MCRB™

An Analysis of Treatment Options, Comparative Effectiveness Research, and Benefit Designs for Rheumatoid Arthritis

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- www.ManagedCareReviewBoard.com is a website devoted to delivering these CE activities

Agenda

6:10 PM	Assessing the Clinical Benefits of Current and Evolving RA Therapies in a Managed Care Setting *Brian Kaye, MD*
6:30 PM	Current Practice Guidelines Review *Neil Minkoff, MD*
6:45 PM	Faculty Idea Exchange
6:50 PM	Current and Emerging CER for Evidence-Based Treatment and Benefit Design Decision Making *Jeffrey Dunn, PharmD, MBA*
7:05 PM	Analyzing the Available Data to Assess the Value of Current and Emerging Treatment Options *Fadia Tohme-Shaya, PhD, MPH*
7:25 PM	Plan Benefit Designs: Maximizing Value for Current and Emerging RA Therapies *Jeffrey Dunn, PharmD, MBA*
7:40 PM	Faculty Idea Exchange and Audience Q&A
7:55 PM	Closing Comments, Post-survey, and Evaluations *Neil Minkoff, MD*

Educational Objectives

After completing this activity, the participant should be better able to:

- Discuss the current clinical practice guidelines to improve outcomes for patients with RA
- Explain the unique role and utility of CER to improve outcomes for the treatment of RA within a managed care setting
- Cite currently available RA data and interpret the results for enhanced managed care decision-making for the treatment of RA
- Apply the use of CER for the treatment of RA within a managed care setting
- Provide accurate and appropriate counsel as part of the managed care treatment team

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Assessing the Clinical Benefits of Current and Evolving RA Therapies in a Managed Care Setting

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Faculty Disclosure

- The ***faculty*** reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

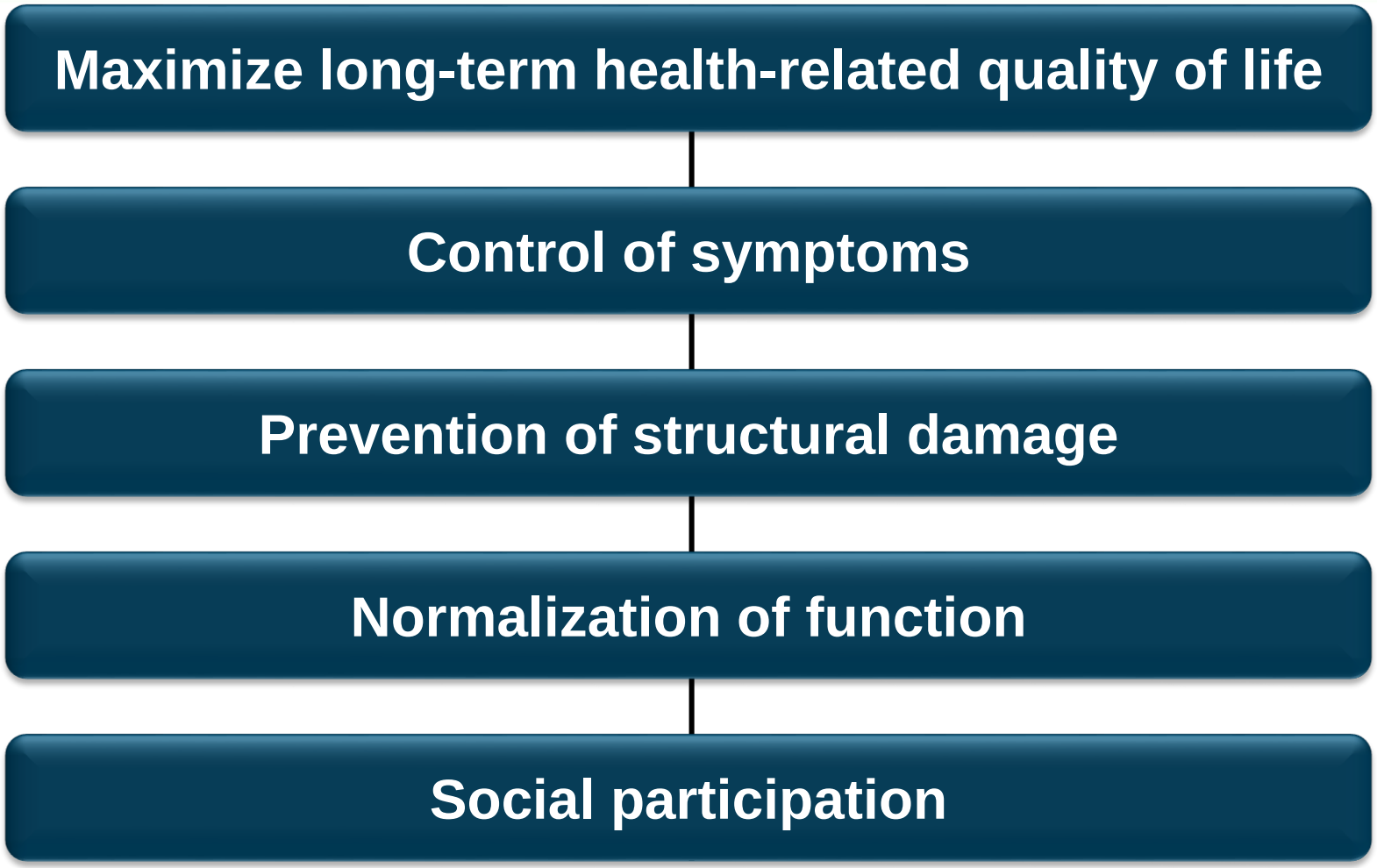
  Brian Kaye, MD, FACP

  - No financial interest/relationships relating to the topic of this activity

Outline

- Overview of RA treatment
  - Principles
  - Goals
  - Strategy
- Measures of disease progression
- Pharmacologic management
  - Approved therapies
  - Emerging therapies

RA Treatment Goals



Smolen JS, et al. *Ann Rheum Dis.* 2010;69:631-637.

RA Treatment Strategy

Early and aggressive treatment

- Attenuate inflammation quickly

Treat-to-target (remission)

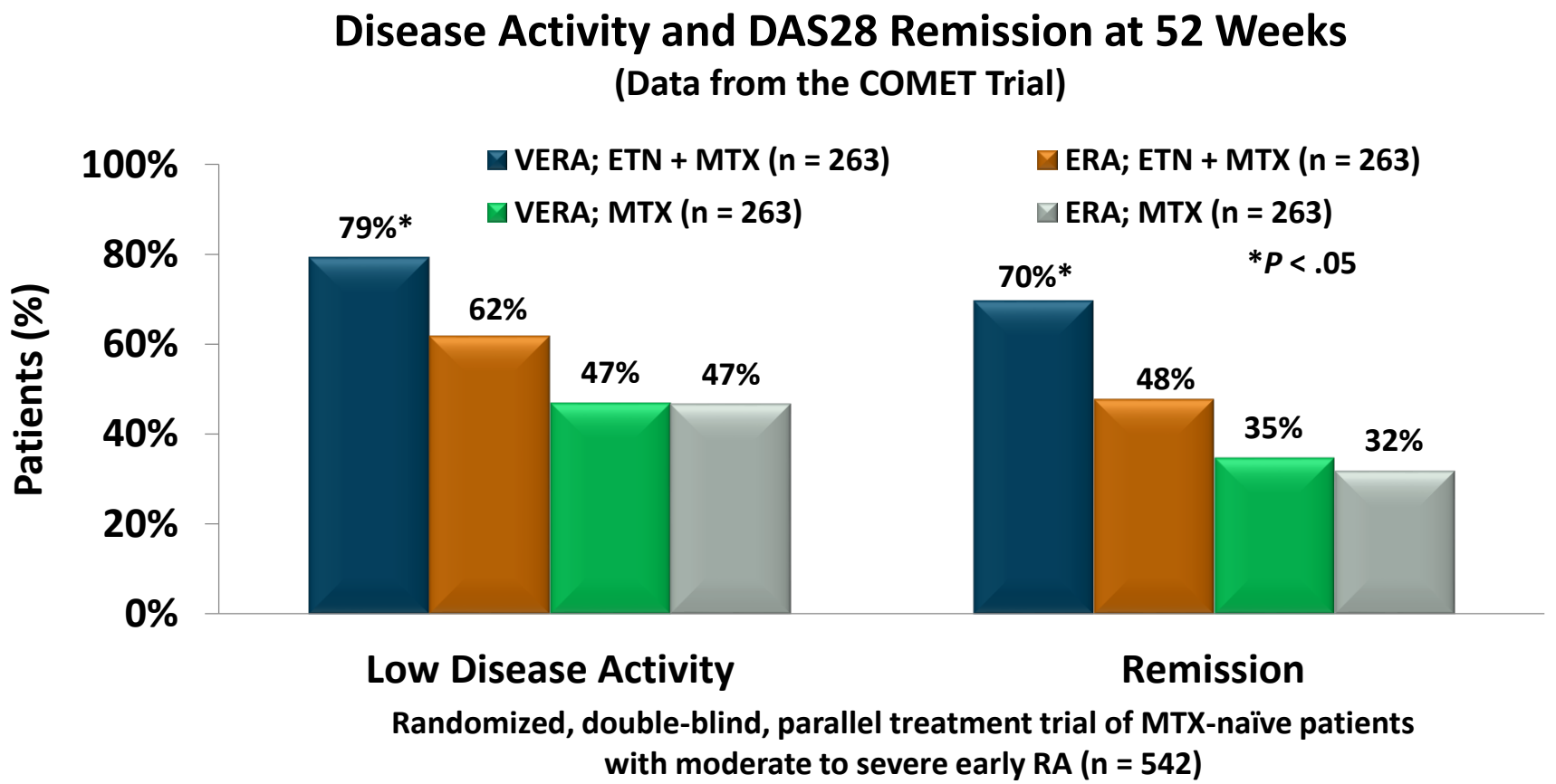
- Achieve minimal or no signs or symptoms of active inflammation

Achieve tight control

- Maintain a low level of disease activity over time through individualized therapy

Smolen JS, et al. *Ann Rheum Dis.* 2015;0:1-13.
Singh JA, et al. *Arthritis Care Res (Hoboken).* 2012;64:625-639.

Early and Aggressive Treatment Elicits Greater Disease Control

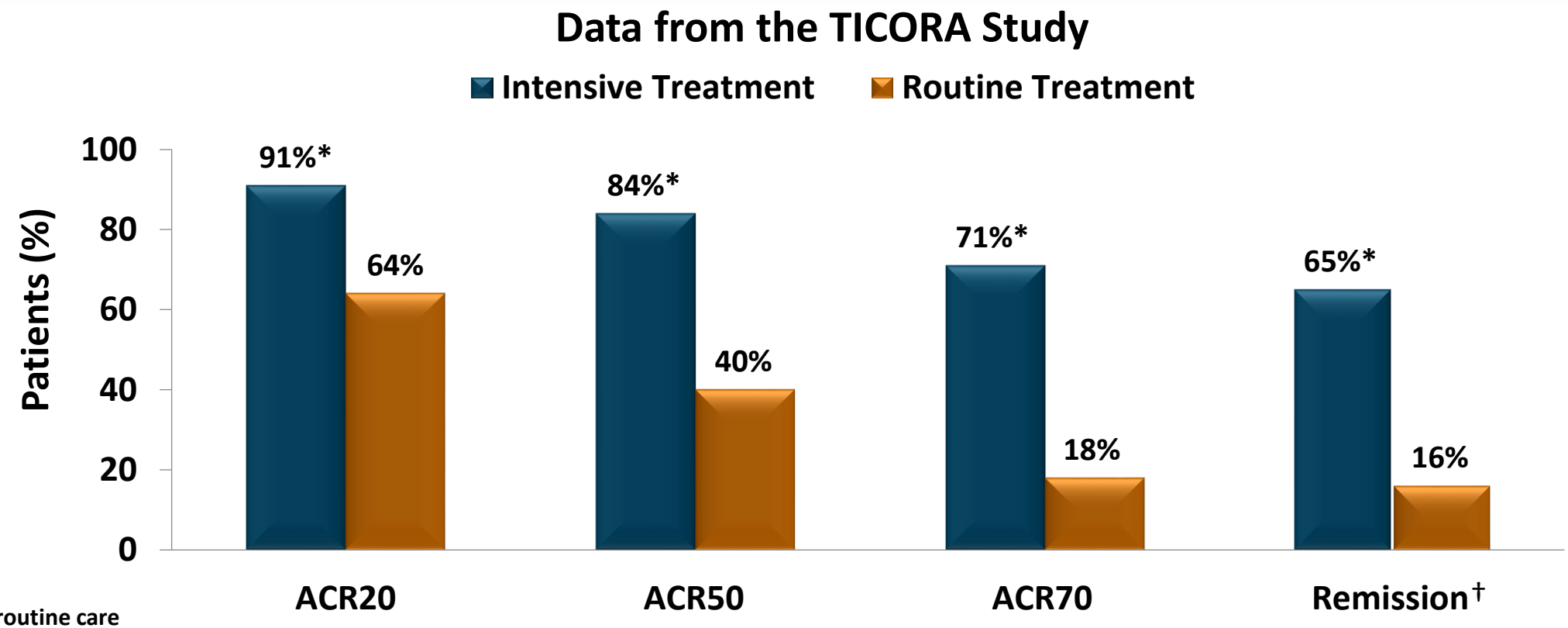


A higher proportions of patients with *very early* RA achieved low disease activity and remission when treated more aggressively

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, et al. *Ann Rheum Dis.* 2012;71:989-992.

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, et al. *Lancet*. 2004;364:263-269.

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, et al. *Arthritis Care Res* . 2014;66:190-196.

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, et al. *Ann Rheum Dis.* 2015;0:1-13. 2. Aletaha D, et al. *Arthritis Rheum.* 2010;62:2569-2581. 3. Hobbs KF, et al. *Rheumatology (Oxford).* 2012;51 Suppl 6:vi21-27. 4. Singh JA, et al. *Arthritis Care Res (Hoboken).* 2012;64:625-639. 5. Anderson J, et al. *Arthritis Care Res (Hoboken).* 2012;64:640-647.

Disease Activity Measures Provide Insight on Patient Response to Treatment

	ACR20	DAS28	SDAI	CDAI	ERAM	GAS	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, et al. *Rheumatology (Oxford).* 2012;51(Suppl 6):vi21-27.

