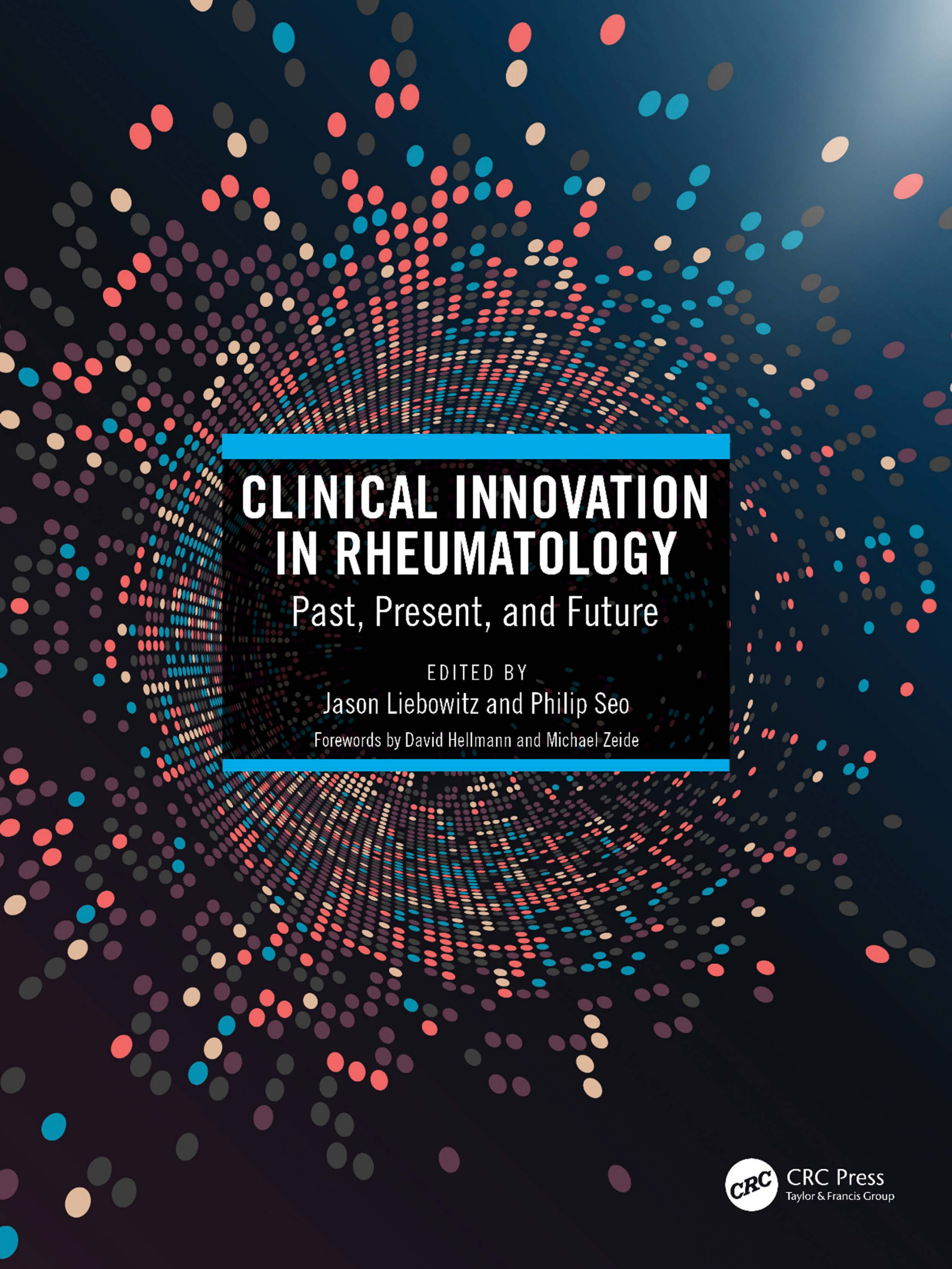
CLINICAL INNOVATION
IN RHEUMATOLOGY
Past, Present, and Future
EDITED BY
Jason Liebowitz and Philip Seo
Forewords by David Hellmann and Michael Zeide
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Clinical Innovation in Rheumatology

Tremendous advances have been made in the field of rheumatology, profoundly changing our understanding of many rheumatologic conditions and creating a new frontier for effective treatments. This book explains the most significant advances in research and care and speculates as to what will be the future of rheumatology over the next several decades, including challenges and lessons learned from past experiences in the field. It highlights landmark research articles and scientific discoveries and discusses how big data, personalized medicine, new biomarkers for disease, and other technological revolutions will shape the future, making it a must-have resource for physicians from all regions of the world.

Key Features

- Includes concise yet thorough descriptions of landmark studies and scientific breakthroughs coupled with easy-to-follow organizational structure of chapters that are accessible to readers at different levels of training.
- Brings together world-leading experts to provide a fresh perspective to trainees, such as residents and fellows-in-training, as well as more senior clinicians and researchers across the field of rheumatology and in specialties such as cardiology, dermatology, pulmonology, nephrology, and neurology, all of whom care for patients with rheumatologic conditions.
- Allows the authors to imagine and speculate about the evolution of the field of rheumatology in the coming decades. Examples of such speculative possibilities include use of synovial biopsy to predict response to treatment in rheumatoid arthritis, replacement of renal biopsy with urinary proteomics in diagnosing and classifying lupus nephritis, use of new therapeutics to obviate the need for steroids in the treatment of ANCA-associated vasculitis, and the use of machine learning to evaluate subtle changes in imaging for management of inflammatory arthritis, and so on.

