

PERSONALIZED MEDICINE IN RHEUMATOLOGY: TOMORROW'S PROMISE OR TODAY'S REALITY?

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Expert Commentary

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As rheumatologists, we are constantly flooded with information from peer-reviewed journals, e-mails, and other easy-to-access sources. Especially in the current electronic age, it takes only a few clicks to find as much data as we want about new drugs, imaging techniques, or disease assessment tools that we can use to better treat our patients today. But what about insight into future patterns and trends? Where can we go to learn about how our practices may need to evolve in the not-so-distant future to take advantage of new technology being tested and developed?

This series of CME-certified publications entitled “Personalized Medicine: Tomorrow’s Future or Today’s Reality?” will attempt to address these issues. You may have recently heard of the term “personalized medicine,” but what does it really mean, and what work is being done in this area that may apply to your current practice? A good deal of the clinical research being done to introduce personalized medicine into the world of rheumatology appears in journals not commonly read by rheumatologists. It is our goal within these publications to highlight some of the key research that has been done and analyze the short- and long-term impact personalized medicine may have on clinical care.

So why should personalized medicine be a topic with which practicing rheumatologists need to become familiar? Here are a few reasons:

1 Personalized medicine seeks to eliminate the variability of group data and individualize therapeutic response.

To date, research studies in rheumatology usually describe group responses. For example, well-controlled studies often describe an entire cohort’s response to therapy using ACR20, ACR50, and ACR70 response rates. However, as demonstrated

in a 2007 study by Wells et al, these data often hide a great deal of variability. In that study, the average DAS28 (ESR) score among patients treated with abatacept was 6.8, although individual patients scored anywhere from 4.8 to 8.8 (95% confidence interval).¹ The introduction of personalized medicine might help decrease this group variability by improving patient selection in clinical trials and in clinical care.

Recently, the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system was introduced to move toward individualizing patient therapy by recommending that trial data include “Number Needed to Treat” or “Number Needed to Harm.”² These descriptors are among those which will better describe individual response.

2 Biomarker research, which has already had a significant impact in other therapeutic areas, is gradually being introduced into rheumatology.

In breast cancer, data has shown that biomarker analysis—specifically, the expression and/or amplification of the human epidermal growth factor receptor 2 (HER-2)—can accurately predict prognosis in untreated patients as well as the

LEARNING OBJECTIVES

- Define personalized medicine, specifically focusing on the potential improvements personalized care may have for patients across the disease spectrum
- Assess the differences between prognostic and predictive factors currently used to help guide patient management and treatment
- Identify at least two specific therapeutic areas where personalized medicine is currently impacting patient care and treatment
- Cite at least two reasons why the introduction of personalized medicine into rheumatology has not been as rapid as it has in other disease states

STATEMENT OF EDUCATIONAL NEED

Personalized medicine is poised to revolutionize the practice of rheumatology. With tests that are able to predict response to therapy, rheumatologists may soon be able to prescribe the right treatment for the right patient at the right time. The next major advance in the treatment of rheumatoid arthritis (RA) may not involve additional new drugs, but rather a dramatic improvement in the rational use of available therapeutic agents to optimize efficacy and cost-effectiveness for individual patients.¹

Given the emerging importance of pharmacogenetics in RA and other rheumatic diseases, rheumatologists and other healthcare providers must prepare for the anticipated arrival of personalized medicine in the rheumatology clinic. Rheumatologists and other clinicians will have to administer a growing number of molecular and genetic tests, make treatment decisions based on risk estimates, and manage new ethical, legal, and reimbursement issues associated with molecular and genetic testing.

likelihood of response to specific therapies. For example, based upon multiple clinical trial results indicating a dramatic beneficial effect of trastuzumab therapy for HER-2 positive patients, guidelines from the American Society of Clinical Oncology were introduced indicating that trastuzumab should be used only in HER-2 positive patients.³ Other examples are highlighted within this issue.