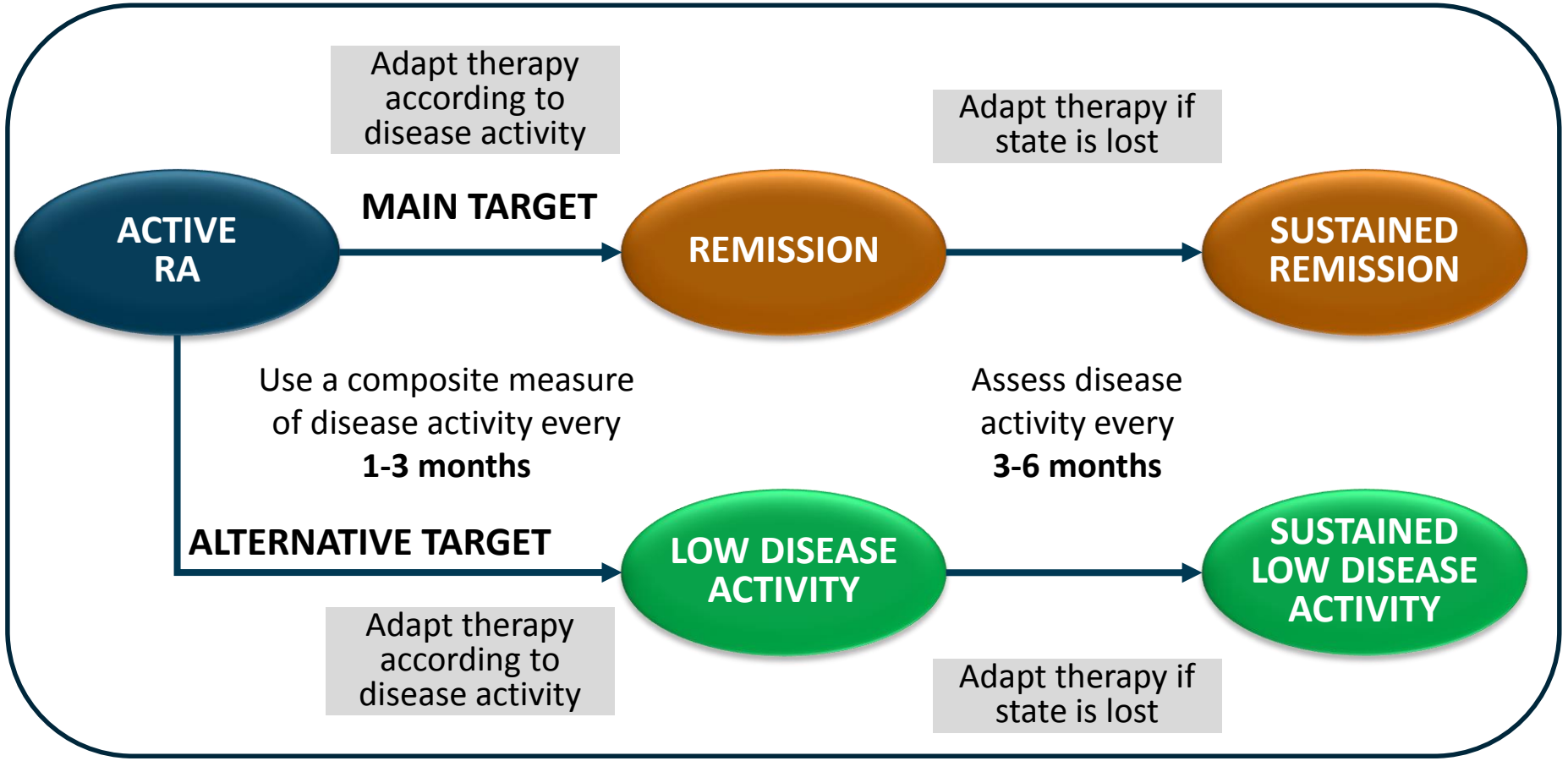
Routine Objective Measurement of Disease Activity Associated with Remission

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, et al. *Lancet*. 2004;364:263-269. 2. Goekoop-Ruiterman YP, et al. *Ann Intern Med*. 2007;146:406-415.

Treat-to-Target Algorithm



Smolen JS, et al. *Ann Rheum Dis.* 2015;0:1-13.

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 response to therapy, disease progression, and effect of different therapies on disease pathways

Rendas-Baum R, et al. *Arthritis Res Ther.* 2011;13:R25.

Pharmacologic Interventions

Corticosteroids

- Methylprednisolone
- Prednisone
- Prednisolone

Non-biologic DMARDs

- Azathioprine
- Hydroxycholorquine
- Leflunomide
- Methotrexate
- Sulfasalazine

Biologics

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

Nonbiologic Disease Modifying Antirheumatic Drugs

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

Currently Available 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 agent (selective costimulator inhibitor)
Tocilizumab[9]	2010	Actemra®	IV infusion or SC injection	IL-6 inhibitor
Tofacitinib[10]	2012	Xeljanz®	Oral	JAK inhibitor

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

1. Enbrel® [PI]. Thousand Oaks, CA: Amgen Inc.; 2015. 2. Remicade® [PI]. Horsham, PA: Janssen Biotech, Inc.; 2015. 3. Kineret® [PI]. Stockholm, Sweden: Swedish Orphan Biovitrium AB; 2012. 4. Humira® [PI]. North Chicago, IL: AbbVie Inc.; 2014. 5. Cimzia® [PI]. Smyrna, GA: UCB, Inc.; 2013. 6. Simponi® [PI]. Horsham, PA: Janssen Biotech, Inc.; 2014. 7. Rituxan® [PI]. S. San Francisco, CA: Genentech, Inc.; 2014. 8. Orencia® [PI]. Princeton, NJ: Bristol-Myers Squibb Company; 2015. 9. Actemra® [PI]. South San Francisco, CA: Genentech, Inc.; 2014. 10. Xeljanz® [PI]. New York, NY: Pfizer, Inc.; 2015.

Emerging RA Therapies

Drug	Mechanism of Action	Dosing and Administration	Status
Baricitinib (LY3009104)	JAK1/2 inhibitor	Once daily oral dosing	Phase 3
Secukinumab (Cosentyx®)	IL-17A antagonist	Monthly subcutaneous injection	Phase 3
Ixekizumab (LY2439821)		Subcutaneous injection	Phase 2
Sarilumab	IL-6 receptor antagonist	Subcutaneous injection	Phase 3
Sirukumab		Subcutaneous injection	Phase 3

IL=interleukin; JAK=Janus kinase; RA=rheumatoid arthritis.

Jacques P, Van den Bosch F. *Expert Opin Emerg Drugs.* 2013;18:231-244.

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

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Current Practice Guidelines Review

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Principal, FountainHead HealthCare

Chief Medical Officer, EmpiraMed, Inc.

Faculty Disclosure

- The ***faculty*** reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

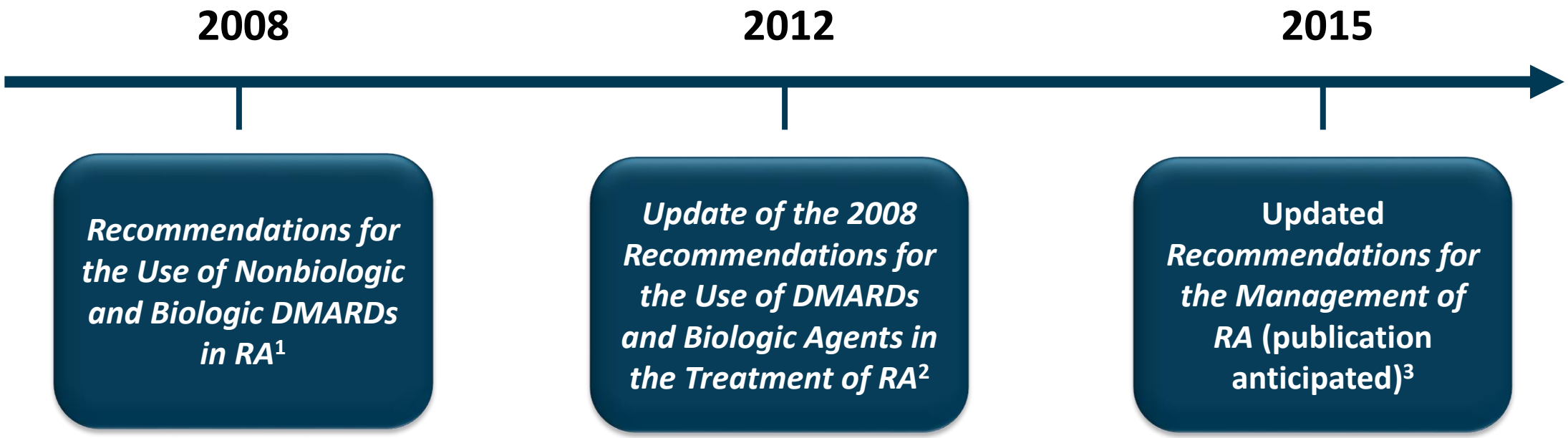
  Neil Minkoff, MD

  - *Consulting Fees*: Bayer Corporation, Boehringer Ingelheim, EMD Serono, Inc., Novartis Pharmaceuticals Corporation, Novo Nordisk, Inc., Salix Pharmaceuticals, Inc., Sanofi US, UCB, Inc., Vertex Pharmaceuticals Incorporated

Outline

- Current American College of Rheumatology (ACR) RA Treatment Guidelines
- Principles guiding the 2015 revision of the document
- Anticipated revisions

American College of Rheumatology RA Treatment Recommendations



DMARDs=disease-modifying antirheumatic drugs.

1. Saag KG, et al. *Arthritis Rheum.* 2008;59(6):762-784. 2. Singh JA, et al. *Arthritis Care Res (Hoboken).* 2012;64(5):625-639. 3. American College of Rheumatology website. http://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Rheumatoid-Arthritis. Accessed September 10, 2015.

Principles Guiding the 2015 Updates

- Focus on common or everyday patients, not exceptional cases
- Optimal dose of medication should be given for 3 months before escalating dose or switching to a new therapy
- Disease activity measurement using one of the ACR recommended measures should be performed in a majority of encounters
- Cost is considered as one of the many possible conditions for the recommendations
- MTX is the initial therapy prescribed for most RA patients
- All RA patients should see a rheumatologist
- Limit corticosteroid treatment to the lowest effective dose for shortest possible time

ACR=American College of Rheumatology; MTX=methotrexate.

First Report Managed Care website. http://www.firstreportnow.com/articles/preview-updated-2015-draft-guidelines-ra-acr-conference-highlight. Accessed September 10, 2015.

Anticipated 2015 ACR Guideline Updates: Employ a Treat-to-Target Approach

Targets

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

Functional Assessment

- **Routine functional assessment using standardized, validated tools**
- **Conducted at least once per year and more often in active RA**

Singh J. Presented at the American College of Rheumatology 2014 Annual Meeting. November 16, 2014.

Anticipated 2015 ACR Guideline Updates: RA Treatment and Comorbidities

- Guidance is anticipated on the approach to treatment in RA patients with
  - Melanoma
  - Lymphoproliferative disorders
  - Hepatitis infection
  - Congestive heart failure
- Guidance will also be provided on the use of biologic therapy and the timing of vaccination

Singh J. Presented at the American College of Rheumatology 2014 Annual Meeting. November 16, 2014.

Anticipated 2015 ACR Guideline Updates: Therapeutic Selection and Sequencing

- Methotrexate remains first-line therapy for all patients
- Corticosteroids should be used at the lowest possible dose for the shortest possible time
- DMARD failure → combination of traditional DMARDs, TNF inhibitor, non-TNF-inhibitor biologic, or tofacitinib (± methotrexate)
- TNF failures
  - Failure of a single TNF inhibitor → another TNF inhibitor or a non-TNF biologic (± methotrexate)
  - Failure of multiple TNF inhibitors → non-TNF-inhibitor biologic or tofacitinib (± methotrexate)

Singh J. Presented at the American College of Rheumatology 2014 Annual Meeting. November 16, 2014.

Anticipated 2015 ACR Guideline Updates: Therapeutic Selection, Sequencing, and Tapering

- Non-TNF biologic failure
  - Failure of a single non-TNF inhibitor biologic → another non-TNF inhibitor biologic or tofacitinib (± methotrexate)
  - Failure of multiple non-TNF inhibitor biologics → tofacitnib or TNF inhibitor biologic (± methotrexate)
- Switching from one therapy to another should only be done at the discretion of the treating physician in consultation with the patient
- Patients with established RA in remission continuing on methotrexate can taper traditional DMARD therapy, TNF inhibitor, non-TNF biologic, or tofacitinib

Singh J. Presented at the American College of Rheumatology 2014 Annual Meeting. November 16, 2014.

Summary

- The updated ACR RA treatment guidelines are expected to emphasize
  - Treating-to-target in both early and established RA
  - Goal is to achieve low disease activity or remission
  - Individualizing treatment
  - Using an optimal dose for 3 months before escalating or switching therapy
  - Routinely assessing disease activity
  - Treating patients with comorbid conditions
  - Tapering of therapy in patients in established remission

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Current and Emerging CER for Evidence-Based Treatment and Benefit Design Decision Making

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  Jeffrey Dunn, PharmD, MBA

  - *Consulting Fees*: Amgen Inc., Pfizer Inc.

Outline

- Overview of comparative effectiveness research (CER)
- Data sources
- Application of CER as a decision support tool

Why Don’t Patients Receive the “Best” Treatments?

Differing underlying assumptions and study designs make comparison of clinical trial results difficult

Confounding variables include

Presence of comorbidities	**Patient age**	**Health reimbursement system**	**Year in which costs are determined**	**Variation in study design**

Why Comparative Effectiveness Research (CER)?

