Rheumatoid Arthritis
Management Strategies:

New Insights for Managed Care

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Clinical Update: Recent Insights for Optimal Treatment

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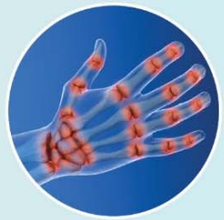
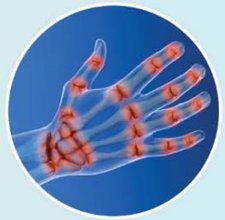
Learning Objective

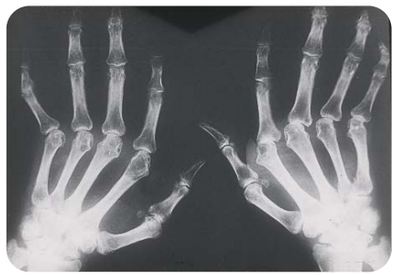


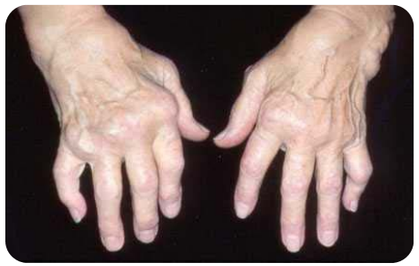
- Review recent insights into the pathophysiology of rheumatoid arthritis (RA) and emerging treatment strategies

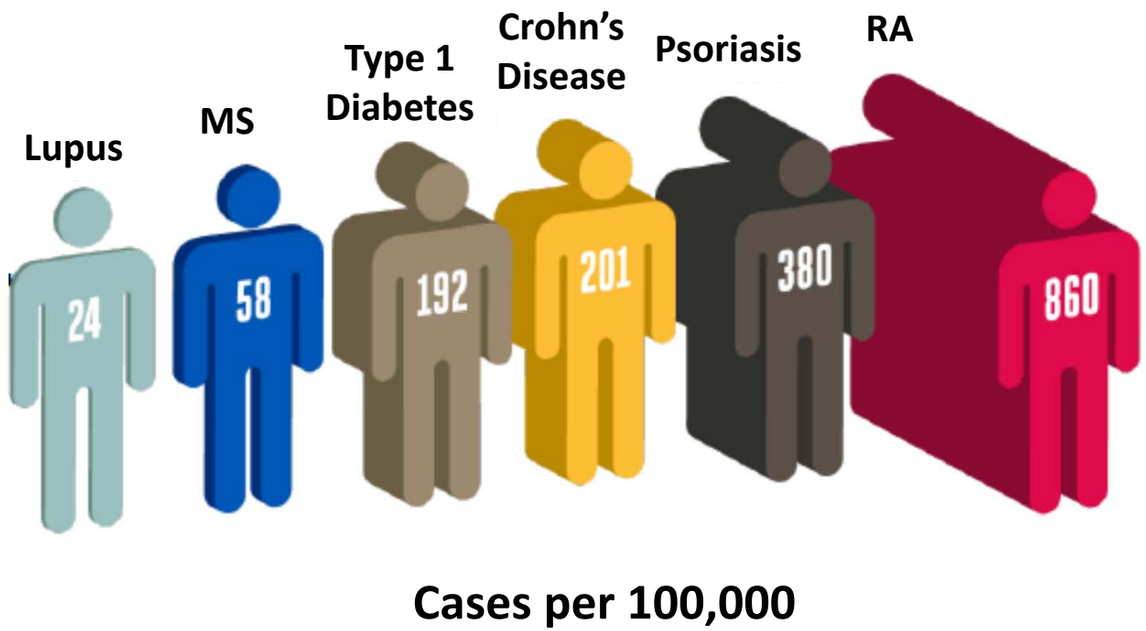
RA is the Most Prevalent Autoimmune Disease



- Affects 1.3 million Americans
- Women 3x more affected than men
- Most commonly occurs between the ages of 30 and 50 years of age
- Typically affects the wrists and small joints of the hands and feet

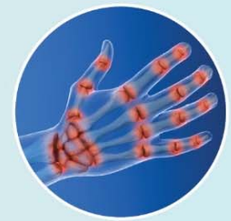






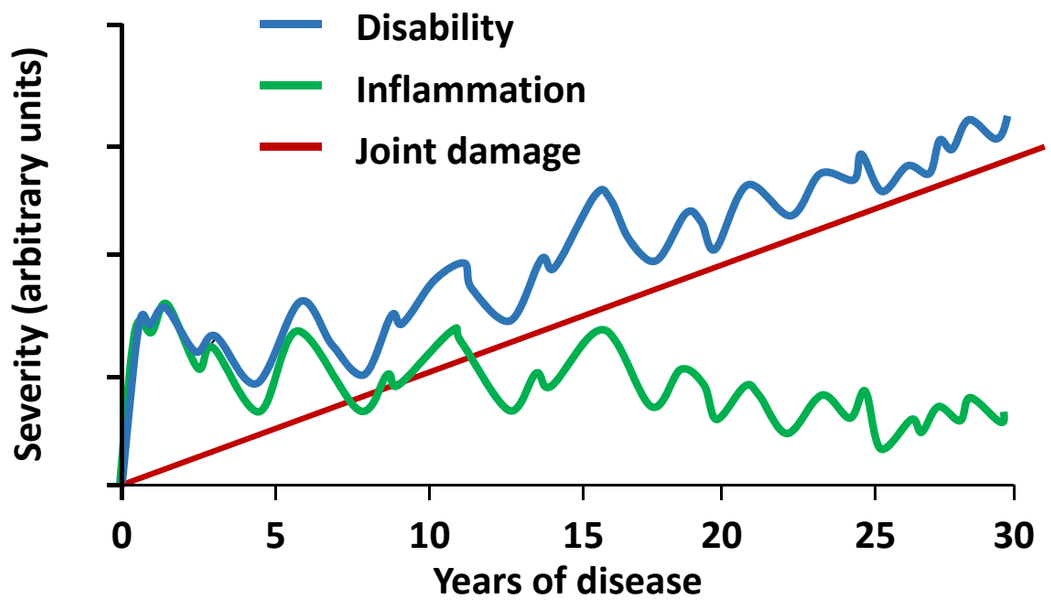
Pal S. *US Pharmacist*. 2016;41(6):11.

RA is a Progressive Disease



- Complex, multifactorial pathogenesis
- Fluctuating clinical course; unpredictable prognosis
- Characterized by
  - Progressive joint destruction
  - Loss of physical function and disability
  - Poor quality of life
  - Increased mortality in severe disease

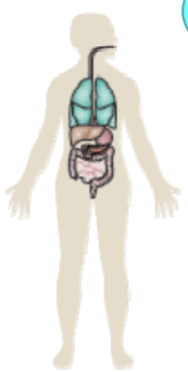
Joint Damage Occurs Early in the Natural History of RA



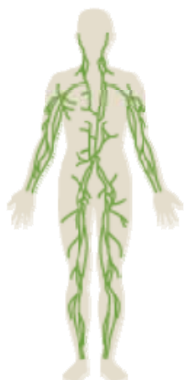
- Inflammatory joint symptoms determine disability early in natural history of the disease
- Joint destruction dominates disability late in disease

Adapted from Kirwan JR. *J Rheumatol*. 2001;28(4):881-6.

Pathogenesis: Mechanisms Involved in the Initiation and Progression of RA



Mucosa (mouth, lung, & gut)



Secondary lymphoid tissues

1 Post-translational modifications

Risk and susceptibility factors

Citrullination and generation of neo-epitopes

Peptidyl arginine → Peptidyl citrulline

Cell activation

APC, Macrophage

Antigen loading and migration

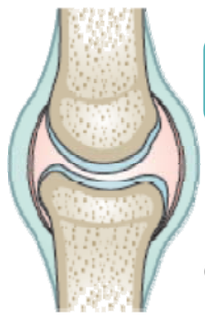
T cell, MHC, TCR, Activated T cell, B cell

Autoantibodies (for example, ACPAs and RF

Leukocyte recruitment and inflammatory responses

2 Adaptive immune response

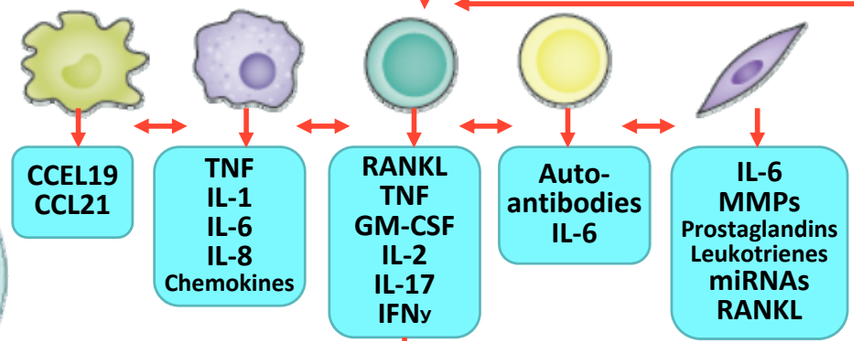
3 Synovial inflammation



Joint

Cartilage and bone

Synovium



CCEL19, CCL21

TNF, IL-1, IL-6, IL-8, Chemokines

RANKL, TNF, GM-CSF, IL-2, IL-17, IFNγ

Auto-antibodies, IL-6

IL-6, MMPs, Prostaglandins, Leukotrienes, miRNAs, RANKL

Second hit

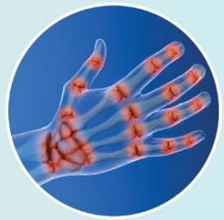
Cartilage destruction
Bone destruction

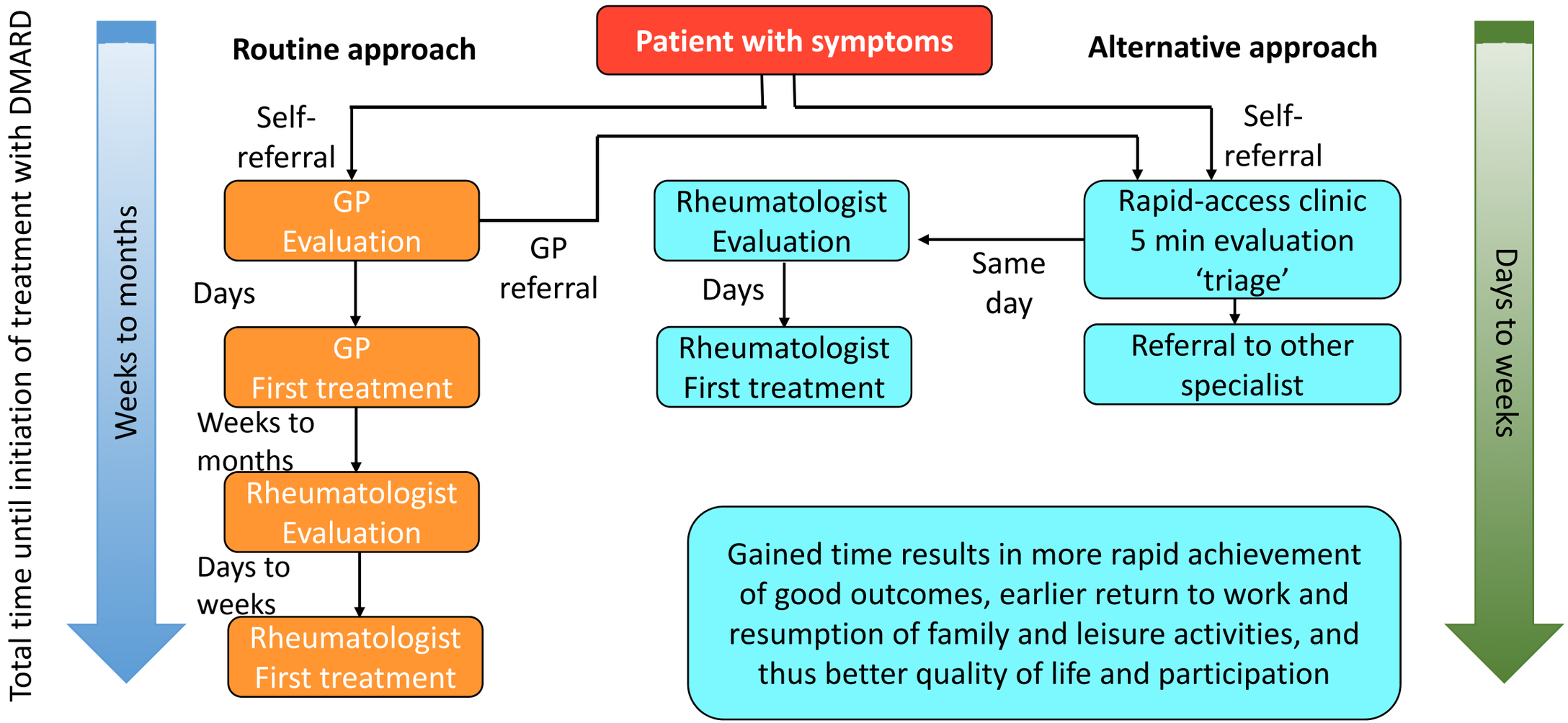
Joint damage

4 Persistent adaptive immune responses

Smolen JS, Aletaha D, Barton A, et al. *Nat Rev Dis Primers*. 2018;4:18001.

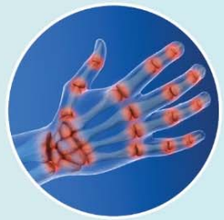
Screening for RA

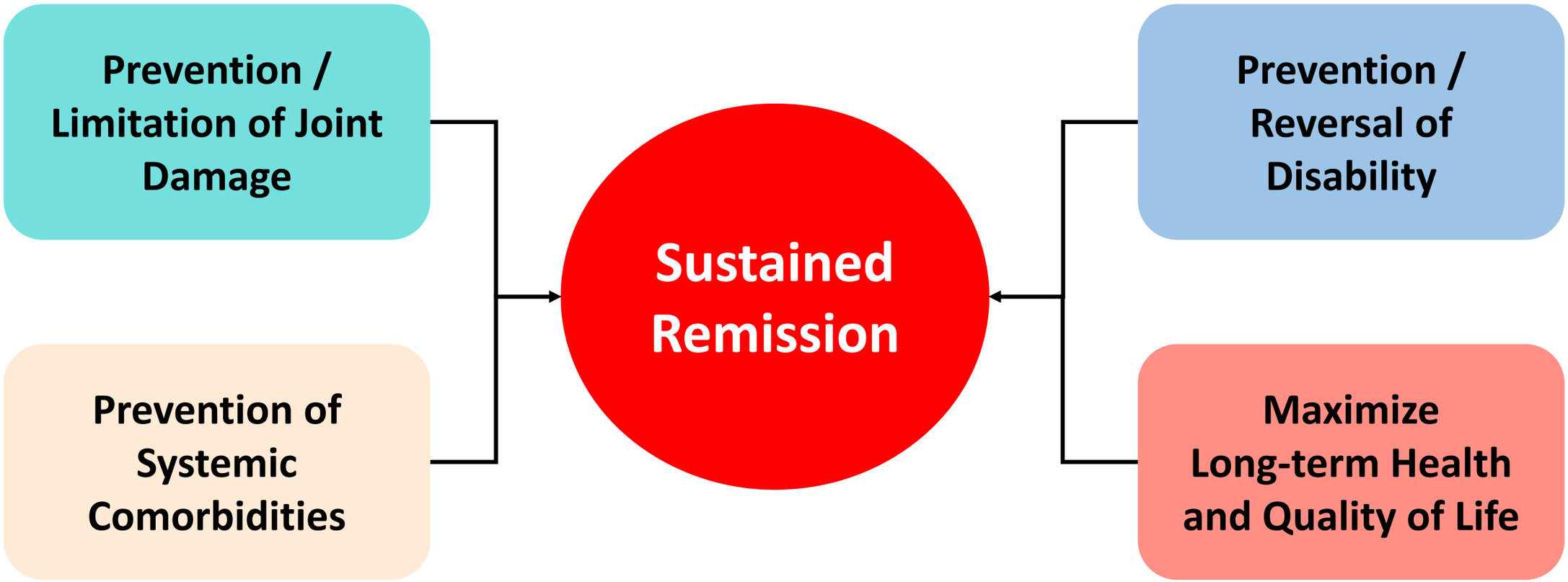




Smolen JS, Aletaha D, Barton A, et al. *Nat Rev Dis Primers*. 2018;4:18001.

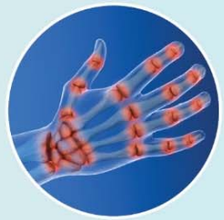
RA Therapeutic Objectives





Smolen JS, Aletaha D, Bijlsma JW, et al. *Ann Rheum Dis*. 2010;69(4):631-7.

RA Treatment Strategy



Early and Intensive Treatment

- Attenuate inflammation quickly

Treat-to-Target

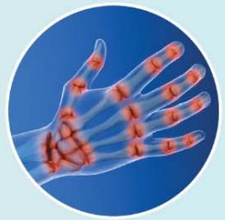
- Achieve remission with minimal/no signs of active inflammation

Achieve Tight Control

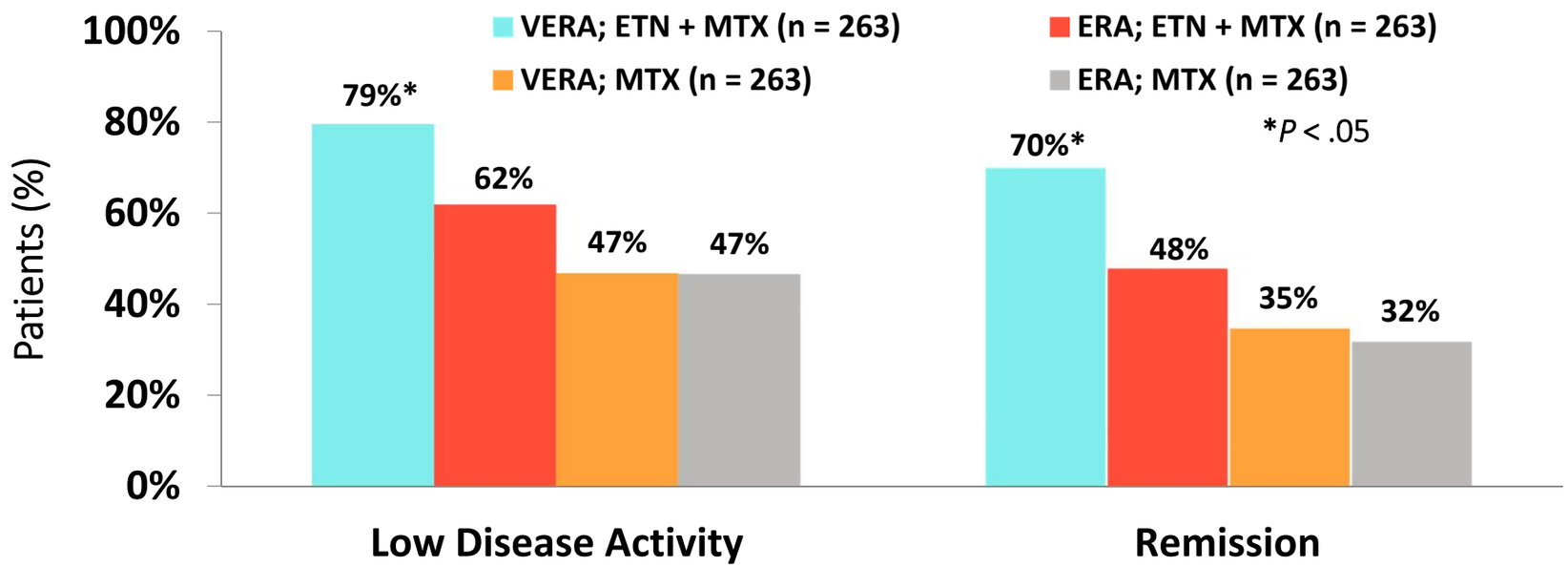
- Maintain remission/low level of disease activity

Smolen JS, Breedveld FC, Burmester GR, et al. *Ann Rheum Dis*. 2016;75(1):3-15.
Singh JA, Saag KG, Bridges SL, et al. *Arthritis Rheumatol*. 2016;68(1):1-26.

