might be able to take a break from these agents; this makes the test an important tool for rheumatologists, patients, and payers.

To that end, Crescendo, which is owned by Myriad Genetics, has embarked on a prospective outcomes study that will report results in 2018. The study will shed light on which patients with RA will benefit from enhanced DMARD therapy versus biologics, and Tobin said, "Managed care plans would very much like to know who those patients are."

Abstracts presented at the ACR meeting covered several topics:

› ***Predicting Radiographic Progression.***[1] In this study, researchers evaluated 180 patients with early RA who took part in the OPERA trial (Optimized Treatment Algorithm for Patients with Early Rheumatoid Arthritis) to see how well the Vectra DA score, taken at baseline, predicted radiographic progression at the 12-month mark and whether it made sense to add the test to the anti-cyclic citrullinated peptide (anti-CCP) test, an older antibody test that has been used to identify patients at higher risk of rapid disease progression.

Results found that patients with a high Vectra DA score (>44 on a scale of 1 to 100)[2] were more likely to see radiographic progression (31%) compared with patients who had a score of 44 or less (3%). Although 34% of the patients who tested positive for anti-CCP and 12% who tested negative had radiographic progression at 12 months, none of the negative patients with a Vectra DA score of 44 or less showed progression, suggesting that the use of the score adds value to the anti-CCP test in predicting future radiographic progression. By contrast, a commonly used functional assessment, Disease Activity Score-C-reactive protein,[3] turned out to have less predictive value in combination with anti-CCP.

› ***Suspending Use of Adalimumab.***[4] This study evaluated how Vectra DA could be used to predict upcoming flares in patients who decided to stop taking the biologic adalimumab after achieving remission. Researchers examined 42 patients who had been taking adalimumab and methotrexate who maintained remission (based on functional assessment) for at least 24 weeks and agreed to stop taking adalimumab. Clinical disease activity, functional status, and joint damage were recorded at the time the patients stopped taking the biologic, and the ability of Vectra DA to predict flares was measured at 6 months and 1 year. After a year, patients' baseline Vectra DA score and corresponding flare rates were: remission, 13.6%; low, 50.0%; moderate, 33.3%, and high, 60.0%. The corresponding sustained remission rates were: remission, 63.6%; low, 33.3%; moderate, 33.3%, and high, 0%.

› ***When to take the test.***[5] Crescendo's David Chernoff, MD, senior vice president for Medical Affairs, presented a study that evaluated the biological variability of Vectra DA scores over a 24-hour period for 28 patients. The study found that patients can take the test at any time during normal business hours without producing meaningfully different results; this is important for patients with RA, who may not prefer an early morning laboratory appointment.

Tobin said that this year's ACR came at a great time, as Vectra DA is gaining acceptance among rheumatologists and making headway with commercial payers and guidelines committees. Medicare already pays for 2 tests a year. Myriad announced during its most recent investor's call that United Rheumatology had included the test on its guidelines. Data provided by the company state that 68% of US rheumatologists use the test and 280,000 of those with RA have received at least 1 test.

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Getting Telehealth Right: Engaging Patients and Providers

Broadly, telehealth is about creating care connections across boundaries. If we get telehealth right, we can potentially reap multiple benefits both at the provider level and the patient level.

Getting telehealth right can reduce the impact of the growing healthcare workforce shortage, while creating a healthier, more engaged patient base. Broadly speaking, telehealth focuses on creating care connections across boundaries—care that encourages patients' independence, prevention, and wellness, and that can be leveraged for needed interventions.

Joseph Kvedar, MD, vice president of Connected Health in the Partners HealthCare System and author of *The Internet of Healthy*

Things, envisions using technology to gather real-time biometric data for chronic disease management. Virtual-provider visits, cloud computing devices, and mobile devices are increasing our capacity for immediate monitoring and chronic disease management.

