Vectra®

& KROGER PRESCRIPTION PLANS

Optimizing Outcomes for Patients with Rheumatoid Arthritis

The impact of RA on quality of life & healthcare economics

- 1.5 million adult cases[1]
- 60-70% higher mortality rate[1]

- Top-5 payer Rx spend3
- $22B annual US spend2
- $20,000 avg OOP per patient[4]

Treatment goals:

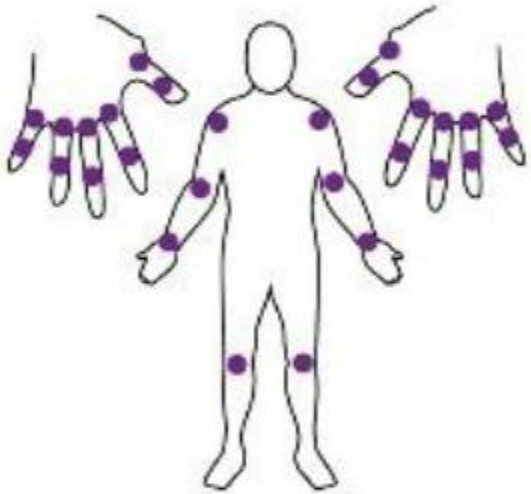
- Control symptoms and joint damage
- Limit disability

How managed today:

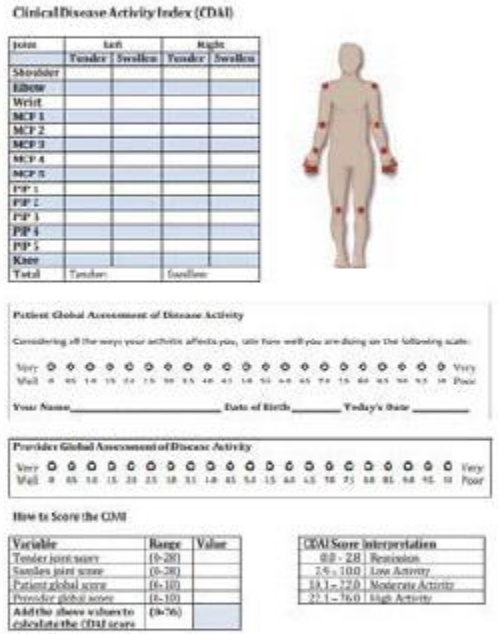
- Frequent assessment and treatment adjustment

1. Arthritis Foundation (2018). 2. American Journal of Managed Care (2018, July 3). 3. Peterson-Kaiser Health System Tracker (2017, December). 4. Health Union LLC (2018).

Traditional disease activity measures are subjective



DAS28 CRP/ESR



Clinical Disease Activity Index (CDAI)

Joint	Left		Right	
	Tender	Swollen	Tender	Swollen
Shoulder				
Elbow				
Wrist				
MCP 1				
MCP 2				
MCP 3				
MCP 4				
MCP 5				
PIP 1				
PIP 2				
PIP 3				
PIP 4				
PIP 5				
Knee				
Total	Tender:		Swollen:	

Patient Global Assessment of Disease Activity

Considering all the ways your arthritis affects you, rate how well you are doing on the following scale:

Very Well 0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10 Poor

Your Name_____ Date of Birth_____ Today's Date _____

Provider Global Assessment of Disease Activity

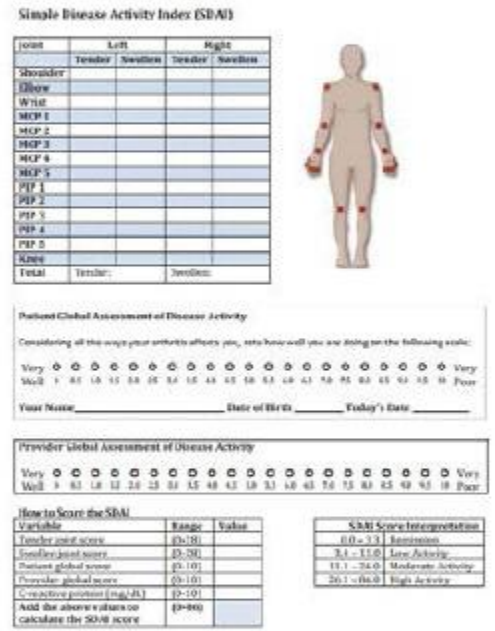
Very Well 0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10 Very Poor

How to Score the CDAI

Variable	Range	Value
Tender joint score	(0-28)	
Swollen joint score	(0-28)	
Patient global score	(0-10)	
Provider global score	(0-10)	
Add the above values to calculate the CDAI score	(0-76)	

CDAI Score	Interpretation
0.0 - 2.8	Remission
2.9 - 10.0	Low Activity
10.1 - 22.0	Moderate Activity
22.1 - 76.0	High Activity

CDAI



Simple Disease Activity Index (SDAI)

Joint	Left		Right	
	Tender	Swollen	Tender	Swollen
Shoulder				
Elbow				
Wrist				
MCP 1				
MCP 2				
MCP 3				
MCP 4				
MCP 5				
PIP 1				
PIP 2				
PIP 3				
PIP 4				
PIP 5				
Knee				
Total	Tender:		Swollen:	

Patient Global Assessment of Disease Activity

Considering all the ways your arthritis affects you, rate how well you are doing on the following scale:

Very Well 0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10 Poor

Your Name_____ Date of Birth _____ Today's Date _____

Provider Global Assessment of Disease Activity

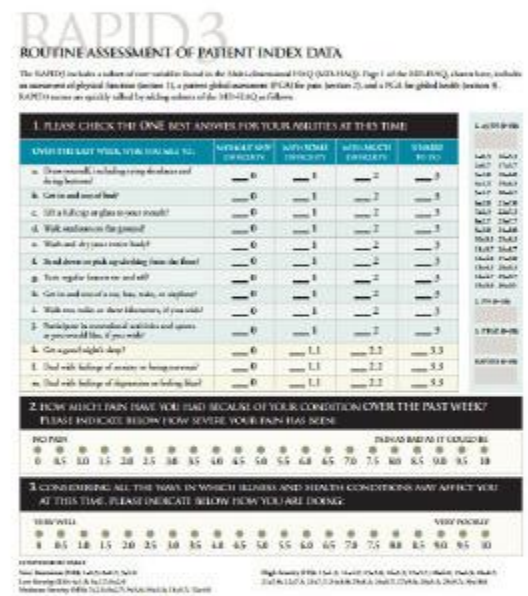
Very Well 0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10 Very Poor

How to Score the SDAI

Variable	Range	Value
Tender joint score	(0-28)	
Swollen joint score	(0-28)	
Patient global score	(0-10)	
Provider global score	(0-10)	
C-reactive protein (mg/dL)	(0-10)	
Add the above values to calculate the SDAI score	(0-86)	

SDAI Score	Interpretation
0.0 - 3.3	Remission
3.4 - 11.0	Low Activity
11.1 - 26.0	Moderate Activity
26.1 - 86.0	High Activity

SDAI



RAPID3

ROUTINE ASSESSMENT OF PATIENT INDEX DATA

1. PLEASE CHECK THE ONE BEST ANSWER FOR YOUR ABILITIES AT THIS TIME

OVER THE LAST WEEK, YOU HAVE NO:	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
a. Dress yourself, including tying shoelaces and doing buttons?	___0	___1	___2	___3
b. Get in and out of bed?	___0	___1	___2	___3
c. Lift a full cup or glass to your mouth?	___0	___1	___2	___3
d. Walk outdoors on flat ground?	___0	___1	___2	___3
e. Wash and dry your entire body?	___0	___1	___2	___3
f. Bend down to pick up clothing from the floor?	___0	___1	___2	___3
g. Turn regular faucets on and off?	___0	___1	___2	___3
h. Get in and out of a car, bus, train, or airplane?	___0	___1	___2	___3
i. Walk two miles or three kilometers, if you wish?	___0	___1	___2	___3
j. Participate in recreational activities and sports as you would like, if you wish?	___0	___1	___2	___3
k. Get a good night's sleep?	___0	___1.1	___2.2	___3.3
l. Deal with feelings of anxiety or being nervous?	___0	___1.1	___2.2	___3.3
m. Deal with feelings of depression or feeling blue?	___0	___1.1	___2.2	___3.3