Early and Aggressive Treatment Elicits Greater Disease Control



Disease Activity and DAS28 Remission at 52 Weeks
(Data from the COMET Trial)



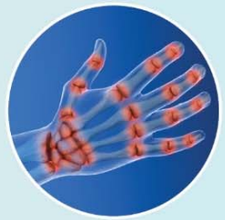
Randomized, double-blind, parallel treatment trial of MTX-naïve patients with moderate to severe early RA (n = 542)

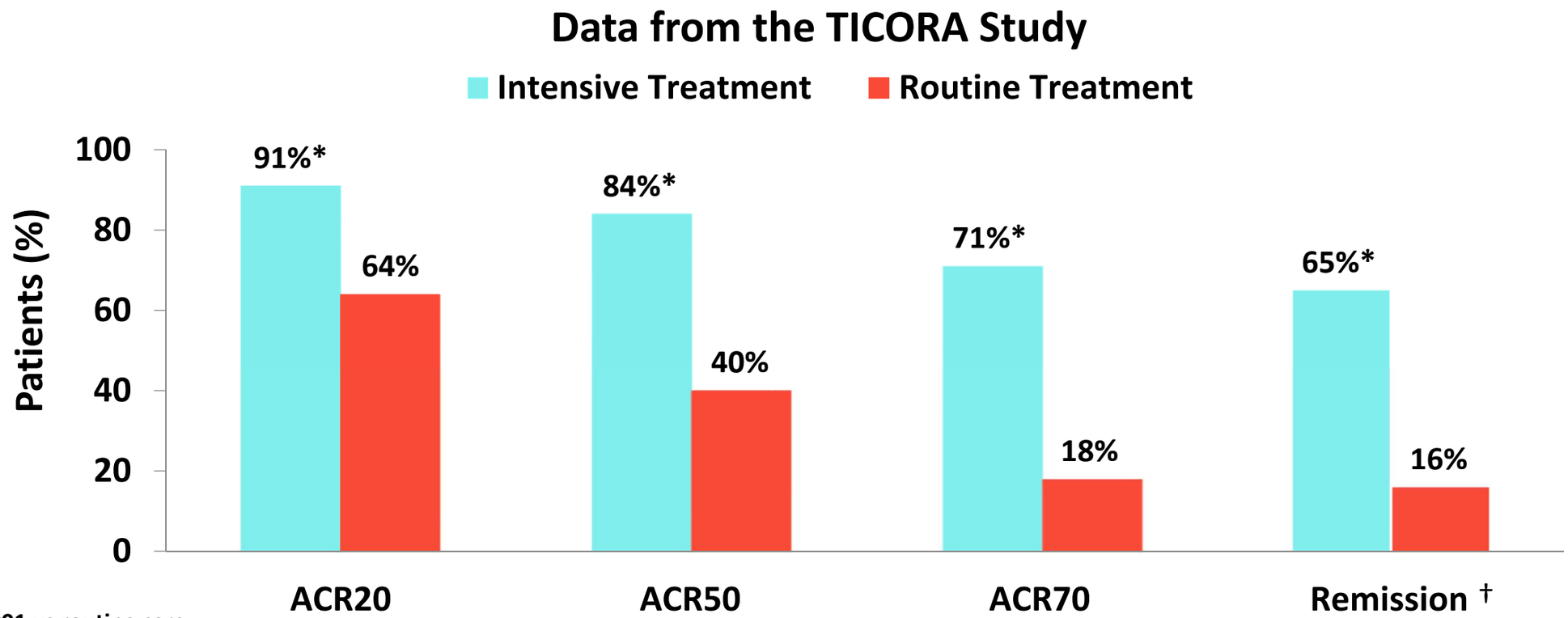
A higher proportion of patients with *very early* RA achieved low disease activity and remission when treated more aggressively

COMET=combination of methotrexate and etanercept in active early RA; DAS28=28-joint Disease Activity Score; DMARD=disease-modifying antirheumatic drug; ERA=early rheumatoid arthritis; ETN=etanercept; MTX=methotrexate; TNF=tumor necrosis factor; VERA=very early rheumatoid arthritis.

Emery P, Kvien TK, Combe B, et al. *Ann Rheum Dis*. 2012;71(6):989-92.

Treat-to-Target Elicited Remission in 65% of RA Patients





****P* < .0001 vs routine care**

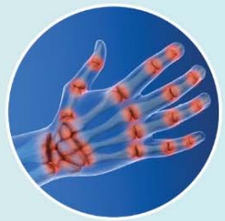
†Disease activity score < 1.6

Intention-to-treat population; n = 111 patients with RA duration < 5 years.

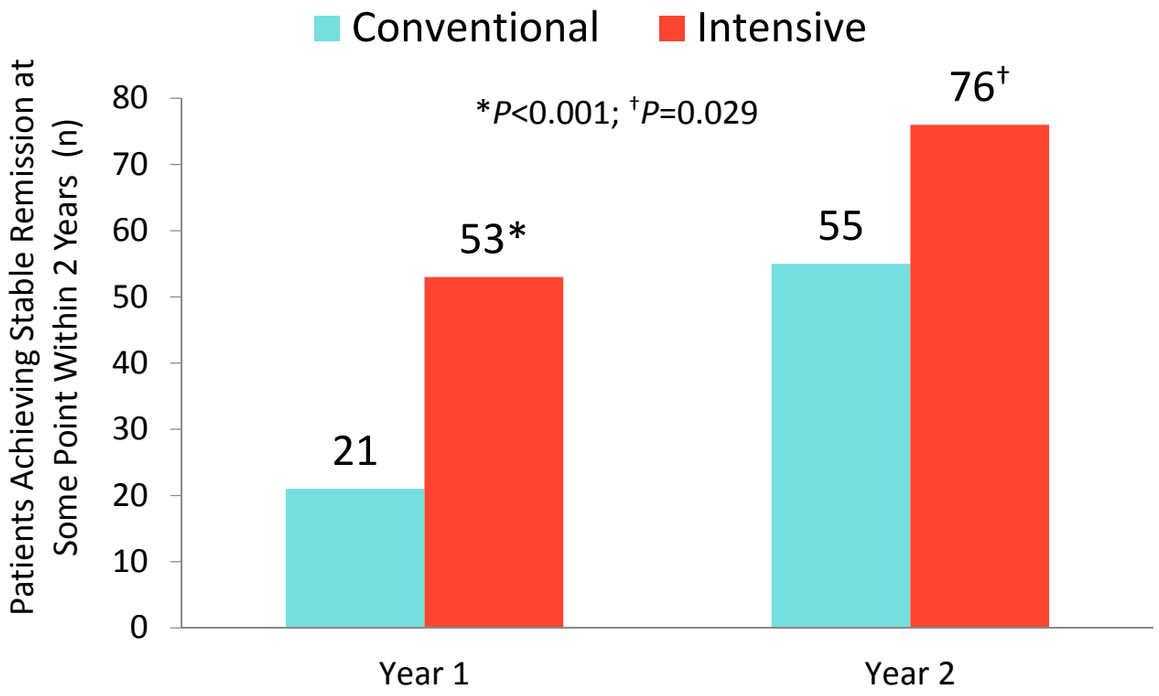
ACR20=American College of Rheumatology 20% improvement criteria; ACR50=American College of Rheumatology 50% improvement criteria; ACR70=American College of Rheumatology 70% improvement criteria; TICORA=Tight Control for Rheumatoid Arthritis

Grigor C, Capell H, Stirling A, et al. *Lancet*. 2004;364(9430):263-9.

Treatment Intensification Achieves Remission More Often, Faster, and For a Longer Period of Time



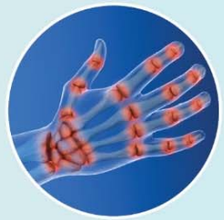
Data from the CAMERA Study‡

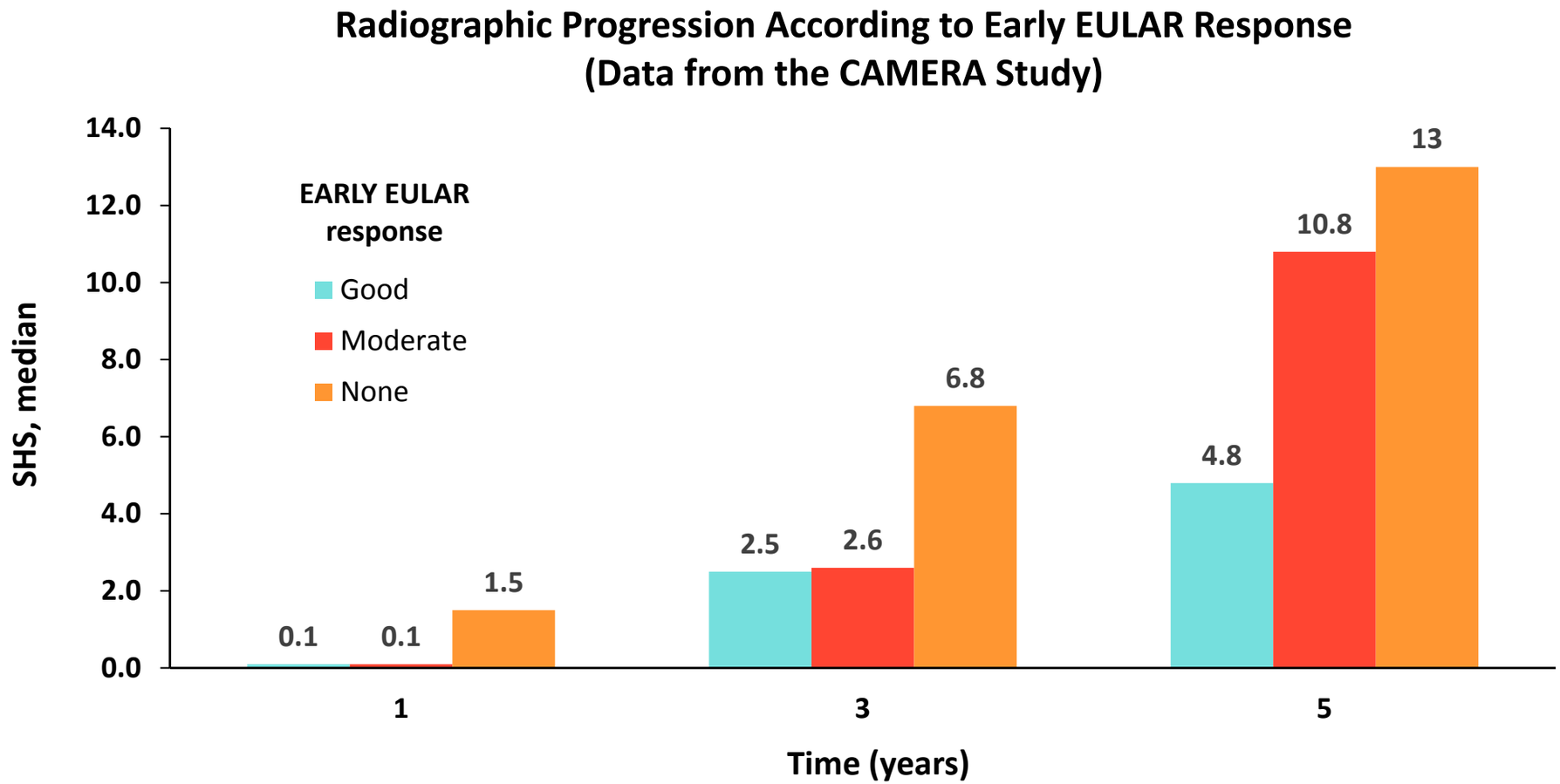


	Conventional	Intensive	*P* value
Time to remission, mo. (95% CI)	14.3 (12.6 – 16.1)	10.4 (9.1 – 11.7)	<0.001
Duration of remission, mo. (95% CI)	9.1 (7.6 – 10.6)	11.6 (10.1 – 13.1)	0.025
Median Area Under the Curve ($IQ_{0.25-0.75}$)			
Morning stiffness	23.7 (12.3 – 56.7)	17.0 (7.5 – 41.2)	0.009
ESR	21.6 (13.0 – 33.6)	17.7 (10.2 – 27.6)	0.007
Tender joint count	5.5 (2.8 – 9.2)	3.6 (1.9 – 6.0)	<0.001
Swollen joint count	4.7 (2.8 – 7.6)	2.7 (1.5 – 5.2)	<0.001

‡Two-year, multicenter, open-label trial of intensive treatment with methotrexate (MTX0 vs conventional therapy). Patients in both groups received MTX (n=299).
Patients in the intensive treatment group came to the outpatient clinic once every month; adjustment of the MTX dosage was tailored to the individual patient on the basis of predefined response criteria. Patients of the conventional strategy group came to the outpatient clinic once every three months; they were treated according to common practice.
Verstappen SM, Jacobs JW, Van der veen MJ, et al. *Ann Rheum Dis*. 2007;66(11):1443-9.

Early Treatment with Intensive DMARD Therapy Slows Radiographic Progression

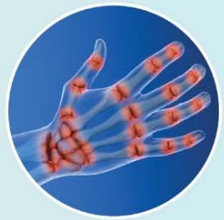




EULAR=European League Against Rheumatism; SHS=Sharp van der Heijde score (median values)

Rantalaiho V, Korpela M, Laasonen L, et al. *Arthritis Res Ther*. 2010;12(3):R122.
Monti S, Montecucco C, Bugatti S, Caporali R. *RMD Open*. 2015;1(Suppl 1):e000057.

Barriers to RA Disease Control

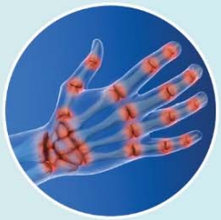


- Factors associated with no adjustment in RA therapy despite documented high or moderate disease activity

Barriers
• Irreversible joint damage
• Patient-driven preference for current therapy
• Non-inflammatory muscle pain
• Insufficient time to assess effect of recently initiated RA therapy
• Safety concerns
• Presence of comorbid conditions
• Resistant disease

Tymms K, Zochling J, Scott J, et al. *Arthritis Care Res* (Hoboken). 2014;66(2):190-6.

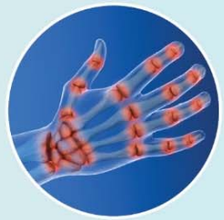
Feasibility of Treat-to-Target Strategy in Clinical Practice



- Success is highly dependent on physician adherence to the strategy in the clinical setting[1]
- Maksymowych et al observed that in 30% to 60% of clinic visits, therapy intensification was not implemented after documentation of moderate to high RA disease activity by any metric[2]
- In nearly 70% of the cases, the primary reason for not following a treat-to-target approach was a belief that current treatment was “acceptable”[3]

1. Lesuis N, Den broeder AA, Hulscher ME, Van vollenhoven RF. *RMD Open*. 2016;2(1):e000195.
2. Maksymowych WP, et al. *Arthritis Rheum*. 2014;66 Suppl 10:S1272
3. Waimann CA, et al. *Arthritis Rheum*. 2014;66 Suppl 10:S1037.

Measures of Disease Activity and Progression Guide Treatment Decisions



Use validated measurements of disease activity/progression to guide treatment decisions and achieve tight control of RA[1]

Biomarkers of inflammation[2]

- ESR and CRP are acute-phase response measures scored as normal or abnormal based on local laboratory standards
  - If results of at least 1 of these 2 tests are abnormal, patient should be scored as having an abnormal acute-phase response

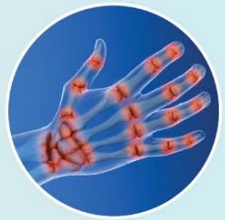
Disease activity scales[1,3-5]

- American College of Rheumatology 20% improvement criteria (ACR20)
- Disease Activity Score-28 (DAS28)
- Simplified Disease Activity Score (SDAI)
- Clinical Disease Activity Score (CDAI)
- Easy Rheumatoid Arthritis Measure (ERAM)
- Global Arthritis Scale (GAS)
- Routine Assessment of Patient Index Data 3 (RAPID3)

CRP=C-reactive protein; ESR=erythrocyte sedimentation rate.

1. Smolen JS, Breedveld FC, Burmester GR, et al. *Ann Rheum Dis*. 2016;75(1):3-15. 2. Aletaha D, Neogi T, Silman AJ, et al. *Arthritis Rheum*. 2010;62(9):2569-81. 3. Hobbs KF, Cohen MD. *Rheumatology* (Oxford). 2012;51 Suppl 6:vi21-7. 4. Singh JA, Saag KG, Bridges SL, et al. *Arthritis Rheumatol*. 2016;68(1):1-26. 5. Anderson J, Caplan L, Yazdany J, et al. *Arthritis Care Res* (Hoboken). 2012;64(5):640-7.