While such dramatic biomarker results have not yet revolutionized rheumatology practices, influential studies have recently been presented. In 2009, Isaacs et al presented data showing that active RA patients who were seropositive for anti-cyclic citrullinated peptide (CCP) antibodies or rheumatoid factor (RF) were approximately 2-3 times more likely to achieve ACR response with rituximab+MTX treatment than anti-CCP or RF seronegative patients.⁴ Additional research has been performed and continues to look for predictors of response for other therapeutic agents in multiple rheumatic conditions.

3 As with biomarkers, specific genetic polymorphisms have been associated with increased rates of response in patients with RA and psoriatic arthritis.

Data presented by Seitz et al in 2007 showed that polymorphisms in the TNF promoter gene were associated with increased rates of response in

patients with RA and psoriatic arthritis. In these patients, those with a specific polymorphism (G/G) at the -308 position of the TNF α gene were significantly more likely to respond to anti-TNF therapy than those with A/A or A/G polymorphisms (P<0.0001).⁵

While these and similar data are complex and typically enroll only small cohorts of patients, future, more robust studies may result in clinical recommendations that impact practicing rheumatologists. Through this educational initiative, we will be reviewing the most significant data in this area of research and explaining its current and future relevance to your practice.

4 One of the reasons we became rheumatologists is our intellectual curiosity—careful, systematic differential diagnosis is a hallmark of our specialty—and serves as the reason we are often called in when a patient diagnosis is unclear.

Keeping up with the literature, which includes ways to improve our diagnostic and therapeutic management skills for each individual patient, is an integral part of who we are. While many aspects of personalized medicine may be unfamiliar, we hope this series of publications will help you understand the potential future role of biomarker and genetic evaluation in daily practice.

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An additional benefit is that you can claim CME credits by reading each publication and completing its post-test.

It is my hope that you will find these educational activities stimulating and useful as you continue to develop your professional skills.

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INTRODUCTION TO PERSONALIZED MEDICINE

WHAT IS PERSONALIZED MEDICINE?

Personalized medicine is an approach to healthcare delivery that tailors treatment for an individual patient according to specific prognostic and predictive factors. Prognostic factors include disease- and patient-specific characteristics, such as age and disease duration, that are associated with prognosis regardless of the type of treatment received. By comparison, predictive factors are clinical, genetic, and molecular markers that predict response to specific treatments. These include variations in genes associated with drug metabolism (eg, drug-metabolizing enzymes) and drug targets (eg, signaling molecules, receptors), any of which can influence a patient's ability to respond to a particular drug. Personalized medicine incorporates all of these characteristics to enable care that accomplishes the following goals:¹

- Improve disease prevention through the early recognition of disease risks, such as genetic susceptibility to future disease
- Allow for the “preemptive” management of disease in its earliest stages through the identification of biomarkers that appear prior to clinical manifestations of disease
- Improve treatment options by allowing physicians to more precisely select drugs and doses that are optimal for specific patients based on their genetic profiles or other predictors of drug response
- Encourage patient participation in healthcare decisions and improve patient compliance

Personalized medicine also allows patients to avoid unnecessary costs and adverse events associated with regimens that are unlikely to work. This shift in treatment paradigm also has the potential to significantly alter the cost-benefit balance of drug therapies.

THE CURRENT MEDICAL, LEGAL, AND REGULATORY LANDSCAPE IN PERSONALIZED MEDICINE

Genetic testing is already a reality in current clinical medicine. Long established in all 50 U.S. states, screening tests for newborns are designed to detect inherited disorders, particularly those requiring early intervention.² Yet despite the known benefit of these newborn screening tests, the public has not yet warmed to the potential benefit of additional routine genetic testing. According to a 2009 survey, there are several reasons for this. Most notably, patients expressed concerns about privacy issues and the confidentiality of genetic testing results, particularly if insurers are able to get access to them.³ Personalized medicine will likely require new health policies, given concerns over confidentiality, access to diagnostic tests, and appropriate use of healthcare resources.