2. HOW MUCH PAIN HAVE YOU HAD BECAUSE OF YOUR CONDITION OVER THE PAST WEEK? PLEASE INDICATE BELOW HOW SEVERE YOUR PAIN HAS BEEN:

NO PAIN 0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10 PAIN AS BAD AS IT COULD BE

3. CONSIDERING ALL THE WAYS IN WHICH ILLNESS AND HEALTH CONDITIONS MAY AFFECT YOU AT THIS TIME, PLEASE INDICATE BELOW HOW YOU ARE DOING:

0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10 VERY POORLY

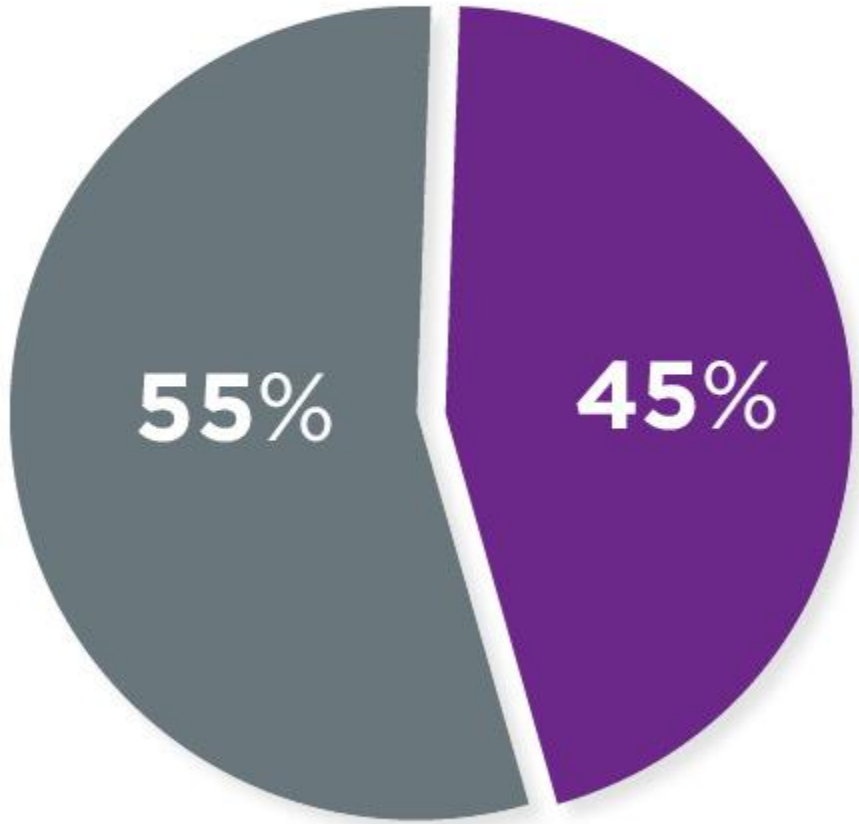
RAPID3

More Than Half of Surveyed US Rheumatologists Did Not Collect Formal Disease Activity Measures*

55% of surveyed rheumatologists did not collect formal measures

Reasons for not collecting formal measures:

- Time required (63%)
- Not on their EMR (32%)
- Just not needed (32%)



N=317

45% of surveyed rheumatologists collect formal measures

Reasons for complementing clinical exams with formal measures:

- Improved care (76%)
- Decision making (67%)
- Ease of use (50%)

*Includes HAQ or MDHAQ, RAPID3, DAS28, CDAI, Vectra, SDAI, ACR20. Cush J, et al. Presented at the ACR Annual Meeting. November 14-19, 2014. Abstract 114.

Vectra®

- A multi-biomarker blood test
- Validated to measure disease activity
- For adults diagnosed with rheumatoid arthritis (RA)
- Categories: Low (≤29), Moderate (30-44), High (>45)
- Prognostic of rapid radiographic progression within one year

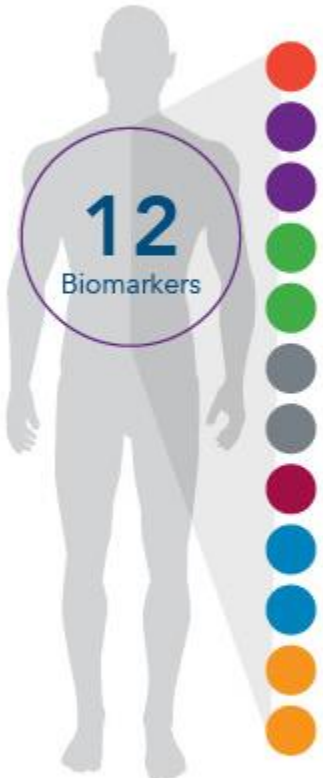
INTENDED USE

- Aid in the assessment of disease activity in RA patients
- Help inform patient management decisions when used with standard clinical assessment

NOT INTENDED OR VALIDATED

- Diagnose RA
- Predict response to specific therapies.

Vectra® Provides Molecular Insights on the Inflammatory State of RA That Can Help Inform Your Medical Managment Decisions



Vectra is a molecular measurement of disease activity and RA inflammation

Adhesion Molecules	Growth Factors	Cytokines/ Receptors	Matrix Metalloproteinases	Skeletal-Related Proteins	Hormones	Acute-Phase Proteins
VCAM-1	EGF	IL-6	MMP-1	YKL-40	Leptin	SAA
	VEGF-A	TNF-RI	MMP-3		Resistin	CRP

Cellular Influx & Tissue Expansion | **Inflammation & Destruction** | **Cartilage Degradation & Joint Damage** | **Stromal Activity & Regulation** | **Systemic Inflammatory Response**

*Interpretation of individual biomarker results has not been validated.

Adapted from: Stedman's online medical dictionary, http://stedmansonline.com/index. Last modified Feb 12. Accessed Feb 12, 2015, Chen G et al. Science. 2002;296:1634-1635, Taylor PC et al. Nat Rev Rheumatol. 2009;10:578-582, Burrage PS, et al. Front Biosci. 2006;11:529-543, Flannery CR et al. J Biol Chem. 1992;267:1008-1014, Suzuki K et al. Biochemistry. 1990;29:10261-10270, Okada Y et al. Ann Rheum Dis. 1989;48(8):645-653, Hakala BE et al. J Biol Chem. 1993;268:25803-25810, Kirkpatrick RB et al. Exp Cell Res. 1997;237(1):46-54, De Ceuninck F et al. Biochem Biophys Res Commun. 2001;285:926-931, Ling H et al. Biochem J. 2004;380(pt 3):651-659, Kotzin BL et al. Proc Natl Acad Sci USA. 2000;97(1):291-296.