Clinical Innovation in Rheumatology

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This book is dedicated to the memory of Dr. Nadia Morgan, a great rheumatologist, colleague, and friend. Although she was taken from us too soon, her legacy lives on through her research and the care she provided to countless patients.

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FOREWORD by Dr. David Hellmann

In 1975, on the first day of my subinternship on the Johns Hopkins Rheumatic Disease Service, Dr. Mary Betty Stevens, the redoubtable director of that service, rushed me into a hospital room to see a patient she said was incredibly rare. The middle-aged man I met that afternoon had an uncommon-enough disease, granulomatous polyangiitis (GPA), but what had gobsmacked Dr. Stevens is that he was still alive (and vibrant) two years after being diagnosed! Two years earlier, Dr. Stevens explained, his once all-but-certain rapid death sentence of a diagnosis had been commuted by Fauci and Wolff's discovery that treatment with cyclophosphamide and prednisone could achieve remission in 75% of patients with GPA. Being in that room on that day with Dr. Stevens and that patient, I felt a frisson of wonder that clarified my previously murky career plans: I would be a rheumatologist.

Little did I know in 1975 that the next forty-seven years would deliver, with increasing speed, many similar moments of wonder. The discovery of the T cell receptor, therapeutic monoclonal antibodies, biologic therapies, the link between scleroderma and cancer, the pathogenesis of Lyme disease, and the adenosine deaminase 2 mutations causing childhood-onset polyarteritis nodosa constitute a Whitman sampler of innovations, which have made rheumatologists smack their lips with pleasure and satisfaction. Given the quickening pace at which the field is delivering these morsels, how fortunate and timely it is that Drs. Jason Liebowitz and Philip Seo, both revered clinicians and teachers, have chosen to memorialize these advances and illuminate the path for future ones with this important book. I believe that everyone interested in rheumatology will relish the many innovations described herein. By tracing the arc of innovation in rheumatology, the editors help us honor our predecessors and anticipate the moments of wonder that will stir our imagination and serve our patients.

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FOREWORD by Dr. Michael Zeide

Although I am a founding member of the American College of Rheumatology, I must admit that I am not a *bona fide* rheumatologist but, rather, an orthopedic surgeon who has always had a keen interest in rheumatology.

I started in orthopedics in 1971 when the United States withdrew from the gold standard in economics but when gold therapy was the "gold standard" for the treatment of rheumatoid arthritis.

In that era, orthopedic surgery was glamorous and driven by applied science, from the development of artificial joint replacements and metallurgy, computed tomography and magnetic resonance imaging scans, and new techniques in arthroscopy, microsurgery, and robotics.

My initial clinical rotation as an orthopedic resident at the Hospital for Joint Disease was a two-month rotation with the legendary Dr. Harry Spiera in rheumatology. Yet at that time, rheumatology still seemed to be in its infancy, with the rheumatologist's arsenal essentially limited to aspirin, phenylbutazone, indomethacin, gold, cortisone, and a good bedside manner. The field of rheumatology kept chugging along with regard to advances in immunology, genetics, molecular biology, and imaging. In terms of treatments, the early successes of ibuprofen, naproxen, and celecoxib were tempered by obstacles posed by failures with benoxaprofen, rofecoxib, and valdecoxib.

Past

Indeed, reviewing the timeline of rheumatology is quite instructive:

1940: American physicians Dr. Bernard Comroe and Dr. Joseph Lee Hollander coin the term *rheumatologist*.
1948: Dr. Charles A. Ragan Jr. rediscovers the rheumatoid factor.
1950: The Nobel Prize in Physiology or Medicine is awarded to Dr. Edward C. Kendall and Dr. Tadeusz Reichstein for the discovery of adrenocorticotropic hormone anti-inflammatory effects in rheumatoid arthritis.
1953: Dr. Marian Ropes and Dr. Walter Bauer publish "Synovial Fluid Changes in Joint Disease."
1958: Publication of the journal *Arthritis and Rheumatism*.
1958: Chloroquine used for rheumatoid arthritis.
1968: Dr. Lee Schlosstein and colleagues note the association between the HLA-B27 antigen and ankylosing spondylitis.
1970: Use of methotrexate for dermatomyositis.
1971: The American Board of Internal Medicine approves rheumatology board certification.
1970s: Dr. John Vane and colleagues demonstrate the blocking of prostaglandin E synthesis by aspirin, paving the way for the development of other anti-inflammatory agents.
1974: The first clinical computed tomography scans are introduced.
1980s: Introduction of magnetic resonance imaging into the medical field.
1985: Founding of the American College of Rheumatology (ACR).
1998: FDA approval of etanercept, a tumor necrosis factor-α inhibitor and the first synthetic biologic disease-modifying antirheumatic medication (DMARD) to be used in rheumatology.

Tempus Fugit

Today, the advances in orthopedic surgery are incremental—improved instrument designs and minimally invasive procedures and developments in stem cell treatments.

In comparison, advances in rheumatology have exploded and continue to expand. The success of conventional, synthetic, and targeted biologic DMARDs, the use of physician- and patient-reported outcomes and treat-to-target approaches, and the increasing evolution of artificial intelligence, machine learning, and other advanced technologies to aid clinicians are remarkable.

Rheumatologists are now at the forefront of extraordinary innovations and treatments across all of medicine.

Future

Dr. Jason Liebowitz and Dr. Philip Seo are to be highly commended for both conceiving and then designing this remarkable textbook on rheumatology. They are master scholars that have compiled a true reference for the increasingly complex field of rheumatology.