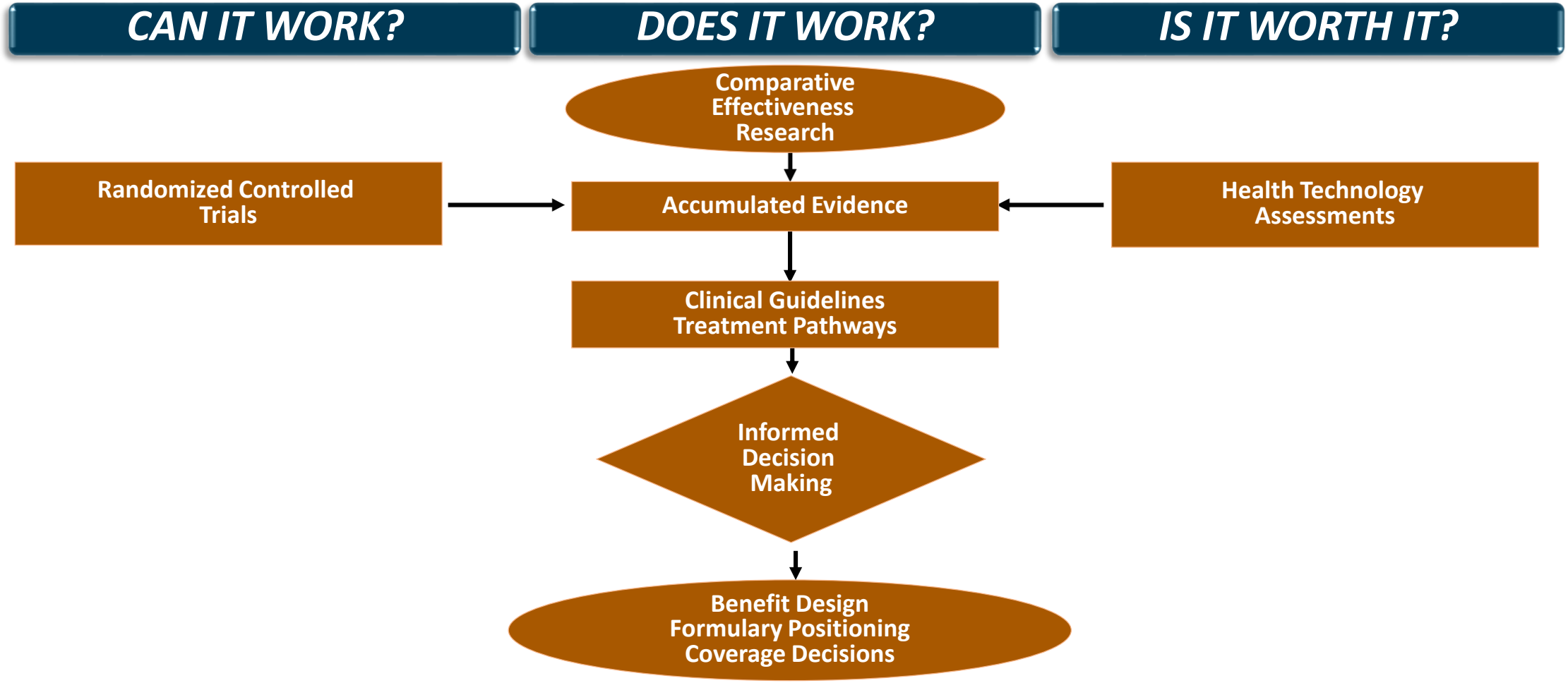
- Pharmacists, physicians, payers, policy makers, and patients must often rely on incomplete data when making health care decisions
- Lack of head-to-head comparisons of competing treatment alternatives can lead to a “trial and error” approach to decision-making
- If effectively designed and conducted, CER can help fill data gaps
  - Used to compare drug therapies in the absence of head-to-head data
  - Applicable to a wide variety of practice settings and diversity of patients

Brixner DI, Oderda G. *J Manag Care Pharm*. 2012;18(Suppl. 4-a):S3-S4.

CER is Not a New Phenomenon

- CER existed before the recent legislative push for health care reform
- Health care decision makers have always compared one treatment with another
- The rise in health care costs has led to renewed emphasis on comparative effectiveness and cost-effectiveness
- Introduction of novel, efficacious, and expensive treatments has led to an increased emphasis on comparing treatments
  - Medications with each other
  - Procedures with each other
  - Procedures compared with medications or physical treatments (exercise, physical therapy, etc)

CER Utilized to Differentiate the Effectiveness vs Efficacy of Treatment Alternatives



Drummond MF, et al. *Int J Technol Assess Health Care*. 2008;24:244-258.

CER Consolidates Evidence From Multiple Sources

- Prospective observational studies
- Peer-reviewed and published retrospective analyses of healthcare data including:
  - Medical or pharmacy claims
  - Electronic health records
  - Registries

Ahmann A. *Am J Manag Care.* 2011;17(2 suppl):S41-S51.
Malone DC. *Am J Pharm Benefits.* 2010;2:301-303.

CER Consolidates Evidence From Multiple Sources (cont'd)

- Systematic reviews/meta-analyses
- Agency for Healthcare Research and Quality (AHRQ) CER reviews
- Cochrane reviews
- Accessible health technology assessment reports (eg, the National Institute for Health and Clinical Excellence [NICE])
- Tailored reviews (technology assessments) using published data
- In-house data analysis

Ahmann A. *Am J Manag Care.* 2011;17(2 suppl):S41-S51.
Malone DC. *Am J Pharm Benefits.* 2010;2:301-303.

CER: How Can it Change Practice?

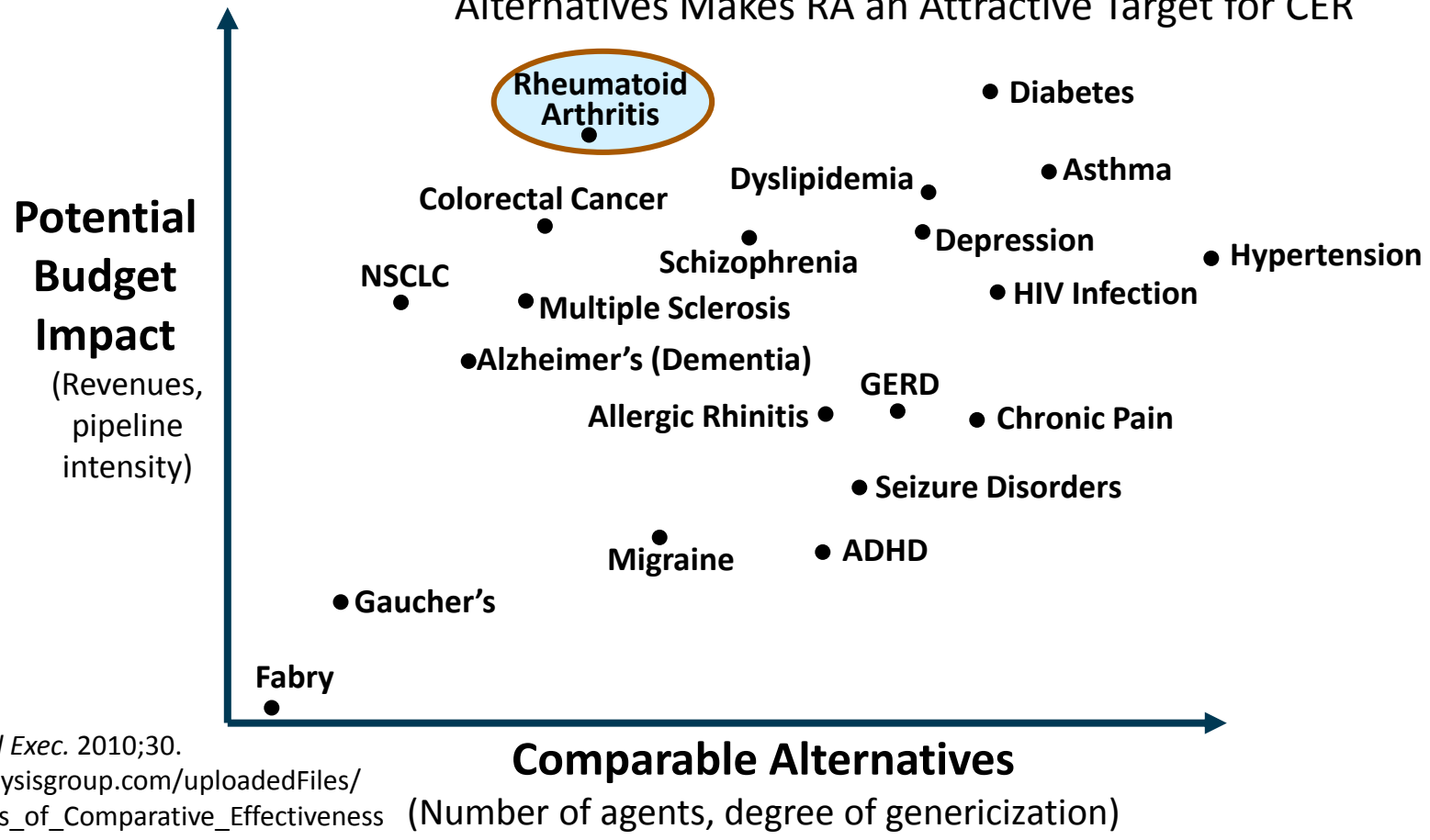
- Establishing parameters to measure improvements
  - Outcomes
  - Reduction in costs
  - Increase in value
- Determining threshold of positive effect to alter current behavior
  - Patients
  - Providers
  - Payers

Zwelling L. Comparative effectiveness research: how can it change practice? http://healthaffairs.org/blog/2011/04/18/comparative-effectiveness-research-how-can-it-change-practice/. April 18, 2011. Accessed September 22, 2015.

Application of CER to Rheumatoid Arthritis

RA is a Prime Target for Comparative Effectiveness Research

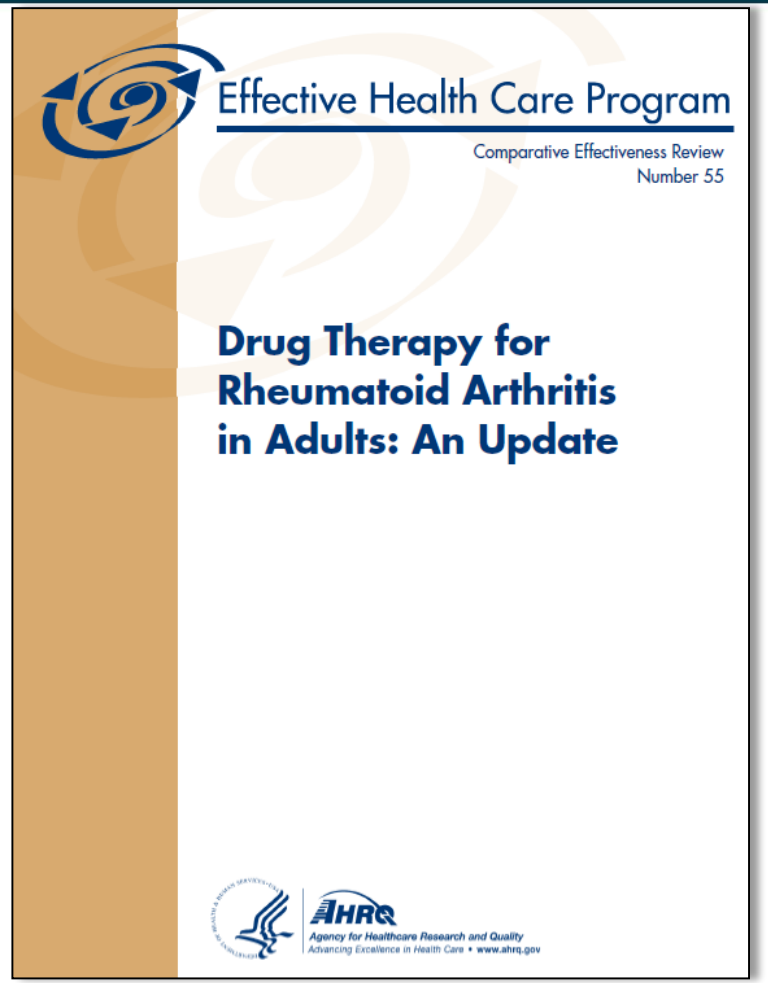
High Budget Impact and Lack of Clear Clinical Superiority Among Biologic Alternatives Makes RA an Attractive Target for CER



Tuttle E, et al. *Pharmaceutical Exec.* 2010;30. Available at: http://www.analysisgroup.com/uploadedFiles/Publishing/Articles/The_Fruits_of_Comparative_Effectiveness.pdf. Accessed September 22, 2015.

AHRQ CER Review Drug Therapy For RA (June 2012)

- Clinical questions addressed include:
  - Do drug therapies for RA differ in their ability to reduce disease activity, to slow or limit the progression of joint damage, or to maintain remission?
  - Do RA drugs differ in their ability to improve patient-reported symptoms, functional capacity, or quality of life?
  - Do RA drugs differ in harms, tolerability, patient adherence, or adverse effects?
  - What are the comparative benefits and harms of drug therapies for RA in subgroups of patients, based on stage of disease, prior therapy, demographics, concomitant therapies, or comorbidities?



Donahue KE, et al. Comparative Effectiveness Review No. 55. Available at: http://effectivehealthcare.ahrq.gov/ehc/products/203/1044/CER55_DrugTherapiesforRheumatoidArthritis_FinalReport_20120618.pdf. Accessed September 22, 2015.

CER Results: Biologic DMARDs

Benefits	Adverse Events
Biologic DMARDs provide greater symptom response and remission rate vs. oral DMARDs for patients with longstanding active RA requiring a change in therapy.	Risk of serious infections increases when patients are treated with biologic DMARDs.
Combining two biologic DMARDs (etanercept with abatacept or anakinra) does improve disease activity, functional capacity, or symptom response more than one biologic DMARD and increases the risk of serious adverse effects.	Combining two biologic DMARDs leads to substantially higher rates of serious adverse events (AEs) than monotherapy.
Comparisons across studies of patients resistant to MTX suggest that there may be clinically observable differences in the efficacy of the biologic DMARDs.	Rate of AEs did not increase over time in long-term studies of adalimumab, anakinra, etanercept, and infliximab.
	No consistent evidence of elevated risk of lymphoma or other cancer types associated with biologic DMARDs (vs oral DMARDs or placebo); actual risk not clear.
	Evidence is insufficient to permit conclusions about differences in risks for rare but serious AEs among biologic DMARDs (demyelination, autoimmunity, hepatotoxicity).

Donahue KE, et al. Comparative Effectiveness Review No. 55. Available at: http://effectivehealthcare.ahrq.gov/ehc/products/203/1044/CER55_DrugTherapiesforRheumatoidArthritis_FinalReport_20120618.pdf. Accessed September 22, 2015.