Vectra®

Kroger Data Discussion

Vectra's Role

Vectra® Guided Care

Disease Management Decision

Baseline at time of treatment change decision

Therapy Initiation or Change:
Until the desired treatment target is reached, drug therapy should be adjusted every 3-6 months

Monitor Treatment Success

Test at 3-6 months after treatment change to evaluate if treatment is working

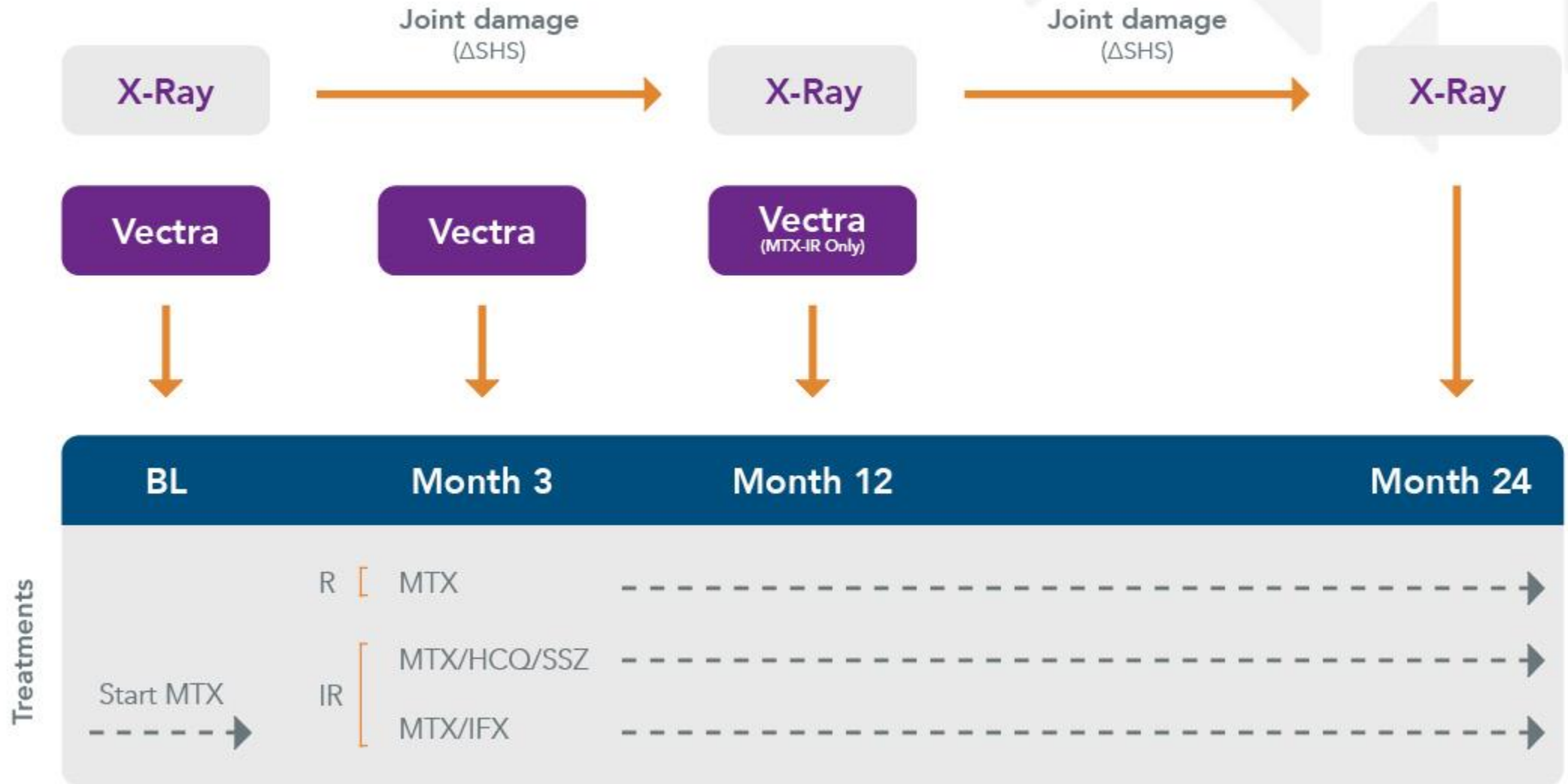
Achieving a state of disease remission in RA is considered a primary treatment goal

Monitor that Inflammation Remains Controlled

Continue to test patient two times a year once in low activity

Monitor that patient is remaining to treatment goal

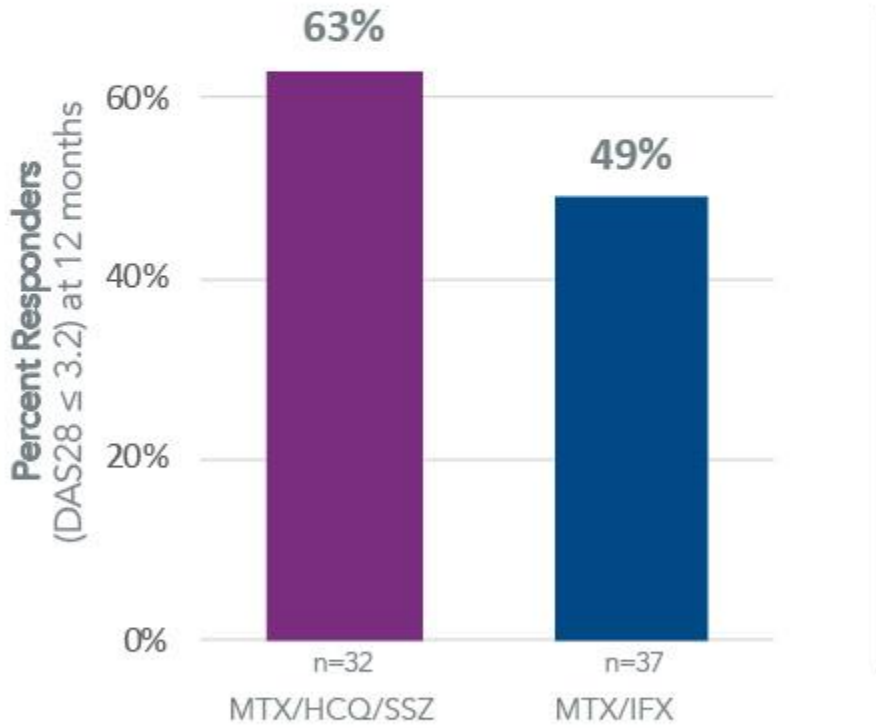
SWEFOT: Study Schema



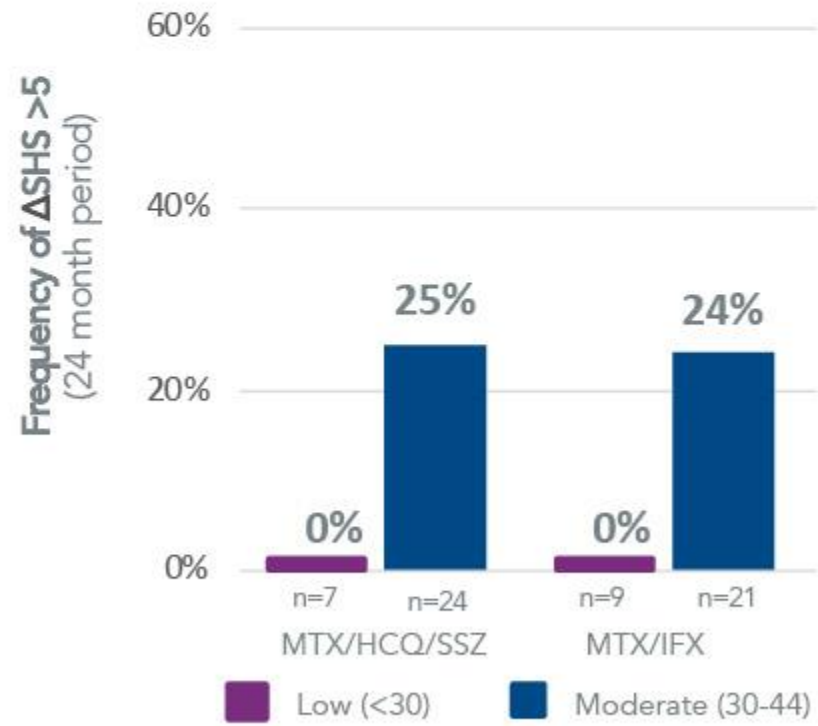
R, responder; IR, inadequate responder (DAS28 >3.2); MTX, methotrexate; HCQ, hydroxychloroquine; SSZ, sulfasalazine; IFX, infliximab; SHS, van der Heijde modified Sharp score. N = 487 for trial initiation, N = 235 for the radiographic subset.
Adapted from Hambardzumyan K, et al. Ann Rheum Dis. 2015;74:1102-1109 and Hambardzumyan K, et al. RMD Open. 2016;2:e000197. doi:10.1136/rmdopen-2015-000197.