This book is special and astute; if this were a canvas, it would represent the multimedia creation of *avant-garde* artists. As a textbook, it resonates with updates on the latest clinical guidelines and research developments and health policy issues impacting patient care and consequential clinical innovations. It is a turning point in textbook writing as it furnishes a framework for understanding the complexities of rheumatology. The chapters are written by leading national and international authorities in the field in a highly organized and lucid style. The structure, organization, and logical approaches to clinical concepts are poignant and insightful.

Medical education, with its conventional approach to patient care, research, and continuing education, presents a conundrum. In this digital age, rheumatology students and clinicians are overwhelmed by the promulgation of myriad journals, podcasts, industry-sponsored supplements, and so forth, but often fail to provide a link between the relevant scientific information and the clinical practice. The complexity of rheumatology requires a new system to present clinical subjects to the clinician in a clear and comprehensive manner.

In this volume, the reader is presented with a review of the current state of the art about rheumatology. This comprehensive work encompasses the new technologies and advances that have been made over the past several decades, from genetics to pathophysiology to biomechanics to artificial intelligence and beyond. The book integrates the scientific knowledge of metabolic, degenerative, and inflammatory diseases with therapeutic research in rheumatic disorders. This book represents an approach that is effective in meeting the needs of today's rheumatologists. Its philosophy is simple: scientific excellence with a vision of the future of rheumatology.

In essence, the authors have translated basic science into state-of-the-art treatment platforms. *Clinical Innovation in Rheumatology: Past, Present, and Future* will be a valuable resource for rheumatologists and other aligned professions for many years to come.

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Jason Liebowitz, MD, attended Johns Hopkins University for his undergraduate studies and was inducted into *Phi Beta Kappa*. He attended medical school at Johns Hopkins University School of Medicine and completed his internal medicine residency at Johns Hopkins Bayview Medical Center, where he was selected Chief Resident. He completed his rheumatology fellowship at Johns Hopkins University and was nominated for the 2019 Distinguished Fellow Award from the American College of Rheumatology. His research has been published in the *New England Journal of Medicine*, *JAMA, JAMA Internal Medicine*, *Arthritis Care and Research*, the *Journal of Rheumatology*, the *American Journal of Medicine*, and *Medical Humanities*. He is also a staff writer for *The Rheumatologist*, a periodical that reaches over ten thousand readers. He greatly enjoys teaching trainees and caring for patients, which he considers a tremendous honor and privilege.

Philip Seo, MD, MHS, is an Associate Professor in the Division of Rheumatology. A graduate of Harvard College and the College of Physicians and Surgeons at Columbia University, Dr. Seo completed his internal medicine training as a member of the Osler Medical Service at the Johns Hopkins Hospital. Since then, he has worked at Johns Hopkins in several capacities, including as a Hospitalist at Johns Hopkins Bayview Medical Center and as an Assistant Chief of service of the Department of Medicine at the Johns Hopkins Hospital, before joining the Division of Rheumatology. Dr. Seo is the Director of the Johns Hopkins Vasculitis Center and the Director of the Johns Hopkins Rheumatology Fellowship Program. His clinical interests lie in the assessment and treatment of patients with systemic vasculitis, in particular, the ANCA-associated vasculitides, which include granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis.

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Chapter 1
RHEUMATOID ARTHRITIS

Brent A. Luedders, Ted R. Mikuls, James R. O'Dell, and Bryant R. England

1.1 Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease with primary manifestations in the synovial joints, though frequently accompanied by extra-articular features. The natural history of untreated or suboptimally treated RA characteristically includes progressive destruction of involved joints, functional disability, systemic complications such as cardiovascular disease, and premature mortality. Nearly 150 years ago, it was described to "[seize] first one joint and then another till all are crippled and deformed, every movement rendered more or less difficult or impossible, and the victim rendered helpless and crippled for all his future life."[1] Fortunately, with the development of several highly effective disease-modifying therapies coupled with earlier diagnosis and a treat-to-target strategy, many patients now avoid irreversible articular damage, resulting joint deformities, and functional limitations. Additional advances in the understanding of the pathogenesis of RA, new diagnostic and therapeutic technologies, and novel management strategies are expected to produce further improvements in quality of life and long-term outcomes as well as reduce treatment-related harms for patients with RA.

1.2 Past and Present Understanding of Rheumatoid Arthritis

1.2.1 Presenting Features and Diagnosis

1.2.1.1 Clinical Features and Diagnosis

RA affects approximately 0.5 to 1.0% of the population and twice as many women as men.[2] While RA is a systemic autoimmune disorder, the primary symptoms that patients present with are related to an inflammatory arthritis. Characteristic articular features include symmetrical swelling, pain, and stiffness, with the small joints of the hands, feet, wrist, and ankles most commonly affected in early disease.[3] Extra-articular manifestations are frequently observed in RA and include inflammatory involvement of the skin, heart, lungs, and eyes, among other organs.[4] Destructive joint changes may appear early in the disease course, with nearly half of patients diagnosed with RA showing radiographic evidence of bone erosions within the first year of disease in some reports.[5]

The diagnosis of RA is made clinically, with many providers utilizing disease classification criteria that were developed for clinical trial purposes to assist in making a diagnosis. Features common to both the initial 1987 American College of Rheumatology (ACR) and revised 2010 ACR / European League Against Rheumatism (EULAR) classification criteria for RA include the presence of small joint arthritis, positive serum rheumatoid factor (RF), and symptom duration of at least six weeks.[6, 7] New components in the 2010 criteria, intended primarily to improve the tool's sensitivity over the preceding version, included the addition of anticitrullinated protein antibodies (ACPA) and elevated acute phase reactants and the removal of rheumatoid nodules and radiographic disease in order to capture patients earlier in the disease course.