Virtual-provider video visits are trending in the healthcare industry and the government sector in part because legal protections have been put in place in response to concerns about provider liability as the potential for telehealth increases exponentially. Walgreens, CVS, and Blue Cross Blue Shield are actively engaged in developing video technologies for care delivery. HHS' Agency for Healthcare Research and Quality has published numerous papers about the potential for virtual-provider visits and using telehealth more broadly. Virtual video production, the agency reported, appears to be a viable approach to patient education and care, professional development, retention, and collaboration.

Cloud computing and mobile devices are increasing the capacity of captured health data and integrated networks, Kvedar said. In 5 years, 20 billion everyday objects will be considered "smart" because they have sensors and networking capabilities. With existing GPS technologies, social networks, and automated motivational messaging augmented by smart day-to-day objects, virtual artificial health beings could motivate humans to take such actions as exercising, resting, and losing weight.

Kvedar also discussed wearables, which measure, record, and report steps, sleep patterns, blood pressure, stress levels, and weight. New and existing technologies need to be able to aggregate and normalize data while meeting user demand for flawless technological design. The end users are both providers and patients, and the technology must be customizable for the patients and normalized to be useful to the providers.

The benefits of employing technology have been shown in several areas: asthma compliance in teens, palliative care pain management, and cancer medication compliance. The strategies used have leveraged subliminal messaging, unpredictable awards, and sentinel events, Kvedar reported. Telehealth has generated changes in self-care and patient outcomes that have the same power as therapeutics.

Teenagers participating in a private Facebook group, which utilized Connect 2 My ACT (an asthma survey) through periodic electronic prompts developed by providers, had an 80% compliance rate compared with the control group's 18% compliance. In another example, palliative care-related telehealth technologies were used to help patients understand how to manage pain. The in-office message to "take the medicine when you need it" often did not resonate at home. However, prompts to rate pain and questions about medicine use were supported by connections to palliative care units when the algorithm-generated response suggested a need for human interaction. Pain levels dramatically improved as a result of these interventions.

Kvedar closed the presentation by promising the audience that telehealth and related technologies will not take the place of doctors: the effect of the patient–provider relationship is lasting. Patients often do not want to disappoint their doctors. If the design of health technologies is provider-driven and supported by doctors, patients will take to the technologies, and medical professionals can expect improvements in health outcomes and patient engagement in their care management. ●

Could the Vectra DA Test Be Used to Predict Cardiovascular Risk?

A test used to predict future disease activity in patients with rheumatoid arthritis (RA) might someday tell physicians which patients are at risk for cardiovascular (CV) events, such as heart attacks or coronary infection, suggest the results of a new study.

A researcher from the University of Alabama Birmingham, Jeffrey R. Curtis, MD, MPH, presented results of a population health study at the 2016 meeting of the American College of Rheumatology in Washington, DC. Using data from 17,000 patients culled from a large Medicare claims database, Curtis and his team examined the relationship between scores on a Vectra DA test, made by Crescendo Bioscience, and the risk of cardiovascular outcomes and infections.

Results showed that a high Vectra DA score was associated with an increased risk for coronary infections that required hospitalization, myocardial infarction, and composite coronary heart disease, including percutaneous coronary intervention and coronary artery bypass graft, according to a press release. In an interview, officials with Crescendo Bioscience emphasized that there are no current plans to pursue the use of Vectra DA to find out which patients with RA face cardiovascular risks. However, they said the findings are not surprising since most of the 1.5 million patients in the United States with RA die of conditions other than the disease.

"Cardiovascular risk with rheumatoid arthritis is very real," said Bernard Tobin, president of Crescendo Bioscience, a subsidiary of Myriad Genetics. "People don't die of swollen joints, but they do die of cardiovascular disease quite often, because it's inflammatory."

Vectra DA is a blood test that examines 12 biomarkers associated with RA. The test generates a score that helps rheumatologists gauge the course of disease progression and guide treatment. Its purpose is to give physicians an objective measure that reduces the guesswork in clinical decision making.

Historically, rheumatologists made treatment decisions, in part, through subjective tests, such as how much pain patients say they feel in their joints during exams.