Disease Activity Scales Provide Insight on Patient Response to Treatment



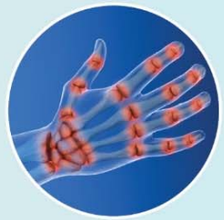
The specific tool used does not matter; it's more important to routinely assess disease activity

							RAPID3
Patient Function	✓					✓	✓
Patient Pain	✓		✓	✓		✓	✓
Patient Global	✓	✓	✓	✓	✓		✓
Physician Global	✓		✓	✓	✓		
Number of Tender Joints	✓	✓	✓	✓		✓	
Number of Swollen Joints	✓	✓	✓	✓	✓		
Acute Phase Response Measures (ESR or CRP)	✓	✓	✓				

ACR20=American College of Rheumatology 20% improvement criteria; CDAI=Clinical Disease Activity Index; CRP=C-reactive protein; DAS28=Disease Activity Score in 28 joints; ERAM=Easy Rheumatoid Arthritis Measure; ESR=erythrocyte sedimentation rate; GAS=Global Arthritis Score; RAPID3=Routine Assessment of Patient Index Data 3; SDAI=Simplified Disease Activity Index.

Hobbs KF, Cohen MD. *Rheumatology* (Oxford). 2012;51 Suppl 6:vi21-7.

Routine Objective Measurement of Disease Activity Associated with Remission

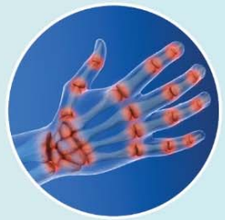


Trial	Factors Associated With Remission	Outcome
TICORA[1]	• Intense treatment • Frequent assessments • Predetermined thresholds for escalation of therapies	10x higher rate of remission in patients receiving frequent objective assessment and intense therapy vs routine care
BeST[2]	• Frequent assessments • Early escalation to combination therapy	Greater number of patients receiving frequent objective assessment and early escalation of therapy achieved remission vs routine care

BeST=The Dutch Behandel Strategieen study; TICORA=tight control for rheumatoid arthritis study.

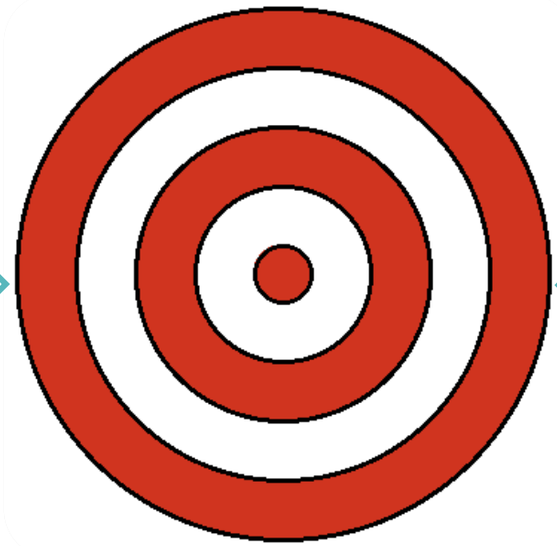
1. Grigor C, Capell H, Stirling A, et al. *Lancet*. 2004;364(9430):263-9.
2. Goekoop-ruiterman YP, De vries-bouwstra JK, Allaart CF, et al. *Ann Intern Med*. 2007;146(6):406-15.

Treat-to-Target is the Recommended Approach to RA Management



Targets

- **Low disease activity**
- **Remission**
- **Other appropriate targets selected by the clinician and patient**

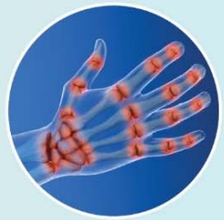


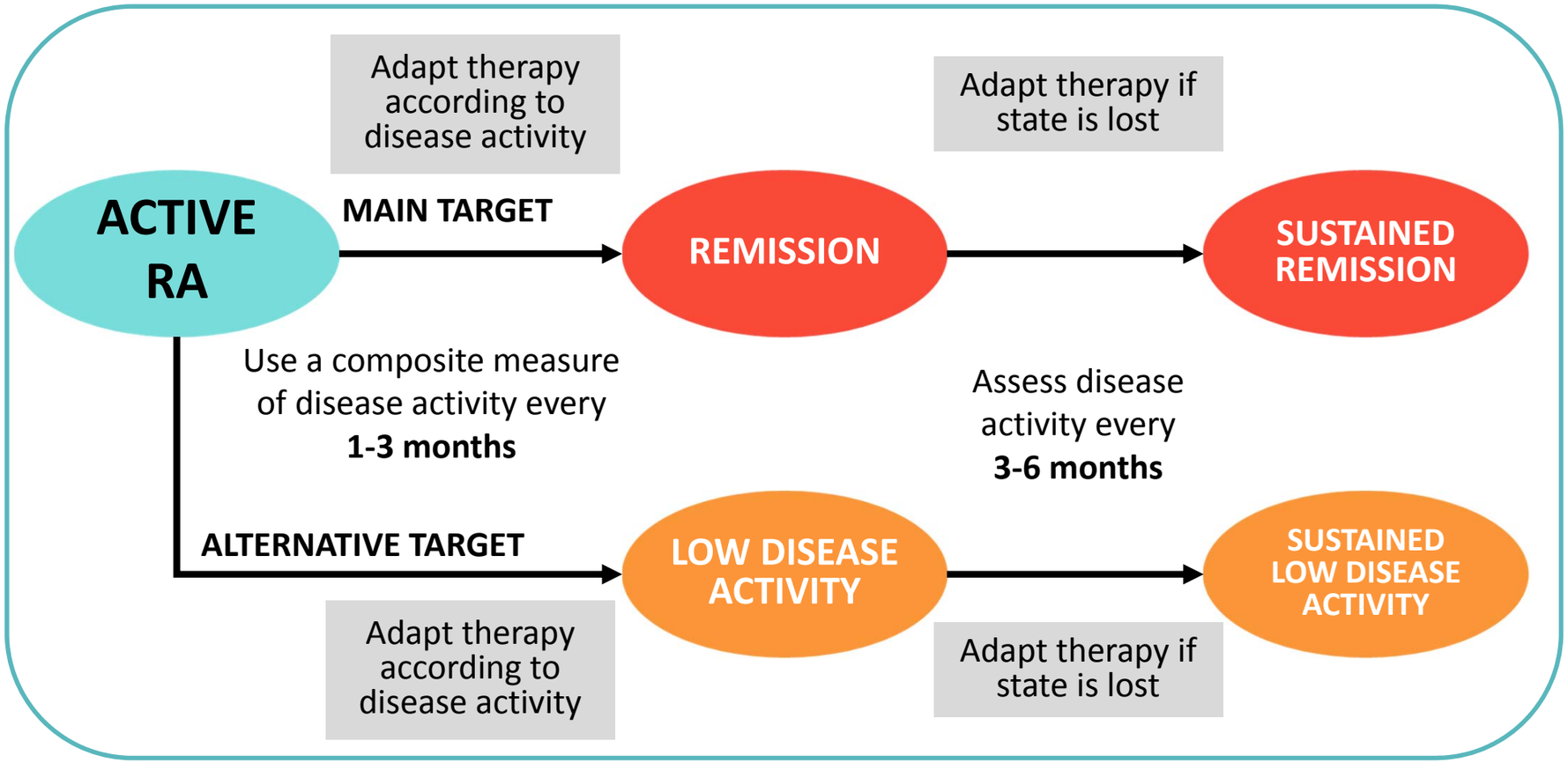
Functional Assessment

- **Assessment using validated tools**
- **Conduct at least once per year and more often in active RA**

Singh JA, Saag KG, Bridges SL, et al. *Arthritis Rheumatol*. 2016;68(1):1-26.

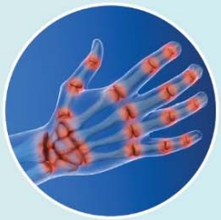
Treat-to-Target Algorithm





Smolen JS, Breedveld FC, Burmester GR, et al. *Ann Rheum Dis*. 2016;75(1):3-15.

Pharmacologic Management of RA: Guiding Principles



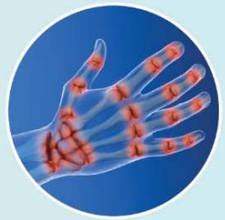
Duration of therapeutic response varies

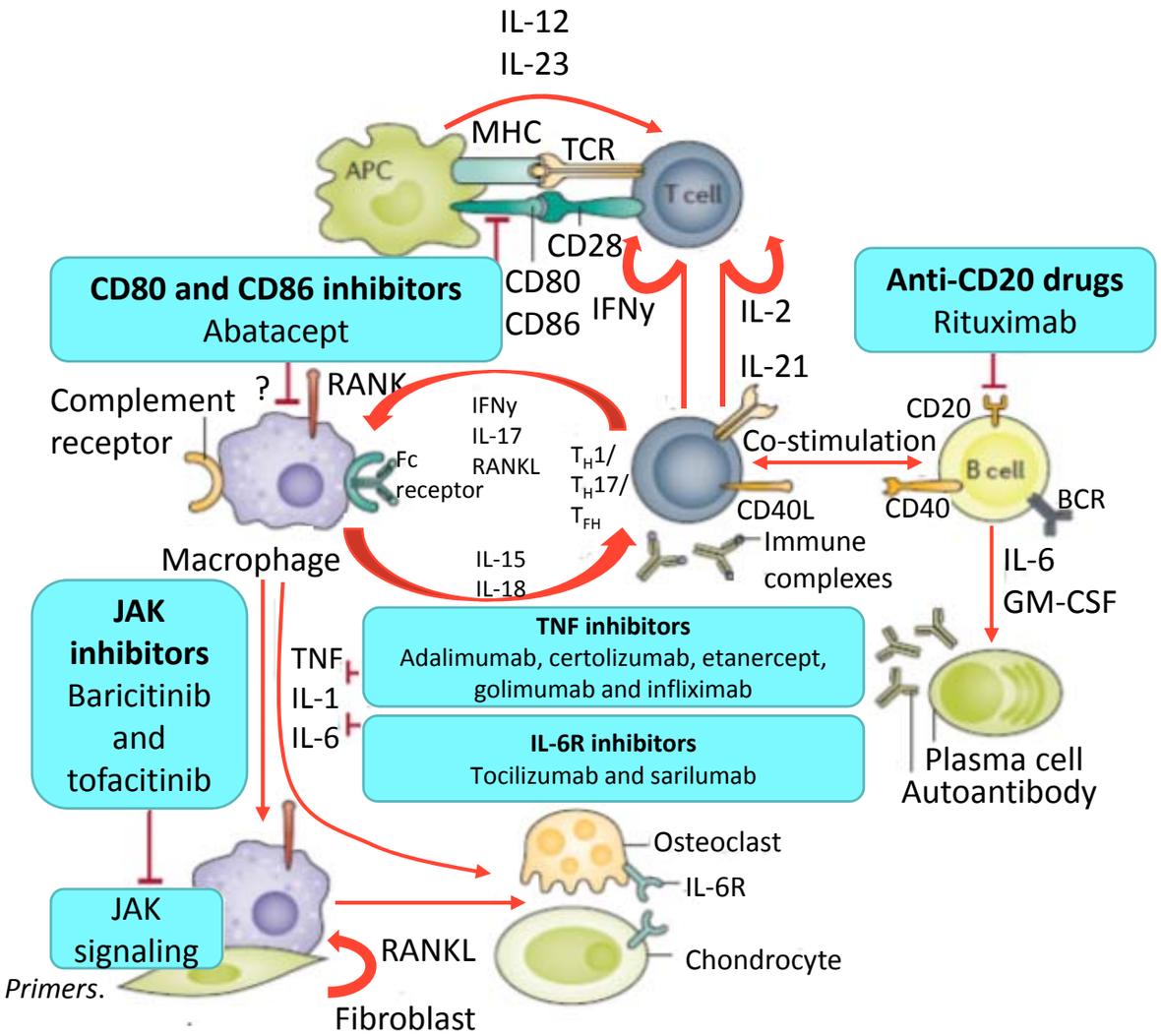
Long-term RA treatment often involves a sequence of different therapies

Optimal sequencing determined by disease activity, response to therapy, and drug mechanism of action

Rendas-baum R, Wallenstein GV, Koncz T, et al. *Arthritis Res Ther*. 2011;13(1):R25.

Management of RA with Disease Modifying Drugs

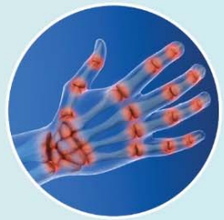




APC, antigen-presenting cell; BCR, B cell receptor; CD, cluster of differentiation; CD40L, CD40 ligand; GM-CSF, granulocyte–macrophage colony-stimulating factor; MHC, major histocompatibility complex; RANK, receptor activator of nuclear factor-κB; RANKL, receptor activator of nuclear factor-κB ligand; TCR, T cell receptor; TFH, T follicular helper cell; TH, T helper cell

Smolen JS, Aletaha D, Barton A, et al. *Nat Rev Dis Primers*. 2018;4:18001.

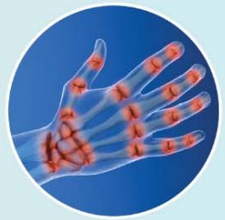
Pharmacologic Interventions



Corticosteroids	Conventional DMARDs	Biologic DMARDs
• Methylprednisolone • Prednisone • Prednisolone	• Azathioprine • Hydroxychloroquine • Leflunomide • Methotrexate • Sulfasalazine	• TNF inhibitors • IL-1 inhibitors • B-cell agents • T-cell agents • IL-6 inhibitors • JAK inhibitors

DMARD=disease modifying anti-rheumatic drugs; JAK=Janus Kinase inhibitor; TNF=Tumor Necrosis Factor.

Corticosteroids

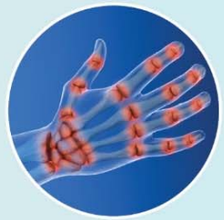


Drug	Initial US Approval	Brand Name	Route of Administration	Mechanism of Action
Prednisone	1955	Generic	Oral	Anti-inflammatory and immunomodulator
Prednisolone[1]	1955	Orapred ODT®	Oral	
Methylprednisolone[2-4]	1957	Medrol®	Oral	
		Solu-Medrol®	IV infusion or IM injection (in office)	
		Depo-Medrol®	IA, IL, IM, or soft tissue injection (in office)	

IA=intraarticular; IL=intralesional; IM=intramuscular; IV=intravenous, ODT=orally disintegrating tablet.

1. Orapred ODT® [package insert]. Florham Park, NJ: Shionogi Inc.; 2013. 2. Medrol® [package insert]. New York, NY: Pharmacia & Upjohn Co.; 2013. 3. Solu-Medrol® [package insert]. New York, NY: Pharmacia & Upjohn Co.; 2014. 4. Depo-Medrol® [package insert]. New York, NY: Pharmacia & Upjohn Co.; 2014.

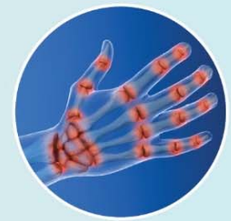
Nonbiologic Disease Modifying Antirheumatic Drugs (DMARDs)



Drug	Initial US Approval	Brand Name	Route of Administration	Mechanism of Action
Sulfasalazine[1]	1950	Azulfidine®	Oral	Not well defined
Methotrexate[2,3]	1953	Generic	Oral	Dihydrofolate acid reductase inhibitor
		Otrexup™	SC injection	
Hydroxychloroquine[4]	1955	Plaquenil®	Oral	Not well defined
Azathioprine[5,6]	1968	Imuran®	Oral or IV infusion	Immunosuppressant
Leflunomide[7]	1998	Arava®	Oral	Pyrimidine synthesis inhibitor

1. Azulfidine® [package insert]. New York, NY: Pfizer, Inc.; 2014. 2. Methotrexate [package insert]. Morgantown, WV: Mylan Pharmaceuticals Inc.; 2013. 3. Otrexup™ [package insert]. Ewing, NJ: Antares Pharma, Inc.; 2014. 4. Plaquenil® [package insert]. Bridgewater, NJ: Sanofi-Aventis US LLC; 2012. 5. Imuran ® for IV injection [package insert]. San Diego, CA: Prometheus Laboratories Inc.; 2014. 6. Imuran ® [package insert]. San Diego, CA: Prometheus Laboratories Inc.; 2014. 7. Arava ® [package insert]. Bridgewater, NJ: Sanofi-Aventis US LLC; 2014.

Available Reference Biologic Agents Indicated for the Treatment of RA



Drug	Initial US Approval	Brand Name	Route of Administration	Mechanism of Action
Etanercept[1]	1998	Enbrel®	SC injection	TNF inhibitor
Infliximab[2]	1998	Remicade®	IV infusion	TNF inhibitor
Anakinra[3]	2001	Kineret®	SC injection	IL-1 receptor inhibitor
Adalimumab[4]	2002	Humira®	SC injection	TNF inhibitor
Certolizumab pegol[5]	2008	Cimzia®	SC injection	TNF inhibitor
Golimumab[6]	2009	Simponi®	SC injection	TNF inhibitor
Rituximab[7]	1997	Rituxan®	IV infusion	B-cell agent (anti-CD20 antibody)
Abatacept[8]	2005	Orencia®	IV infusion or SC injection	T-cell costimulation inhibitor
Tocilizumab[9]	2010	Actemra®	IV infusion or SC injection	IL-6 inhibitor
Tofacitinib[10]	2012	Xeljanz®	Oral	JAK inhibitor
Sarilumab[11]	2017	Kevzara®	SC injection	IL-6R antagonist
Baricitinib[12]	2018	Olumiant®	Oral	JAK inhibitor

IL=interleukin; IV=intravenous; JAK=Janus kinase; SC=subcutaneous; TNF=tumor necrosis factor.

1. Enbrel® [package insert]. Thousand Oaks, CA: Amgen Inc.; 2015. 2. Remicade® [package insert]. Horsham, PA: Janssen Biotech, Inc.; 2015. 3. Kineret® [package insert]. Stockholm, Sweden: Swedish Orphan Biovitrium AB; 2012. 4. Humira® [package insert]. North Chicago, IL: AbbVie Inc.; 2014. 5. Cimzia® [package insert]. Smyrna, GA: UCB, Inc.; 2013. 6. Simponi® [package insert]. Horsham, PA: Janssen Biotech, Inc.; 2014. 7. Rituxan® [package insert]. S. San Francisco, CA: Genentech, Inc.; 2014. 8. Orencia® [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2015. 9. Actemra® [package insert]. South San Francisco, CA: Genentech, Inc.; 2014. 10. Xeljanz® [package insert]. New York, NY: Pfizer, Inc.; 2015. 11. Kevzara® [package insert]. Bridgewater, NJ: Regeneron Sanolfi Genzyme. 2017. 12. Olumiant® [package insert]. Indianapolis, IN: Lily USA, LLC. 2018.