CER Results: Combining Oral and Biologic DMARDs

Benefits	Adverse Events
In patients with inadequate disease control who required a change in treatment, combination therapy with a biologic DMARD and MTX achieved greater improvements in some outcomes than either a biologic DMARD or MTX alone.	Combining MTX or other oral DMARDs with a biologic DMARD does not alter the adverse event (AE) rate found with the biologic DMARD alone.
In patients whose RA failed to respond to first-line MTX, combination therapy with MTX and a biologic DMARD was not more successful than monotherapy with a biologic DMARD.	Combining MTX and biologic DMARDs demonstrates a better tolerability profile than MTX alone.
In MTX-naive patients or those not recently on MTX, combination therapy is superior to monotherapy with a biologic DMARD for functional capacity and quality of life.	The evidence is insufficient to estimate differences in rates of specific AEs between the biologic and oral DMARDS.

Donahue KE, et al. Comparative Effectiveness Review No. 55. Available at: http://effectivehealthcare.ahrq.gov/ehc/products/203/1044/CER55_DrugTherapiesforRheumatoidArthritis_FinalReport_20120618.pdf. Accessed September 22, 2015.

CER Results: DMARDs For Patients With Early RA

Benefits	Adverse Events
Combination strategies that use corticosteroids plus 2 to 3 oral DMARDs are more effective than oral DMARD monotherapy for improving symptom response, disease activity, and functional capacity in the short-term and reducing radiographic evidence of progression and joint erosion in the longer term (≥1 year).	Adding prednisone to treatment with one or multiple oral DMARDs does not increase treatment discontinuation rates.
Combining one oral DMARD with prednisone reduces radiographic progression and joint erosion more than the DMARD alone.	Combining oral DMARDs (sulfasalazine and MTX) increases withdrawal from treatment due to adverse events.
For MTX-naive patients with early, aggressive RA, combining MTX with a biologic DMARD (abatacept, adalimumab, etanercept, or infliximab) provides greater improvement than biologic DMARD monotherapy for symptom response, clinical remission rates, and radiographic progression	

Donahue KE, et al. Comparative Effectiveness Review No. 55. Available at: http://effectivehealthcare.ahrq.gov/ehc/products/203/1044/CER55_DrugTherapiesforRheumatoidArthritis_FinalReport_20120618.pdf. Accessed September 22, 2015.

CER in Formulary and Benefit Design: How to Evaluate Without Head-to-Head Trials

- Identify and target key trials with similar patient characteristics, outcome measures, inclusion/exclusion criteria, etc.
- Evaluate drug benefit minus placebo benefit over defined time frame of defined and appropriate outcome measure(s)
- Determine appropriate costs over same time period
- Divide cost into drug benefit
- Compare cost to achieve predefined response
  - "How much do we pay for an outcome with all of the drugs?"
- Have to hold industry accountable

Summary

- Incomplete data can impact decision-making in health care decisions
- Comparative effectiveness research can be utilized to generate and/or synthesize data to support health care decision-making
  - Intent of CER is to describe whether a treatment works for the average patient in the average practice
- CER requires valid and feasible data from multiple sources
- A comprehensive CER analysis of 211 studies of drugs used to treat RA was conducted by the AHRQ

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Analyzing the Available Data to Assess the Value of Current and Emerging Treatment Options

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Professor and Vice Chair for Academic Affairs PHSR

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Faculty Disclosure

- The ***faculty*** reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

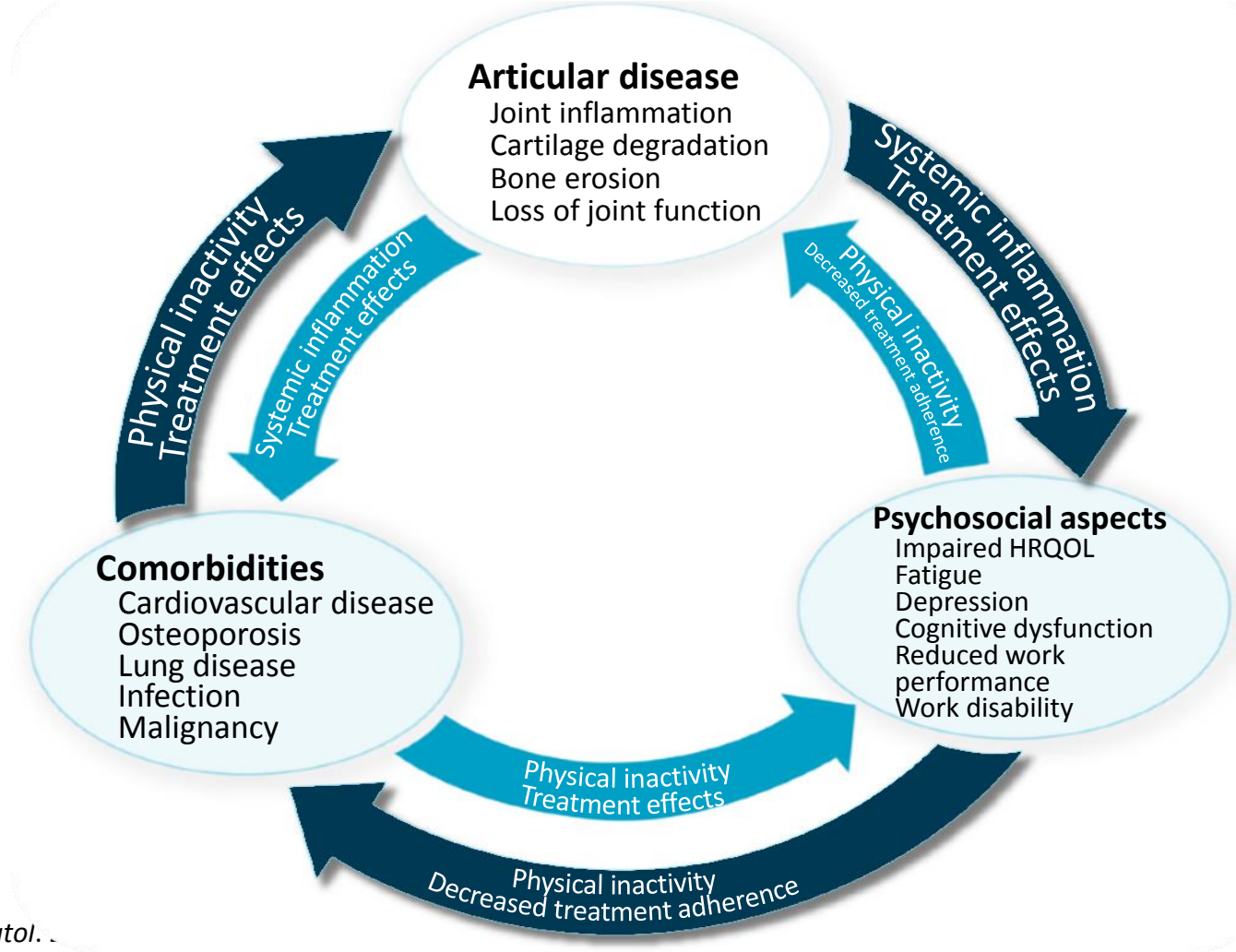
  Fadia Tohme-Shaya, PhD, MPH

  - No financial interest/relationships relating to the topic of this activity

Outline

- Clinical and economic burden of rheumatoid arthritis (RA)
- Determining the value of current and emerging RA treatment regimens
- Application to patient care and managed care decision-making

RA Disease Burden Extends Beyond the Joint



Cutolo M, et al. *Sem Arthritis Rheumatol*.

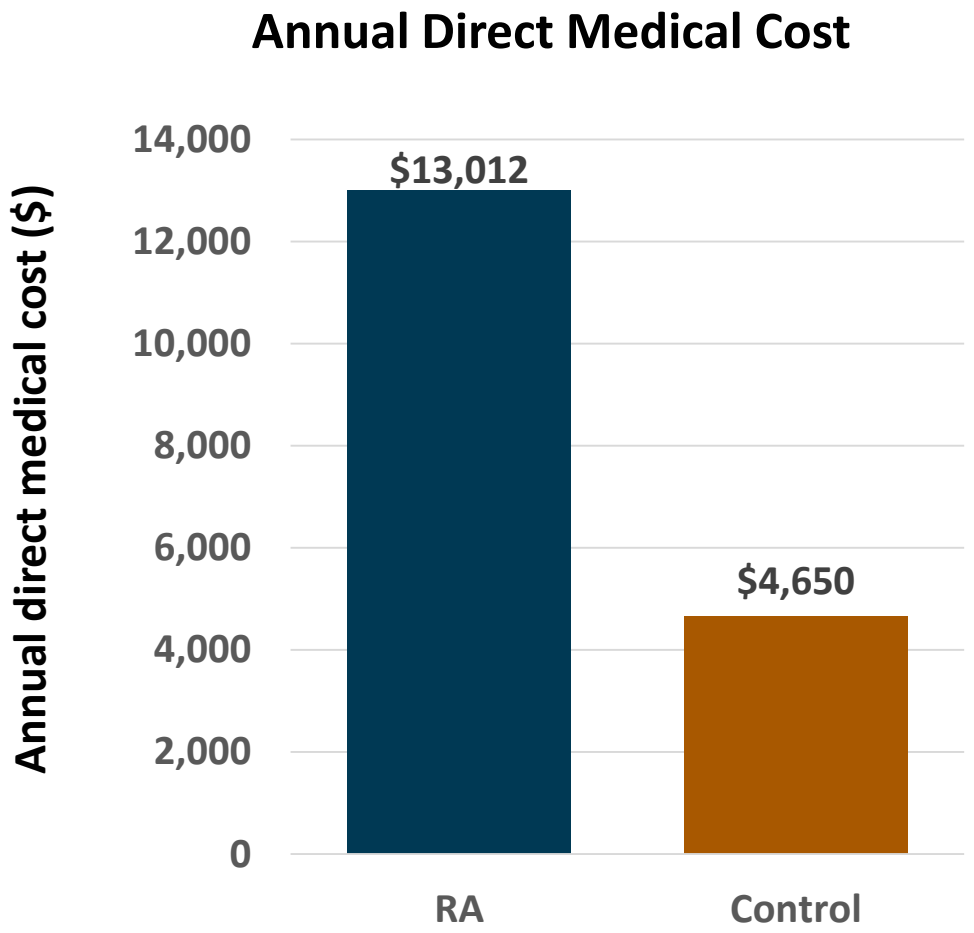
Clinical Burden of RA

- **Prevalence**: ~0.5 to 1.0% of the US population[1]
- **Ambulatory care events**: 2.9 million ambulatory care visits
- **Hospitalizations**: >15,000 hospitalizations with RA listed as the principle diagnosis
- **Cardiovascular (CV) risk**: 5x higher CV event rate vs general population
- **Disability**: Many RA patients are unable to work within 10 years of onset
  - Pre-biologic era: 50%[2]
  - Current: 26%[3]
- **Excess deaths**: Mortality rate is 1.5 to 1.6-fold higher in RA patients vs general population

1. Centers for Disease Control. http://www.cdc.gov/arthritis/basics/rheumatoid.htm. 2015. Accessed September 24, 2015.
2. Yelin E, et al. *Ann Intern Med*. 1980;93:551–556.
3. Verstappen SM, et al. *Rheumatology*. 2010;49:1570-1577.

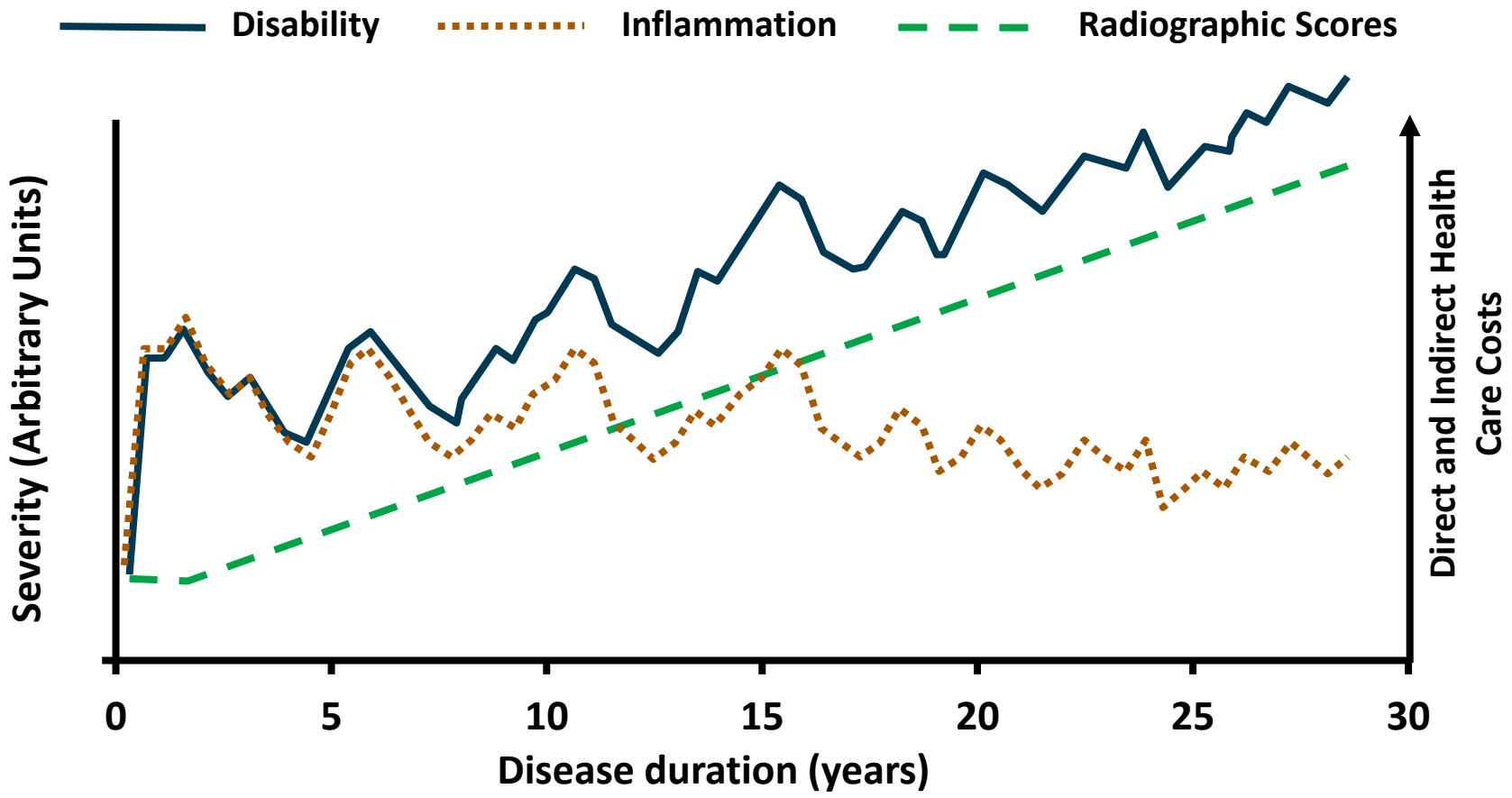
Economic Burden of RA

- RA exerts considerable incremental economic burden on the health care system
- Excess costs include expenditures on
  - Pharmacy
  - Office visits
  - Emergency care
  - Inpatient stays
- Total incremental expenditure of all RA patients: ~$22.3 billion



Kawatkar AA, et al. *Arth Care Res*. 2012;64:1649-1656.