David Chernoff, MD, Crescendo's senior vice president for medical affairs, said there's a great deal of work that occurs with cardiovascular risk profiling among patients with diabetes and obesity—conditions that also involve inflammation—to assess whether drugs for these conditions put patients at higher risk for CV events. (The FDA has required large studies, known as cardiovascular outcomes trials, for all new diabetes and obesity drugs since 2008.) But less has been done to identify which patients with RA are at high risk, despite the known connections between the disease and CV events.

"Just having RA doubles the risk" of having a heart attack or stroke, Chernoff said. Using Vectra DA to identify which patients face increased cardiovascular risks would require much more study and larger data sets, and Crescendo has no plans to pursue the question right now. But it would fulfill an unmet need, Chernoff said. It's possible that in the future, Vectra DA could identify a patient whose RA is not progressing rapidly, but, he said, "the test would indicate they need to be treated aggressively for cardiovascular outcomes."

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Creating a Culture of Care Focused on Health, Not Illness

Clinicians who marry technical skills with knowledge in the humanities can see their patients and themselves in a different context.

The goals of medicine are function and health. Clinicians who marry technical skills with humanities knowledge can see their patients and themselves in the larger context of family, society, history, politics, and economics. As a result, barriers to medication compliance and treatment are better understood and improvements in health outcomes are more likely.

Providers can meet patients' needs for dignity, health, and comprehensive clinical care while concurrently fulfilling obligations to capture patient data in this electronic age of payment reform and meet the demand for provider productivity through an understanding and appreciation of the humanities. Providers who understand and apply humanities—the study of the intersection of art, history, the individual experience, science, anthropology, and language—relate better to their patients and create environs for promoting health. This was the overarching message of the session, "Culture, Health and Healing: Humanities in Inter-Professional Collaboration and Patient Centered Care" presented by Paulette Hahn, MD, at the American College of Rheumatology's 2016 Annual Meeting.

Providers who seek to enable patient health, rather than limit their practice to the treatment of disease, broadly accept that to treat the patient, the provider must see the ailment as preventing the fullness of socio-emotional and physical engagement with society. Clinicians, Hahn pressed, must be the first to extend a hand to help a patient to bridge illness to health.

Hahn explained how Maslow's Hierarchy of Needs is relevant to the study and practice of medicine. The intersection of these needs—physiology, safety, love, esteem, and self-actualization—is the human condition, the humanities. An understanding of humanities helps providers better identify with their patients, improves clinical care, and generates positive health outcomes. Clinicians who combine their technical skills with the ability to see their patients and themselves in the larger context of family, society, history, politics, and economics more easily discern barriers to medication compliance and treatment.

After the session, Hahn further discussed the importance of presence in the context of competing demands (eg, the need for recording information in the electronic medical record). She encouraged clinicians to see their patients in the details of the patients' hands, to see their patients in the context of the room, to see their face fully, to value the history they wear, speak, and bear—these are all of value to patient visits. The conversations generate recall and let clinicians more fully populate the medical record, she said. Notes can serve as triggers for conversations. Quality reporting is improved.

During the presentation, Hahn spoke of the act of listening as providing attention to self and others. Clinicians who pause outside a patient's door before entering acknowledge their work as vital and important and each patient as their focus. These clinicians are more likely to connect with patients and have an impact on their health.

There was consensus in the room with Hahn's statement that all staff members need to be engaged in seeing the patient. Questions must be asked not to the computer screen, but to the patient's face. Taking notice of patient responses can trigger conversations that speak to the underlying barriers to health rather than the presenting problem of illness.

Hahn called on clinicians to be contemplative, curious, collaborative, and creative. Patient–provider relationships centered on the larger human condition are often less likely to be plagued by challenges with compliance, adherence, and follow-up. Provider productivity is only sometimes compromised in these relationships because patients value provider time, show up on

time, and are less likely to be no shows; providers waste less time clarifying patient responses by providing their full attention to the patient; and quality drives the patient–provider encounter.