1.2.1.2 Laboratory Evaluation

Measurement of serum RF and ACPA is part of the routine evaluation of suspected RA. RF is elevated in approximately two-thirds of RA patients,[8] but the specificity for RA is limited as RF may also be present in healthy patients as well as in patients with a variety of rheumatic and nonrheumatic diseases, including systemic lupus erythematosus, Sjögren's syndrome, and various bacterial and viral infections.[9] The discovery of ACPAs has helped to more accurately diagnose RA, as its sensitivity is similar to RF but it has a specificity for RA approaching 95%.[8] In addition to supporting the diagnosis of RA, these autoantibodies also prognosticate a more severe RA disease course,[10, 11] including the presence of extra-articular manifestations.[4]

Evidence of an acute phase response, including elevations in the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level, may be helpful to identify inflammation associated with active RA. However, normal ESR or CRP does not rule out RA as these may be normal in up to 40% of RA patients at the time of presentation.[12] Additional nonspecific features of systemic inflammation that may be present in RA include anemia of chronic inflammation and reactive thrombocytosis. Arthrocentesis of affected joints, while not routinely performed for typical disease presentations, will reveal inflammatory synovial fluid with a white blood cell count in the range of 2,000 to 50,000 cells/mm^3 with a predominance of polymorphonuclear cells.[13]

1.2.1.3 Natural History

RA is recognized to advance through a series of phases. Initially, an individual is predisposed to RA through genetic and environmental factors without clinical or laboratory evidence of autoimmunity. In what has been termed the preclinical or prediagnostic phase, autoimmunity (presence of RA-related autoantibodies) develops without clinical signs or symptoms of disease or with nonspecific arthralgias but with the absence of inflammatory arthritis. Transition to clinically apparent RA is marked by the development of inflammatory arthritis or, in a minority of patients (<5%), extra-articular features, such as interstitial lung disease (ILD) or rheumatoid nodules.[14] Prior to the era of effective DMARD therapies, RA was typically characterized by a progressive, disabling disease course. Uncontrolled inflammatory arthritis resulted in bone erosions and frequent joint deformities that impose substantial physical limitations and frequently require joint surgery. Devastating extra-articular manifestations may also occur as a result of uncontrolled, long-standing disease, driving premature mortality in patients with RA. Fortunately, the poor functional, economic, social, and survival outcomes for RA patients[15] appear to be improving as a result of advances in therapeutic approaches.[16, 17]

1.2.2 Pathogenesis

1.2.2.1 Genetic Factors

The heritability of RA is estimated to be approximately 60%,[18] and the strongest genetic associations with RA risk lie within the *HLA-DRB1* region on chromosome 6. The "shared epitope," consisting of a shared five amino acid sequence between amino

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acid position 70 and 74 in *HLA-DRB1*, was found to confer an increased risk of RA.[19, 20] Subsequent studies have revealed the link between SE alleles and RA risk to be driven by ACPA-positive RA.[21, 22] Within *HLA-DRB1*, genetic haplotypes defined by amino acids both within and outside the shared epitope region (e.g., valine at position 11) have been strongly associated with RA risk, autoantibody concentrations, and RA-related outcomes.[23, 24] Beyond *HLA-DRB1*, genome-wide association studies have identified more than one hundred additional risk loci for RA, with the strongest of these being *PTPN22*.[25]

1.2.2.2 Environmental Factors and Gene/Environment Interaction

Numerous environmental factors have been identified as risk factors for developing RA, of which the strongest and most consistently identified is cigarette smoking.[26] There is mounting evidence that chronic mucosal inflammation, including periodontitis,[27] dysbiosis of the gut and distal airway microbiome,[28, 29] and airway inflammation,[30–32] may each contribute to the risk of developing RA. With females being affected by RA two to three times more commonly than men,[33] sex hormones are hypothesized to influence RA risk.[34] Occupational inhalant exposures (e.g., silica) have also been recognized to meaningfully influence RA risk,[35, 36] a risk that appears in most studies to disproportionately impact men. Being overweight and obesity have been associated with an increased risk for developing RA.[37] Viral infections, including Epstein Barr Virus, have long been implicated as a possible risk factor for RA.

Genetic and environmental risk factors appear to act in concert in mediating RA risk. This gene-environment interaction is best exemplified by the markedly increased risk of ACPA-positive RA accompanying the presence of both SE alleles and cigarette smoking.[38] Mirroring these findings, exposure to military burn pits was associated with the presence of ACPAs in US veterans with RA, particularly among those with shared epitope alleles.[39]

1.2.2.3 Autoantibodies

RF and ACPA are the most clinically relevant autoantibodies in RA. RF targets the Fc region of IgG,[40] whereas ACPAs target citrullinated peptides resulting from the posttranslational modification of arginine facilitated by peptidyl arginine deiminase (PAD) enzymes.[41] While enzymatically mediated protein citrullination is not specific to RA, tolerance loss to these peptides is. Several antigen-specific citrullinated proteins have been found to be the targets of ACPAs in RA, including α-enolase, fibrinogen, filaggrin, vimentin, and type II collagen, among others.[42] Studies leveraging biobanked blood samples of RA patients from the prediagnostic period have shown that RF and ACPA antibodies are detectable in the serum years before the development of clinical signs or symptoms of inflammatory arthritis.[43–45] In the absence of joint inflammation, it is hypothesized that RA-related autoimmunity may originate at mucosal sites, such as the lung, intestine, or oral mucosa.[46] Evidence suggests that RF and ACPA antibodies may be pathogenic through the ability to stimulate pro-inflammatory cytokine production, an effect that is synergistic among those dual positive for RF and ACPA,[47] as well as through direct activation of osteoclasts and pain receptors.[48]