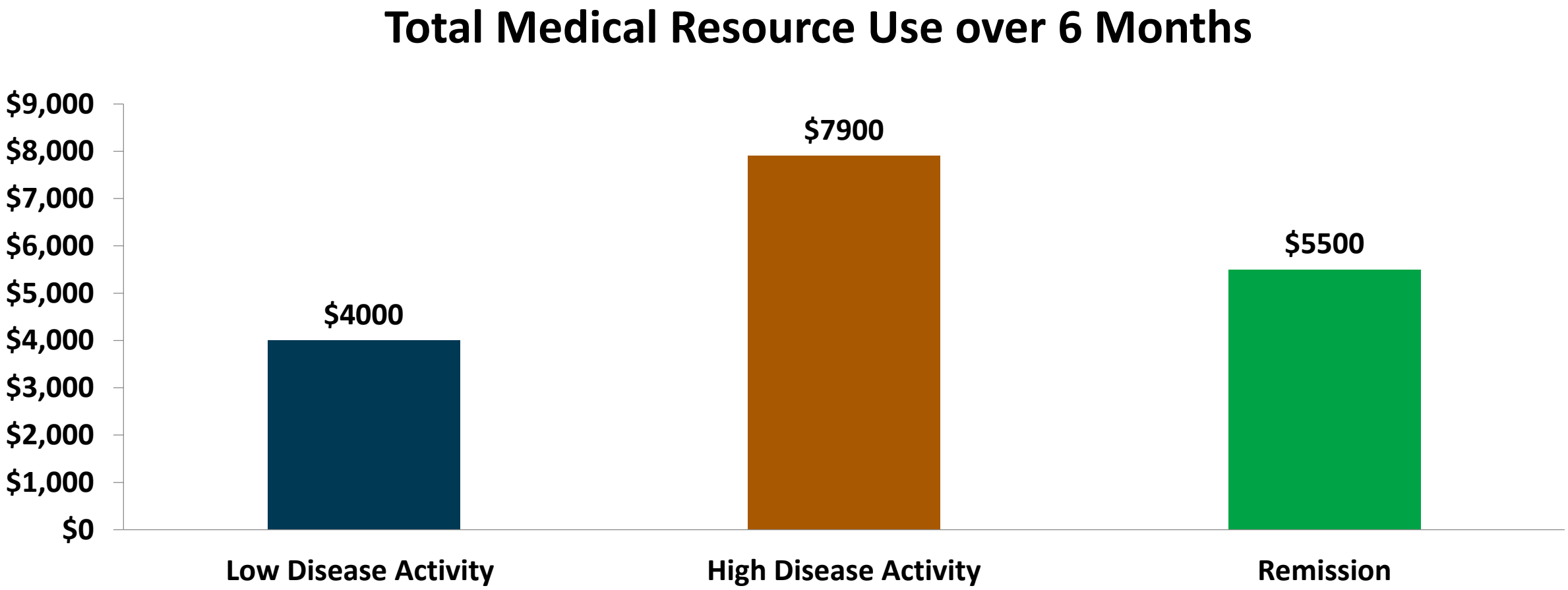
Cost of RA Treatment Increases Over Time as Function Declines



Kirwan J. *J Rheumatol*. 1999;26:720-725.
Wolfe F, Cathey MA. *J Rheumatol*. 1991;18:1298-1306.
Fautrel B. *Rheumatology*. 202;51:iv21-iv26.

*50% rates of loss of function based on Health Assessment Questionnaire (HAQ) scores.

Medical Resource Utilization is Highest in Patients with Highly Active RA



Beresniak A, et al. *Clin Exp Rheumatol*. 2013;31:400-408.

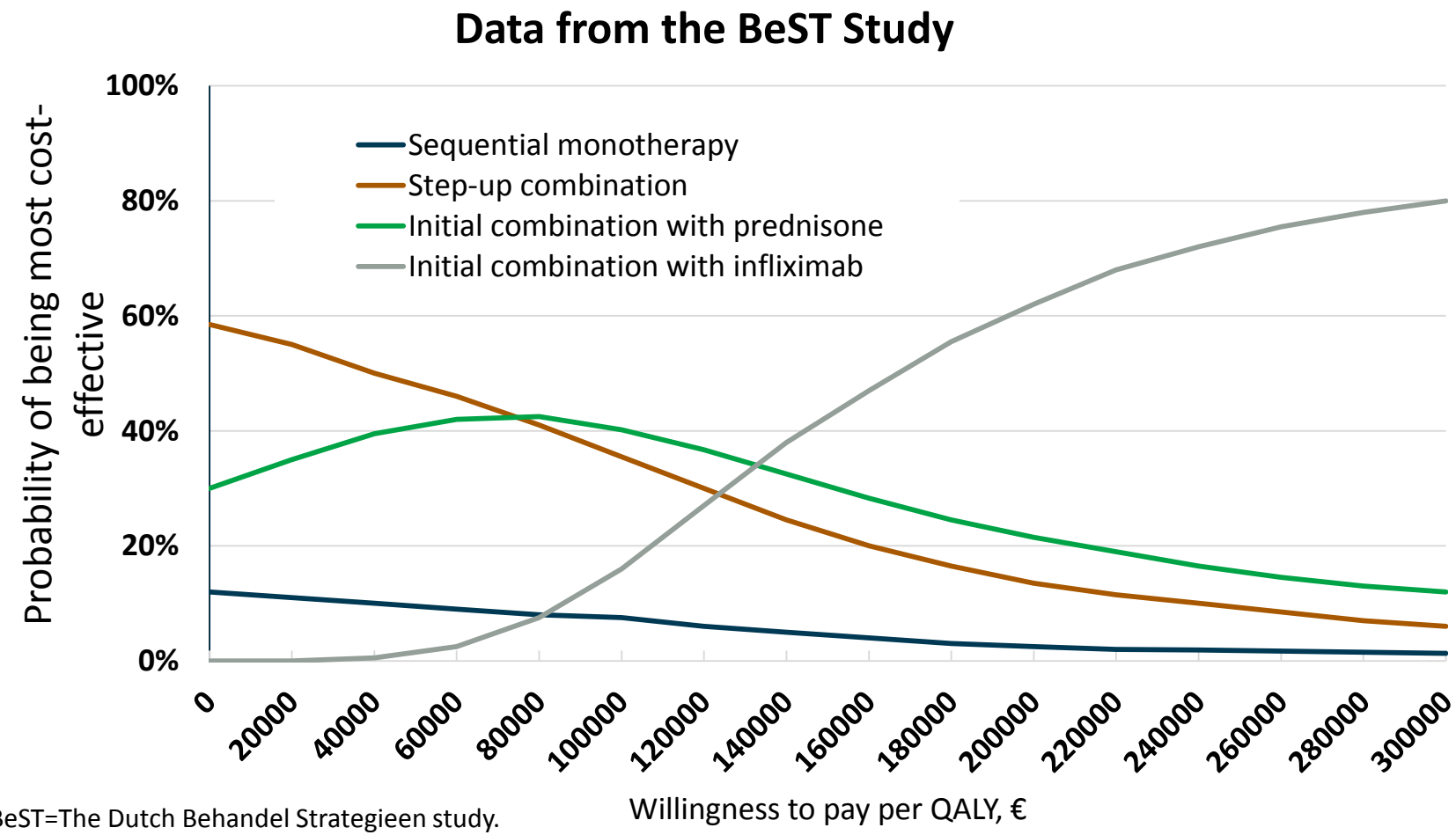
Determining the Value of RA Treatment Options

Determining the Value of RA Treatments

- The relatively high cost and expanding use of biologics make them an important target for economic evaluation
- Economic evaluation tools include
  - Cost-effectiveness analysis (CEA) compares the cost and effectiveness of two or more treatments
  - Cost-utility analysis (CUA) is a subtype of CEA, applying quality-adjusted life-years (QALY) as a measure of effectiveness
    - Primary outcome measure in CUA is the incremental cost-effectiveness ratio (ICER)
    - ICER describes the ratio of the additional costs of a treatment (vs an alternative) to QALYs gained

Joensuu JT, et al. *PLoS ONE*. 10(3): e0119683. doi:10.1371/journal.

Biologics Do Not Appear to be Cost-Effective as First Line Therapy



- Anti-TNF agents are less cost-effective vs conventional DMARDs for newly diagnosed, treatment-naïve patients[1,2]

BeST=The Dutch Behandel Strategieen study.

1. Tsao NW, et al. *Best Pract Res Clin Rheumatol*. 2012;26:659-676.
2. van den Hout WB, et al. *Arthritis Rheum*. 2009;61:291-299.

ICERs Favor Treatment with Conventional DMARDs in the First Line

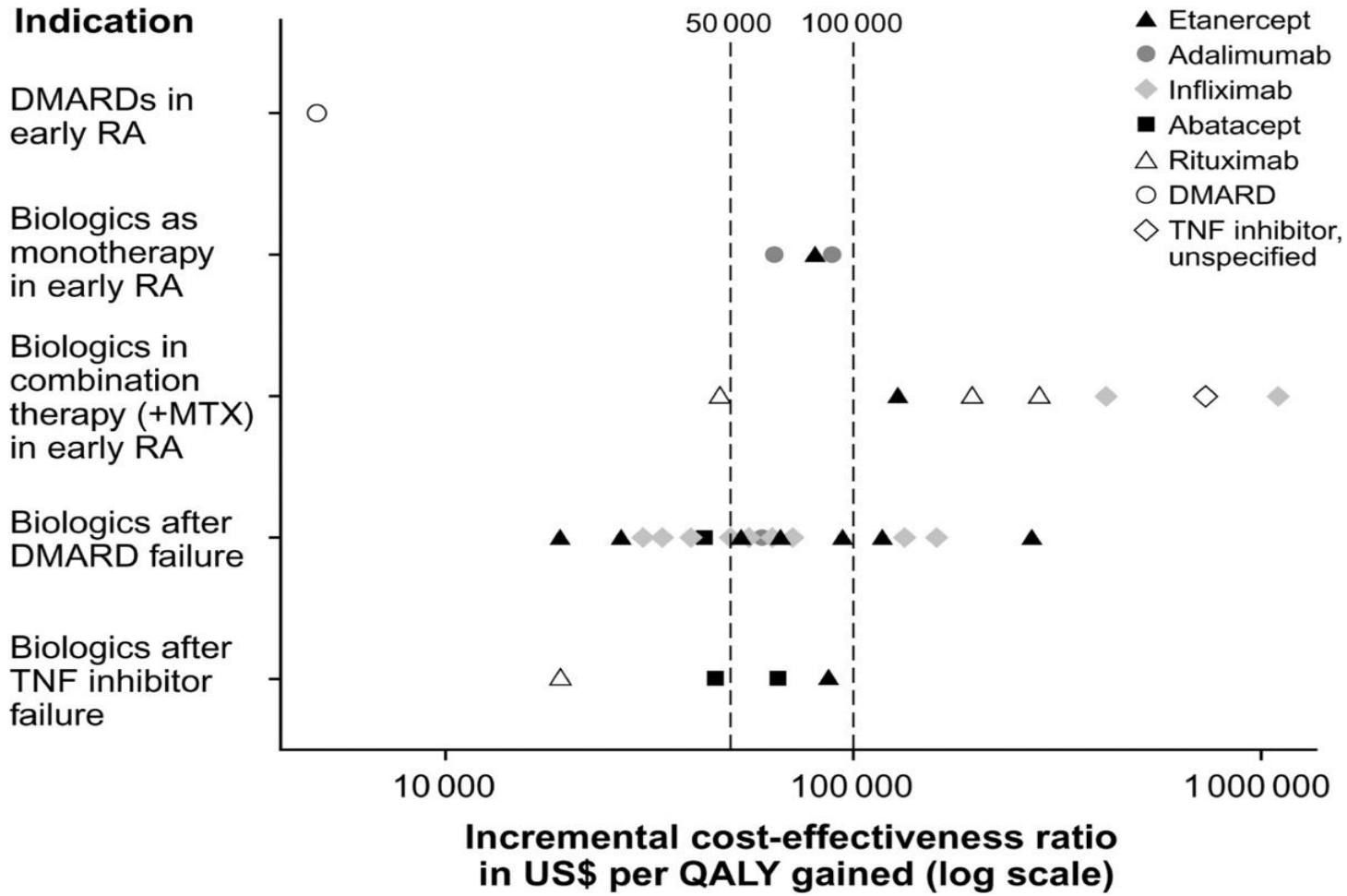
Cost Utility Analyses

Conventional DMARD vs	ICER ($/QALY)
	Payer Perspective
Adalimumab	$63,281 to $382,982/QALY
Infliximab	$71,936 to $1,464,344/QALY
Etanercept	$110,389 to $175,721/QALY
TNFa inhibitors (class)	$139,744
	Societal Perspective
Infliximab	$141,827
TNFa inhibitors (class)	$137,843

- These (and similar) findings lead most payers to require a trial of conventional DMARDs in treatment-naïve patients

Tsao NW, et al. *Best Pract Res Clin Rheumatol*. 2012;26:659-676.

Biologics Begin to Be Cost Effective After Failure of a Conventional DMARD



- Early treatment should be with nonbiologic therapies
- Biologic treatments become cost effective after failure of therapy a conventional DMARD

Schoels M, et al. *Ann Rheum Dis*. 2010;69:995-1003.

ICERs Favor Treatment with Biologics in DMARD Inadequate Responders (IR)

Sequential use/switching to another DMARD vs	ICER ($/QALY) Payer Perspective
Tocilizumab	$29,654/QALY
Abatacept	$58,376/QALY
Etanercept	$32,465 to $154,057/QALY
Adalimumab	$33,396 to $317,650/QALY
Infliximab	$37,225 to $313,144/QALY
TNFa inhibitors (class)	$53,802 to $291,531/QALY
Societal Perspective	
Infliximab	$59,924/QALY
Etanercept	$25,727 and $76,089/QALY
Adalimumab	$34,183/QALY
Tocilizumab	$29,707/QALY

Tsao NW, et al. *Best Pract Res Clin Rheumatol*. 2012;26:659-676.