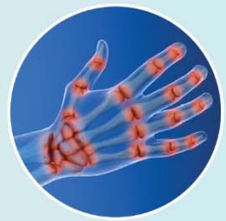
Biosimilar Agents Indicated for the Treatment of RA

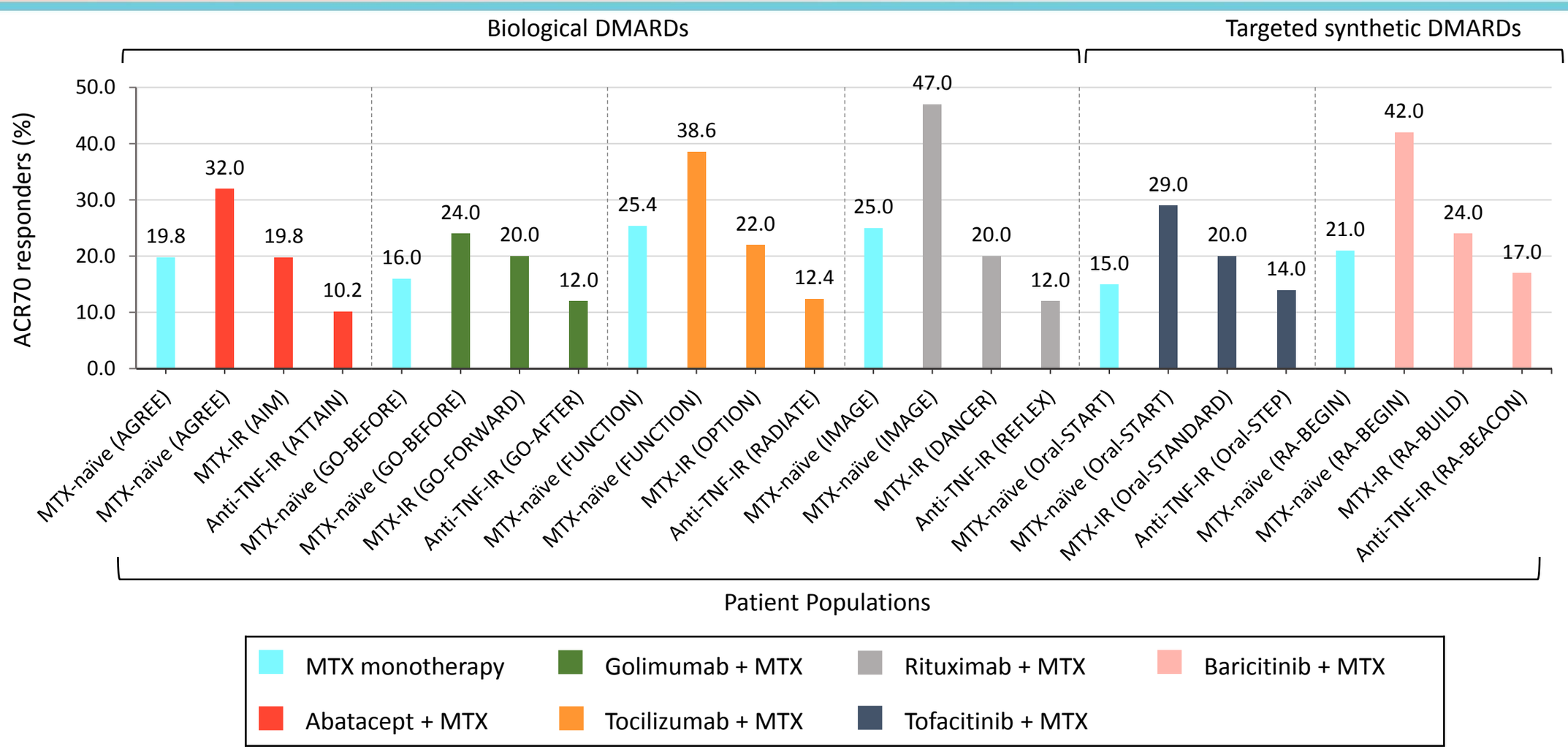
Drug	Date of US Approval	Brand Name	Route of Administration	Mechanism of Action	Status
Infliximab-dyyb	2016	Inflectra®	IV infusion	TNF inhibitor	Available
Infliximab-abda	2017	Renflexis®	IV infusion	TNF inhibitor	Available
Infliximab-qbtx	2017	Ixifi®	IV infusion	TNF inhibitor	Not available
Etanercept-szzs	2016	Erelzi®	SC injection	TNF inhibitor	Not available
Adalimumab-atto	2016	Amjevita®	SC injection	TNF inhibitor	Not available
Adalimumab-adbm	2017	Cyltezo®	SC injection	TNF inhibitor	Not available

IV=intravenous; TNF=tumor necrosis factor.

Biosimilar Approval Status. Biosimilar Review and Report website. https://biosimilarsrr.com/us-biosimilar-filings/. Updated October 10, 2018 Accessed October 2018.

ACR70 Responses to DMARDs





Smolen JS, Aletaha D, Barton A, et al. *Nat Rev Dis Primers*. 2018;4:18001.

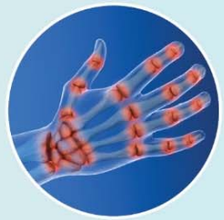
Common Adverse Events Associated with DMARDs

Drug	Dermatological	GI	Hematological	Respiratory	Other
MTX	Stomatitis	Nausea; vomiting; increased liver enzymes	Leukocytopenia; macrocytic anemia; thrombocytopenia	Pneumonitis; atypical pneumonia	Fever; headache; depression
SSZ	Exanthema; pruritus	Nausea; abdominal pain; diarrhea; cholestasis; hepatitis and pancreatitis	Hyperchromia; thrombocytopenia; leukopenia	Not observed	Headaches; fatigue; polyneuropathy; depression; psychosis
LEF	Eczema; alopecia; rash; urticaria; pruritus	Diarrhea; nausea; vomiting; increased liver enzymes	Leukocytopenia; anemia	Interstitial lung disease	Hypertension; dizziness; headaches; weight loss
TNF inhibitor	Injection site reaction; rash; cellulitis; psoriasis	Increased liver enzymes; reactivation of hepatitis B	Leukocytopenia; thrombocytopenia	Infections; pneumonia; tuberculosis	Demyelination; new onset / exacerbation of CHF
ABT	Rash, herpes infection	Abdominal pain; nausea; diarrhea; hyperlipidemia; reactivation of hepatitis B	Leukopenia; thrombocytopenia	Bronchitis; cough; infections	Fatigue; weight loss; hypertension; headaches
Rituximab	Hypersensitivity reactions	Dyspepsia; reactivation of hepatitis B	Leukopenia; thrombocytopenia	Infections; bronchial spasms	Infusion reactions
JAK inhibitor	Injection site reaction; cellulitis	Hyperlipidemia; increased liver enzymes; reactivation of hepatitis B	Neutropenia	Infections; pneumonia	Hypersensitivity reaction; increased risk for herpes zoster

Table is not comprehensive. ABT, abatacept; DMARD, disease-modifying antirheumatic drug; JAK, Janus kinase; LEF, leflunomide; MTX, methotrexate; SSZ, sulfasalazine; TNF, tumor necrosis factor inhibitor.

Smolen JS, Aletaha D, Barton A, et al. *Nat Rev Dis Primers*. 2018;4:18001.

Emerging RA Therapies

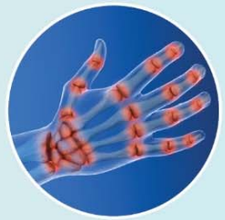


Candidate Drug	Mechanism of Action	Status
Upadacitinib	JAK1 inhibitor	Phase 3
Filgotinib	JAK1 inhibitor	Phase 3
Peficitinib	JAK inhibitor	Phase 3
Vobarilizumab	IL-6R antagonist	Phase 3
Olokizumab	IL-6 antagonist	Phase 3
Clazakizumab	IL-6 antagonist	Phase 2
Mavrilimumab	GM-CSF antagonist	Phase 2
Evobrutinib	Bruton tyrosine kinase (BTK) inhibitor	Phase 2

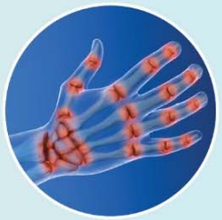
JAK=Janus kinase; IL=interleukin; RANKL, receptor activator of NF-κB ligand ; GM-GSF=granulocyte–macrophage colony-stimulating factor.

Chaudhari K, et al. *Nat Rev Drug Discov*. 2016;15:305-306.
Clinical Trials.gov. Accessed September 2018.

Summary



Treatment Goals	• Achieve remission, relieve symptoms, prevent joint and organ damage, improve physical function and well-being, and reduce long-term complications
Treatment Strategy	• Early and aggressive treatment • Treat-to-target (remission) • Achieve tight control through individualized therapy
Measures of Disease Activity/Progression	• Use validated measurements to guide treatment decision-making
Pharmacologic Management	• Long-term treatment often involves a sequence of different therapies • Optimal sequencing is determined by response, disease progression, and effects of therapies on disease pathways



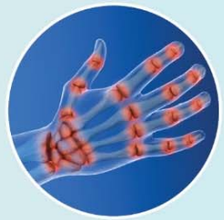
Care Management Strategies to Improve Clinical and Economic Outcomes

James Kenney, Jr. RPh, MBA

Manager, Specialty and Pharmacy Contracts

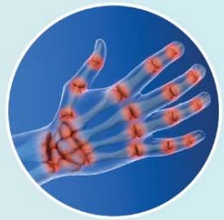
Harvard Pilgrim Health Care

Learning Objectives

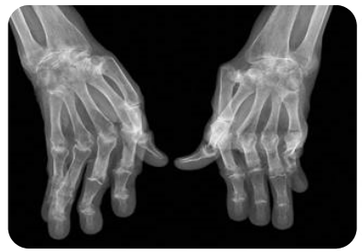


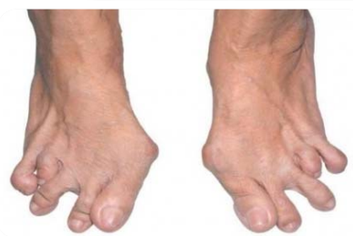
- Employ specialty pharmacy and disease management services for rheumatoid arthritis (RA) patients
- Describe care pathways and their application as a cost management tool in RA

The Challenge of Managing the Cost of Care While Improving Outcomes



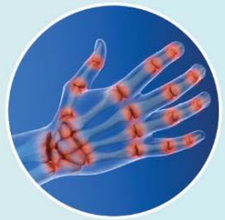
- RA is a chronic, progressive disease that exerts a tremendous toll on patient quality of life and places a significant economic burden on patients, employers, and payers
- Managed care organizations must weigh the direct and indirect costs of RA care when making informed decisions about treatment approaches
  - This often involves identifying opportunities to reduce costs while maintaining quality



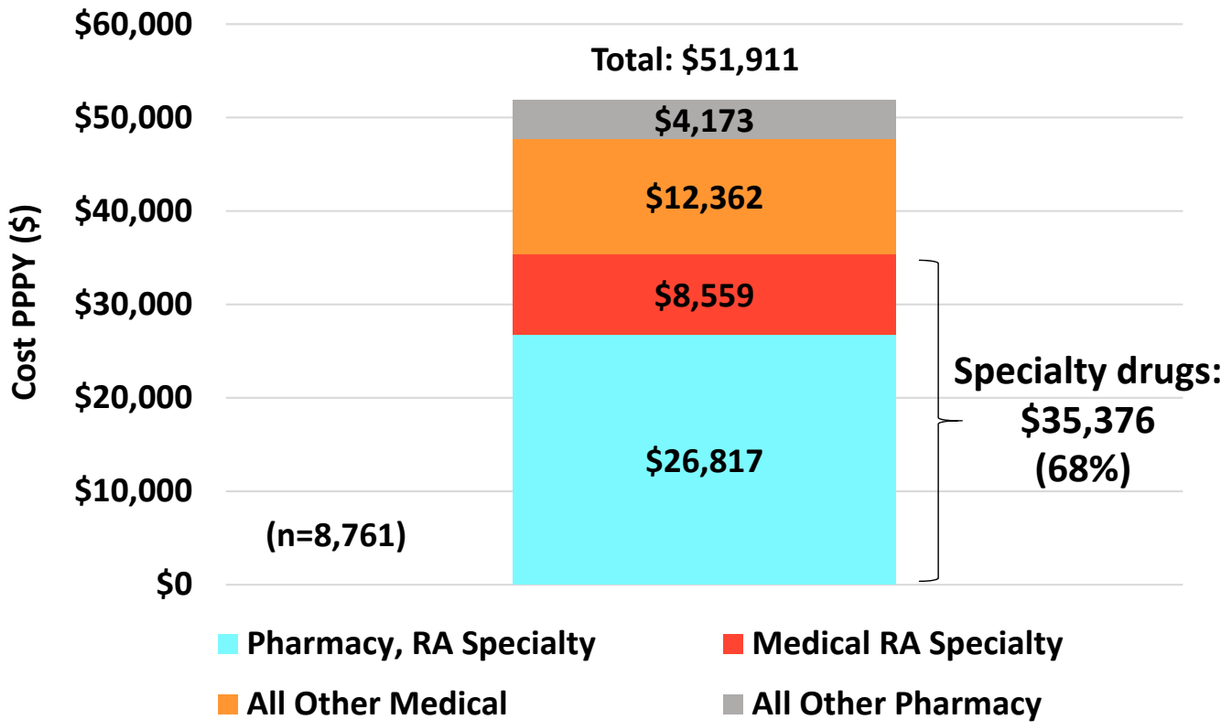


Cardarelli WJ. *Am J Manag Care*. 2016;22:S462-S469.

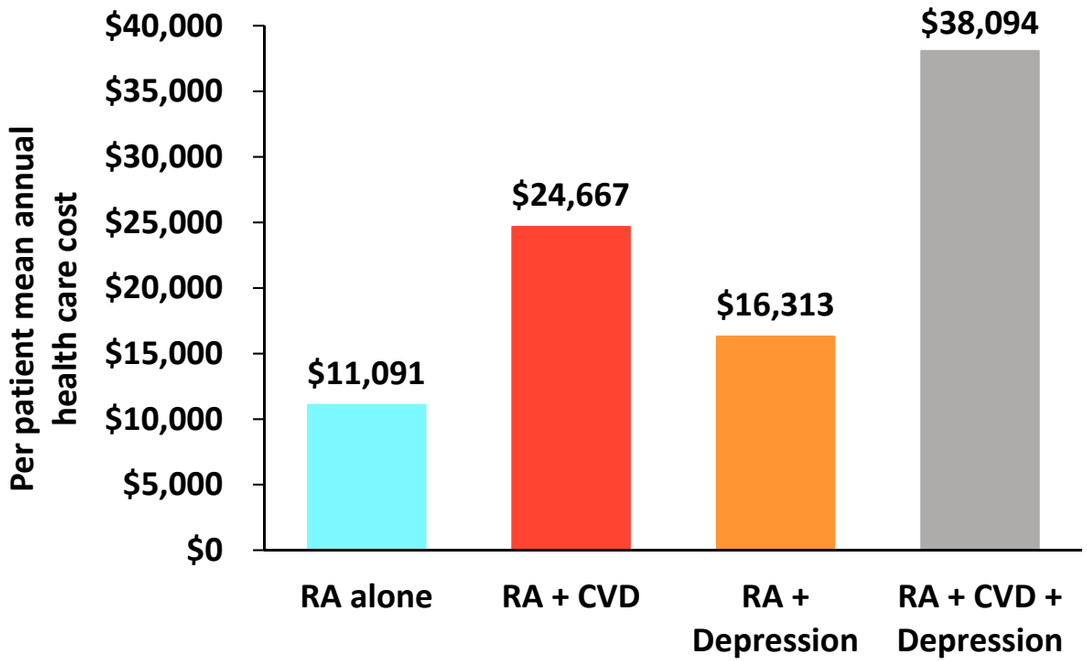
Costs Associated with RA are Substantial



Medical and Pharmacy Costs: Per Patient Per Year (2016)[1]



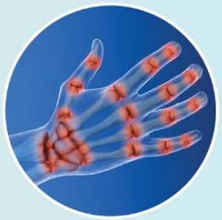
Annual Per Patient Cost of Care for RA With and Without Comorbidities[2]



Analysis of pharmacy and medical claim database of patients with a diagnosis of RA continuously enrolled in a commercial plan between 2013-2016.

1. Bowen K, et al. Abstract 408-5B. Presented at: The Academy of Managed Care Pharmacy Annual Meeting; October 16-19, 2017; Dallas, Texas.
2. Joyce AT, Smith P, Khandker R, Melin JM, Singh A. *J Rheum*atol. 2009;36(4):743-52.

Care Management Strategies to Control Costs and Improve Outcomes



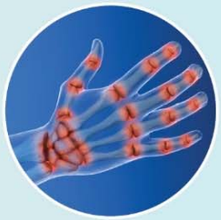
Care (Clinical) Pathways

Chronic Care Management Programs

Specialty Pharmacy

Care (Clinical) Pathways

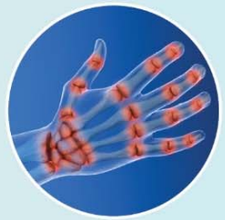
Care Pathways: A Tool to Manage Patient Care and Improve Outcomes



- **Definition:** a multidisciplinary treatment plan that provides guidance on:
  - Medical decision making
  - Psychosocial management
  - Ancillary services that go with that treatment
- **Goal:** make the treatment of complex, high-cost diseases as cost-effective as possible by improving quality, reducing variation, and increasing efficient use of health care
- Pathways are generally expected to reduce the overall costs of treatment
  - Many are designed to encourage efficient use of medical resources, particularly specialty drugs

Chawla A, Westrich K, Matter S, Kaltenboeck A, Dubois R. *Am J Manag Care*. 2016;22(1):53-62.

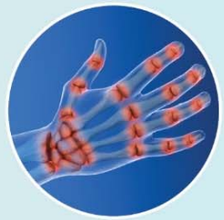
Impact of a Rheumatoid Arthritis Pathway on Patterns of and Costs of Care: Methodology



- RA treatment pathway developed as a collaborative effort between CareFirst BlueCross BlueShield, Cardinal Health and network rheumatologists
- Components
  - Use of a real-time decision-support and data-capture tool
  - Requirement for a clinical disease activity index (CDAI) at each physician visit
  - Use of disease-modifying antirheumatic drugs as first-line treatment for at least 12 weeks before use of biologic agents
  - Requirement that dose, schedule, and adjustments for biologic agents follow package label prescribing guidelines

Feinberg BA, Olson T, Matsumoto AK, Baraf HS, Miller PB, Winn D. Abstract PHS170. *Value Health*. 2014;17(3):A154.