Hahn noted that patients who have developed relationships with a healthcare provider are more likely to set and meet health goals. "Health" and "care" are the active verbs in relationships where clinicians and patients value and engage in conversations regarding course of action, toxicity, and personal achievement. This is not soft science: humanities are the essence of the patient–provider relationship, Hahn explained. ●

Following the Path of Antibody Structures to Biosimilars: A Journey in Innovation

The challenge for biosimilars is that in addition to developing an antibody, researchers must consider such issues as culture conditions, purification, and formulation.

During a session at the Annual Meeting of the American College of Rheumatology, John D. Isaacs, MD, PhD, FRCP, stated that his goal was not just to review regulatory perspectives, but to convey the essence of the biology: how can we craft antibodies to our own purposes? From that, he said, one can look at the implications for creating and using biosimilars—a bio-therapeutic product similar in terms of quality, safety, and efficacy to a previously licensed and referenced bio-originated product—in clinical practice.

He then took the audience on a "journey" along the path of the biological revolution of antibody structure/function and its attendant posttranslational complexities, beginning in the late 19th century, when 2 individuals developed an antitoxin for diphtheria, and continuing in to the late 20th century, when scientists realized they could clone antibodies. Isaac next presented detailed explanations of how researchers went from DNA to antibody heavy chains to antibody diversity, before making fully human antibodies. He then examined the pros and cons of nanobodies, followed by a discussion of the development of technology that permits the creation of bispecific monoclonal antibodies—with the whole point being to link an antibody with a function at the other end. This technology paved the way for the development of biosimilars.

> The challenge researchers have with biosimilars is to analyze what is in the bio-originator and then replicate it.

There are numerous steps along the way of developing and manufacturing a novel monoclonal antibody—including initial development, purification, drug substance, and formulation/sterilization. Because of the profusion of steps, however, the resulting product will vary. The challenge researchers have with biosimilars, Isaac said, is to analyze what is in the bio-originator and then replicate it. Because researchers are creating this product from human cells, however, they can only try to copy the bio-originator due to a concomitant lack of control inherent in using a living system. In addition, when dealing with optimization of a therapeutic antibody, researchers must also consider such issues as culture conditions, purification, and formulation.

Regulatory requirements for new drugs follow a conventionally approved pathway that ends with several clinical studies. The biosimilar approval pathway, however, is essentially reversed. Most of the money goes into analyzing the original antibody to make the biosimilar as alike as possible. Comparative in vitro nonclinical studies—an array of side-by-side comparisons—must look similar all the way through. Also, safety and immunogenicity must be comparable and continue to be assessed post marketing. This process ends with at least 1 large clinical study to demonstrate clinical equivalence and safety derived from the meta-analysis of randomized controlled trials of the bio-originator.

Isaac delineated some of the advantages of using biosimilars. They are cheaper (their manufacturing processes are much more efficient), the regulatory requirements are abbreviated, the risk of failure is reduced (because they are using a drug that is already working), and the bio-originator becomes better characterized. However, there are also disadvantages. These include different processes (eg, cell line and culture) that could result in unpredicted effects or impurities in the final product. This, in turn, could influence half-life, aggregate formation, and immunogenicity.

Currently, pharmacists may not implement interchangeability (switching from the physician's proscribed bio-originator to a biosimilar). Isaac did think that this could change in the future, but stressed the critical importance of physicians prescribing by brand names. He reiterated that the bio-originators in use today are not the same as those used 20 years ago, because researchers have found better ways of producing antibodies. Posttranslation modifications are more difficult to control, so

they are not, and, he emphasized, cannot be identical to the bio-originator product.