The complex issues surrounding personalized medicine have captured the attention of policy makers, who have authored legislation, created high-level positions, and made other efforts to facilitate the birth of this new era in healthcare. In 2008, passage of the Genetic Information Non-Discrimination Act (GINA), which ensures that all genetic information is protected against misuse by health insurers and employers, was an important milestone on the path to personalized medicine.⁴ Also in 2008, the President's Council on Science and Technology published a report entitled, “Priorities for Personalized Medicine,” that emphasized the development of technology and modernizing regulation and reimbursement.⁵ At the Department of Health & Human Services, the Secretary's Advisory Committee on Genetics, Health, and Society recently released recommendations related to the ethical, legal,



and social implications of genomics in medicine.⁶ In 2009, the U.S. Food and Drug Administration (FDA) created a new position, the Senior Genomics Advisor, to coordinate genomics activities in its Office of Chief Scientist.⁷ Together, these initiatives are setting the stage for widespread implementation of personalized medicine throughout healthcare sectors.

The FDA's new Critical Path Initiative aims to modernize the drug development process by incorporating novel tools into product evaluation. In particular, the initiative recommends including biomarker assays that correlate the presence of specific genes or proteins to the likelihood that a patient will respond to a new therapy.⁸ Although only a handful of diagnostic tests with personalized medicine implications are approved for use by the FDA, a growing number of genetic tests are recommended to be used with specific therapeutic agents to determine their appropriateness in individual patients along with correct dosages. Currently, more than 200 product labels either recommend genetic testing or refer to the influence of genetic variation on treatment response or safety.⁹ As an example, the FDA recently updated the product label for warfarin to include genetic testing in the calculation of its optimal dose, bringing personalized medicine to one of the most widely prescribed drugs in medicine.¹⁰

PERSONALIZED MEDICINE IN CURRENT CLINICAL PRACTICE

Since the mapping of the human genome in 2003, pharmacogenetic research has accelerated rapidly. Several real-world examples now demonstrate the

potential for personalizing medicine to improve diagnosis, optimize therapy, and avoid unnecessary toxicity in patients with debilitating diseases. One of the biggest success stories is occurring in patients with breast cancer.

Studies have shown that approximately 25–30% of patients with breast cancer have tumors that overexpress human epidermal growth factor receptor 2 (HER2). Trastuzumab, a monoclonal antibody that targets HER2, improves survival in patients with high levels of HER2 expression or gene amplification in both the adjuvant and metastatic disease settings, but provides no benefit in patients who do not overexpress HER2.¹¹ Consequently, the FDA's Center for Biologics Evaluation and Research now requires that a diagnostic assay be used in situations where the decision to use a specific therapy is dependent on a patient's HER2 status. The HercepTest, an immunohistochemical assay for HER2 expression, was approved by the FDA along with trastuzumab in 1998.¹² Since then, several other HER2 assays have been developed, including those that evaluate HER2 expression based on fluorescence in-situ hybridization (FISH) assays.¹²

The Oncotype DX[®] breast cancer assay is another example of how personalized medicine has been introduced into the management of patients with breast cancer. This 21-gene assay calculates the likelihood of disease recurrence among patients with estrogen receptor (ER)-positive, node-negative breast cancer.¹³ Based upon assay results, a score is calculated to help patients and clinicians decide whether to pursue treatment with adjuvant chemotherapy. Patients with a low risk of disease

recurrence can avoid toxic and debilitating chemotherapy without harming their long-term health, while those with a high risk of recurrence will be more confident of the need for chemotherapy. Oncotype DX is now reimbursed by Medicare and all major insurance payers and is a standard component involved in managing women with ER-positive, node-negative breast cancer.

Personalized medicine is also integral to the treatment of non-small cell lung cancer (NSCLC) and colorectal cancer. In both of those settings, specific therapeutic agents (erlotinib for NSCLC, cetuximab and panitumumab for colorectal cancer) have been found to be more beneficial in patients with specific tumor types.^{14–17} Testing for gene status in patients with those diseases has become commonplace prior to the introduction of therapy.

Recently developed tools may also be used to identify patients who may benefit from more rigorous surveillance. To date, the most dramatic example of genetic susceptibility to disease involves mutations in the BRCA1 and BRCA2 genes, which carry such a high risk of breast and ovarian cancer (approximately 85%) that some carriers opt for prophylactic radical mastectomy and oophorectomy.^{18,19} Other tests, such as the deCODEme genetic test for susceptibility for prostate, lung, colorectal, and other cancers, are also available to calculate the lifetime risk of developing these diseases.