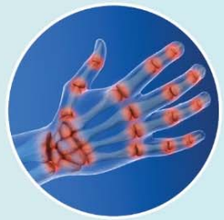
Impact of a Rheumatoid Arthritis Pathway on Patterns of Care



- **Results**
  - A total of 1,800 unique RA patients entered the program
  - CDAI capture through the decision support tool exceeded 70% of visits
  - DMARD rule compliance resulted in an 8% reduction in overall biologic agent use
  - Claims-validated compliance with initial infused biologic agent dose and schedule by label increased from 40% to 53%
  - Pathway adherence was without a consequent increase in CDAI scores
- **Conclusions**
  - High-level pathway program adoption suggests the feasibility of pathway-guided care in RA
  - Label-based prescribing of DMARD and biologic agents was not associated with higher CDAI scores, confirming that evidenced-based algorithms do not jeopardize patient outcomes

Feinberg BA, Olson T, Matsumoto AK, Baraf HS, Miller PB, Winn D. Abstract PHS170. *Value Health*. 2014;17(3):A154.

Use of a Rheumatoid Arthritis Clinical Pathway Reduced Cost of RA Care

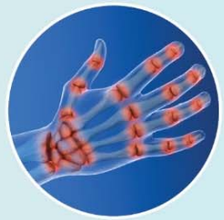


- **Results**
  - DMARD use increased by 7.4% over the first year contributing to a lower cost of care annualized at $1,069,790
  - Control of biologic “dose-creep” contributed $80,230 to further lowering cost annually
  - Average hospital facility costs per biologic infusion were near double that of community practice ($5,000 vs $2,500, respectively)
  - Participating providers had 80% fewer facility infusions than nonparticipating providers (11% vs 55%, respectively)
- **Conclusion**
  - RA pathway algorithm-compliant prescribing behavior for DMARDs and biologics resulted in measurable cost savings

Feinberg BA, Olson T, Matsumoto AK, Baraf HS, Miller PB, Winn D. *Value Health*. Abstract PHS79. 2014;17(3):A138.

Care Management Programs

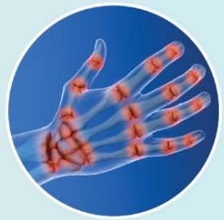
Care Management Programs May Control Health Care Costs and Improve Outcomes



- **Definition**: a set of activities designed to enhance patient care, reduce the need for medical services, and improve outcomes
- **Strategies**
  - Identify and engage patients at high risk for poor outcomes and high resource utilization
  - Conduct a comprehensive health assessment
  - Follow guideline-recommended care
  - Initiate early treatment
  - Assess appropriate use of biologics
  - Maximize adherence
  - Employ coordinated, multidisciplinary care
  - Improve management of comorbidities

Hong CS, Siegel AL, Ferris TG. Caring for High-Need, High-Cost Patients: What Makes for a Successful Care Management Program. The Commonwealth Fund website. http://graceteamcare.indiana.edu/content/Care%20Management%20Complex%20High%20Cost%20Hong%20TCF%202014%20(2).pdf. Published August 2014. Accessed September 2018.

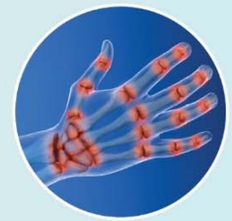
Common Elements of Successful Care Management



Success Factor	Description
Communication	• Patient satisfaction increases when the health care team explains information clearly, and tries to understand the patient's experience, and provides viable treatment/management options
In-person encounters	• Face-to-face interaction is necessary for effective care management • Care management relying solely on telephone and/or electronic encounters has not been shown to be successful
Training and personnel	• Programs with specially trained care managers working as part of a multidisciplinary team are most successful
Physician involvement	• Placing care managers with physicians in primary care practices may help facilitate physician involvement
Informal caregivers	• Patients with complex health care needs, particularly those with physical or cognitive functional decline, often need the assistance of informal caregivers to actively participate in care management
Coaching	• Involves teaching patients and their caregivers how to recognize early warning signs of worsening disease

Goodell S, Bodenheimer T, Berry-Millet R. Care management of patients with complex health care needs. Robert Wood Johnson Foundation website. https://www.rwjf.org/content/dam/farm/reports/issue_briefs/2009/rwjf49853. Published December 2009. Accessed September 2018.

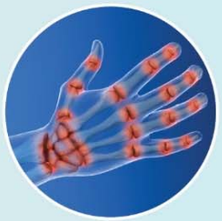
Examples of Care Management Programs



Program	Payer Type	Definition of Complex Patient	Primary Care Enhancement or High Risk	Level of Primary Care Integration	Operational Control	Funding
AtlantiCare Special Care Center (NJ)	Commercial	• Health risk assessment based on diagnoses, medication counts, acute care utilization, psychosocial issues	High risk	Integrated as part of the primary care team	Delivery system	Payer / employer
Geisinger ProvenHealth Navigator (PA)	All payer	• Risk score • Referral	PCMH	Integrated part of primary care team/off-site with frequent interaction	Payer / delivery system	Payer / health system
Health Quality Partners (PA)	Medicare Advantage	• Aetna Medicare Advantage Risk score plus ≥1 high-risk chronic conditions	High risk	Off-site with frequent interaction	Regional CM organization	Payer

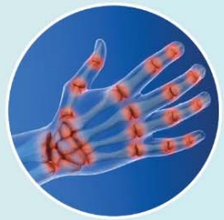
Sutter Care Coordination Program (CA)	Commercial	• Referral
		• Any one of the following:
		  • Unplanned readmission within 30 days
		  • ≥2 admissions in past year
		  • ≥2 ED visits in past year
		  • ≥7 medications
		  • Diagnosis of CHF, COPD, or pneumonia
		  • ≥3 chronic conditions
			High risk	Embedded/off-site with regular interaction	Payer / Delivery system	Payer / health system

Hong CS, Siegel AL, Ferris TG. Caring for High-Need, High-Cost Patients: What Makes for a Successful Care Management Program. The Commonwealth Fund website. http://graceteamcare.indiana.edu/content/Care%20Management%20Complex%20High%20Cost%20Hong%20TCF%202014%20(2).pdf. Published August 2014. Accessed September 2018.



Specialty Pharmacy

Specialty Pharmacy is Well-Positioned to Support Care Management Activities



Specialty Pharmacy Links Care Providers

Physician

Payer

Pharma

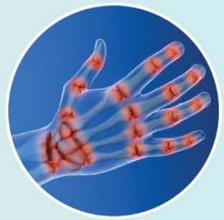
Results
- Safety
- Adherence
- Education
- Improved outcomes

Patient Data
- Lab values
- Medical history and exam results
- Treatment history and current plan

Adherence and Benefits
- Benefit design
- Fill/refill history
- Prior authorization
- Step edits
- Copay support

Safety and Outcomes
- Safety and efficacy data
- Dosage and administration
- Storage and handling
- Cost-effectiveness data

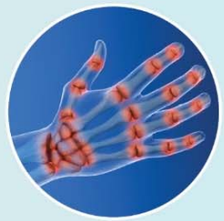
Services Provided by Specialty Pharmacy to Improve Care and Outcomes



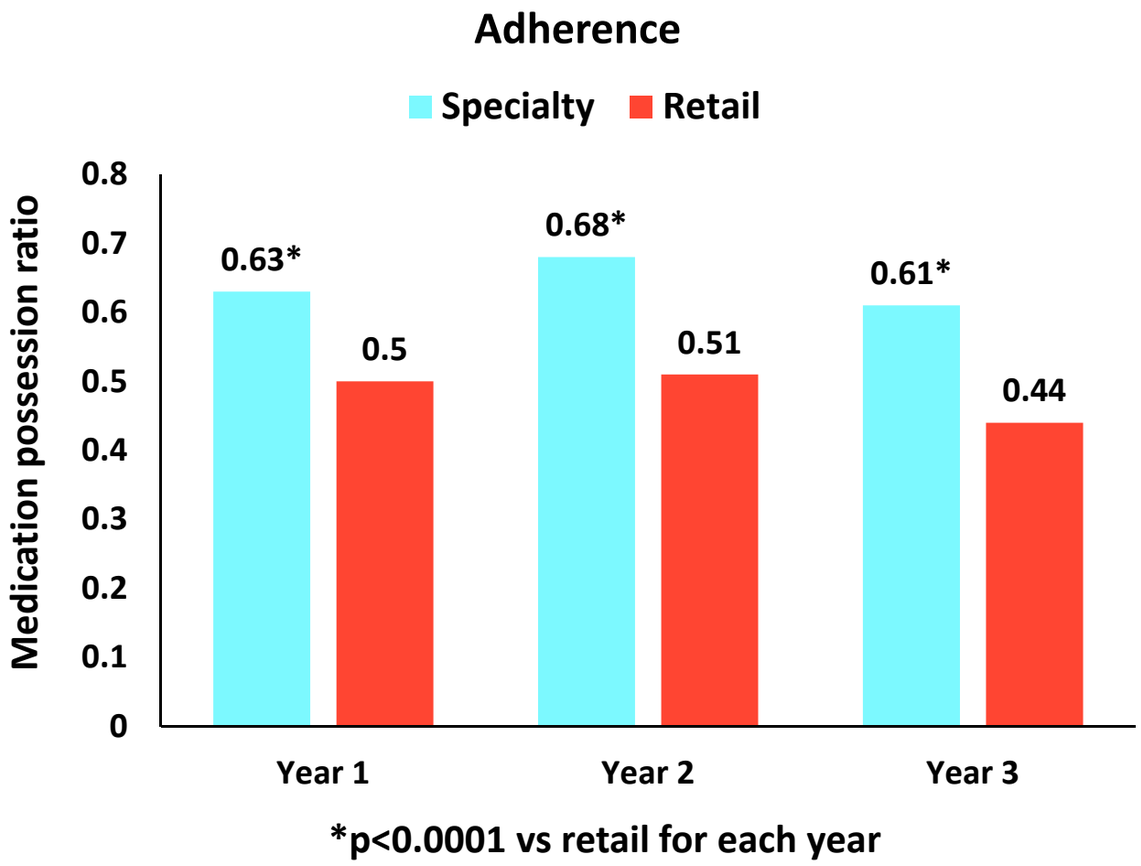
Patient Education	Drug Administration	Drug Dosing	Monitoring

• Therapy expectations
• Dosing
• Adverse events
• Follow up
• Shipping and storage requirements
• Patient access/insurance
	• Train patients and caregivers
	  • Drug preparation
	  • Proper administration techniques
	  • Proper handling, storage, and disposal
		• Individualization of dosing
		• Dosing frequency
			• Adherence support
			• Concurrent medications
			• Adverse events
			• Drug interactions
			• Comorbidities

Use of a Specialty Pharmacy Increased Adherence to Biologic Agents

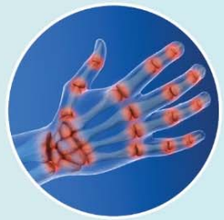


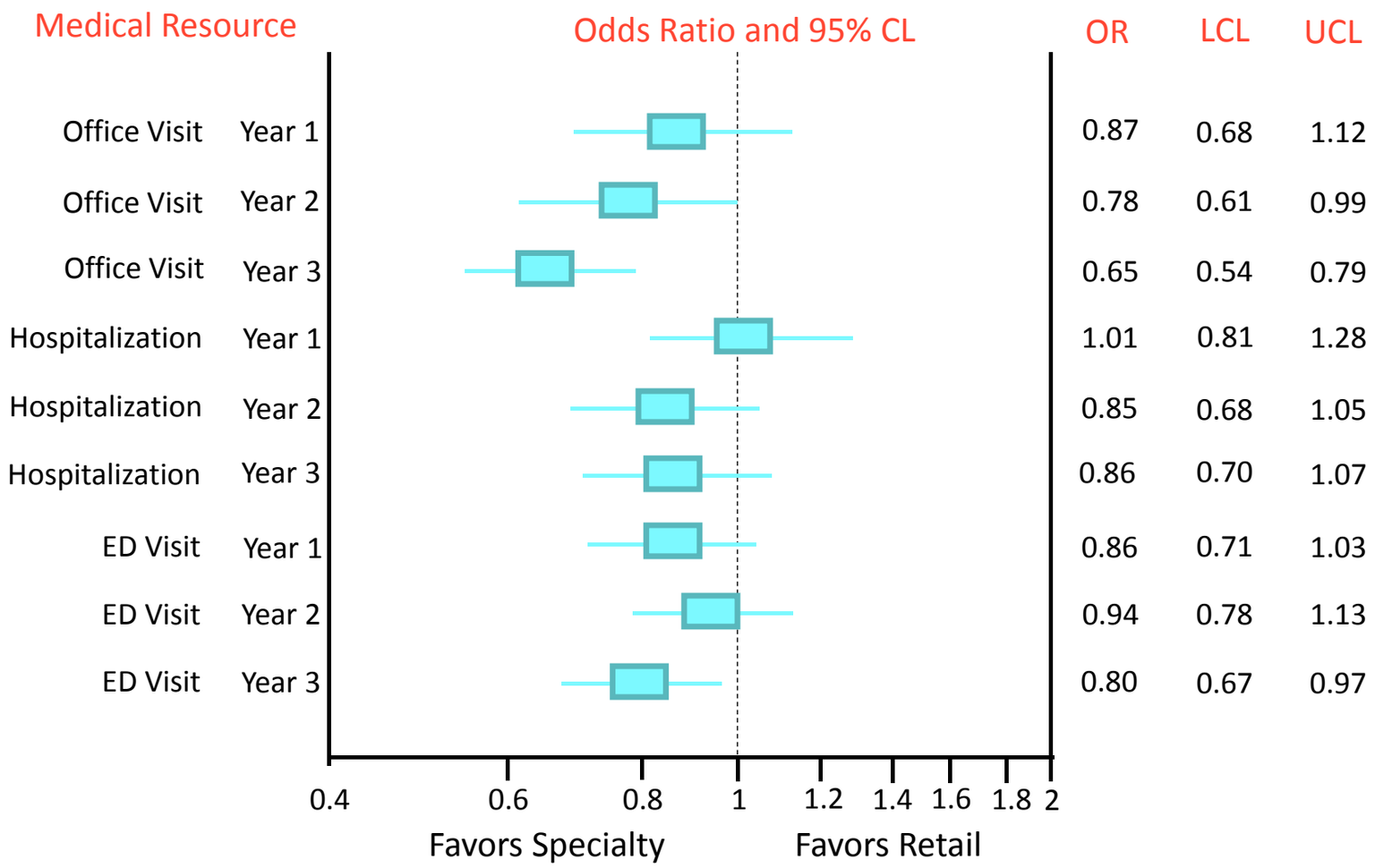
- Retrospective assessment of the impact of mail-order specialty pharmacy vs community-based retail pharmacy on patients with RA (n=31,678) treated with biologics over 3 years
- Primary outcome measures
  - RA medication adherence
  - Occurrence of office visit
  - Hospitalization
  - Emergency department visit
  - Drug costs
  - Medical costs



Barlow JF, Faris RJ, Wang W, Verbrugge RR, Garavaglia SB, Aubert RE. *Am J Pharm Benefits*. 2012;4(Special Issue):SP49-SP56.

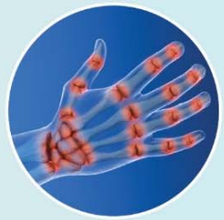
Patients Using Specialty Pharmacy Services Tended to Use Fewer Medical Resources



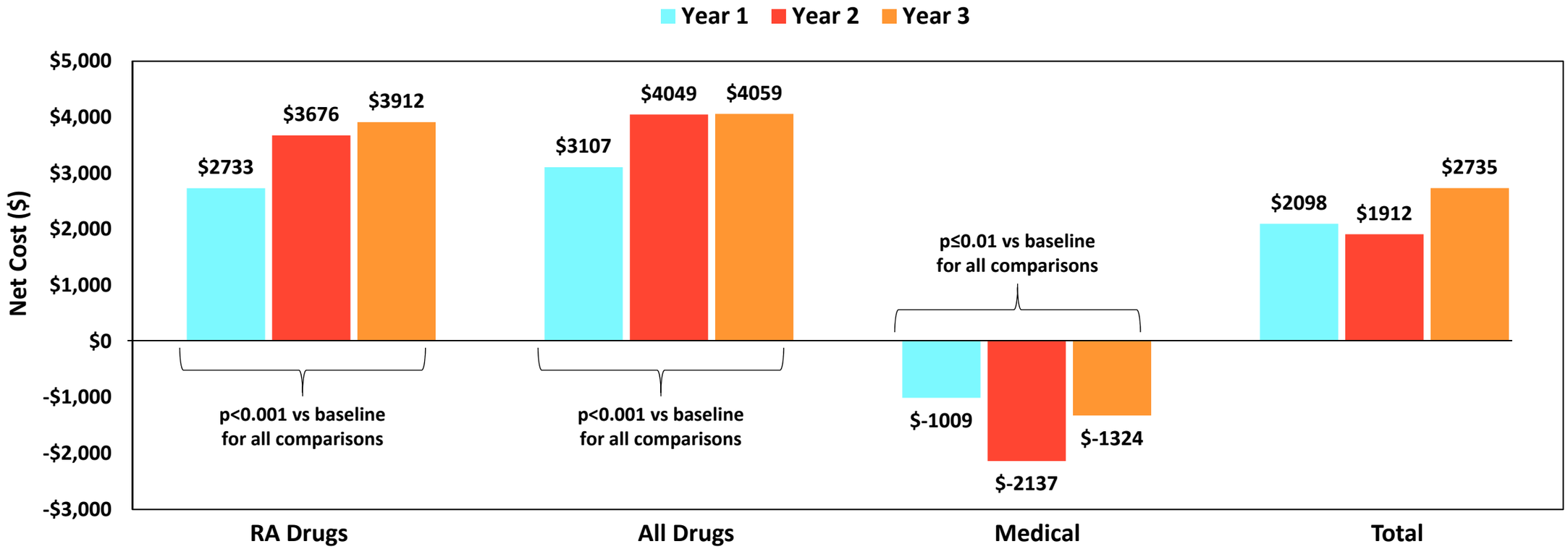


Barlow JF, Faris RJ, Wang W, Verbrugge RR, Garavaglia SB, Aubert RE. *Am J Pharm Benefits*. 2012;4(Special Issue):SP49-SP56.