Lastly, Issac addressed cost. In Norway, which uses a competitive process, biosimilars cost one-third less than the reference product. In the United Kingdom, biosimilars are about 20% less expensive than originator drugs. Isaac expects a 20% to 30% reduction in biosimilar costs in most countries in the near future. ●

Claims-Based Analysis of the Cost-Effectiveness of Cyclers Versus Switchers in Patients With Less-Than-Adequate Tumor Necrosis Factor Inhibitors

During a session at the Annual Meeting of the American College of Rheumatology, Jeffrey Curtis, MD, discussed treatment considerations for patients with rheumatoid arthritis (RA).

Jeffrey Curtis, MD, a rheumatologist from Birmingham, Alabama, discussed the ways in which patients with RA who demonstrate a less-than-adequate response to a tumor necrosis factor inhibitor (TNFi) can be treated with another disease-modifying antirheumatic drug (DMARD), either by changing to another TNFi ("cyclers") or by changing to a drug with a new mechanism of action (MoA) (new MoA "switchers"). Acknowledging that clinicians have many choices in the management of RA, and citing growing analytical evidence on which option might be best physically, the study by Curtis et al focused on what steps to take when a patient does not respond adequately to TNFi therapy.

The study covered patient data from 2010 to 2014, with 8517 patients meeting inclusion criteria. Although Curtis cited several data sources, he relied mainly on Truven Health Analytics Market Scan. Inclusion criteria consisted of patients with RA having manifested moderate or high disease activity for at least 3 months. Patients excluded from the study included those currently on TNFi therapy for any other disease, as well as those with a history of cancer.

During the study, patients must have used a TNFi for at least 12 months and for a subsequent 12 months after starting a new therapy. Among additional requirements, patients could not stop taking the drugs, nor could they change to a new MoA DMARD. If the patient was on steroids, he or she could not increase the dosage.

The costs of DMARD/biological treatments and total RA-related healthcare were standardized to December 2015 dollars. The study's main outcome variable was the cost per "effectively treated" patient in the first year after TNFi cycling or new MoA switching, with treatment effectiveness being defined according to an identified algorithm. Curtis et al examined the average 12-month postindex cost per patient divided by the percent of patients categorized as effectively treated. For example, if main costs per treatment cohort were $50,000, but only 50% of patients were effectively treated, then the cost per effectively treated patient was $100,000. With regard to patient characteristics, compared with TNFi cyclers, MoA switchers were slightly older and more likely to have used corticoids.

Concerning treatment effectiveness, 23.3% of cyclers met all the efficacy criteria compared with 26% of new MoA switchers. As to why the former group had a higher failure percentage, Curtis remarked that some patients moving to the next therapy just gave up.

Most RA costs are related to drug treatment. Over the course of the year, the overall cost per effectively treated patient was lower for the switcher cohort ($165,200 for cyclers vs $126,991 for switchers). What accounts for the difference, he said, is the adherence issue, not switching to a new MoA.

In summing up the results, Curtis noted that a higher proportion of new MoA switchers were effectively treated and had significantly lower costs per effectively treated patient than TNFi cyclers. He pointed out, however, that the direction of bias is always against a new drug, so if differences favor the new drug, they are more likely to be real.

> What's next when there is inadequate response to tumor necrosis factor inhibitor therapy?

Nevertheless, there are limitations to keep in mind, including that this was strictly an observational study; thus, causality could not be claimed. He added that the true costs and true differences may be of greater magnitude than those observed. Additionally, clinical outcomes were not included in the claims-based treatment effectiveness algorithm; therefore, the researchers did not know, for example, why a patient stopped using the drug or switched, as that information was not captured in the data. Curtis also acknowledged that the perspective in this analysis is somewhat different from previous studies, in that it examined the cost of medications over time relative to whether patients were effectively treated. ●

Genes, the Environment, and Autoimmune Disease

Understanding genetic variation in response to therapy will be critical in treating autoimmune diseases.

David Hafler, MD, chairman of the Department of Neurology at the Yale School of Medicine, spoke of exciting times in the field of genome-wide association study (GWAS)—specifically speaking to neurology, genetics, the environment, and the autoimmune response.