Beyond the oncology setting, personalized medicine is routinely used in the treatment of conditions ranging from HIV infection to heart transplantation. Patients who carry the HLA-B*5701 allele are at high risk of developing a

hypersensitivity reaction to abacavir, a nucleoside analog reverse transcriptase inhibitor (NRTI) used to treat HIV infection. Therefore, prior to initiating therapy with abacavir, routine screening for the HLA-B*5701 allele is recommended.²⁰ In the heart transplantation setting, the AlloMap[®] multi-gene assay profiles the expression of genes associated with rejection. AlloMap[®] findings identify patients with a low probability of moderate or severe rejection, thus allowing patients to avoid biopsy in certain clinical settings.²¹

PERSONALIZED MEDICINE IN RHEUMATOLOGY

Biologic therapies, beginning with the introduction of the first tumor necrosis factor (TNF) inhibitor a decade ago, have dramatically improved the care of patients with RA. Even though the therapeutic use of TNF blockade is well established, patients show a considerable heterogeneity in response to therapy. Approximately one-third of patients with RA have minimal or no response to TNF inhibitors, and there is currently no way to predetermine which patients are more or less likely to respond to therapy.^{22,23} Moreover, TNF inhibitors are expensive and can be associated with significant toxicity, including an increased risk of infection and malignancy.^{24–26}

Given the high cost and safety risks associated with biologic therapy, breakthroughs related to personalized medicine could greatly benefit patients, physicians, and payors. However, while it is making inroads in other therapeutic areas, the application of personalized medicine into the treatment of rheumatic diseases has been slow. Several barriers specific to RA and other rheumatologic conditions currently prevent its introduction, including the following:

Disease phenotypes — RA consists of multiple distinct disease phenotypes, each of which lead to the common signs and symptoms associated with what is clinically defined as RA. For example, physicians have long recognized the different natural histories of RA in patients who test positive vs. those who test negative for anti-cyclic citrullinated peptide (anti-CCP) antibodies.²⁷ In addition to differences in disease severity, patients with different RA phenotypes may experience highly variable responses to treatment, with considerable differences in both efficacy and toxicity.

Multiple genes — RA is a complex disease with multiple genes that affect response to therapy, including efficacy and toxicity. Several studies have focused on polymorphisms in genes known to be involved in RA pathogenesis, genes encoding TNF receptors, or genes implicated in TNF metabolism. One SNP, the –308G A/G



MOLECULAR TECHNOLOGY IN PERSONALIZED MEDICINE

Molecular diagnostics play an important role in the development of personalized medicine. Common diagnostic assays include those that evaluate gene expression, individual genetic polymorphisms, and genome-wide genetic signatures.

GENE EXPRESSION ASSAYS

Assays based on immunohistochemistry or FISH have been measuring degrees of gene expression in tissue samples for decades. FISH is currently used to evaluate HER2 expression in breast cancer tumors and other tumor samples.¹²

ASSAYS FOR GENETIC POLYMORPHISMS

DNA variants of one base, called single nucleotide polymorphisms (SNPs), account for approximately 80% of all known polymorphisms. They can be associated with disease susceptibility and/or drug response.⁴¹ Some assays target SNPs to perform a “spot check” on the status of single genes by tagging haplotypes or groups of SNPs inherited in blocks. In clinical practice, rheumatologists could test patients for specific SNPs that are known to be associated with drug response to determine which drug regimen best fits a patient's genetic profile.

GENOME-WIDE ASSAYS

Recent genome-wide association (GWA) studies have scanned hundreds of thousands of SNPs to identify genetic loci associated with susceptibility to RA. Ideally, personalized medicine will eventually involve the use of automated genotyping to determine an individual patient's profile with regard to genes involved in the pathogenesis of disease, the metabolism and disposition of candidate drugs, and targets of drug therapy.