Vectra® low/moderate patients had similar radiographic outcomes despite DMARD therapy

Responders at 12 months in MTX-IRs with low/moderate Vectra Score



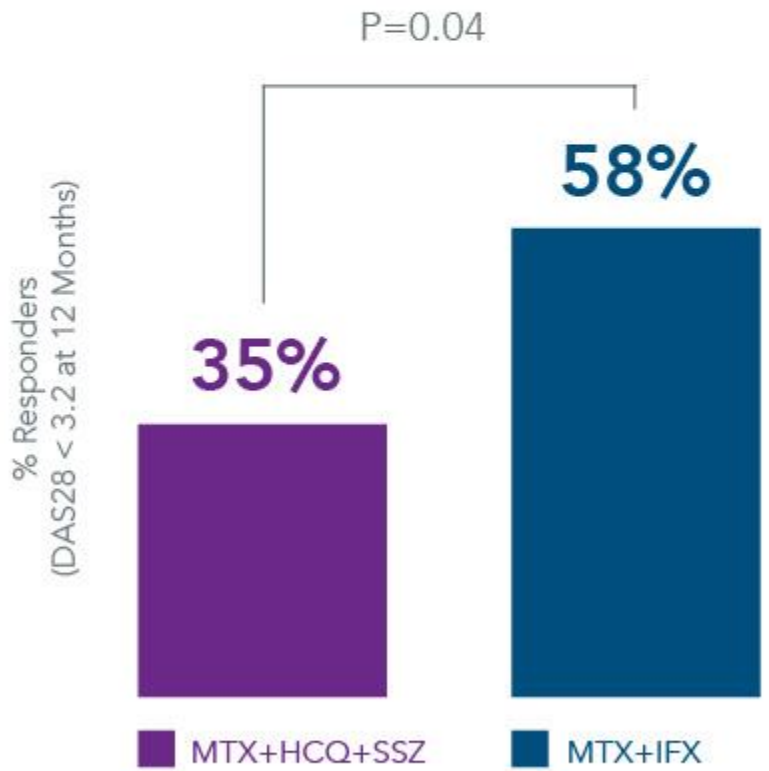
MTX-IRs with RP over 24 months with low/moderate Vectra score
(Vectra Score at Month 3)

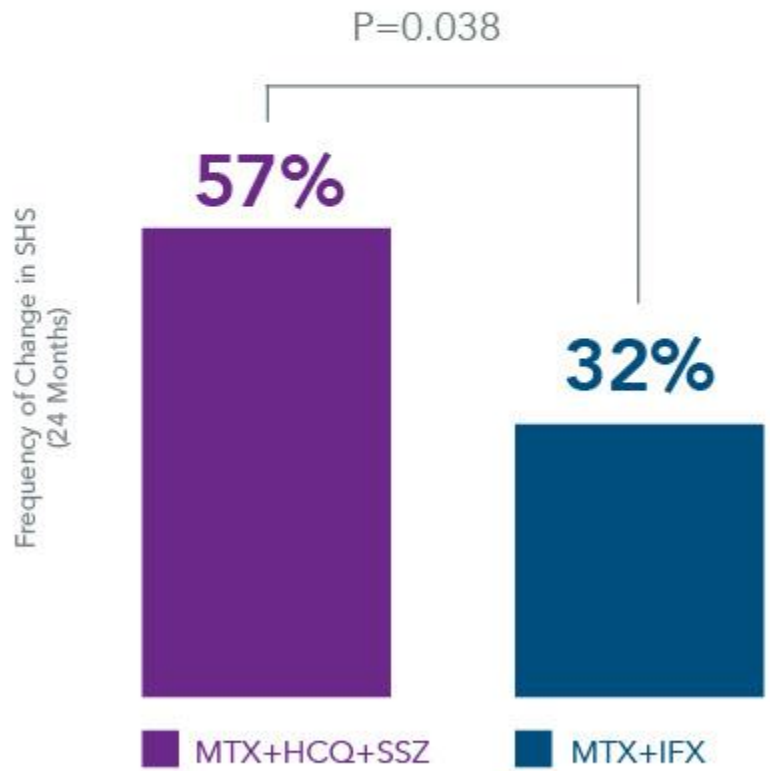


Adapted from Hambardzumyan K, et al. Arthritis Rheumatol. 2015;67(suppl 10). http://acrabstracts.org/abstract/the-multi-biomarker-disease-activity-score-in-methotrexate-incomplete-responders-predicts-clinical-responses-to-non-biological-versus-biological-therapy-in-early-ra/. Accessed May 6, 2016 and Hambardzumyan K, et al. RMD Open. 2016;2:e000197. doi:10.1136/rmdopen-2015- 000197.

Vectra®: Addressing suboptimal use of bDMARDs

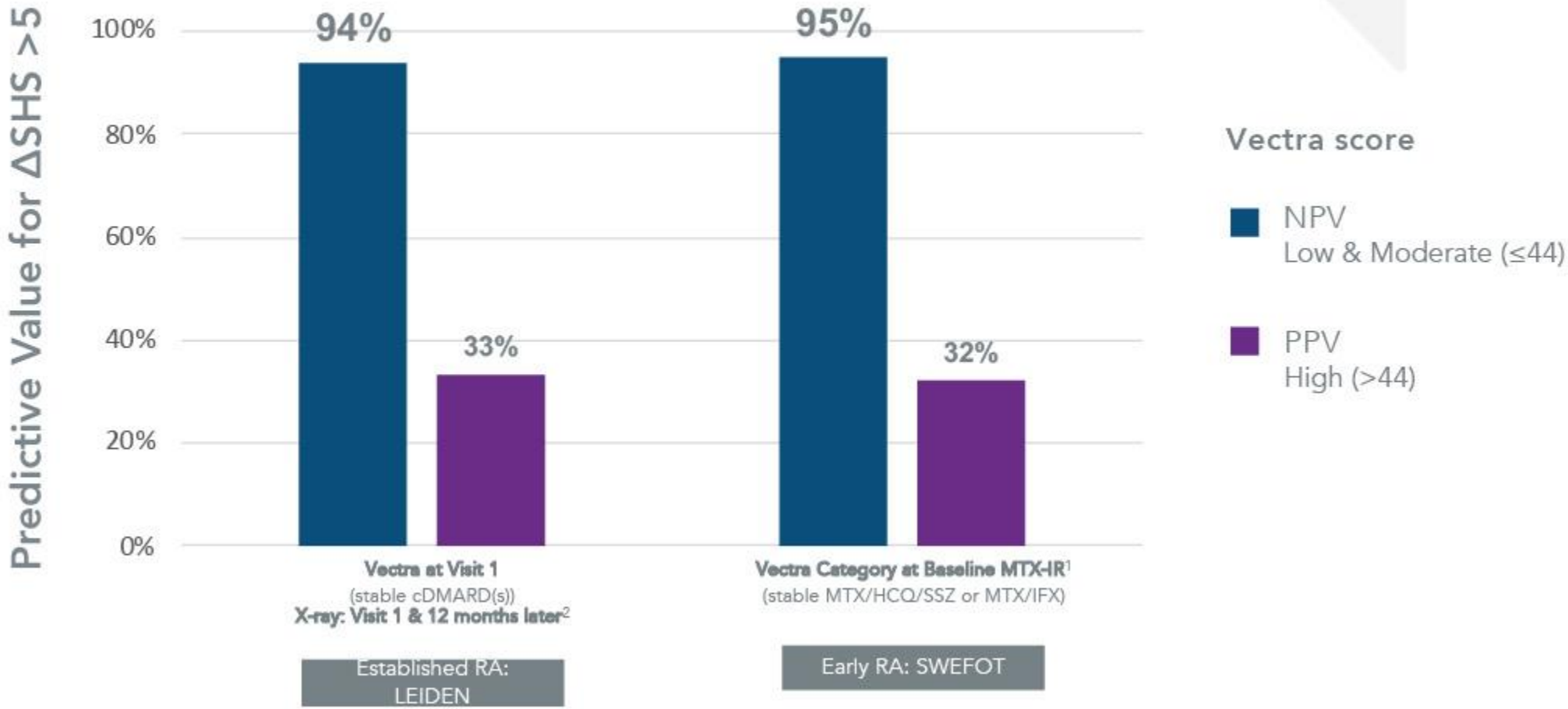
Conversely, patients with **high** Vectra scores (56%) should not discontinue bDMARD therapy because they have an increased risk of radiographic progression