1.2.2.4 Immune Effector Cells and Inflammatory Cytokines

While the roles of innate and adaptive immune responses in RA pathogenesis are incompletely understood, the crucial roles of $CD4^+$ T cells and immune effector cells have been well established. While type 1 T helper (TH1) cells have historically been thought to be most crucial in RA, there is increasing evidence that upregulation of TH17 cells and downregulation of regulatory T cells additionally play an important role in RA pathogenesis. Through autoantibody production as well as presentation of autoantigens and production of inflammatory cytokines, B cells also play a key role in disease pathogenesis. As such, therapies inhibiting both B cells (i.e., rituximab) and T cells (i.e., abatacept) have proven effective in treating RA. Cells of the innate immune system, including macrophages, neutrophils, and mast cells, are of central importance in propagating and sustaining synovial inflammation, producing pro-inflammatory cytokines, and causing local tissue damage.[49] Pro-inflammatory cytokines and chemokines have also served as therapeutic targets of effective RA therapies, such as tumor necrosis factor alpha (TNFα), interleukin (IL)-6, and IL-1.[50]

1.2.2.5 Synovial Inflammation and Fibrosis

In RA synovium, increased expression of pro-inflammatory cytokines, upregulation of adhesion molecules, and release of matrix metalloproteinases characterize the dysregulation of fibroblast-like synoviocytes. As a result, the synovium in RA becomes hyperplastic, invades and destroys the cartilage, and causes periarticular bone erosions via osteoclasts.[49] This propensity for fibrosis can additionally occur in extra-articular sites, such as in the lungs, where it results in ILD.

1.2.3 History of DMARD Therapy in RA

The mainstay of treatment for RA is disease-modifying antirheumatic drug (DMARD) therapy, therapies that alter the natural history by reducing the progression of structural joint damage in RA. The first DMARD to be widely used in RA was gold, which was administered primarily by intramuscular (IM) injection, although a less efficacious oral preparation was also used. Forestier[51] reported the use of IM gold salt injections in 1928 in Paris after observing that the medication had shown some utility in the treatment of tuberculosis (Figure 1.1). DMARD therapies such as gold were initially reserved for patients with only the most advanced forms of arthritis,[52] whereas a majority of patients were treated initially with nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin (which have not been shown to have disease-modifying activity in RA).

Several advances to RA treatment occurred in the midtwentieth century. "Compound E," now better known as cortisone, was found to lead to rapid and dramatic improvement in the clinical features of RA[53] and led to Hench and Kendall being awarded the Nobel Prize in 1950. While they are highly efficacious for treating the manifestations of RA, the risk of adverse effects[54] with long-term glucocorticoids has limited their use with preference for other agents with better long-term safety profiles in contemporary practice. Both sulfasalazine and hydroxychloroquine were approved for the treatment of RA in the 1950s and remain widely used today. In 1968, tetracycline was reported as a treatment for RA in Brazil,[55] and minocycline was subsequently shown to be effective in RA treatment,[56] specifically in the context of RF-positive early disease, though these are not FDA-approved therapies for RA.

Reports of methotrexate (MTX) use for RA from uncontrolled studies first appeared in the 1970s, with subsequent controlled trials in the mid-1980s establishing its efficacy in the treatment of RA.[57–60] Despite initial use at lower doses than currently prescribed, MTX was as effective or superior to other DMARDs commonly used at that time,[61] in addition to being

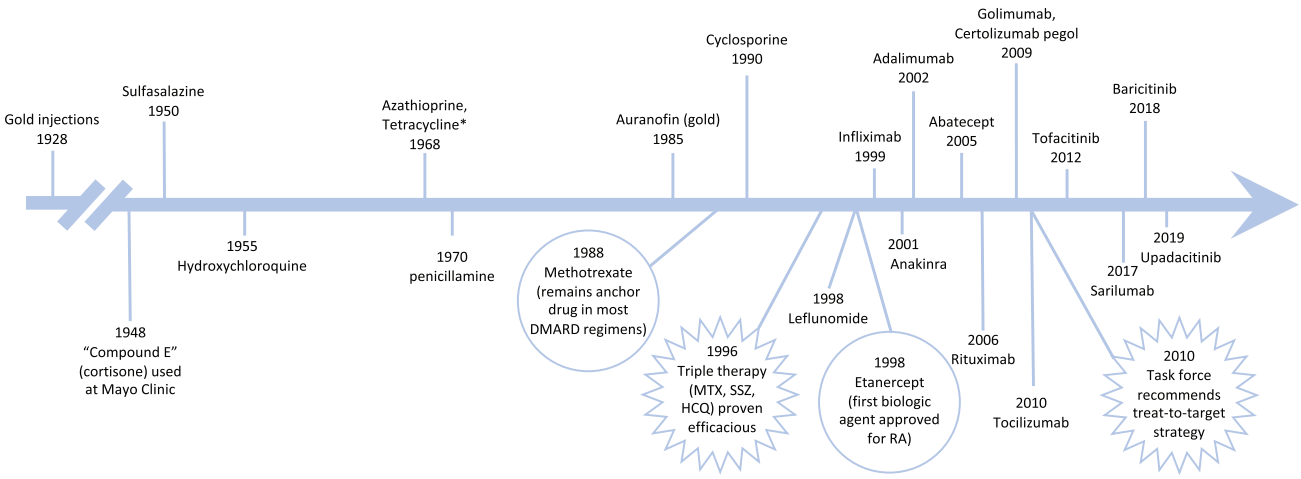

FIGURE 1.1 Timeline of important drug approvals and milestones in rheumatoid arthritis treatment. The first use of disease-modifying treatments for RA was reported in the 1920s with the injection of intramuscular gold salts. FDA approvals for RA were limited throughout the twentieth century; however, an explosion of FDA approvals began around the turn of the century following the approval of the first biologic for RA, etanercept.
* Not FDA approved for RA but efficacy has been proven.
Abbreviations: RA, rheumatoid arthritis; DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; SSZ, sulfasalazine; HCQ, hydroxychloroquine.