Regardless of the particular assay, rigorous quality control and biomarker standardization is critical for ensuring consistent and reliable results with molecular diagnostics. In 2007, the American Society of Clinical Oncology (ASCO) published guidelines for the use of tumor marker tests used in the prevention, screening, treatment, and surveillance of breast cancer,⁴² as well as guidelines specifically focused on HER2 testing in breast cancer.¹² Such guidelines may serve as models for future standards of diagnostic testing across disease states.



polymorphism, has shown promise as a predictor of response to TNF inhibitors.²⁸⁻³¹ In a trial of etanercept in RA, researchers identified a multi-gene signature that was able to predict treatment response based on differentially expressed gene pairs or gene triplets.³² Gene polymorphisms, including interleukin-1 receptor (IL1RN), transforming growth factor beta (TGFB1), interleukin-10 (IL-10), TNF, and lymphotoxin alpha (LTA) have also been associated with treatment response to TNF inhibitor therapy.³³ Despite these findings, however, it should be acknowledged that no current genetic test can robustly predict treatment response.

Tissue access — In cancer patients, tumor tissue is routinely biopsied for analysis. However, in RA, synovial tissue is rarely obtained as part of diagnosis. Instead, diagnostic studies and studies of disease activity often rely on peripheral blood as a surrogate marker of pathologic events in the synovial tissue.¹

Personalized medicine may also impact other rheumatologic conditions, although genetic research is significantly more advanced in RA than other disease states. Psoriatic arthritis is treated through a blockade of TNF, yet not all patients

show a response to treatment.^{34,35} To date, only the -308 A/G polymorphism of the TNF gene appears to predict response to TNF blockade in patients with psoriatic arthritis.³⁶

Researchers have also identified several genes associated with disease susceptibility in ankylosing spondylitis, including SNPs of the endoplasmic reticulum aminopeptidase (ERAP1) and interleukin-23 receptor (IL-23R) genes.^{37,38} These early characterizations of ankylosing spondylitis may lead to the identification of genetic determinants of treatment response.

Finally, personalized medicine may soon impact the treatment of systemic lupus erythematosus (SLE) patients, especially those treated with biologic therapy. Makers of AlloMap®, the multi-gene assay that monitors immune response in heart transplant patients, are developing a test to monitor the effectiveness of abatacept in the treatment of SLE.³⁹ Other research in SLE has shown that response to antimalarial drugs is influenced by polymorphisms of the IL-10 (-1,082 A/G) and TNF (-308 A/G) promoter genes.⁴⁰

The next step in bringing personalized medicine to the rheumatology clinic is validating these potential markers of treatment response in

prospective, randomized clinical trials. Toward this end, multiple groups of researchers are dedicated to identifying clinical biomarkers for the management of autoimmune diseases, including RA.

Much more detail about the potential current and future impact of personalized medicine in rheumatology will be included in future issues of this publication.

SUMMARY

Personalized medicine is changing the delivery of care by providing tools to improve drug selection, identify optimal dosing, maximize drug efficacy, and minimize the risk of toxicity. While personalized medicine has been slow to impact rheumatology, rheumatologists may soon be able to select a course of treatment based on a patient's clinical and genetic characteristics, thereby improving clinical outcomes and optimizing the use of healthcare resources. Ongoing research continues to identify patient subgroups with genetically determined responses to specific therapies.



IMAGE 1



IMAGE 2



IMAGE 3

Her past medical history is unremarkable, although a review of her family history notes that Courtney's maternal grandmother had severe rheumatoid arthritis (RA). Courtney says she takes hydrocodone 10 mg/acetaminophen 500 mg twice daily, as needed, for pain, but otherwise is not currently on any prescribed medication. A systems review indicates an unintentional 35-pound weight loss and marked fatigue.

A musculoskeletal exam reveals pain with passive range of motion of the shoulders and a 10-degree flexion contracture of the right elbow with active synovitis. Decreased range of motion is apparent upon dorsiflexion of both wrists, with active bilateral synovitis. Active synovitis of several PIP joints is also present (see Image 1). There is a moderate-sized left knee effusion with joint tenderness, along with swelling and tenderness of the right ankle. Courtney reports tenderness bilaterally after a metatarsophalangeal joint squeeze, but there is no palpable swelling.