Medical Costs Were Significantly Lower for Specialty Pharmacy Patients

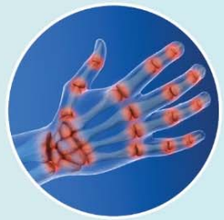


Net Direct Costs Associated with Specialty Pharmacy Management

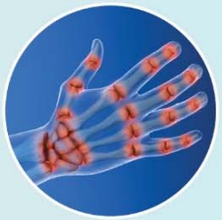


Barlow JF, Faris RJ, Wang W, Verbrugge RR, Garavaglia SB, Aubert RE. *Am J Pharm Benefits*. 2012;4(Special Issue):SP49-SP56.

Summary

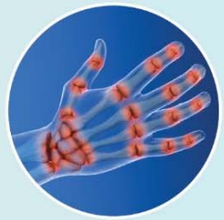


- RA is associated with substantial medical and pharmacy costs
- Several care management strategies have been devised to manage cost and improve RA treatment outcomes including care pathways, care management programs, and use of specialty pharmacies
  - Care pathways improve the use of guideline-directed care and are associated with reduced costs
  - Care management programs identify patients at high risk for poor outcomes despite excessive health care resource utilization
  - Specialty pharmacy is well-positioned to link providers, payers, and pharmaceutical manufacturers in order to increase adherence and reduce costs



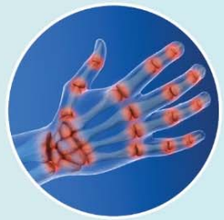
Benefit Design and Specialty Pharmacy Services for Effective RA Management

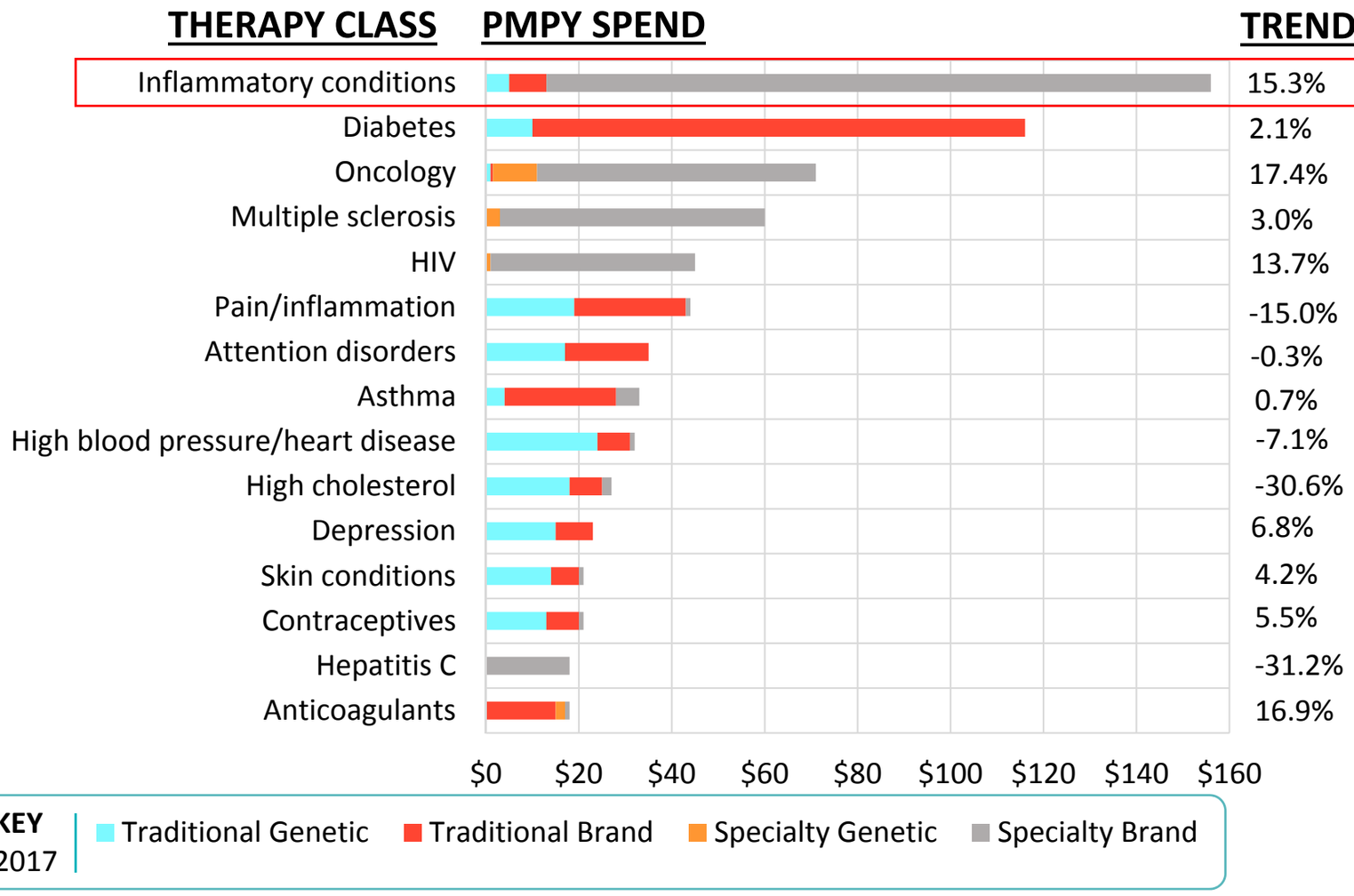
Learning Goal



- Assess benefit design strategies to improve overall patient outcomes for rheumatoid arthritis (RA)

Inflammatory Conditions Lead All Classes in PMPY Spending for Commercial Members

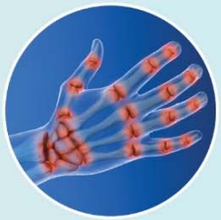




- **RA remains one of the top drivers of specialty drug trend**
- **RA accounts for approximately one fourth of all specialty drug spending in the US**

2017 Drug Trend Report. Express Scripts. http://lab.express-scripts.com/lab/drug-trend-report/2017-dtr. Published 2018 Accessed September 2018.

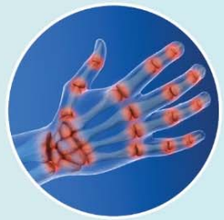
RA Management Challenges: Increasing Number of Biologic Agents



- Growing number of biologic agents for the treatment of RA
  - Not every biologic agent works for every RA patient
  - Little understanding of the cause of variation of drug efficacy between patients
- Clear guidance on the use of biologics to optimize RA treatment outcomes are lacking
  - Importance of understanding the optimal use of these agents magnified by their high cost
- Physicians, patients, and plan managers need better data to compare the effectiveness of the different biologics

Levesque MC. *BioDrugs*. 2012;26(2):65-70.

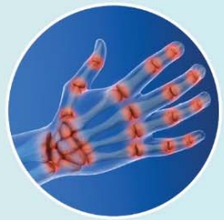
Comparative Effectiveness Research: The Value of Evidence-Based Medicine Review of Medications

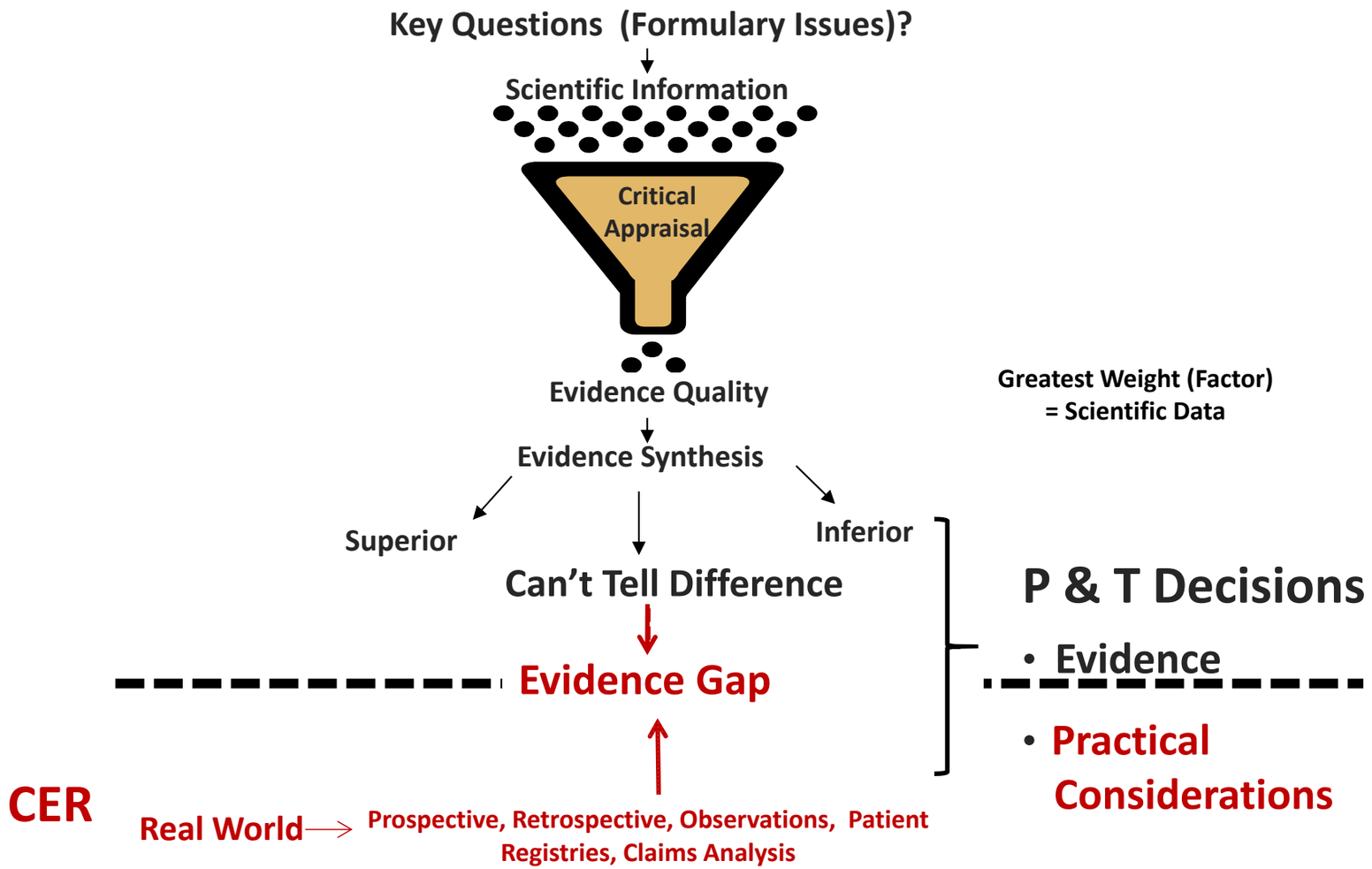


- Comparative effectiveness research (CER) addresses key questions that formulary decision-makers need to consider regarding a medication
- Builds a foundation in developing a comprehensive EBM formulary drug review
- Addresses challenges associated with:
  - Reviewing and critically appraising large amounts of data
  - Analyzing several products in a class or across classes
- Identifies evidence gaps for future research
- Provides information for practical considerations

EBM Formulary Drug Review

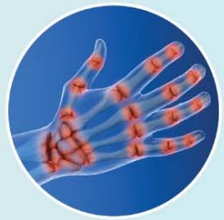
Practical Use of CER to Address Evidence Gaps





Perfetto EM, Anyanwu C, Pickering MK, Zaghab RW, Graff JS, Eichelberger B. *J Manag Care Spec Pharm*. 2016;22(6):609-16.

CER Application: Outcomes and Overall Cost of Rheumatologic Biologics



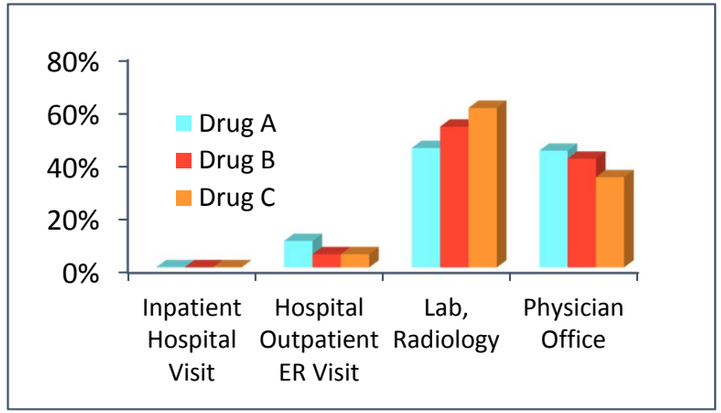
Clinical Trial Data

- Reliable quality evidence for biologics in rheumatologic conditions (rheumatoid arthritis, psoriatic arthritis/psoriasis, ankylosing spondylitis)
- Compared to standard treatments (ie, with/without methotrexate)
- Limited evidence for direct head-to-head comparison

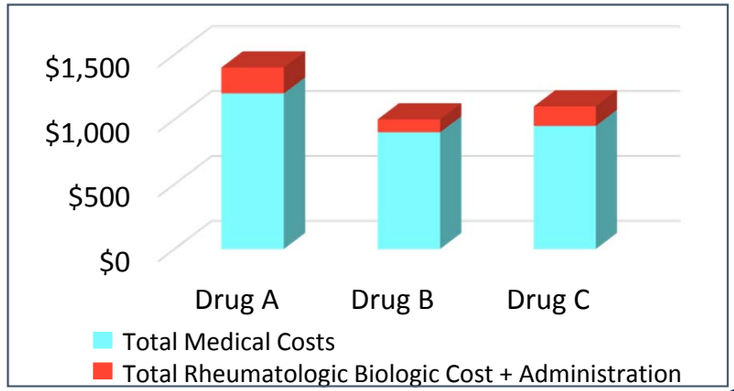
Real-world CER

- Compared to Drug A for rheumatologic conditions, Drugs B or C *associated* with:
  - Fewer outpatient hospital, ER visits
  - Lower monthly medical costs per utilizing member
  - Lower overall monthly costs per utilizing member (medical/drug/administration costs)

% Health Care Utilization per Year (as % of Total Medical Claims)

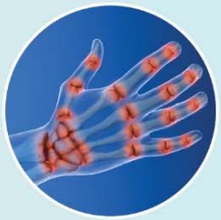


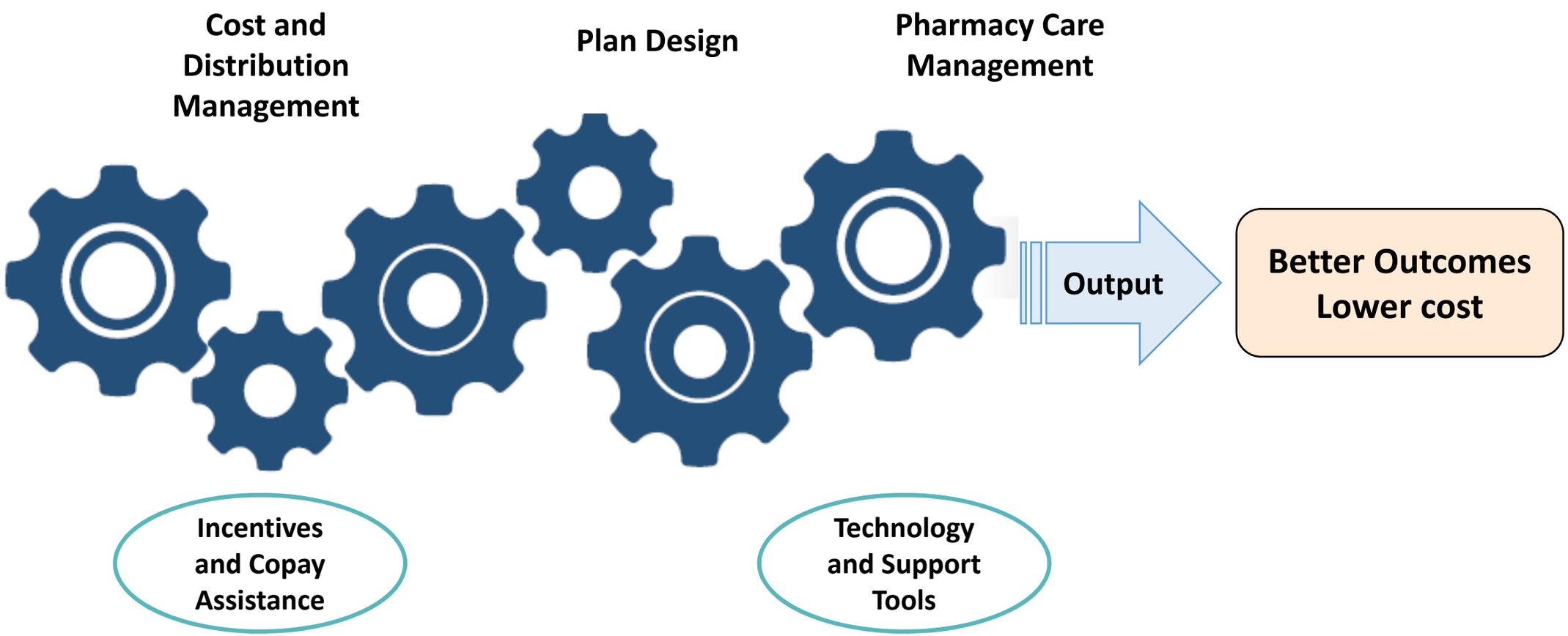
$ Cost Per Utilizing Member Per Month



Hudson M, Tascilar K, Suissa S. *Nat Rev Rheumatol*. 2016;12(6):358-66.