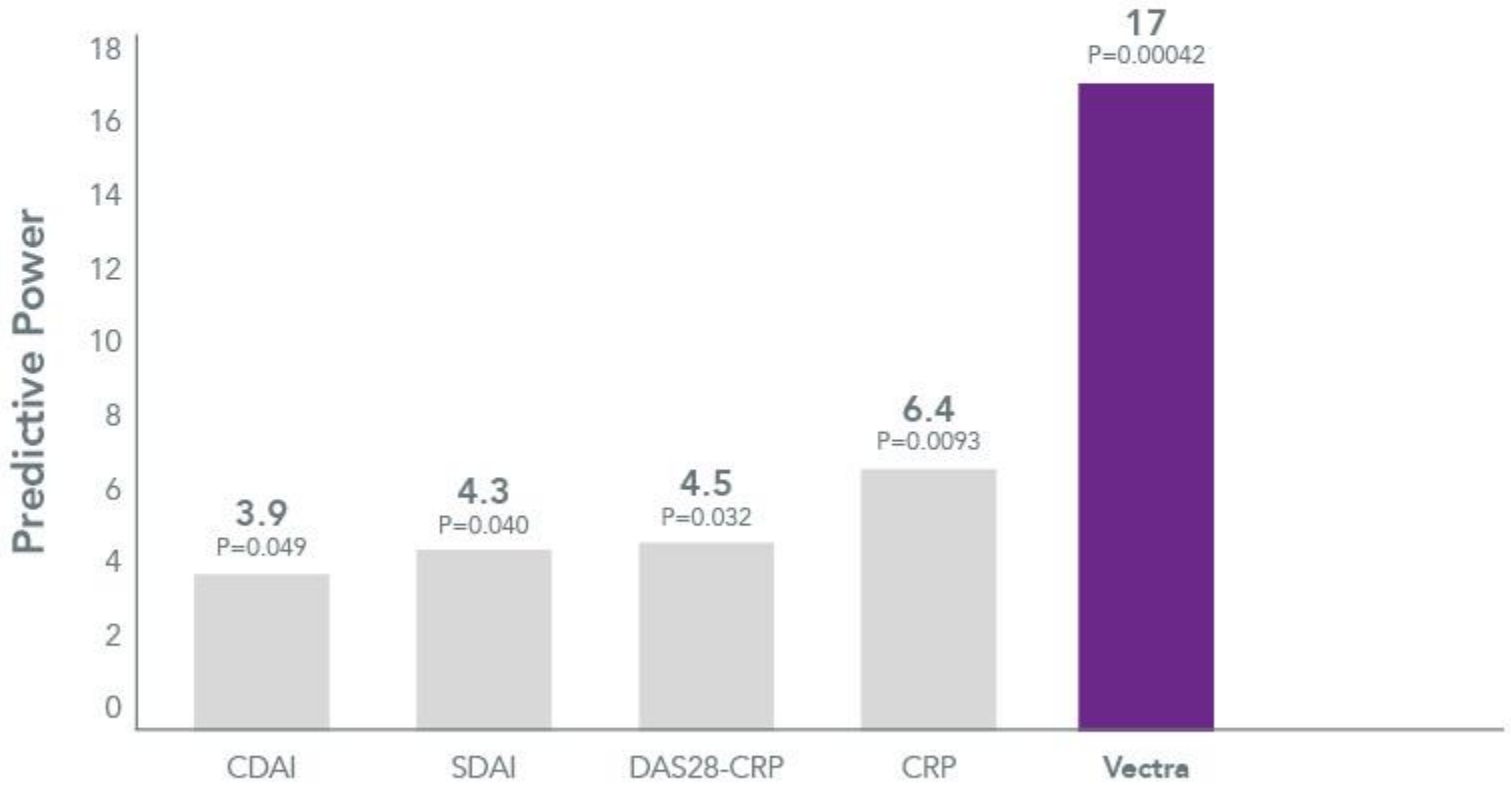
DMARD, disease modifying anti-rheumatic drug; IR, inadequate responder (DAS28 >3.2); MTX, methotrexate; HCQ, hydroxychloroquine; SSZ, sulfasalazine; IFX, infliximab. 8 patients were missing radiographs at either baseline or 24 months.
Adapted from Hambardzumyan K, et al. Arthritis Rheumatol. 2015;67(suppl 10). http://acrabstracts.org/abstract/the-multi-biomarker-disease-activity-score-in-methotrexate-incomplete-responders-predicts-clinical-responses-to-non-biological-versus-biological-therapy-in-early-ra/. Accessed May 6, 2016 and Hambardzumyan K, et al. RMD Open. 2016;2:e000197. doi:10.1136/rmdopen-2015- 000197.

Powerful NPV in Vectra Low/Moderate categories in both early and established RA



1 Hambardzumyan K, et al. Ann Rheum Dis 2015;74:1102-1109. (Additional information: Supporting online material, Table S3 is available at http://ard.bmj.com/content/suppl/2014/05/02/annrheumdis-2013-204986.DC1/annrheumdis-2013-204986supp_table2.pdf).
2 Adapted from Hambardzumyan K, et al. Ann Rheum Dis. 2014;73(Suppl2):382-383.

Vectra is Unsurpassed in Predicting Radiographic Progression



Vectra®

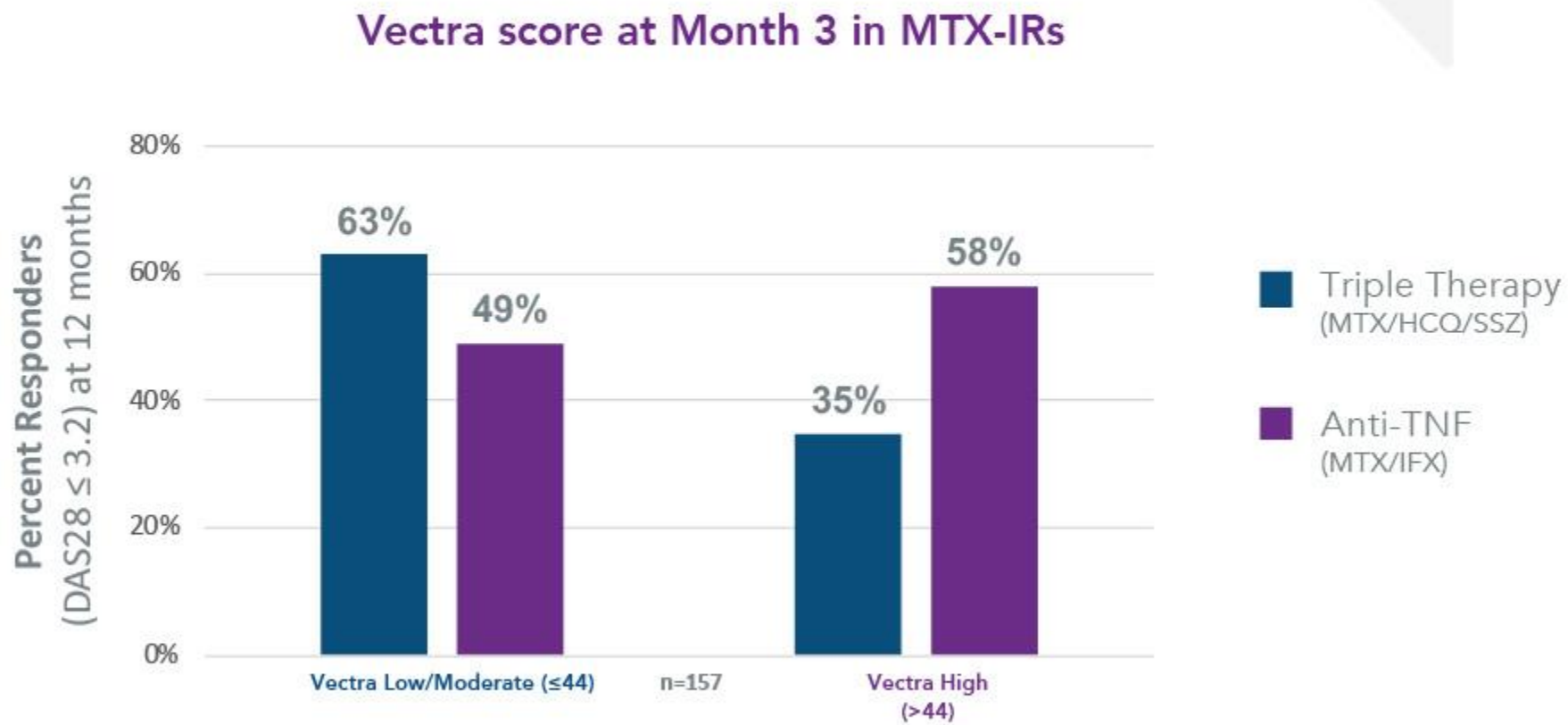
Superior predictor of Radiographic Progression