Cost-effective Strategy in the Treatment of TNF-IR Patients

- Anti-TNF agents are frequently used sequentially in case of an inadequate response (IR) or intolerance to another anti-TNF agent
- Switching between biologic agents is common in medical practice
  - However, there is limited evidence that compares the overall costs and effectiveness of such a strategy

Beresniak A, et al. *Clin Exp Rheumatol*. 2013;31:400-408.

Cost-effective Strategy in the Treatment of TNF-IR Patients

Sequential use/switching to another anti-TNF vs	ICER ($/QALY)
	Payer Perspective
Abatacept	$78,303 to $270,539/QALY
Rituximab	$26,314 to $40,868/QALY

- Rituximab was found to be the most cost-effective alternative compared to other biologics among the patients with an insufficient response to an anti-TNF agent

Tsao NW, et al. *Best Pract Res Clin Rheumatol*. 2012;26:659-676.

Cost-effectiveness of JAK Inhibitors as First Line Therapy

- Comparison of treatment of patients with moderate-to-severe RA using an anti-TNF agent or an oral JAK inhibitor
- Cost-utility analysis (societal perspective) of the phase 3 placebo-controlled Oral Rheumatoid Arthritis Trial (ORAL)
  - Efficacy assessed using ACR response rates, converted to the changes in Health Assessment Questionnaire-Disability Index (HAQ-DI) score
  - HAQ-DI scores were mapped onto utility values to calculate outcomes in terms of quality-adjusted life-years (QALYs)
  - Costs were analyzed from a societal perspective
  - Cost-effectiveness is presented in ICERs

Lee MY, et al. *Clin Ther*. 2015;37:1662-1676.

1st Line Treatment with Oral JAK Inhibitors in Moderate-to-Severe RA Appears to be Cost-effective

- 1st line use of oral JAK inhibitors increased QALYs gained vs standard-of-care, resulting in an ICER of ~$13,000 per QALY
  - Treatment with the oral JAK inhibitor also increased costs and QALYs gained when incorporated as a 2nd, 3rd, or 4th line therapy
- JAK inhibitor-associated increases in costs were attributable to the increased lifetime drug costs
- Sensitivity analyses yielded ICERs in the range of ~$6,000 to $32,000/QALY
- From a societal perspective, the inclusion of an oral JAK inhibitor as a treatment strategy for moderate-to-severe RA is cost-effective

Lee MY, et al. *Clin Ther*. 2015;37:1662-1676.

Summary

- RA is associated with significant clinical and economic costs
- Anti-TNF agents are less cost-effective options for 1st line treatment vs conventional DMARDs
- Treatment with an anti-TNF agent in patients refractory to previous DMARD therapies is more cost-effective, vs switching to another conventional DMARD
- In TNF-IR patients, rituximab appears to be more cost-effective than switching to another anti-TNF agent
- Treatment with an oral JAK inhibitor for moderate-to-severe RA appears to be cost-effective across the treatment sequence

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Plan Benefit Designs: Maximizing Value for Current and Emerging RA Therapies

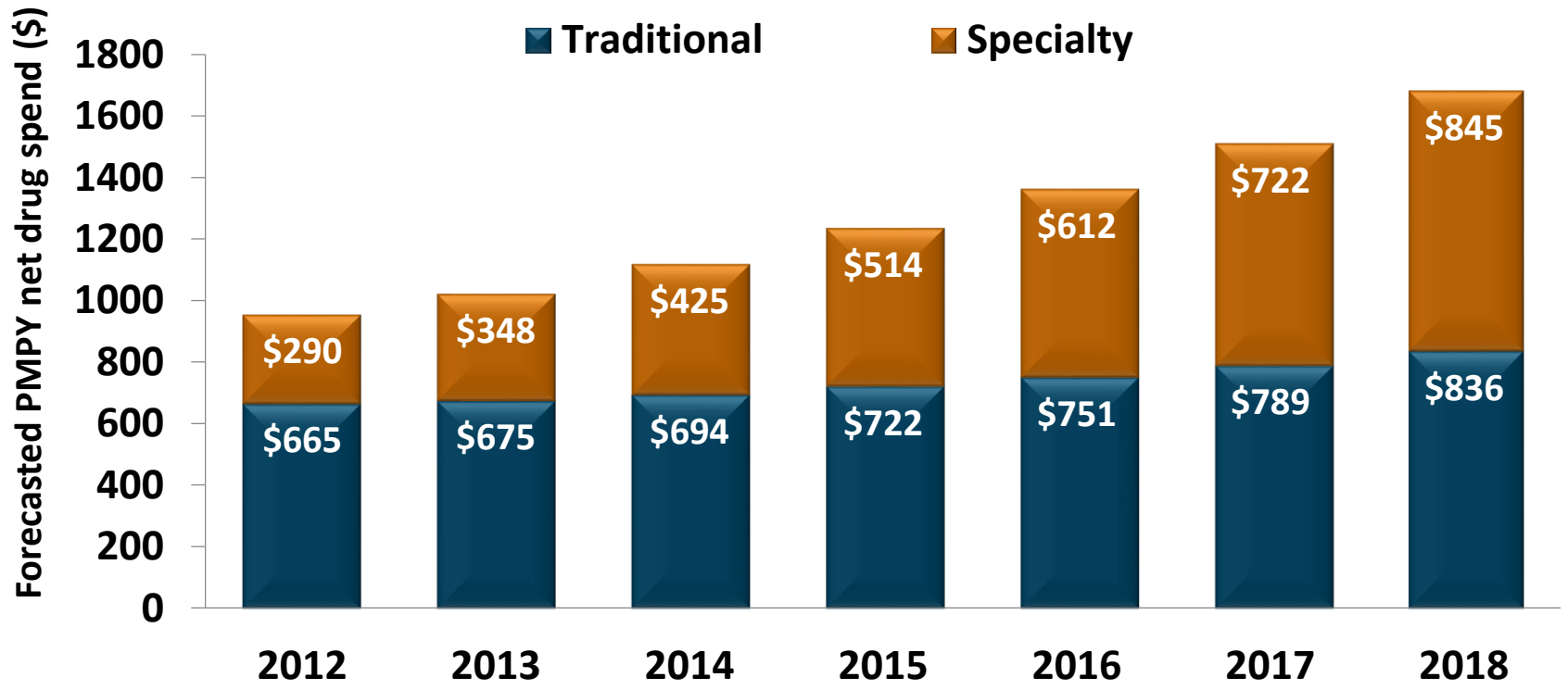
Jeffrey Dunn, PharmD, MBA
Chief Clinical Officer
Senior Vice President
VRx Pharmacy Services, LLC

Outline

- Coverage strategies for current RA therapies
- Impact of advances in RA therapeutics on benefit design

Sales of Specialty Drugs Continues to Grow

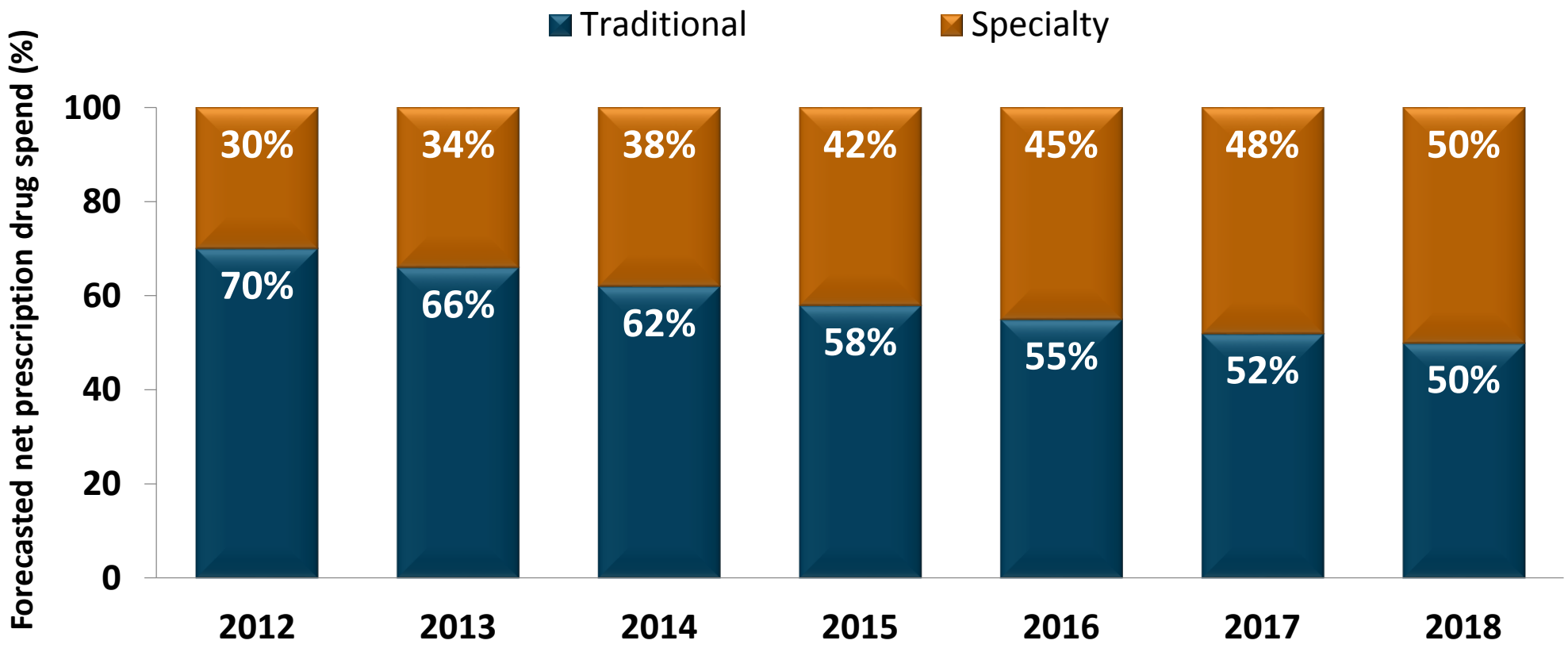
Spending on Specialty Drugs Projected to Surpass Sales of Traditional Agents by 2018



PMPY=per member per year

Artemetrx. Specialty drug trends across the pharmacy and specialty benefit. 2013. Available at: http://www.artemetrx.com/wp-content/uploads/2014/08/artemetrx-specialty-drug-trends.pdf. Accessed September 22, 2015.

Growth of Pharmacy Spending on Specialty Drugs in Commercial Plans Expected to Grow as Coverage is Shifted Out of the Medical Benefit



Artemetrx. Specialty drug trends across the pharmacy and specialty benefit. 2013. Available at: http://www.artemetrx.com/wp-content/uploads/2014/08/artemetrx-specialty-drug-trends.pdf. Accessed September 22, 2015.

Specialty Categories Under the Pharmacy Benefit

			TREND		
RANK	**THERAPY CLASS**	**PMPY SPEND**	**UTILIZATION**	**UNIT COST**	**TOTAL**
1	Inflammatory Conditions	$80.03	8.5%	15.7%	24.3%
2	Multiple Sclerosis	$52.36	3.2%	9.7%	12.9%
3	Oncology	$41.64	8.9%	11.7%	20.7%
4	Hepatitis C	$37.95	76.1%	666.6%	742.6%
5	HIV	$27.24	4.5%	10.3%	14.8%
6	Miscellaneous Specialty Conditions	$11.10	27.3%	8.2%	35.6%
7	Growth Deficiency	$9.98	-0.9%	7.5%	6.6%
8	Hemophilia	$5.49	-0.8%	17.6%	16.9%
9	Pulmonary Arterial Hypertension	$5.41	7.6%	6.2%	13.8%
10	Transplant	$5.13	0.8%	-3.1%	-2.3%
	TOTAL SPECIALTY	**$311.11**	**5.8%**	**25.2%**	**30.9%**

PMPY=per member per year.

Express Scripts. http://www.drugtrendreport.com/commercial/specialty-trend-by-therapy-class. Accessed April 28, 2015.

RA Management Challenges: Drug and Disease Cost Issues and Trends

Drug Costs

- Drug acquisition
  - Pipeline burgeoning with novel biologic agents
  - Price increases vs rebates

Administrative Burden

- Elusiveness of data to determine total costs due to lack of transparency driven by medical/ pharmacy benefit designs
- Parity laws
- Patient education/health management programs
- Management of safety monitoring

Total Costs to be Evaluated

- Direct and indirect
- Contract implications of indications
- Role of Patient Assistance Programs

RA Management Challenges: Increasing Number of Biologic Agents

- No standardized outcomes measures used in clinical practice
- 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
- Guidelines on how biologics should be used 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;26:65-70.

Benefit Design: Multi-tier Structure

- All specialty is NOT created equal
- 12 of 36 health plans with specialty strategy have multi-tier specialty cost share
  - Accounts for 45% of covered lives
- 93% of PBMs plan to increase use of specialty tier in next 24 months

- Proposal:
  - Multi-tier specialty formulary
    - Generic specialty tier
    - Preferred specialty tier
    - Non-preferred specialty tier
- Optional to clients but structure in place for those that want to participate in specialty strategy

EMD Serono Specialty Digest, 9th Edition. Managed care strategies for specialty pharmaceuticals http://www.amcp.org/EMDSeronoSpecialtyDigest9th.pdf. Accessed September 22, 2015.