Using GWAS, there is growing consensus that multiple sclerosis (MS) and rheumatoid arthritis (RA) display similar autoimmune genetic pathways. GWAS clearly shows that RA and MS are genetically mediated autoimmune reactions to clonal expansions of autoreactive T cells that trigger cellular responses of B cells and macrophages, which then suppress regulatory T cells. Scientists have been able to create models of the reaction, which have been validated by therapies.

MS, RA, and lupus have low genetic odds ratios of 1.0 or 1.2, leaving many scientists questioning why the ratios are so low. The answer appears to be in the gene-environment interactions which influence phenotypes. Each genetic variant has a small effect, and interactions with the environment magnify disease presentation.

Hafler and colleagues studied more than 14,000 cases of MS and 23,000 controls, looking for rare combinations of events. A small group emerged that was able to provide enough information to suggest casual variance, with scientists now able to tell what cell types cause immune diseases. It appears that a greater potential for disease presentation is associated with the presence of H3K27ac histone modifications at enhancer regions on chromosomal DNA. Data available in the public domain support these disease-associated variants as markers of targeted gene expression.

Variation drives the risk of disease. Hafler described the incidence of autoimmune disease as epidemic. For example, smoking is a risk factor for MS only for carriers who have a specific single nucleotide polymorphism positional variant. For those carriers, smoking increases the risk of disease presentation by 5 times; for carriers without the genomic variant, the risk is minimal. Vitamin D deficiency is an independent risk factor for MS, and variation drives that risk.

Hafler discussed studies of the effect of sodium chloride (salt) on the immune response. Salt appears to induce regulatory T-cell suppression. Scientists who effectively block the pathways involving salt can restore the function of regulatory T cells. The effect of salt and the counter activity of blocking salt have shown promise in both in vivo and assay studies. The in vivo studies evaluated a high-salt diet in animals with encephalomyelitis. Animals with a higher salt content in their diet died much faster than animals with lower salt intakes.

Countering doubts that a high-salt cellular inducton of inflammatory response cannot be created from diet, Hafler stated that it is the small intestine that mediates the effect of salt in the gut microbiome. He pointed out that salt is part of an ancient stress response. It is clear, he stated, that scientists will need to look at multiple time points in the salt signature to understand its effect and to concurrently study the range of carrier genetic variance. The overarching message is that understanding genetic variation in response to therapy will be critical in treating autoimmune disease.

To date, the genetic research has not translated to clinical practice; however, drugs that have shown tremendous promise in trials are expected to be available soon. By focusing on B cells, some drugs are showing a 98% decrease in new lesions in disease-specific target studies, said Hafler. ●

Sarilumab in Patients With Rheumatoid Arthritis Who Had Inadequate Response to Methotrexate

Cem Gabay, MD, professor of medicine at the University of Geneva, presented the results of a study on the use of sarilumab on circulating biomarkers of bone and joint destruction in patients with rheumatoid arthritis who had shown an inadequate response to methotrexate. By way of background, he stated that researchers know that synovial inflammation leads to bone damage. There is also a cascade of signaling events that contribute to this damage. In addition, he noted that more recently, different synovial phenotypes have shown different responses to biologic agents.

Gabay briefly explained the study's methodology, which included the measurement of biomarkers using validated enzyme-linked immunosorbent assays, random selection of subsets of patients receiving different amounts of a drug, and evaluation of changes (modest differences in some biomarker levels) in patients classified as anti-cardiolipin (aCL) responders and non-aCL responders at 6 months. Information on demographics and disease characteristics at baseline were presented. Notably, this study included older patients. Baseline characteristics, including baseline serum levels of most biomarkers, were similar between groups.

Among the findings were that sarilumab reduced disease activity and improved physical function—all superior to methotrexate alone. Some of these results could be observed as early as 2 weeks after just one injection, suggesting a subset of the biomarkers may be associated with a decrease in disease activity. Specifically, sarilumab:

- Significantly reduced serum concentrations of C-reactive protein (CRP) compared with placebo at all time points in the evaluation.
- Significantly increased a marker of bone formation and decreased a marker of bone resorption.
- Significantly decreased markers of synovial inflammation and tissue remodeling—a rapid reduction at week 2 and again at week 24.
- Significantly decreased a marker of collagen type 1 destruction.