Guides Treatment

Drives Cost Savings

Curtis JR, Brahe CH, Østergaard M, Lund Hetland M, Hambardzumyan K, Saevarsdottir S, Wang X, Flake Ii DD, Sasso EH, Huizinga TW. Predicting risk for radiographic damage in rheumatoid arthritis: comparative analysis of the multi-biomarker disease activity score and conventional measures of disease activity in multiple studies. Curr Med Res Opin. 2019 Sep;35(9):1483-1493. doi: 10.1080/03007995.2019.1585064. Epub 2019 Mar 14. PMID: 30777458.

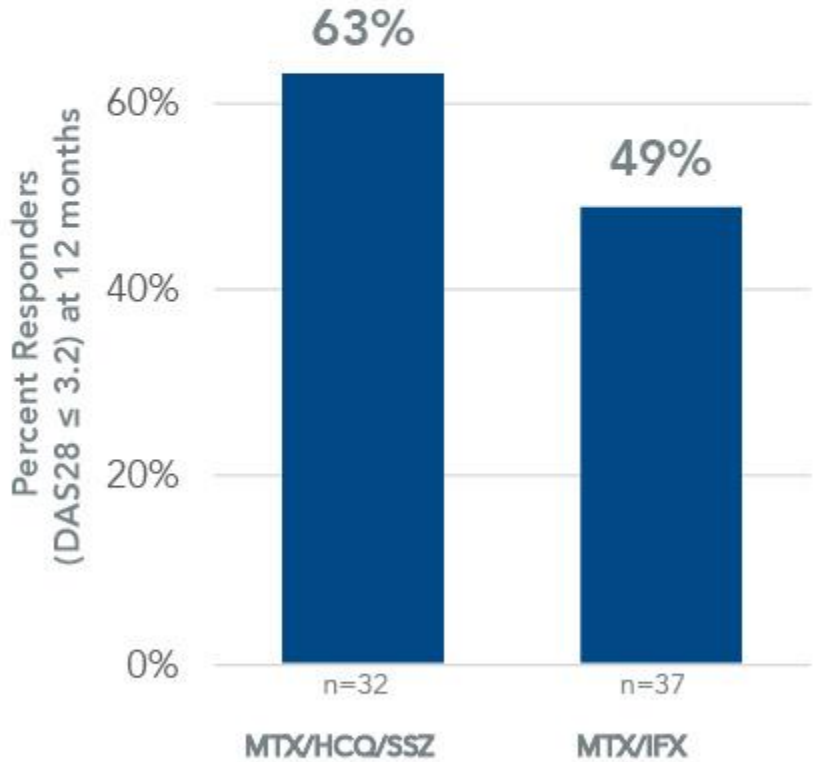
Many patients with Low/Moderate Vectra Scores responded at 12 months on cDMARDs



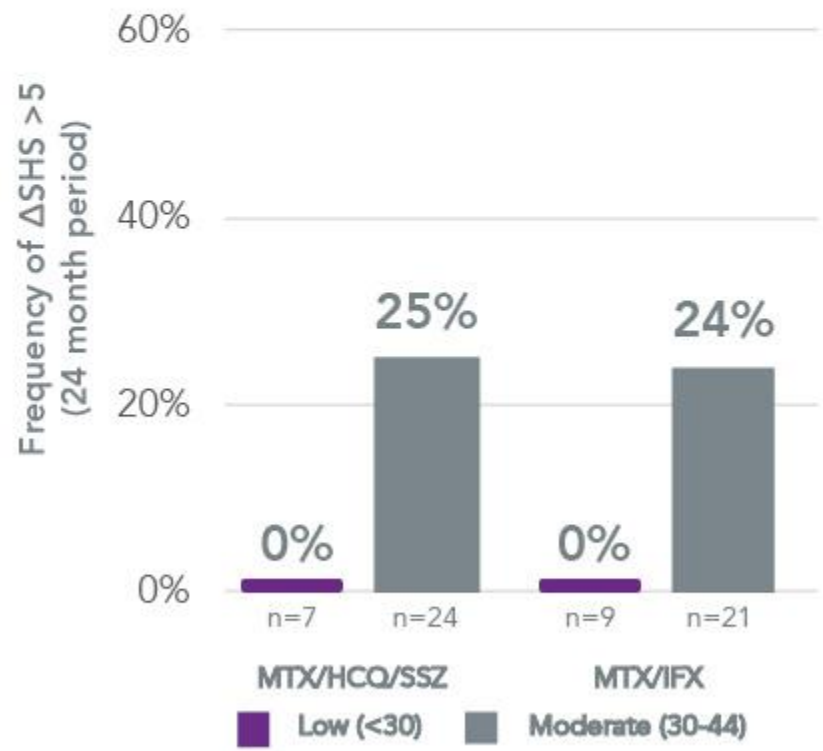
Adapted from Hambardzumyan K, et al. Arthritis Rheumatol. 2015;67(suppl 10). http://acrabstracts.org/abstract/the-multi-biomarker-disease-activity-score-in-methotrexate-incomplete-responders-predicts-clinical-responses-to-non-biological-versus-biological-therapy-in-early-ra/. Accessed May 6, 2016.

Vectra® Low/Moderate patients had similar radiographic outcomes despite DMARD therapy

Responders at 12 months in MTX-IRs with low/moderate Vectra score



MTX-IRs with RP over 24 months with low/moderate Vectra score (Vectra score at Month 3)



Adapted from Hambardzumyan K, et al. *Arthritis Rheumatol*. 2015;67(suppl 10). http://acrabstracts.org/abstract/the-multi-biomarker-disease-activity-score-in-methotrexate-incomplete-responders-predicts-clinical-responses-to-non-biological-versus-biological-therapy-in-early-ra/. Accessed May 6, 2016 and Hambardzumyan K, et al. *RMD Open*. 2016;2:e000197. doi:10.1136/rmdopen-2015- 000197.

Vectra

SAMPLE

ORDERING PHYSICIAN: Physician Name, MD

RECEIVING HEALTHCARE PROVIDER
Clinic United Partnership Example of Oklahoma University
1234 Pennsylvania Ave, Bldg 100, Ste 123,
Dept of Rheumatology
Anytown, OK 12345
Phone: 555-555-1234 / Fax: 555-555-1234

SPECIMEN
Collection Date: JUL-24-2020
Receipt Date: JUL-25-2020

REPORT
Report Date: JUL-30-2020

PATIENT
Name: Jane Doe
Date of Birth: JUN-20-1971
Patient ID: 000-000-0000
Gender: Female
TRF ID: 00000000-00

Vectra Molecular Result

Vectra Score	Risk of RP	Change in Score	Vectra Score Interpretation
58 HIGH (45-100)	11% 1-Year Risk of Radiographic Progression	Meaningful Change Not Calculated. Multiple Vectra Scores Required for Meaningful Change Calculation	High Vectra Score: 58. Patient has a High Vectra Score and is at increased risk for radiographic progression. Consider adjusting treatment regimen to reduce inflammation, and retesting at the next clinical visit.