a more durable therapy than other conventional agents when used as monotherapies.[62] The subsequent discovery that folic acid supplementation improved the tolerability of MTX without compromising its efficacy[63, 64] has been critical in supporting dose escalation and treatment persistence. MTX remains the first-line therapy for RA and an anchor drug in combination regimens for the treatment of RA.

A major shift in RA management occurred during the 1990s when combinations of DMARDs were shown to be highly effective and possess a favorable safety profile.[65] Prior to this, DMARDs were used almost exclusively as monotherapies in a sequential fashion, out of concern there may be unacceptable risks of toxicity posed by combination DMARD use. Combination DMARD therapy, however, allowed a greater proportion of RA patients to achieve better disease control and prevent RA progression as well as improve more rapidly by avoiding cycling through DMARDs one at a time. Additional studies, including COBRA,[66] MTX/cyclosporine combinations,[67] FIN-RACo,[68] and MTX/leflunomide combinations,[69] firmly established the efficacy and tolerability of combination DMARD therapy. Despite earlier concerns, all these combinations resulted in little to no incremental toxicity compared to monotherapy.

The late 1990s signaled the beginning of the use of biologic DMARDs (bDMARDs) for RA following the approval of etanercept in 1998. This class of medication consists of proteins produced by recombinant DNA technology with mechanisms of action generally targeting cytokines, their receptors, or other cell-surface molecules. While the initial agents approved for the treatment of RA were anti-IL-1 (anakinra) and TNF-targeted therapies (e.g., etanercept, infliximab, adalimumab), subsequent bDMARDs have targeted IL-6 (tocilizumab, sarilumab), B cells through the CD20 receptor (rituximab), and T cells through cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) (abatacept). Biosimilar agents, which are biologics highly similar to the previously approved bio-originator in safety and effectiveness, are available for several RA bDMARDs and will hopefully lead to lower costs and improved patient access.[70]

The newest class of DMARDs is the Janus kinase inhibitors (JAKi), which, in contrast to bDMARDs that necessitate either an injection or infusion, are available in oral formulations. Tofacitinib was the first JAKi approved by the FDA for RA in 2012. Additional JAKi have subsequently been approved and differ based on their selectivity for specific JAK isoforms (JAK1, JAK2, JAK3).

Recognizing the need to provide guidance to providers given the expanding therapeutic armamentarium, the ACR published the first clinical practice guidelines for the management of RA in 1996.[71] As treatment options have evolved, updates to these guidelines and those of other professional societies, including EULAR,[72] have regularly occurred, with the most recent ACR guidelines being published in 2021.[73]

1.2.4 Current Treatment Strategy

1.2.4.1 Treat-to-Target Strategy

1.2.4.1.1 Treat-to-Target Strategy

In the early 2000s, a novel treatment strategy was tested in RA whereby disease activity would be routinely assessed and treatment escalated toward predefined treatment targets (Figure 1.2). This "treat-to-target" strategy was shown to result in greater improvements in disease activity, functional status, and less radiographic progression in the transformative tight intensive control of RA (TICORA) trial.[74] Other early treat-to-target trials of systematic disease activity measurement both with (Computer-Assisted Management in Early RA [CAMERA][75]) and without[76] protocolized treatment confirmed these benefits. A meta-analysis of these treat-to-target clinical trials demonstrated that not only did systematic measurement of disease activity improve patient outcomes but also that even greater improvements were achieved when medication adjustments were performed on a protocolized basis after disease activity measurement.[77] This body of evidence led an international task force