The study showed that patients using sarilumab showed a significantly higher magnitude of change in biomarkers of inflammation and bone or joint degradation compared with patients treated with methotrexate. Further, for some of these markers, the difference was observed as early as 2 weeks after treatment began.

Sarilumab significantly reduced biomarkers of synovial inflammation and bone remodeling. What this means, explained Gabay, was that clinicians learned which biomarkers to follow to monitor the response of patients to this drug. Although Gabay was not surprised at the results of using sarilumab, he was surprised at the speed with which they were produced—that the medication worked as quickly as 2 weeks. The results he displayed for CRP were well known, he said, but for other markers of synovial inflammation, it was a good surprise that the changes occurred so quickly. ●

Treat-to-Target Approach Beneficial for Rheumatoid Arthritis Treatment

John M. Davis, MD, MS, described the treat-to-target approach and his own perspectives in managing rheumatoid arthritis and common comorbidities.

Treat-to-target has largely become the preferred method for physicians treating patients with rheumatoid arthritis (RA). "I think there's room for further data and evidence, but in general, I think we use this in our patients for the benefits of joint preservation, enhancing work productivity, improving quality of life, and enhancing the probability of remission," said John M. Davis, MD, MS, vice chair of Rheumatology at Mayo Clinic.

Davis presented on this topic at the American College of Rheumatology (ACR) Annual Meeting. He focused on the importance of this treatment approach for adults with RA, as well as the updated guidelines from the ACR. He also discussed his own perspectives in managing RA and common comorbidities.

"The main goal of treat-to-target is to have patients achieve remission quickly and safely. The goal of patients with severe rheumatoid arthritis may be to achieve low disease activity," Davis said.

Treat-to-target requires physicians to measure a patient's disease activity every 1 to 3 months until the desired outcome is reached; disease activity is then measured every 3 to 6 months thereafter. If disease activity becomes unstable, it needs to be monitored more often and treatment must be adjusted. However, medications, side effects, cost, and health care burdens could present limitations for this treatment approach, according to Davis. The shift toward treat-to-target was based on results of the Tight Control of Rheumatoid Arthritis (TICORA) and Dutch Behandel Strategieen (BeSt) clinical trials, which were both conducted in the early 2000s.

At that time, the standard care was a pyramid scheme, Davis said in the session. Physicians would initiate treatment with a nonsteroidal anti-inflammatory drug or hydroxychloroquine and then wait 6 months before determining if the patient responded. The newly-revised ACR guidelines expand on an earlier version of the guidelines, now recommending treat-to-target for these patients. The new recommendations were revised using the GRADE methodology that incorporates a transparent and aggressive assessment of evidence.

Recommendations for treatments are categorized as strong or conditional. A strong recommendation means that a majority of patients should receive it; conditional means that there should be an open discussion about whether this is a beneficial treatment option.

Davis also discussed what physicians should do if their patients do not achieve the treatment goal or do not respond to the treatment. For patients who do not respond optimally to methotrexate, there are other strong recommendations for treatments based on clinical trials and conditional recommendations for patients who fail to respond.

When patients experience treatment failure, barriers to care must be discussed. Factors such as medication adherence, caregiver support, smoking, weight, mental health conditions, and a wrong diagnosis should be discussed in this care, Davis said. Another issue, and one that can contribute to depression, is if patients and physicians are not in agreement about the disease. If patients believe their disease is less or more severe than their physician does, this discordance can increase the risk of depression.

"Both situations can be problematic, although I think the one that is most challenging for us is the situation in which the patient is struggling and having high levels of pain and disability," Davis said.

By implementing a treat-to-target strategy and understanding the new guidelines, physicians can treat patients in the most beneficial manner. ●