Laboratory evaluations reveal an elevated platelet count of 542,000 but no anemia. Rheumatoid factor (RF) and anti-CCP antibody are both negative. Courtney's erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels are both normal, at 16 and 9.88, respectively.

Radiographs of her hands and feet reveal marginal erosions typical of RA (see Images 2 and 3).

Are you confident that Courtney has RA despite having negative RF and CCP antibody, as well as normal ESR and CRP levels?

According to the American College of Rheumatology's (ACR's) 1987 criteria, Courtney meets the definition of RA as she fulfills criteria Nos. 1–4 as well as criterion No. 7. The ACR criteria indicate that 4 of the following 7 components must be present (criteria Nos. 1–4 must be present for at least 6 weeks) to satisfy a diagnosis of RA:¹

1. Morning stiffness lasting for at least 1 hour
2. Simultaneous arthritis of 3 or more joints
3. Arthritis of hand joints
4. Symmetrical arthritis
5. Rheumatoid nodules
6. Abnormal serum rheumatoid factor
7. Radiographic changes typical of RA on posteroanterior hand and wrist radiographs

In addition, Courtney meets the definition of RA according to the newly proposed ACR/EULAR diagnostic criteria presented at ACR's 2009 annual meeting.² On this scale, she scores >6 points, which was set as the threshold defining the presence of RA, due to measurable synovitis on exam in >10 joints involved with inflammation (tenderness and/or swelling) and ≥6 weeks of symptoms. This new set of criteria was designed to classify patients who have RA earlier in the disease process and also identify those who have a more active disease course. As noted in Table 1, these criteria rely heavily on the presence of polyarticular

involvement and elevation of biomarkers, including acute phase reactants, RF, and anti-CCP. Of note, published data shows that the anti-mutated citrullinated vimentin (MCV) assay has slightly greater sensitivity than anti-CCP or RF, picking up approximately 10% of early RA patients who test negative for anti-CCP and RF.³

One possibility we should consider is, based upon clinical and laboratory results, whether Courtney may have a disease other than RA. Although she fulfills both the traditional ACR and new ACR/EULAR criteria for RA and most likely will end up with this diagnosis, it is possible that her disease could evolve into another type of inflammatory arthritis.

Are we able to predict whether Courtney will have a mild, moderate, or severe course of disease?

Courtney displays several features that suggest a more active disease course, including symptom severity (polyarticular pain, swelling, flexion contracture of the elbow, prolonged morning

CASE STUDY

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“Courtney,” a 20-year-old caucasian female, presents to the rheumatology clinic chiefly complaining of joint pain, swelling, and stiffness for the past 6 months.

She says that her symptoms began 4 months after she gave birth to her son and initially manifested as pain in the left shoulder and elbows. Her symptoms quickly progressed to involve her ankles, knees, wrists, and fingers. Courtney complains of approximately 4 hours of daily morning stiffness.

She was seen in a local emergency department several times over the past 4 months and was given intramuscular corticosteroid injections each time. Unfortunately, each injection provided only a few days of partial relief.

Courtney is married and expresses difficulty caring for her 10-month-old son. Courtney was recently forced to quit her job as a waitress because it required her to spend extended amounts of time on her feet. She has no medical insurance at the time of her initial clinic visit.



TABLE 12009 ACR/EULAR Diagnostic Criteria for RA²**PATIENTS WHO SCORE ≥6 POINTS ARE CONSIDERED TO HAVE RA****JOINTS (0–5 POINTS)**

1 LARGE JOINT	0
2–10 LARGE JOINTS	1
1–3 SMALL JOINTS (<i>large joints excluded</i>)	2
4–10 SMALL JOINTS (<i>large joints excluded</i>)	3
>10 JOINTS (<i>at least 1 small joint</i>)	5

SEROLOGY (0–3 POINTS)

NEGATIVE RF AND ACPA	0
LOW POSITIVE (<i>more than the upper limit of normal but not higher than three times the upper limit of normal</i>) RF OR ACPA	2
HIGH POSITIVE (<i>more than three times the upper limit of normal</i>) RF OR ACPA	3