Costs Effectively Managed by Aligning Distribution, Plan Design and Pharmacy Care Management





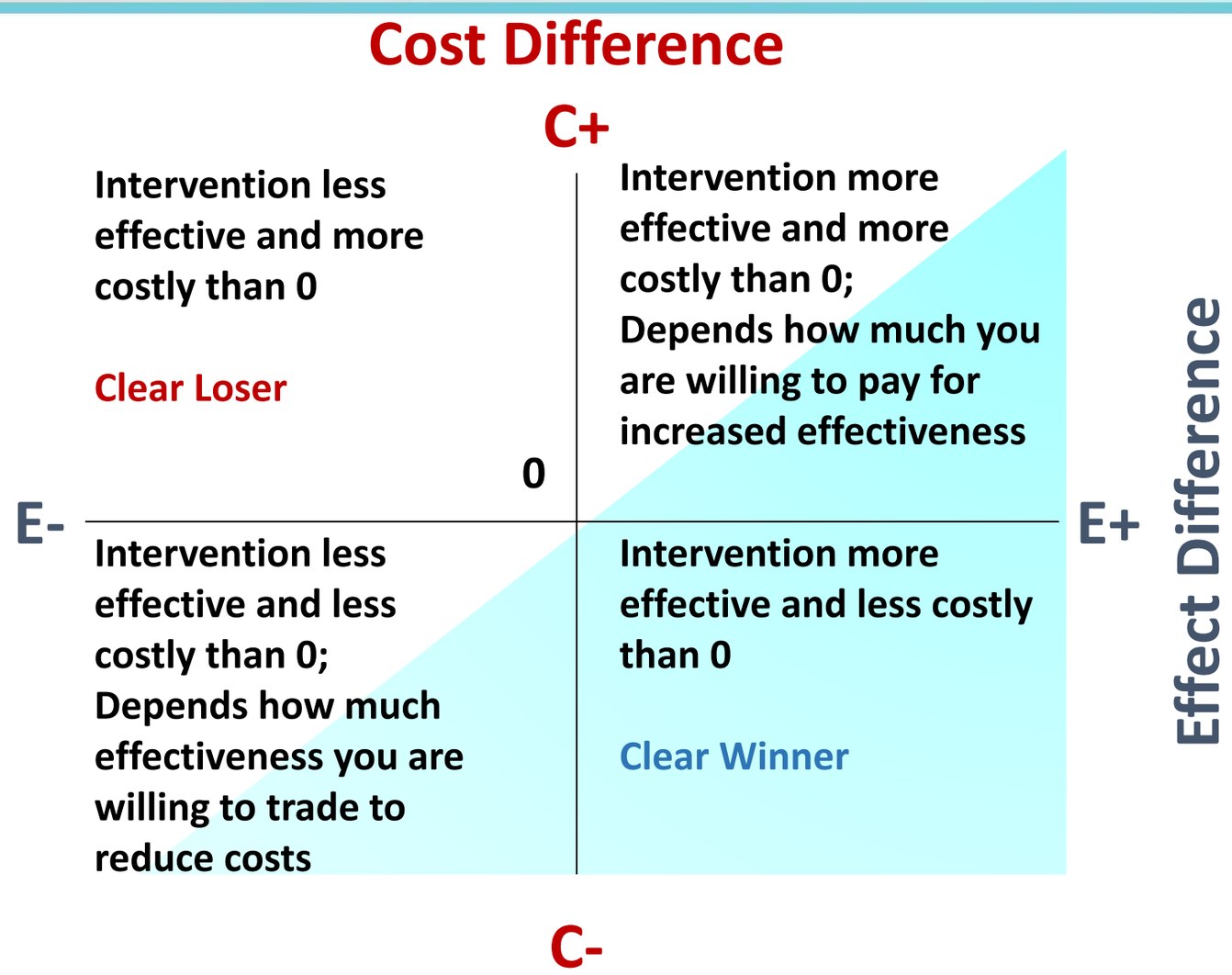
Basic Tenets of the Specialty Drug Benefit

Utilization Management	• Reduce costs by aggressively managing drug utilization
Preferred Drug Management	• Establish preferred products and formulary tiers • Use cost sharing to drive use of preferred products, but not limit adherence
Contract Management	• Aggressively negotiate rebates • Incent providers to utilize the most cost-effective drugs
Channel Management	• For pharmacy, optimize the distribution network • Optimize site of care
Care Management	• Provide counseling and education to patients and caregivers • Incent coordinated care

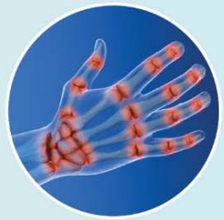
Starner CI, Alexander GC, Bowen K, Qiu Y, Wickersham PJ, Gleason PP. *Health Aff* (Millwood). 2014;33(10):1761-9.

Value = Cost Effectiveness

- Efficacy
- Price
- Cost per event avoided
- Cost per % improvement
- Helps compare agents
  - When there are no head-to-head trials



Elements of the RA Benefit Design: Formulary Tiers

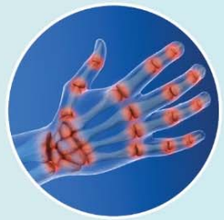


- Trend is toward multi-tier formularies
- Patient cost is dependent on the formulary tier
  - Tier 1: lowest cost
  - Tier 2: slightly higher cost
  - Tier 3: higher cost
  - Tier 4 (specialty drugs): highest cost
- Formulary positioning depends on the demonstrated value of the drug as assessed by the plan sponsor

Tier 1 Generic	Tier 2 Preferred	Tier 3 Non-preferred	Tier 4 Specialty
$	$$	$$$	$$$$
Least expensive, including all generics and select brands	**Brand name drugs proven to be most effective** in their class	**Non-preferred brand names** not considered to be the most effective as well as **preferred specialty drugs**	The most expensive drugs; typically **non-preferred, branded specialty drugs**

2018 Aetna Pharmacy Drug Guide. Aetna website. https://fm.formularynavigator.com/FBO/41/premier_pdf.pdf. Accessed September 2018.

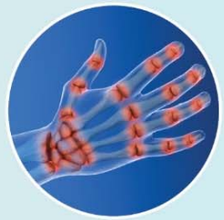
Example: RA Formulary Design

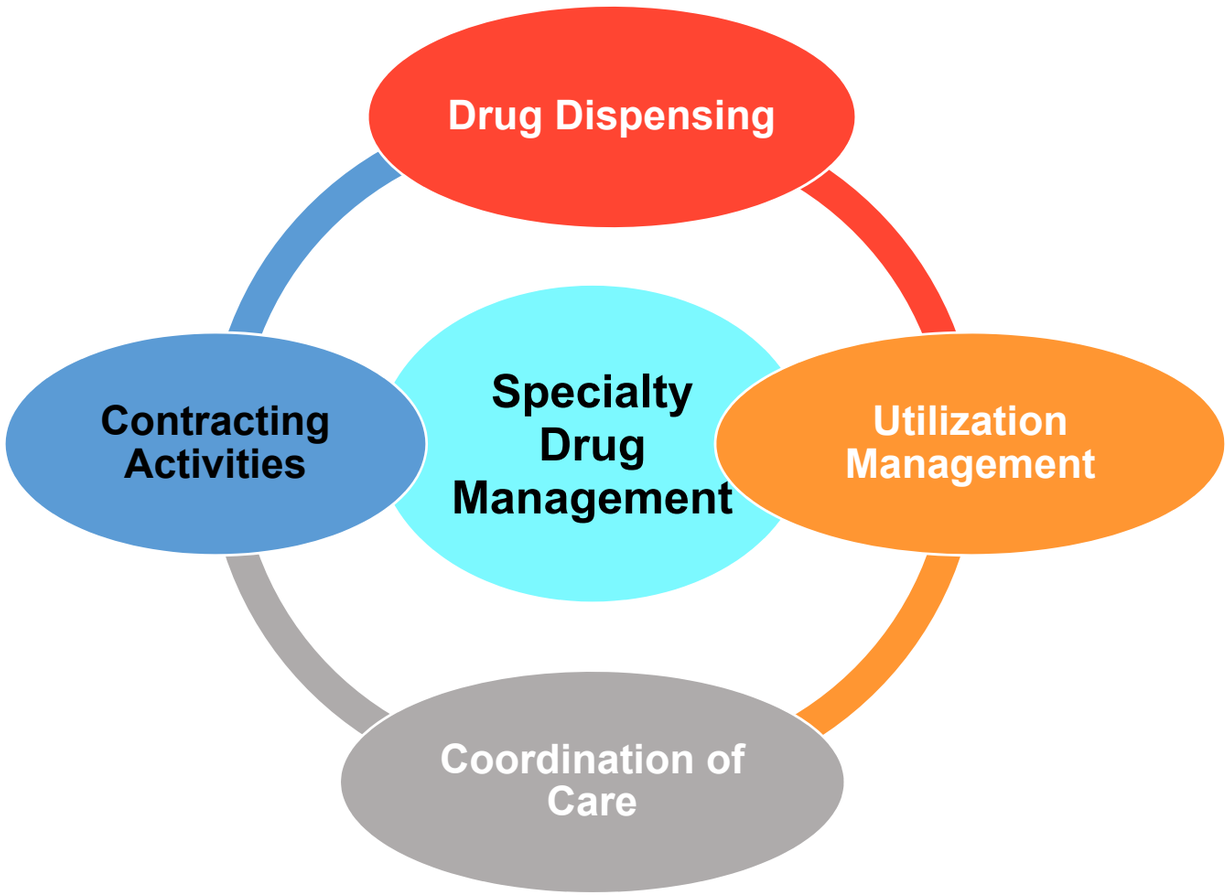


Pharmacy Benefit		
Tier	**Drug**	**Cost**
Preferred generic		$5
Non-preferred generic		$10
Preferred brand		$50
Non-preferred brand		$100
Preferred specialty		10%
Non-preferred specialty		20%

Medical Benefit		
Tier	**Drug**	**Cost**
Non-specialty		NA
Preferred specialty		10%
Non-preferred specialty		20%

Utilization Management

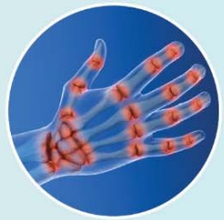




- Prior authorizations
- Step-therapy
- Quantity limits
- Partial fill
- Site of care
- Reporting

5-7% Savings

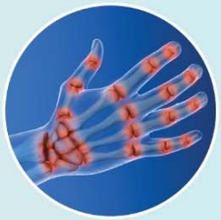
Medicare Advantage Prior Authorization and Step Therapy for Part B Drugs

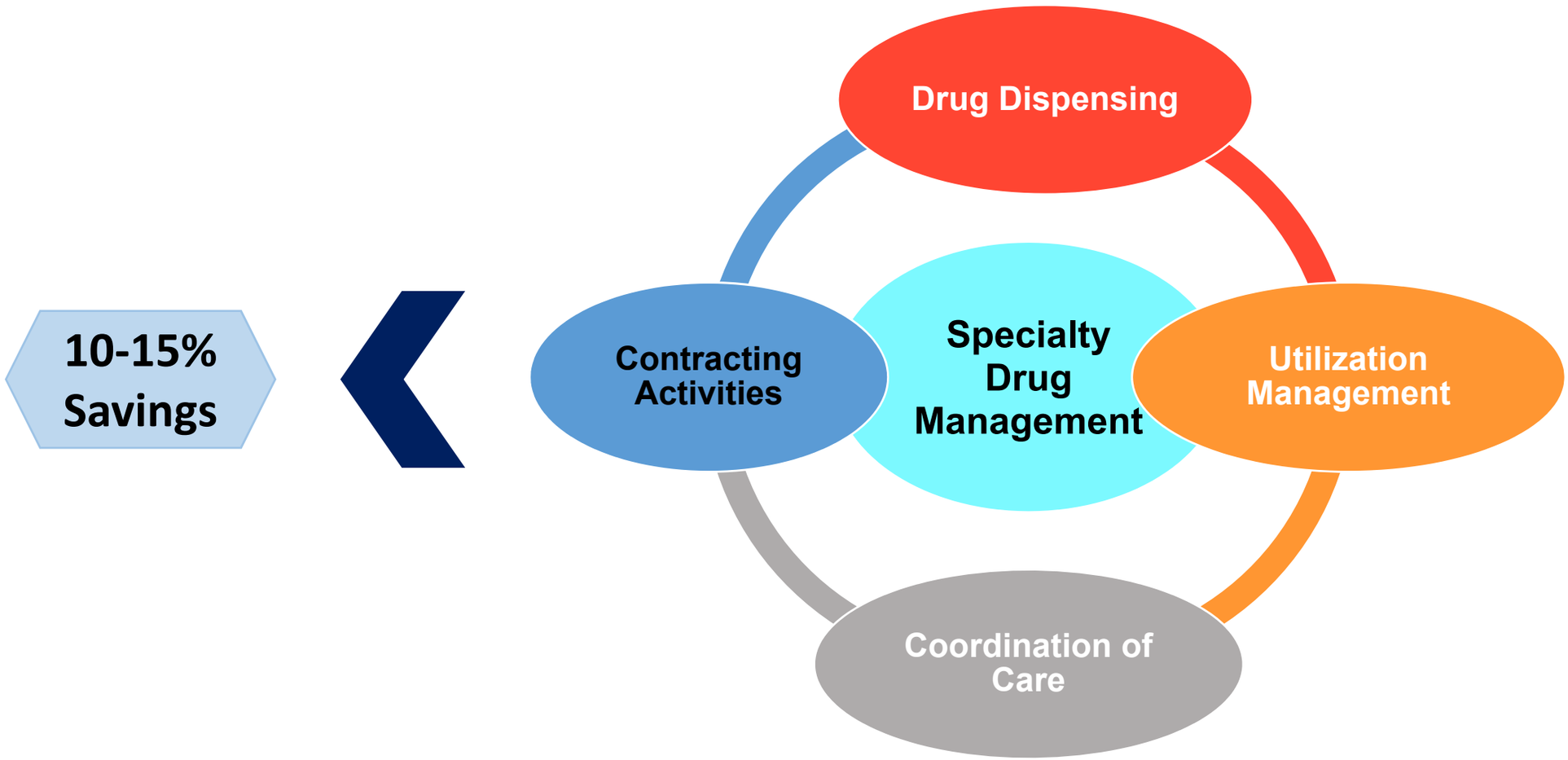


- Beginning January 1, 2019, CMS will provide Medicare Advantage (MA) plans the option of applying step therapy for physician-administered and other Part B drugs
- MA plans choosing to offer Part B step therapy must couple step therapy with new patient-centered care coordination services for beneficiaries
- Care coordination services must include
  - Discussing medication options with beneficiaries
  - Providing beneficiaries with educational material and information about their medications
  - Implementing adherence strategies for beneficiaries on their medication regimen
- MA plans will be required to pass savings on to beneficiaries through the rewards furnished as part of the drug management care coordination program

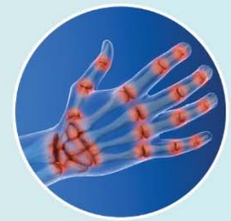
Medicare Advantage prior authorization and step therapy for Part B drugs. Centers for Medicare and Medicaid Services website. https://www.cms.gov/newsroom/fact-sheets/medicare-advantage-prior-authorization-and-step-therapy-part-b-drugs. Published August 7, 2018. Accessed September 2018.

Preferred Product Management: Contracting and Rebates





Contracting and Rebates for Preferred Products

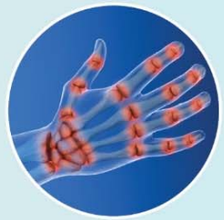


- Create “preferred” products within key therapeutic classes
  - Maximize rebate potential
  - Control utilization

Example of Preferred Product Categories	
Multiple sclerosis (im/sc)	Growth hormone
Rheumatoid arthritis (sc)	Psoriasis
Rheumatoid arthritis (im)	Crohn’s disease
Hepatitis C virus (oral)	Hepatitis C virus (sc)

im=intramuscular; sc=subcutaneous

Value-based Effectiveness Contracting for RA



- Amgen entered into a 2-year agreement with Harvard Pilgrim linking the cost of etanercept to its real-world clinical efficacy
- The goal is to reimburse based on value to the patient and not solely on volume of medicine sold
- This is the only outcomes-based contract of its kind for the treatment of moderate to severe RA
- Harvard Pilgrim will pay less for the drug if patients score below certain levels on measurements of 6 criteria including
  - Patient adherence to the drug
  - Switching drugs
  - Adding drugs
  - Dose escalation
  - Steroid interventions

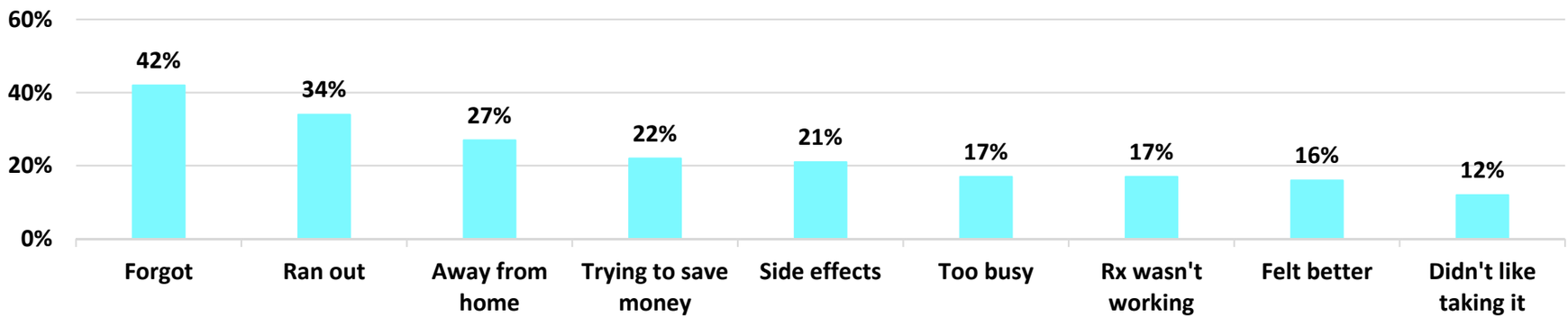
Harvard Pilgrim Signs Outcomes-Based Contract with Amgen for Enbrel. Harvard Pilgrim HealthCare Press Release. https://www.harvardpilgrim.org/public/news-detail?nt=HPH_News_C&nid=1471912468296. Published February 22, 2017. Accessed September 2018.

Risk-Sharing with a Specialty Pharmacy Provider: Adherence

Factors Impacting Patient Adherence[1]

- Patient-related
- Health care system
- Therapy-related
- Disease-related
- Cost-related
- Socio-economic

Reasons for Non-Adherence[2]



- Segment patient adherence using multiple parameters
- Target opportunities for adherence interventions
- Evaluate for differences in adherence due to prescriber, drug, age, reported reasons for non-adherence, etc.

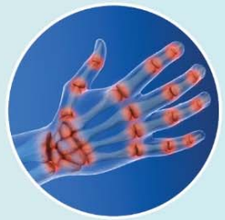
1. Patient Adherence: The Next Frontier. 9th edition. Capgemini Consulting. http://pharma-smart.com/wp-content/uploads/2015/03/Patient_Adherence__The_Next_Frontier_in_Patient_Care.pdf. Published 2011. Accessed September 2018.
2. Medication in America. National Community Pharmacists Association. http://www.ncpa.co/adherence/AdherenceReportCard_Full.pdf. Published 2013. Accessed September 2018.