VECTRA SCORE DESCRIPTION

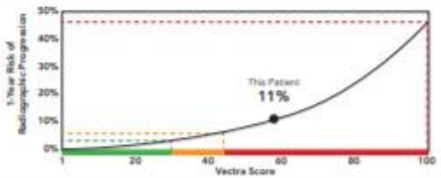
Vectra Disease Activity Levels: Low: 1 to 29 Moderate: 30 to 44 High: 45 to 100

Vectra Score measures the concentrations of 12 serum proteins. An algorithm is applied to these concentrations to calculate a disease activity score on a scale of 1 to 100. The Vectra Score is personalized based on the age, gender, and adiposity of the patient.

RISK OF RADIOGRAPHIC PROGRESSION (RP)

The risk of RP is shown as a function of Vectra Score (see graph, right). The definition of RP is a 1-year total Sharp score change of >5 units. Increased risk of RP means a greater chance of irreversible joint damage.

Patient serostatus may affect the risk of radiographic progression. Thus, the actual risk of radiographic progression may be higher if this patient is seropositive and lower if this patient is seronegative.



CHANGE IN SCORE DESCRIPTION

Change in Score is assessed in relation to the Minimally Important Difference (MID) for Vectra. The MID for patients with a Moderate or High Vectra Score is 8.0.

VECTRA SCORES OVER TIME Complete score history shown on last page. Low Moderate High

*As of December 4, 2017 the Vectra Score is adjusted based on the age, gender and adiposity of the patient.

While the Vectra Score provides important objective data, it is intended for informational purposes only and does not constitute a recommendation. Medical management decisions should be made by a healthcare provider with an understanding of the full medical history and clinical assessment of the patient. For full test specifications and related publications, please visit VectraScore.com.

Laboratory Director: Bruce F Arnold, MD, FCAP
Crescendo Bioscience, Inc. a Myriad Genetics Company
200 Wakara Way, Salt Lake City, UT 84108
VectraScore.com | P: 1-877-743-8440 | F: 1-877-743-8439

The Vectra test is intended for clinical use. Crescendo Bioscience Inc. and Myriad Genetics, Inc. developed Vectra and determined its performance characteristics. The Crescendo Bioscience Clinical Laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity clinical testing and is a College of American Pathologists Accredited Laboratory.

Vectra

PATIENT: Jane Doe	DOB: 1/1/1980	PATIENT ID: 000-000-0000	GENDER: Female

Clinical Validation

Vectra was validated in adults with RA, 230 who previously tested positive for rheumatoid factor (RF) and/or antibodies to cyclic citrullinated peptide (anti-CCP) and 141 who tested negative for both RF and anti-CCP. The performance of the test may differ between these two populations[5]. The Vectra disease activity thresholds shown on the first page of this report reflect the Vectra score equivalents to DAS28CRP cut-offs of 2.67 (low to moderate) and 4.09 (moderate to high), respectively[10], and were calculated by converting the DAS28 scale (0 to 9.4) to the Vectra Scale (1 to 100).

Individual Biomarker Results

TYPE	BIOMARKER	RESULT / UNITS	RA RANGE‡	RA PERCENTILE*
ACUTE PHASE PROTEINS	SAA	3.1 ug/mL	0.29 - 85	8%
	CRP	0.32 mg/L	0.19 - 92	64%
ADHESION MOLECULES	VCAM-1	0.41 ug/mL	0.09 - 1.2	68%
CYTOKINE-RELATED PROTEINS	IL-6	2.9 pg/mL	2.5 - 200	6%
	TNF-R1	1.2 ng/mL	0.6 - 3.9	2%
GROWTH FACTORS	EGF 3	190 pg/mL	12 - 430	27%
	VEGF-A	330 pg/mL	75 - 790	26%
HORMONES	LEPTIN	59 ng/mL	1.5 - 120	58%
	RESISTIN	5.7 ng/mL	2.5 - 21	51%
MATRIX METALLOPROTEINASES	MMP-1	5.6 ng/mL	1.3 - 23	23%
	MMP-3	17 ng/mL	7.9 - 160	30%
SKELETAL-RELATED PROTEINS	YKL-40	45 ng/mL	22 - 540	5%

‡ These 95% reference ranges were established from 125,761 patient samples tested at Crescendo Bioscience Clinical Laboratory.
§ Inversely correlated with disease activity
* Subject's biomarker level relative to levels in RA patient specimens from which the RA ranges were determined.

Please note: The individual biomarker results, which are expressed in two significant figures, are required inputs into the algorithm used to calculate the Vectra Score. Clinical interpretation of individual biomarker levels, which have different weights in the Vectra algorithm, has not been established.

References

1. Wuker CH, Östergaard M, Johansen J, et al. Predictive value of a multi-biomarker disease activity (MBDA) score for clinical remission and radiographic progression in patients with early rheumatoid arthritis (RA) – a post hoc study of the OPERA trial. Scandinavian journal of rheumatology. 2019;48:351–358.

2. Hambardzumyan K, Bolce R, Saevarsdottir S, et al. Achievement multi-biomarker disease activity score and radiographic progression in early RA: results from the SWEFOT trial. Annals of the rheumatic diseases. 2020;79:1500–8.

3. Hambardzumyan K, Bolce RJ, Saevarsdottir S, et al. Association of a multibiomarker disease activity score at multiple time points with radiographic progression in rheumatoid arthritis: results from the SWEFOT trial. RMD open. 2016;2(2):e000377. doi: 10.1136/rmdopen-2016-000377.

4. Li MX, Saco BR, van der Helm-van Mil AH, et al. Relationship of multi-biomarker disease activity score and other risk factors with radiographic progression in an observational study of patients with rheumatoid arthritis. Rheumatology (Oxford). 2016;55:257–66.

5. Markusse IM, Dirven L, van den Broek M, et al. A multibiomarker disease activity score for rheumatoid arthritis predicts radiographic joint damage in the BeSt study. Journal of rheumatology. 2016;43:2153–9.

6. VanDerHelm-Van MHAH, Knevel R, Coenen G, et al. On evaluation of molecular and clinical remission in rheumatoid arthritis by assessing radiographic progression. Rheumatology (Oxford). 2013;52:439–46.

7. Curtis JR, et al. Uptake and Clinical Utility of the Multi-Biomarker Disease Activity Testing in the U.S. J Rheumatol. 2018 Nov 15.

8. Chernoff R et al. Determination of the minimally important difference (MID) in multi-biomarker disease activity (MBDA) test scores: impact of diurnal and daily biomarker variation patterns on MBDA scores. Clin Rheumatol. 2018 Aug 29.

9. Curtis JR, et al. Validation of a novel multibiomarker test to assess rheumatoid arthritis disease activity. Arthritis Care Res. 2010; 62 (12): 1792–1801.

10. Inoue E, et al. Comparison of Disease Activity Score (DAS)28- erythrocyte sedimentation rate and DAS28- C-reactive protein threshold values. Ann Rheum Dis 2007; 66: 407–409.

Crescendo Bioscience, Inc. a Myriad Genetics Company
200 Wakara Way, Salt Lake City, UT 84108
VectraScore.com | Fax: 1-877-743-8440 | TOLL-FREE: 1-877-743-8439

The Vectra test is intended for clinical use. Crescendo Bioscience Inc. and Myriad Genetics, Inc. developed Vectra and determined its performance characteristics. The Crescendo Bioscience Clinical Laboratory is certified under the Clinical Laboratories Improvement Act of 1988 (CLIA) as qualified to perform high complexity clinical testing and is a College of American Pathologists Accredited Laboratory.

Laboratory Director: Bruce F Arnold, MD, FCAP

Note: Third page contains Complete Vectra score history for that patient

Kroger Prescription Plans

Vectra Slides
Kevin Favro, PharmD, BS
{10.15.20}

Our Mission Starts with Core Values

Transparency & Value

Financial transparency equals value, leading to an industry-leading platform designed to help you achieve success.

Personalization & Service

Helping people live healthy lives begins with personalized care, robust programs, excellent guidance and great service.