DURATION OF SYNOVITIS (0–1 POINTS)

<6 WEEKS	0
≥6 WEEKS	1

ACUTE PHASE REACTANTS (0–1 POINTS)

NORMAL CRP AND ESR	0
ABNORMAL CRP OR ESR	1

stiffness, prominent fatigue, physical disability, and elevated platelet count consistent with inflammation), and the presence of erosive change in peripheral joint radiographs. However, she does not display elevation of key laboratory biomarkers such as anti-CCP antibody or CRP that are predictive of an aggressive course. Consequently, although her disease would not be considered mild, it is not clear whether it would be classified as moderate or severe in nature. Future availability of different, more sensitive, and more specific biomarkers should allow us to more accurately predict her disease course. Therapy could then be planned accordingly.

Even in the absence of such serum markers, the presence of early erosions is suggestive enough of an aggressive disease course that Courtney should be treated accordingly. Currently, additional laboratory testing or imaging is unlikely to provide significantly useful information, although rapid and inexpensive testing of genetic variations associated with disease severity (e.g., HLA-DRB1 alleles encoding the so-called shared epitope) are in development that may be of significant future clinical value.

What would be your initial treatment recommendation for Courtney?

After appropriate education about the diagnosis and the treatment options available to treat RA, I would recommend a number of pharmacologic and non-pharmacologic treatments at this juncture based upon 2008 ACR recommendations.⁴ I would have her consider four medications to start with—a nonsteroidal anti-inflammatory drug, methotrexate (MTX), folic acid, and, as a short-term bridge until we can assess the effectiveness of MTX, low-dose prednisone. Prednisone can be used in an attempt to quickly reduce Courtney's physical disability.

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Courtney should be started on a dose of MTX of at least 15 mg per week, rapidly escalating to 20–25 mg per week depending on her clinical response and tolerability. Her progress should initially be monitored with a validated tool such as the DAS28 on a monthly basis. If, after 3 months of treatment, she has not reached a state of low disease activity (DAS28≤3.6) or remission (DAS28≤2.4),⁵ strong consideration should be given to initiating an anti-TNF or other biologic medication.⁴ In addition, I would offer to aspirate her knee joint effusion and inject corticosteroids intra-articularly.

Currently, our ability to reliably predict potential efficacy or side effects of MTX through individualized biomarker/genomic testing has not yet evolved. However, if Courtney's response is inadequate with standard oral dosages, one new test, the methotrexate polyglutamate assay, has shown promise in helping to guide dosing.⁶ Other tests will hopefully be available in the near future.

What questions may advances in personalized medicine be able to answer about Courtney's condition that currently stump rheumatologists?

This is perhaps the most exciting development to watch for—what breakthroughs tied to individualizing care will allow us to better serve our patients in the future? Research continues that focuses on answering the following questions:

- Would therapy aimed at one particular disease pathway or target (ie, TNF, B cells, T cells, IL-6) be any more effective at reducing disease activity and radiographic progression in this patient? If so, which one?
- What is the optimal dose of our drug of choice?
- What is the likelihood of toxicity, infection, or other adverse events from the drug of choice in this patient?

Activity Learning Assessment Request for Credit and Evaluation Form

ACTIVITY INSTRUCTIONS & CRITERIA FOR SUCCESS

To successfully complete this activity and obtain a certificate of credits awarded, the learner is required to read the entire newsletter, complete the post-test learning assessment, and complete the activity evaluation form. Learners are required to correctly answer 75% of the post-test questions. Certificates of credit will be forwarded via e-mail within 2 to 3 weeks of your submission. All forms must be received by February 15, 2011, to be eligible for CE credits.

- Please fax both sides of this evaluation to ICHE at (215) 592-9085, OR
- Please complete the evaluation online by going to www.iche.edu and clicking on **Enduring Materials**.