Multi-tier Structure

Benefits

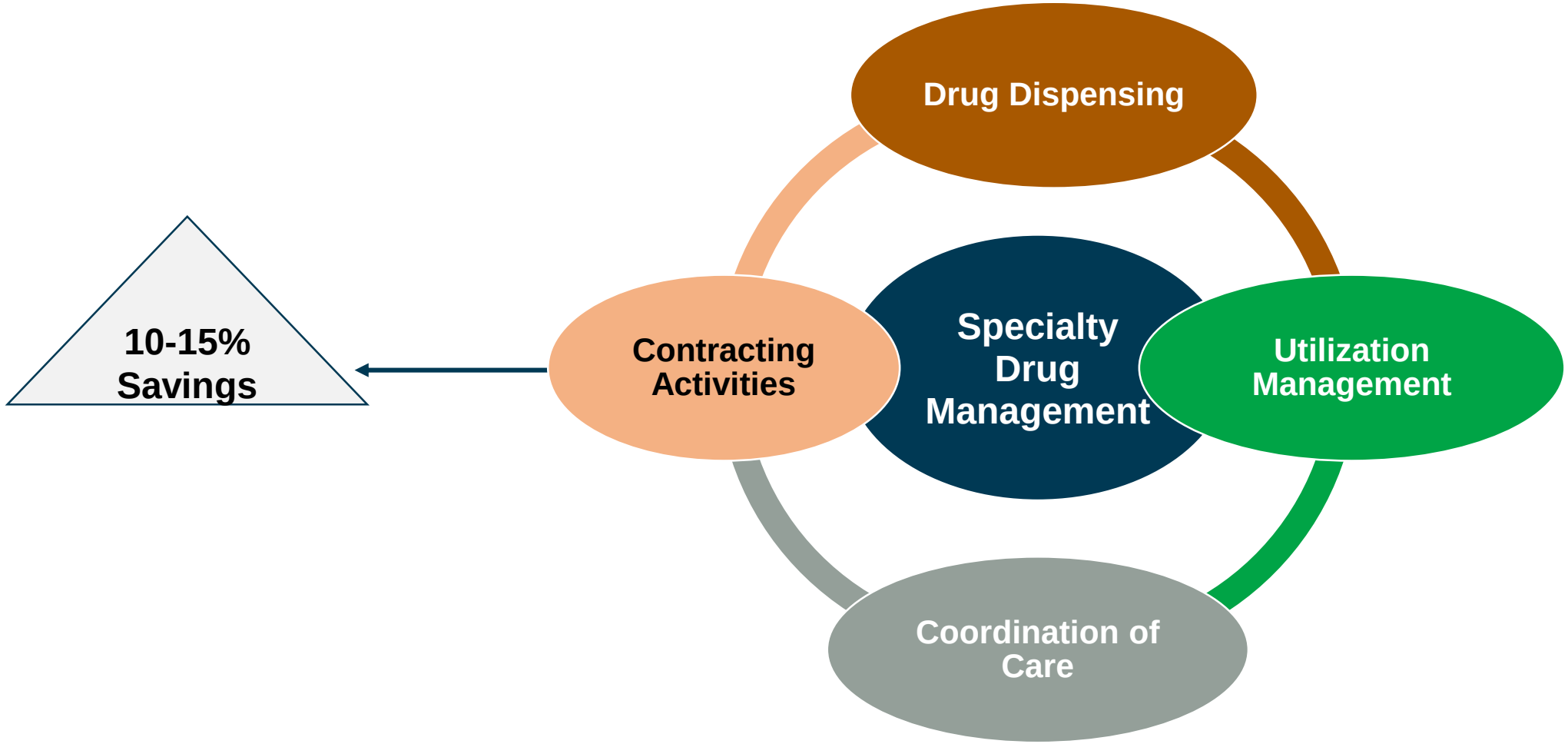
- Further differentiation of specialty class
  - Cost management
  - Ability to manage specialty classes
- Contracting benefits
- Provides a strategy solution for employer groups and health plans

Tier	Specialty "Opt In"	"Opt out"
4 (generic)	10%	20%
5 (preferred)	20%	20%
6 (non-preferred)	40%	20%

Possible Difficulties

- Multiple layers adds confusion
  - Client
  - Member
  - Customer Service
  - Internal
- More time spent managing the formulary

Contracting and Rebates for Preferred Products



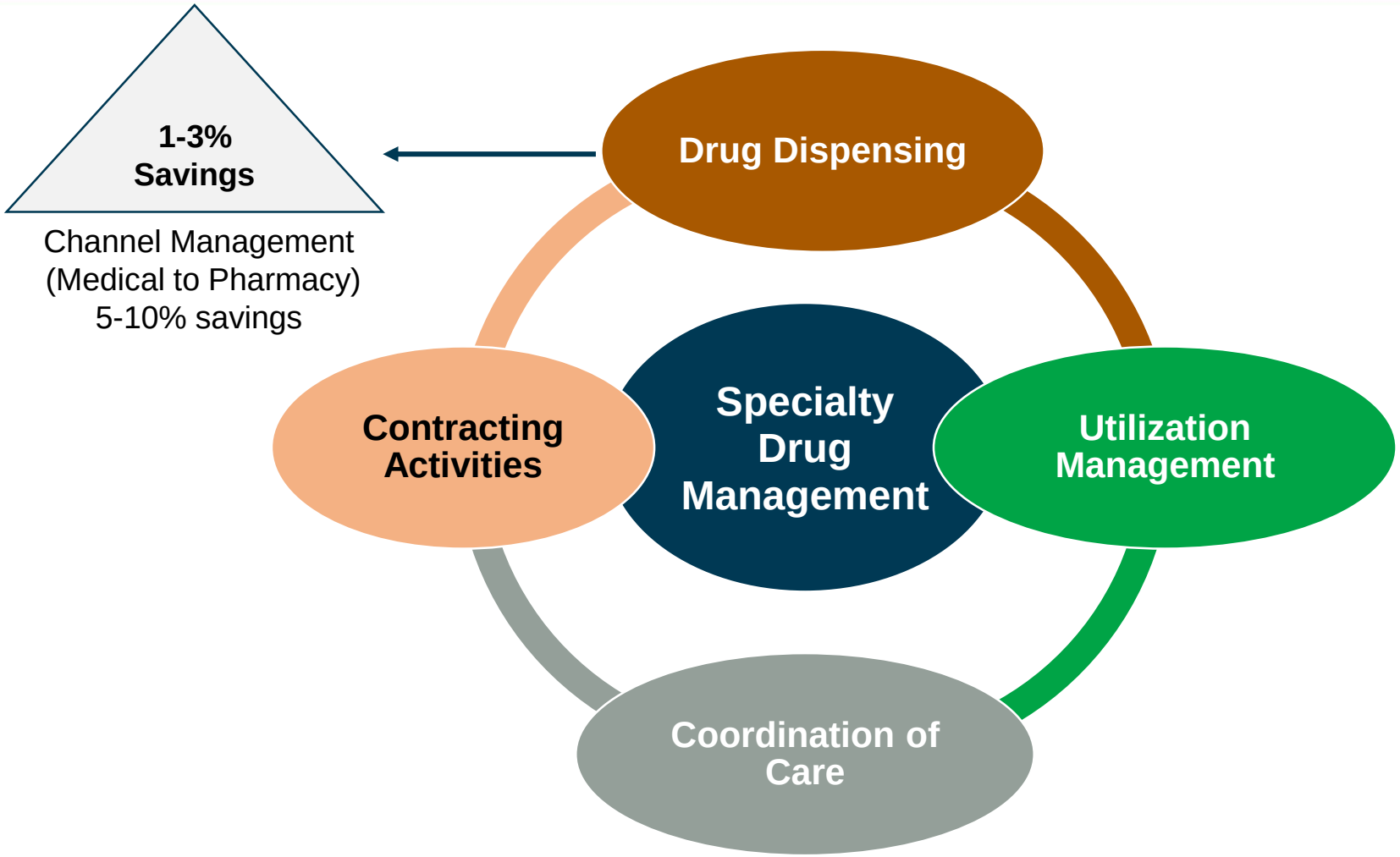
Contracting and Rebates

- Create "preferred" products within key therapeutic classes
  - Maximize rebate potential
  - Control utilization
- 2013 EMD Serono Specialty Report identifies 15 therapeutic classes where health plans have preferred products

Preferred Product Categories	
MS (IM/SC)	Growth hormone
RA/CD (SC)	Psoriasis
HCV (oral)	HCV (SC)
ESAs	PAH (oral/inhaled)
RA/CD (IV)	HA derivatives

EMD Serono Specialty Digest, 9th Edition. Managed care strategies for specialty pharmaceuticals http://www.amcp.org/EMDSeronoSpecialtyDigest9th.pdf. Accessed September 22, 2015.

Channel Management: Drug Dispensing



Drug Dispensing

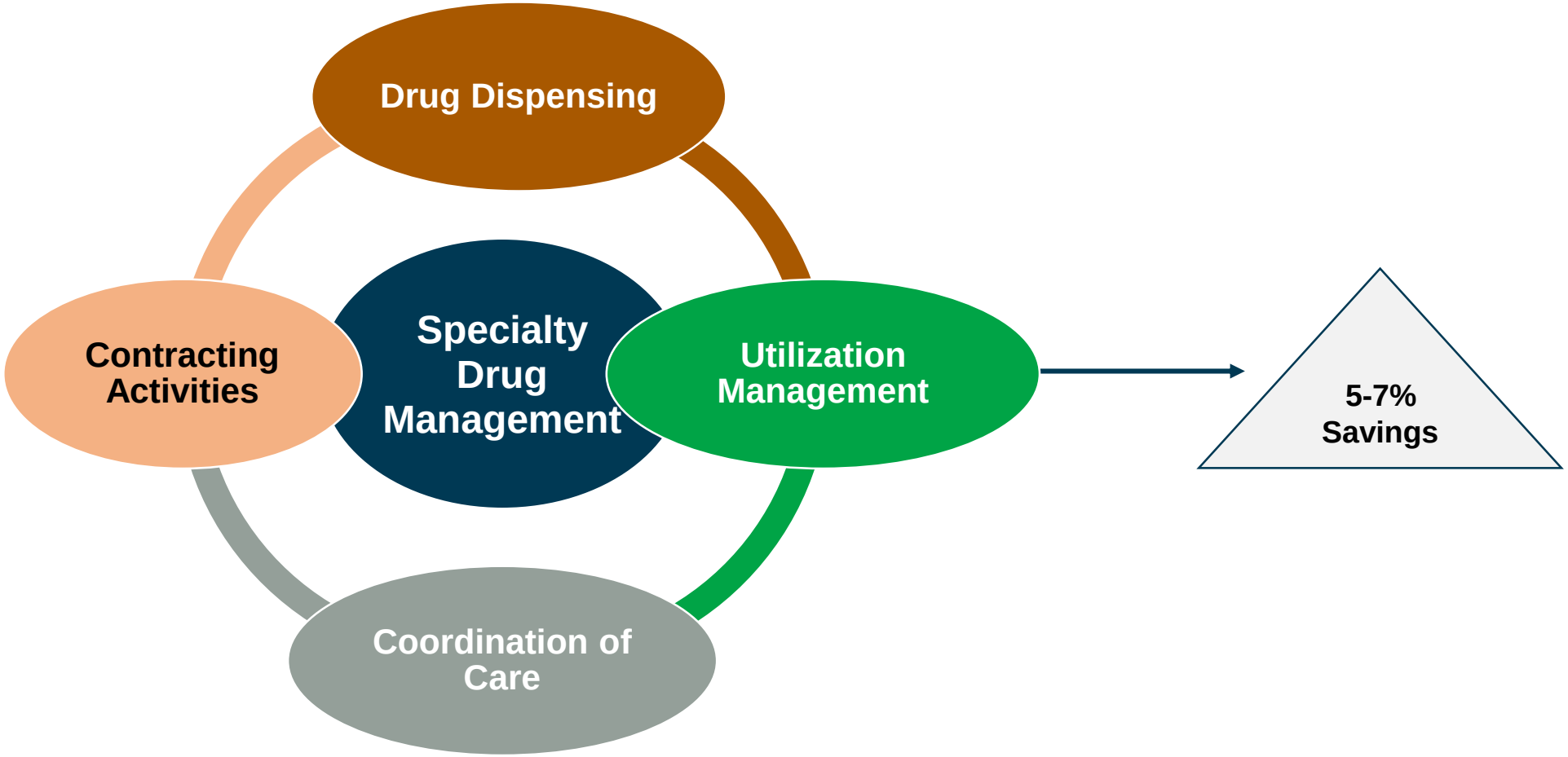
- Channel management
  - Medical claim Site-of-Care Optimization
  - Pharmacy channel management

Remicade® Site-of-Care Example

Place 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**

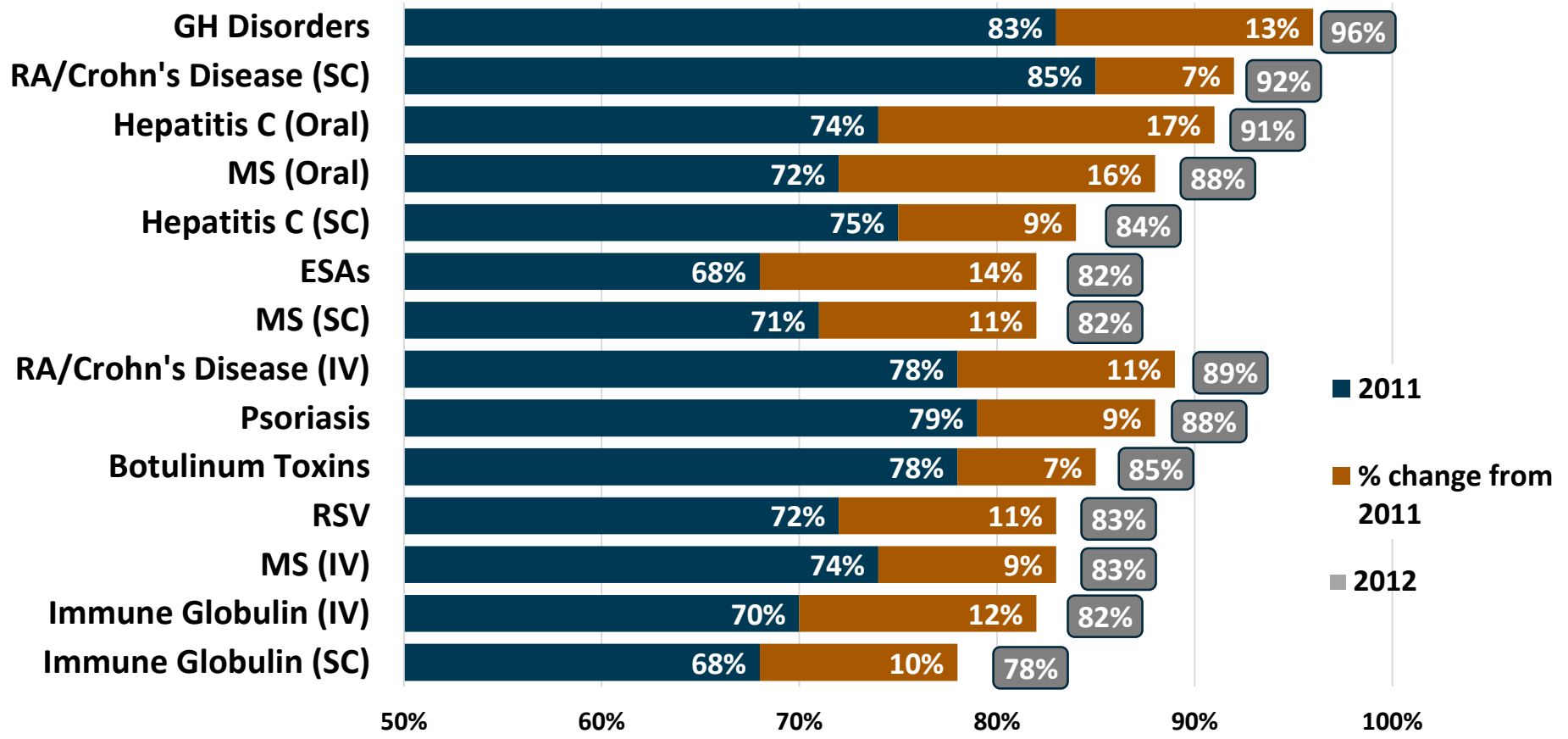
HOPD=hospital outpatient department.
Internal utilization and pricing data.