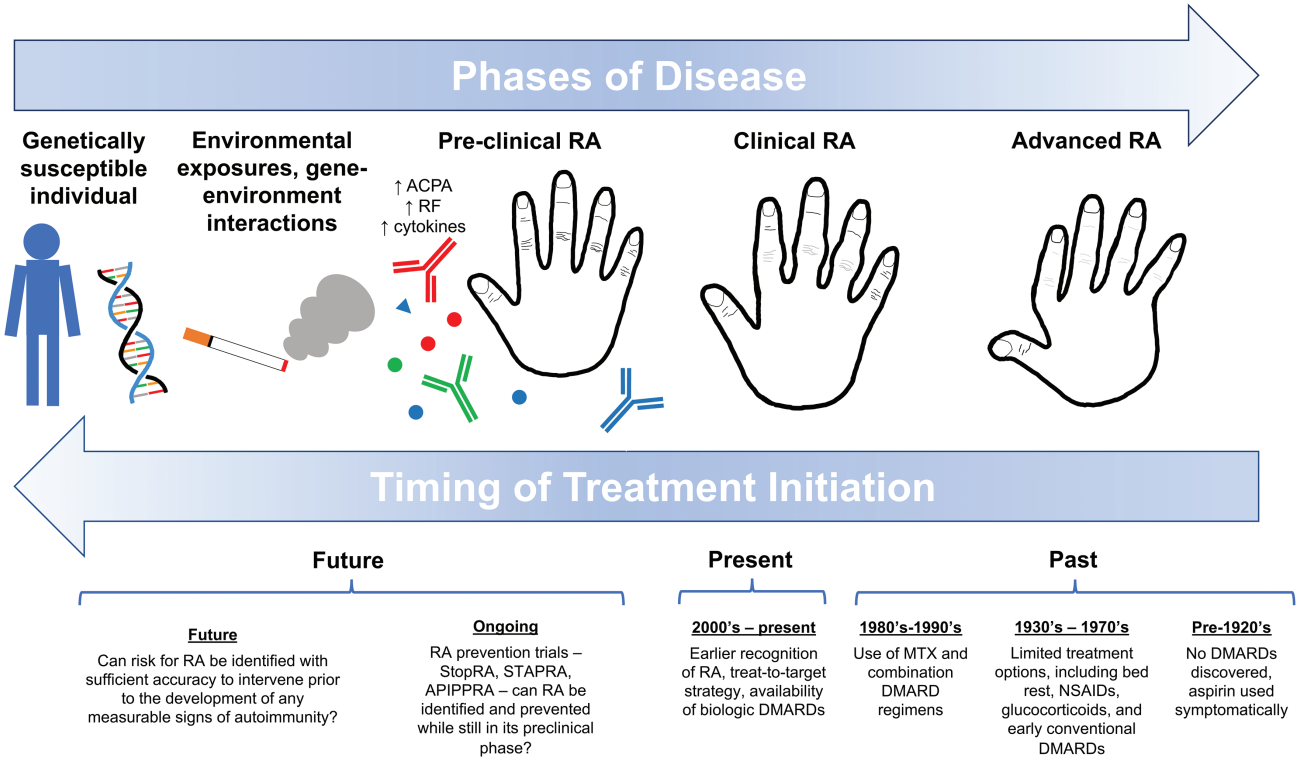

FIGURE 1.2 Treatment of rheumatoid arthritis moving to earlier phases of disease over time. With the understanding that earlier treatment of RA leads to better outcomes, coupled with the discovery of highly effective DMARD therapy, the treatment of RA has been moving to earlier phases of the disease over time. While previous treatment strategies reserved DMARD therapy for patients with more advanced disease, current practice involves initiating DMARDs at the time of diagnosis. Trials are currently underway to evaluate the prevention of RA in the preclinical phase with pharmacotherapy, and with further understanding of the pathogenesis and risk factors for RA, it may become possible to intervene prior to the development of autoimmunity and prevent the development of clinical disease.
Abbreviations: RA, rheumatoid arthritis; ACPA, anticitrullinated protein antibody; RF, rheumatoid factor; MTX, methotrexate; DMARD, disease-modifying antirheumatic drug; NSAID, nonsteroidal anti-inflammatory drug.

to recommend a treat-to-target strategy in RA in 2010,[78] and a treat-to-target strategy remains core to current RA treatment guidelines.[72, 73]

1.2.4.1.2 Assessment of RA Disease Activity

Implementing a treat-to-target strategy requires the regular measurement of disease activity. With several disease activity measures available, the ACR has established working groups to evaluate and recommend optimal RA disease activity measures. The five composite RA disease activity measures currently recommended for regular use in clinical practice based on their psychometric/clinimetric performance and feasibility[79] are listed in Table 1.1. All these measures include patient-reported data with or without formal joint counts, provider global assessment, and acute phase reactants.

Major RA treatment guidelines recommend treating to a target of remission or low disease activity according to recommended RA disease activity measures.[73] However, "remission" can be defined in other ways, such as the absence of synovitis on advanced imaging modalities (e.g., magnetic resonance imaging, musculoskeletal ultrasound), or according to specific criteria for RA remission (e.g., Boolean remission). Clinical trials assessing the treat-to-target strategy using clinical measures versus advanced imaging modalities as the target have found no differences in patient outcomes.[80, 81]

TABLE 1.1: Recommended RA Disease Activity Measures

Disease Activity Measures	Components
Clinical Disease Activity Index (CDAI)	28 TJC, 28 SJC, Patient Global VAS, Provider Global VAS
Disease Activity Score in 28-joints (DAS28)	28 TJC, 28 SJC, Patient Global VAS, ESR or CRP
Patient Activity Scale II (PAS-II)	Health Assessment Questionnaire-II, pain VAS, Patient Global VAS
Routine Assessment of Patient Index Data with 3 Measures (RAPID-3)	Multidimensional Health Assessment Questionnaire, pain VAS, Patient Global VAS
Simplified Disease Activity Index (SDAI)	28 TJC, 28 SJC, Patient Global VAS, Provider Global VAS, CRP

Abbreviations: TJC, tender joint count; SJC, swollen joint count; VAS, visual analogue scale; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

1.2.4.1.3 Treat-to-Target in Real-World Settings

Despite the benefits of a treat-to-target strategy demonstrated in trial settings, implementation of the treat-to-target strategy in clinical practices appears to be suboptimal.[82] Analysis of data from the ACR Rheumatology Informatics System for Effectiveness (RISE) registry revealed low rates of change to DMARD regimens among patients with moderate to high disease activity levels in real-world settings.[83] The use of learning

collaboratives has shown promise for improving adoption of the treat-to-target approach.[84] Financial incentives tied to achieving quality measures (e.g., Merit-based Incentive Payment System) for regularly reporting RA disease activity may further encourage adoption across practices.