NAME _____ DEGREE/CERTIFICATION _____

ACTIVITY LEARNING ASSESSMENT QUESTIONS (*Please circle the letter that matches the correct response to each question below*)

- John is a 28-year-old new patient of yours. He has measurable synovitis in three PIP joints that has persisted for approximately 3 months, negative RF and ACPA, and normal CRP and ESR. According to the October 2009 ACR/EULAR Diagnostic Criteria, does John meet the definition of RA?**
 - Yes
 - No
 - Not enough information has been presented to make a clear determination
- Which of the following can be considered primary goals of personalized medicine?**
 - Fostering disease prevention through surgical manipulation of an individual's genetic profile
 - Improving treatment options by allowing physicians to more appropriately select drugs and doses that are optimal for specific patients based on genetic predictors of drug response
 - Allowing patients to serve as sole arbiters of their course of treatment based upon data presented to them by their healthcare team
 - All of the above
- Approximately how many current drug labels currently recommend genetic testing or refer to the influence of genetic variation on treatment response or safety?**

a. 50	c. 200
b. 100	d. 500
- In which of the following disease states has personalized medicine currently had the least impact?**

a. Breast cancer	c. Colorectal cancer
b. HIV	d. Rheumatoid arthritis
- What was the primary focus of the 2008 Genetic Information Non-Discrimination Act?**
 - All genetic information must be protected against misuse by health insurers and employers
 - Medicare must set up a special committee to review the clinical efficacy of genetic tests and determine reimbursement rates
 - The Food and Drug Administration must determine a strict pathway by which specific genetic tests will be approved for use
 - The drug development process must be modernized to incorporate novel tools into product evaluation
- The GRADE system was recently introduced recommending the use of which of the following descriptors in clinical trials?**
 - Number Needed to Treat
 - Number Needed to Cure
 - Number Needed to Harm
 - Both A and C
 - All of the above
- Rheumatologists' ability to reliably predict potential efficacy or side effects of methotrexate in individual patients through the use of individual biomarker/genomic tests has progressed enough so that these tests are currently recommended for use in all RA patients.**

a. True	b. False
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- Treatment response to TNF inhibitors has been shown in trials to be associated with which of the following gene polymorphisms?**

a. -308G A/G	c. Lymphotoxin alpha
b. Interleukin-10	d. All of the above

The learning objectives designed for this activity (listed below) can help me strive toward:	Nothing at this time	Reinforcement of current practices	Moderate Improvement	Significant Improvement
Define personalized medicine, specifically focusing on the potential improvements personalized care may have for patients across the disease spectrum	1	2	3	4
Assess the differences between prognostic and predictive factors currently used to help guide patient management and treatment	1	2	3	4
Identify at least two specific therapeutic areas where personalized medicine is currently impacting patient care and treatment	1	2	3	4
Cite at least two reasons why the introduction of personalized medicine into rheumatology has not been as rapid as it has in other disease states	1	2	3	4

Please indicate the extent of your agreement with the following statements:	Strongly Disagree		Not Sure		Strongly Agree	
1. The information presented in this newsletter was pertinent to my professional needs.	1	2	3	4	5	6
2. The content of this newsletter contributes valuable information that will assist me in improving patient outcomes.	1	2	3	4	5	6
3. Based on my experience, I would recommend future newsletters to my colleagues	1	2	3	4	5	6
4. Were you able to locate information about faculty disclosure at the beginning of the newsletter?	YES				NO	
5. Did you perceive any bias or commercial influence in the newsletter? If so, your help in identifying it is appreciated: _____	YES				NO	

6. Do you think personalized medicine will have a significant clinical impact in rheumatology practices within the next five years?

- a. Definitely
- b. Maybe
- c. I doubt it

7. Which of the following would you consider to be the most significant barrier to the introduction of biomarker assays and genetic tests into your current practice?

- a. Lack of proven applicability of results
- b. Reimbursement issues
- c. Insufficient knowledge about the tests themselves
- d. Concerns about the confidentiality of test results

8. The following is the primary barrier to implementing change at my facility:

- a. Lack of knowledge regarding evidence-based strategies
- b. Misperceptions of or negative attitudes about research and evidence-based care
- c. Demanding patient workloads
- d. Fears about practicing differently from peers

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Signature _____ Date _____

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