Risk-Sharing for Members

Adherence Contracts

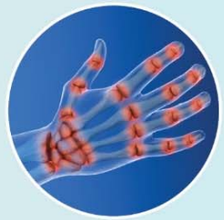
- Increasingly utilized
- Engages members and increases ownership of their care
- Advantages vs disadvantages
  - What happens with patients who are <50% adherent?

Current Environment of Copay Assistance



- While copay cards may improve patient access, affordability and adherence, some plan sponsors believe they may increase costs via:
  - Removing barriers to unnecessary testing/procedures by limiting patients' stake
  - Incentivizing patients to utilize non-preferred drugs that are less cost-effective
- In response to these issues and as a way to drive greater savings for plan sponsors, two new specialty copay card programs were introduced in 2017: *accumulator adjustment* and *copay allowance maximization*
  - However, when applied to high-cost/high-value drugs, these programs may create a barrier to patients' utilization of more complex therapies

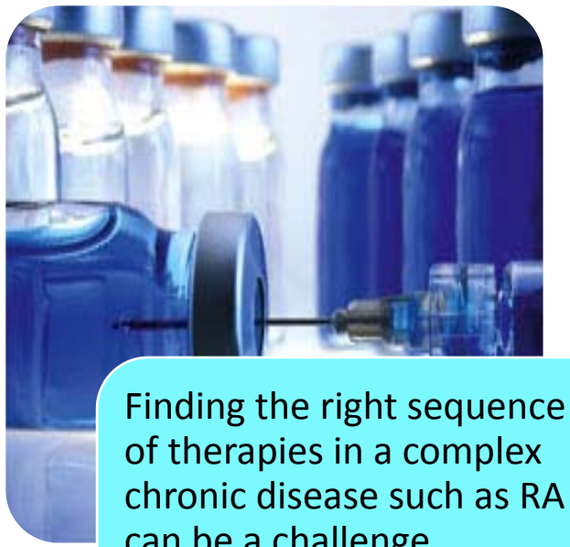
Accumulator Adjustment and Copay Allowance Maximization Programs



- There is a trend among pharmacy benefit managers towards the use of promoting “copay accumulator” programs to health plan sponsors
- The effect of these programs is to shift much of the cost burden for specialty drugs toward patients and manufacturers
- With copay accumulator adjustment programs in place, the copay coupon still allows the patient to access his or her medication, but the patient no longer receives deductible credit

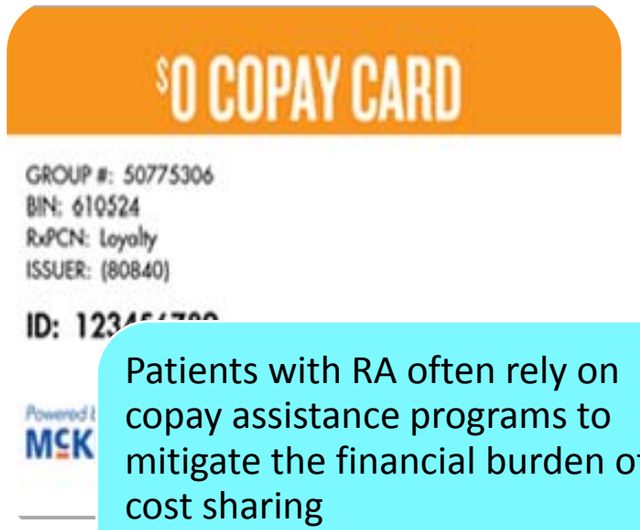
Feldman MA. The Physician’s Perspective. http://1yh21u3cjptv3xjder1dco9mx5s.wpengine.netdna-cdn.com/wp-content/uploads/2018/06/IfPA_Copay-Accumulator-Adjustment-Programs_June-2018.pdf. Published June 2018. Accessed September 2018.

Copay Assistance Mitigates Patient Cost Burden, but Accumulator Adjustment Programs Can Reintroduce Financial Barriers to Access



Finding the right sequence of therapies in a complex chronic disease such as RA can be a challenge

- Treatment adherence can result in improved Quality of Life and decreased health care utilization



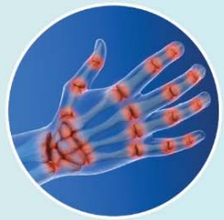
Patients with RA often rely on copay assistance programs to mitigate the financial burden of cost sharing

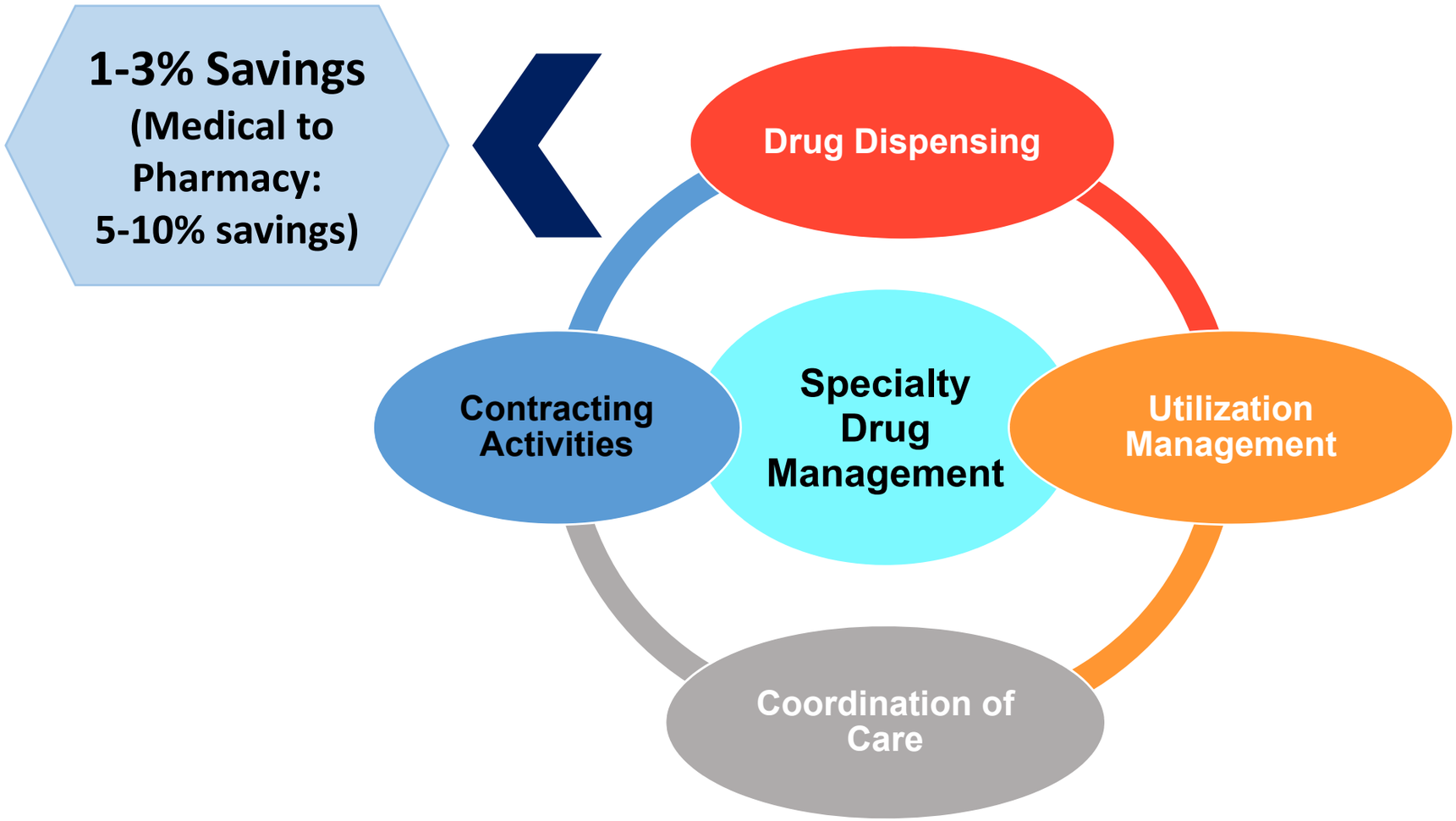
- A significant proportion of patients now only have high-deductible plan options
- Copay assistance programs are offered by manufacturers of specialty drug products

Copay Accumulator Programs interfere with a vital lifeline for patients with chronic conditions necessitating specialty drugs

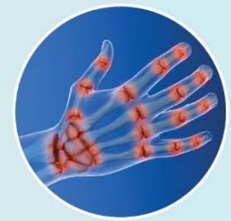
- Accumulator adjustment and copay allowance maximization negate the benefits of copay assistance programs and reintroduce financial barriers to care

Channel Management: Site of Care





Drug Dispensing



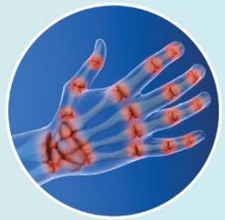
- Channel management
  - Medical claim Site-of-Care Optimization
  - Pharmacy channel management

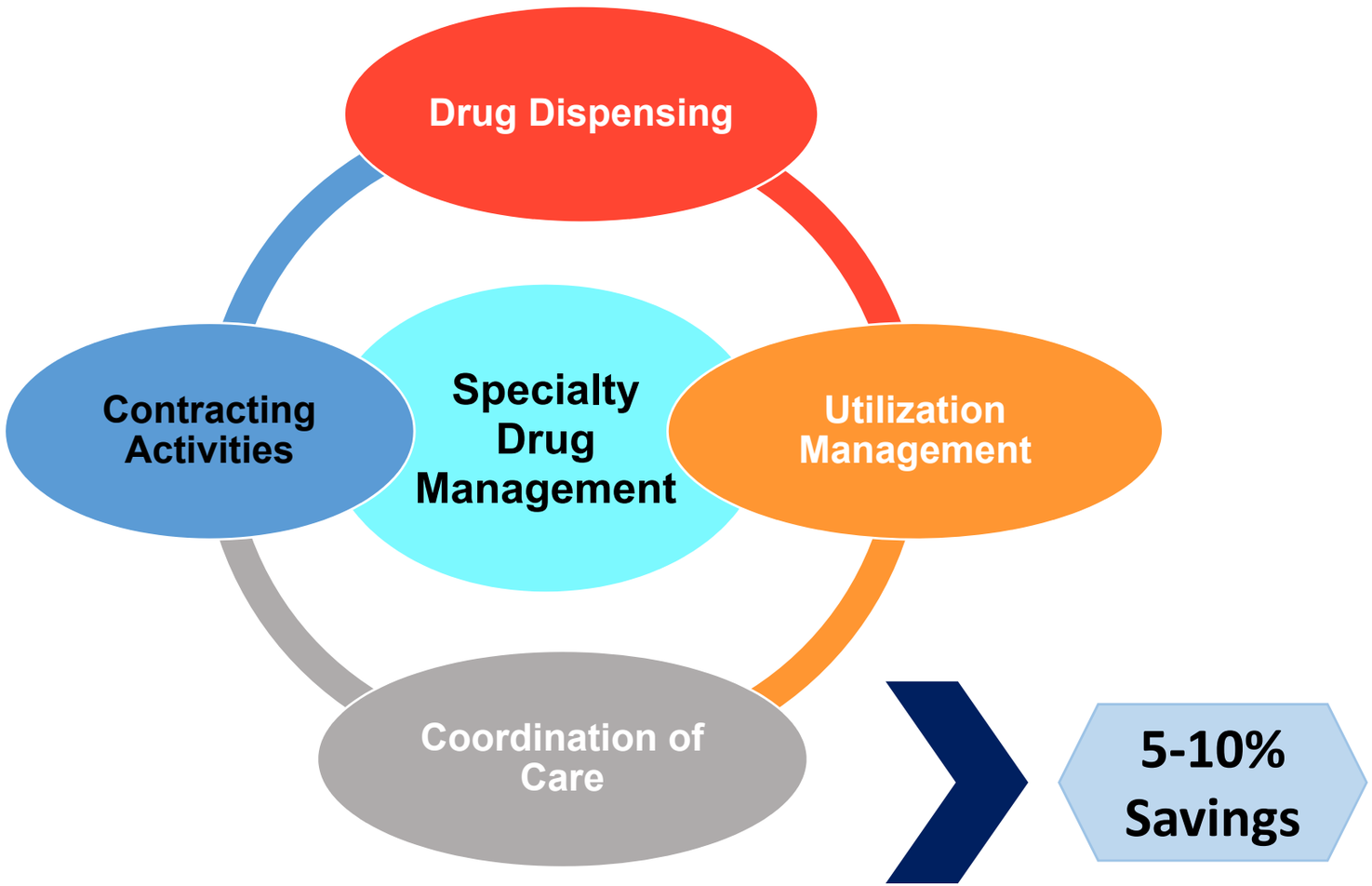
Infliximab Site-of-Care Example

Site of Service	Cost per unit	Units	Cost per claim	Claims per year	Annual Cost
MD office or home infusion	$70	50	$3,500	7	$24,500
HOPD (average)	$111	50	$5,500	7	$38,850
HOPD (highest cost hospital)	$360	50	$18,000	7	$126,000

HOPD=hospital outpatient department.
Internal utilization and pricing data.

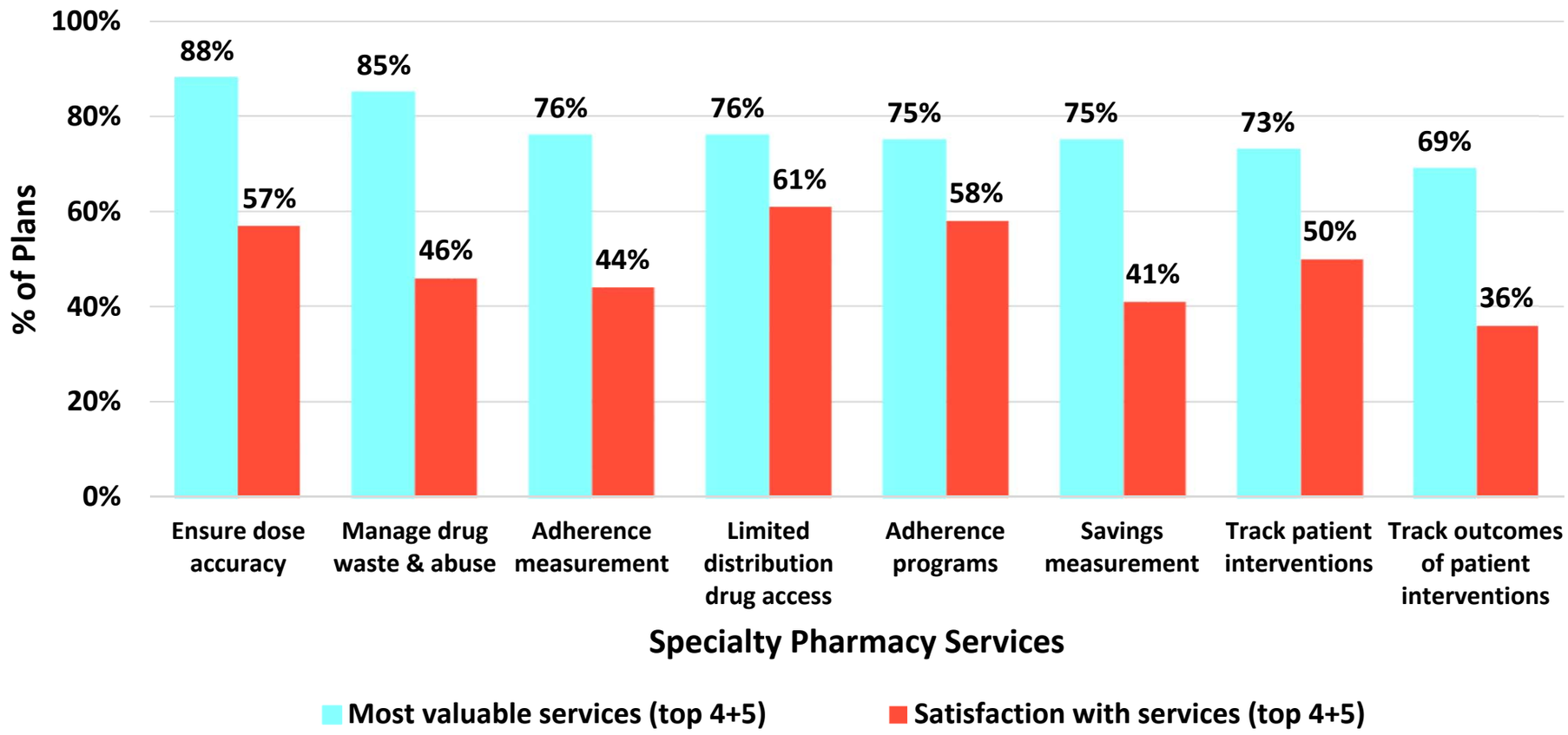
Care Management





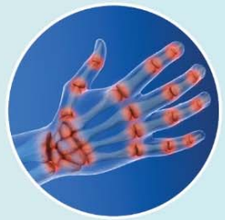
Care Management

- **Opportunity**
  - Costs will continue to rise (How to get the most out of drug spend?)
- **Fill the specialty pharmacy "gap"**
  - Education on use
  - Education on side effects
  - Adherence
  - Site-of-care optimization



EMD Serono Specialty Digest, 9th Edition. Managed care strategies for specialty pharmaceuticals. Academy of Managed Care Pharmacy website. http://www.amcp.org/EMDSeronoSpecialtyDigest9th.pdf. Published 2013. Accessed September 2018.

Specialty Pharmacy Care Management



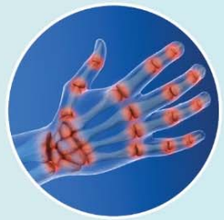
Program

- Specialty Pharmacy MTM
  - Integration with care management
  - Coordinate site-of-care
  - Ensure appropriate dosing
  - Adherence
  - Education on use
  - Expectation management

Actions

- Design program workflow and integration with care management
- Analyze utilization to select targeted drugs/disease states
- Train personnel:
  - Specialty diseases
  - Medications
  - Site-of-care logistics

Summary



- The number of biologic agents for the treatment of RA continues to increase
- While many patients stand to gain with the growth in the number of therapeutic options, these benefits will come at a higher cost
- To ensure patient access to these innovative therapies, the RA benefit must evolve to maintain a balance between access, appropriate use, and cost management