Channel Management: Utilization Management



Utilization Management

- Prior authorizations
- Step-therapy
- Quantity limits
- Reporting



Use of Prior Authorizations by Disease State

EMD Serono Specialty Digest, 9th Edition. Managed care strategies for specialty pharmaceuticals http://www.amcp.org/EMDSeronoSpecialtyDigest9th.pdf. Accessed September 22, 2015.

Utilization Management (cont'd)

Analysis

- Review of specialty database for clinically appropriate quantity limits and PAs
  - Opportunities exist to further control utilization by implementing PAs and QLs on medications
- Evaluate PA/step-therapy effectiveness

Actions

- Multiple layers adds confusion
  - Client
  - Member
  - Customer Service
  - Internal
- More time spent managing the formulary

PA=prior authorization; QL=quantity limits.

Utilization Management (cont'd)

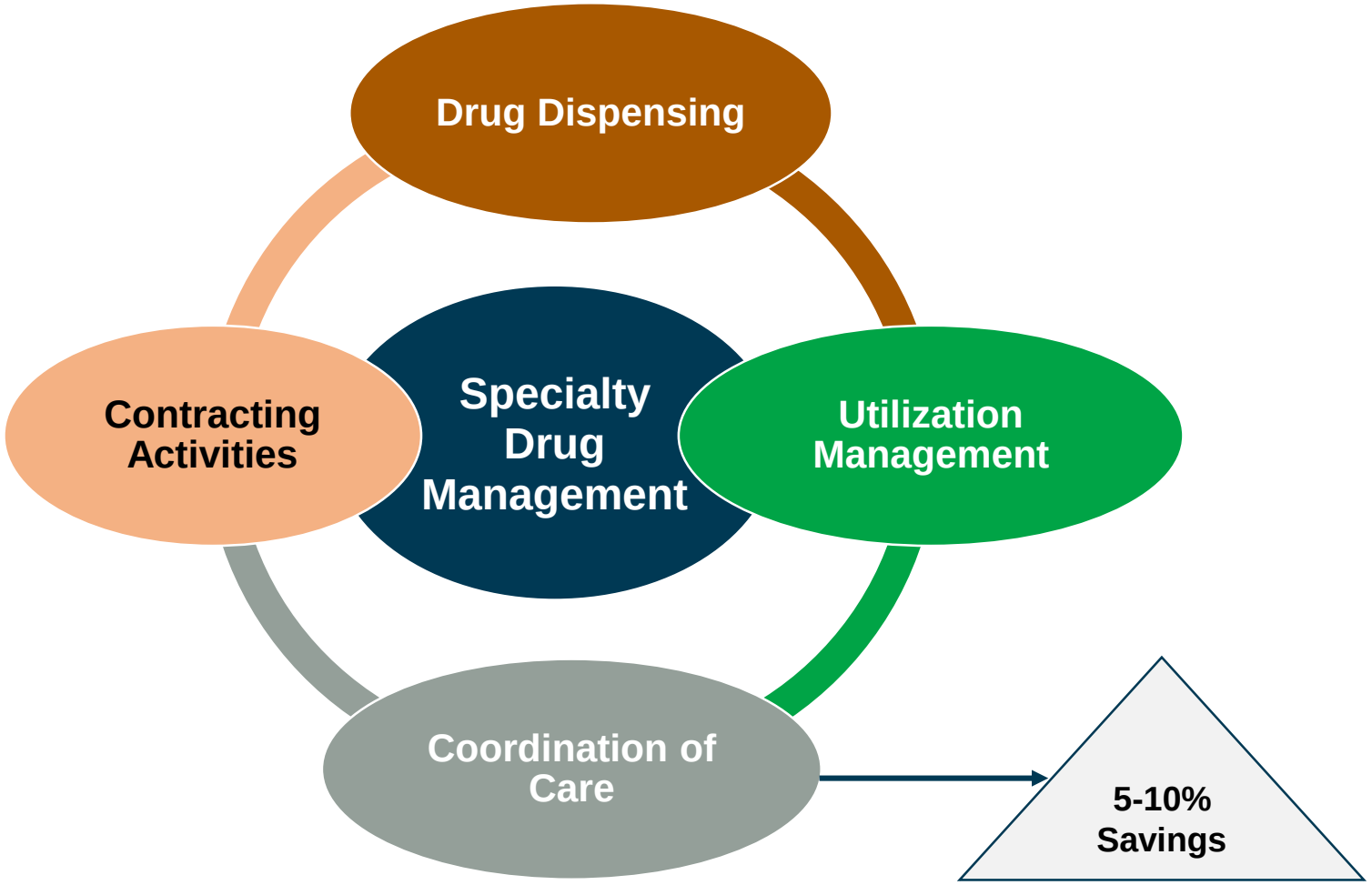
Plan

- Reporting
  - Control utilization through analysis of medications that require special dosing
    - Medical therapy management (MTM) outreach/education on these medications

Actions

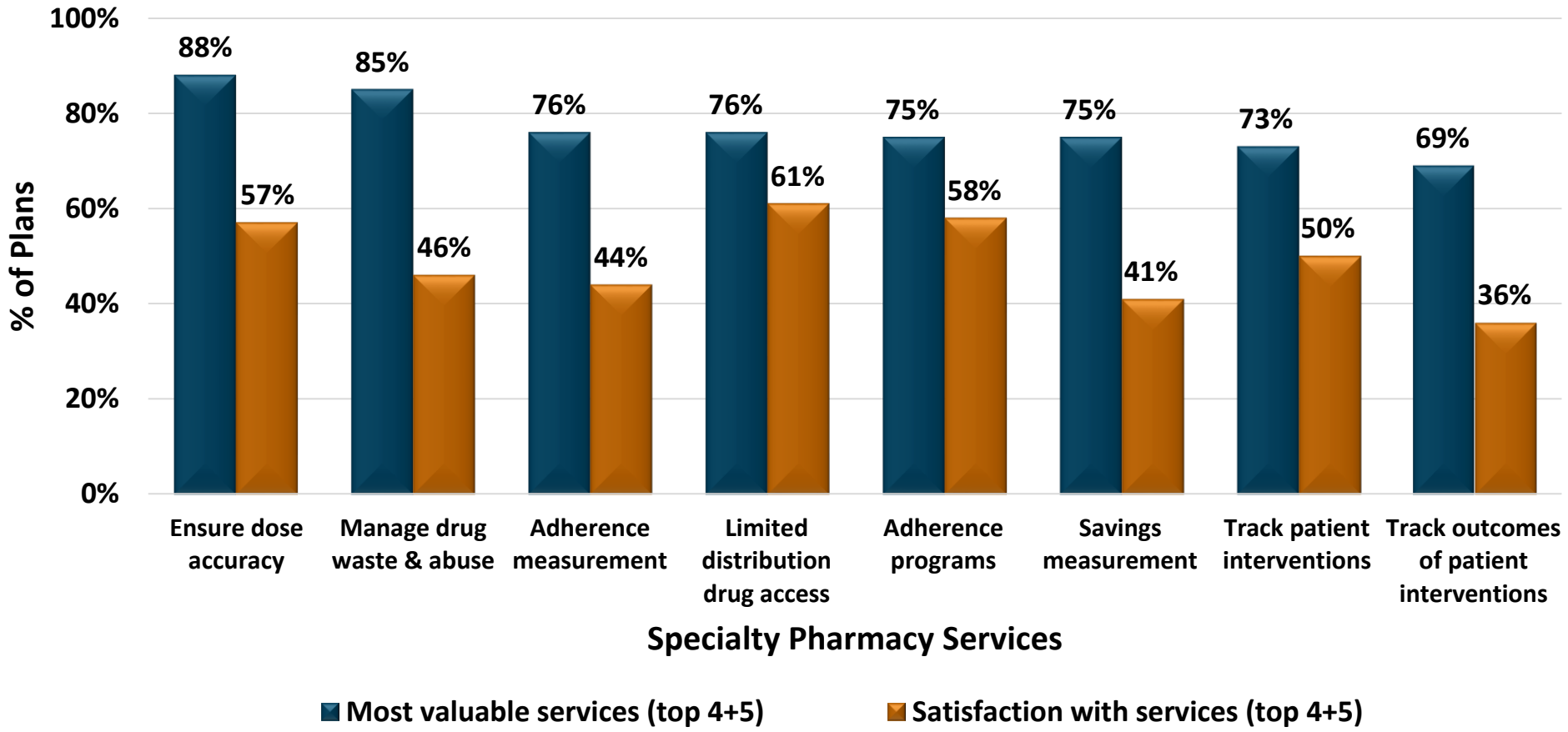
- Create list of targeted medications
- Develop reporting system in claims system
- Implement intervention in MTM program

Channel Management: 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 http://www.amcp.org/EMDSeronoSpecialtyDigest9th.pdf. Accessed September 22, 2015.

Specialty 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

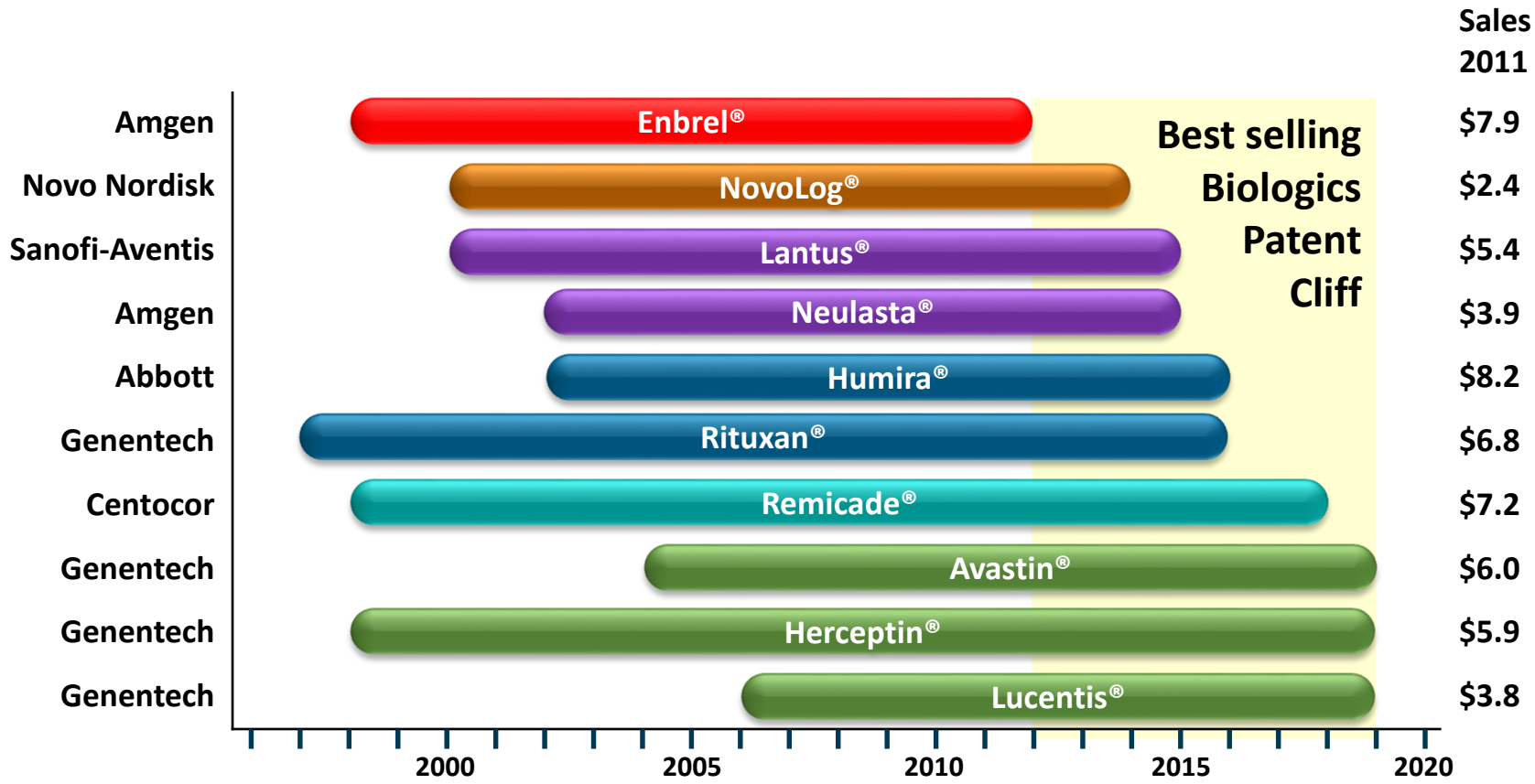
What is a Biosimilar (Then)?

Close, but…?

What is a Biosimilar (Now)?

Close, but…?

Issues with Biosimilars



- Rating/interchangeability
- Data extrapolation/indications
- Safety
- Manufacturing
- Cost

Summary

- Spending on specialty drugs projected to surpass sales of traditional agents by 2018
- RA drugs represent a significant proportion of the specialty spend and the number of available biologic agents continues to increase
- Strategies include multi-tier specialty formularies, contracting activities, channel management, utilization management, care management, and specialty pharmacy management
- Biosimilars are poised to enter the RA biologic market
- It remains challenging to identify the most effective allocation of agents for optimal RA management

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