When implementing treat-to-target in clinical practice, providers are faced with deciding how strictly to adhere to the treat-to-target strategy. Situations arise where providers and patients may determine through shared decision-making that the optimal treatment decisions do not strictly follow treat-to-target, for example, patients with multimorbidity (with inherent concerns about treatment escalation) who have improved their disease activity meaningfully with their current DMARD regimen and are functioning as desired but have persistent moderate to high RA disease activity. Additionally, there are situations when disease activity measures may not accurately capture RA disease activity, such as in patients with fibromyalgia or chronic low back pain.

1.2.4.1.4 Choice of Specific DMARDs

DMARDs should be started as early as possible after the diagnosis of RA. Unless contraindicated, MTX should be the initial DMARD of choice for most patients due to its established efficacy, safety, and cost. Unfortunately, MTX use is currently suboptimal in clinical practice, with most patients escalating to combination therapy or bDMARD/JAKi before optimizing the MTX regimen through dose escalation or parenteral administration.[85] Initial combination DMARD treatment may result in earlier improvements than MTX monotherapy, but longer-term outcomes are similar as long as a treat-to-target protocol is followed.[65, 86, 87]

For patients improving but not reaching treatment targets on MTX monotherapy, additional DMARDs should be added. The addition of hydroxychloroquine and sulfasalazine to MTX (i.e., Triple Therapy) was found to be as effective as adding etanercept in randomized controlled trials of early[86] and established[88] RA. When patients need to escalate to a biologic or targeted-synthetic DMARD therapy, agents with different mechanisms of action are available. Without clear superiority of one bDMARD/JAKi over another based on efficacy and safety, this choice is typically driven by contraindications, subtle but important differences in side effect profiles, insurance coverage, route and frequency of administration, and patient and provider preferences. Similar factors guide selection of subsequent bDMARD/JAKi when a treatment switch is required. The paucity of evidence to guide these decisions is reflected by recent ACR RA treatment guidelines which give only conditional recommendations for RA patients not at target after MTX treatment.[73]

Glucocorticoids are well recognized to provide timely and often important relief of RA symptoms in addition to their disease-modifying effects. Due to their known long-term toxicities and the availability of many other effective DMARDs, long-term and early systematic use is diminishing and not recommended in recent treatment guidelines.[73] When necessary, such as in the setting of a RA flare, providers should use the lowest dose for the shortest period possible.

1.2.4.2 Management of Extra-Articular Manifestations

Extra-articular manifestations typically accompany severe RA, resulting in a poor prognosis for patients and complicating treatment decisions. Multidisciplinary management with other subspecialty providers may be required. Fortunately, the presence of serious extra-articular manifestations appears to be decreasing, with the exception of RA-associated lung disease.[89] RA-associated interstitial lung disease (RA-ILD) clinically affects 5–10% of patients and carries a median survival after diagnosis of three to seven years.[90, 91] Treatment strategies for RA-ILD include glucocorticoids, DMARDs effective for RA and/or utilized for other connective tissue disease-ILD (e.g., azathioprine, mycophenolate mofetil), and avoidance of therapies that may cause lung toxicity.[92] Antifibrotics used in idiopathic pulmonary fibrosis have recently become available, though they are not expected to impact the course of articular disease.

1.2.4.3 De-escalation of Therapies

It is evident that early treatment of RA[93, 94] and advances in therapeutic regimens[95] have led to better patient outcomes. With more patients achieving treatment targets, an important question has emerged whether DMARDs can be reduced or discontinued in patients experiencing sustained remission without worsening of disease. Trials addressing this have shown that many patients can maintain disease control on reduced DMARDs. Flares will occur in other patients during treatment de-escalation, though most regain disease control quickly after resuming their prior treatment regimen.[96–98] Patients with "deeper" levels of remission and who have been at target for longer periods of time are less likely to flare when de-escalating therapies. For patients treated with combination DMARDs, an optimal tapering sequence has not been established, a fact reflected in differing recommendations in the most recent ACR[73] and EULAR[72] guidelines. Very few patients will achieve sustained, drug-free remission, exemplifying RA as a chronic and currently incurable disease.

1.3 The Future of Rheumatoid Arthritis

Tremendous advancements have transpired in RA over the prior decades, yet RA remains an incurable, albeit highly treatable, chronic disease that has the potential to dramatically impact patients' lives. In this section, the future of RA is contemplated, focusing on select areas that offer substantial potential for advancing RA management and optimizing patient outcomes (Table 1.2).

1.3.1 Elucidating Subtypes of RA

RA is a heterogeneous disorder, most commonly subdivided based on the presence or absence of RF and/or ACPA. This classification is useful for establishing the diagnosis of RA and provides prognostic information for the disease course, with seropositive patients tending to have a more aggressive disease course and a higher incidence of extra-articular features. While seropositive patients may also have a better response to DMARD therapies,[99, 100] these autoantibodies are not able to meaningfully predict a differential response to therapies,[101] and in order to improve future RA outcomes, factors that predict differential treatment response (i.e., which patients will respond to which therapies) are immensely needed. Moreover, approximately 30% of RA patients are seronegative for RF or ACPA. Discovery of additional and antigen-specific RA autoantibodies could improve disease subtyping to facilitate earlier and more accurate diagnoses, prognosticate disease course, guide treatment, and spurn research to uncover different risk factors and pathophysiologic mechanisms in RA.

Several novel RA autoantibodies show promise for filling these roles. Antibodies to malondialdehyde-acetaldehyde (MAA) are elevated in the serum and synovium of RA patients and correlate with ACPA positivity.[102] Anti-MAA antibodies