Innovation & Access

With innovation and integrity at the forefront of our offerings, health decisions are made easy and accessible.

Program Highlights

Covered Benefit for 165,000 Members Effective 1/1/2019

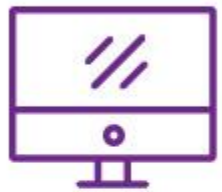
Value Based Contract

600 Members Eligible for Test

Low to Moderate Scores Targeted for Delayed (6 Month) Biologic DMARD Initiation

Process

Member Prescribed Non-bDAMRD



Member Flagged for Intervention

Pharmacist Evaluates Vectra Fit

Process

Pharmacist Educates Member on Vectra

Member Referred to Healthcare Provider

Healthcare Provider Receives Test-Related Documents

Case Study and Score Distribution

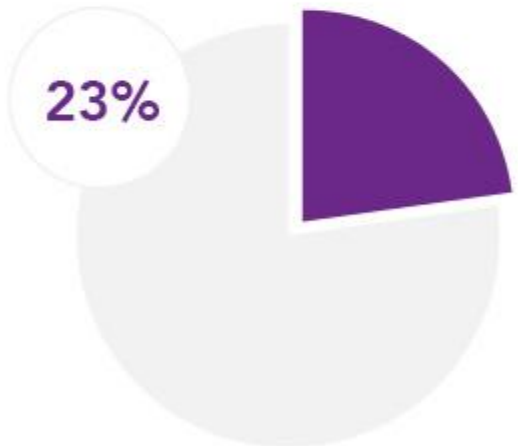
42 of 56 Members Tested are 6 Months Post-Test

19 Members Not Eligible for Analysis

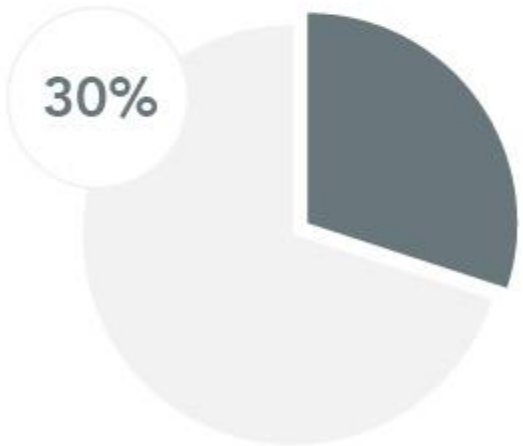
- 13 on bDMARD Before Test
- 6 Received High Test Scores

23 Members Receive Low or Mod Score

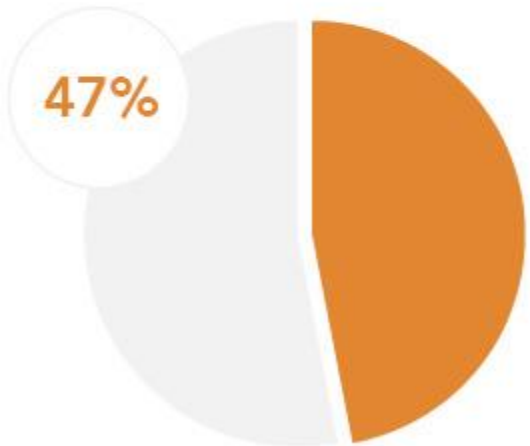
- 22 Avoided bDMARD (95%)
- 1 Initiated bDMARD (5%)



Low (<30)



Moderate (30-44)



High (>44)

Clinical Programs Mean Customized Care

95%

Avoided bDMARD With Low/Moderate Scores

$30k

Savings Per Compliant Patient Per Year

$571k

Confirmed Annual Drug Savings Compared to Treatment as Usual

*6 months of savings is based on $4,540 per-month net cost for bDMARD; savings after paying for cost of testing.

Employee Wellness

- Support medication selection at key moments within the patient's healthcare journey
- Personalize care
- Use pharmaceutical spend more effectively
- Improve patient outcomes

Vectra Preferred RA Guideline

1

Vectra Test Required

Covered at Zero Cost to Member

2

Require 3-Month Trial

One DMARD Therapy

3

Require 3-Month Trial

Dual DMARD Therapy

Vectra®

Advancements to Vectra since the Kroger Program

ACR has Included Vectra® in Recommendations for Disease Activity Measures in Patients with Rheumatoid Arthritis (RA)

The new recommendations were published in the Arthritis Care & Research Journal

Vectra is among 11 disease activity measures that met a minimum standard for regular use

Clinicians can utilize any of the 11 disease activity measures for integration into their care for RA patients

These recommendations can assist clinicians with adhering to a treat-to-target approach for patients with RA

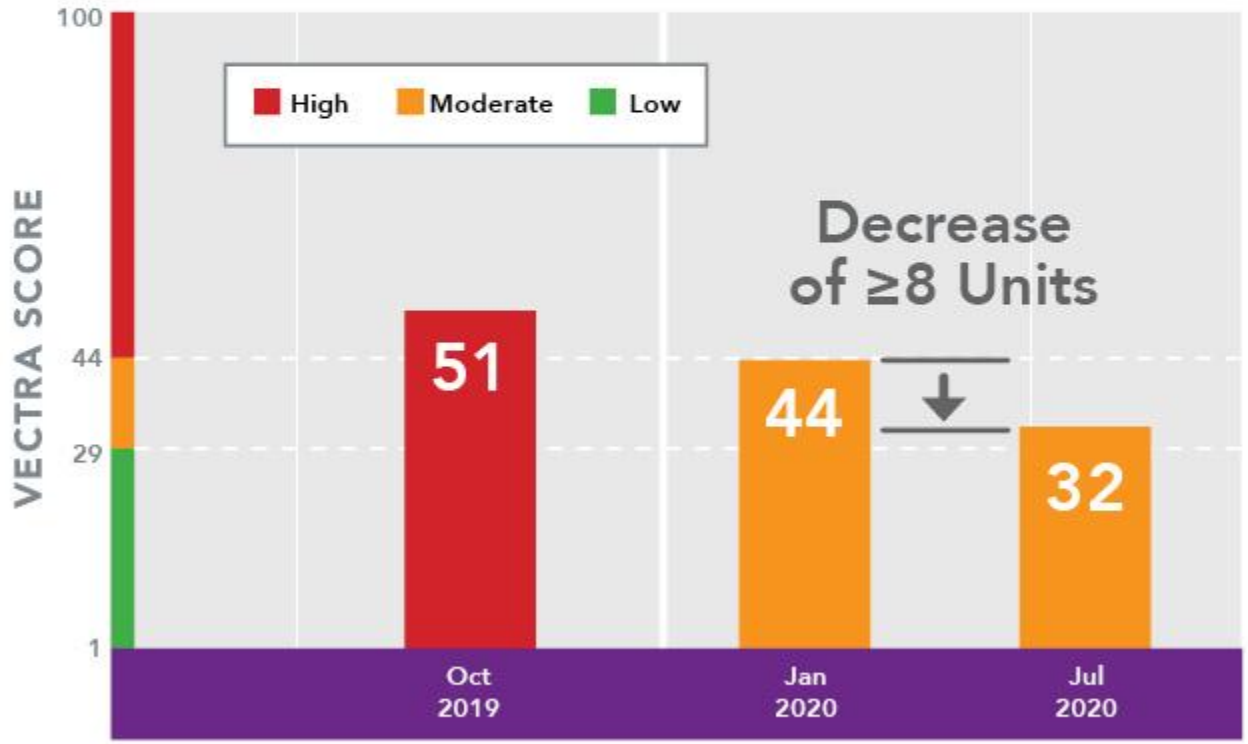
Vectra was one of the five most frequently studied RA disease activity measures among the 46 evaluated

Reference: England, B. R., Tiong, B. K., Bergman, M. J., Curtis, J. R., Kazi, S. , Mikuls, T. R., O'Dell, J. R., Ranganath, V. K., Limanni, A. , Suter, L. G. and Michaud, K. (2019), 2019 Update of the American College of Rheumatology Recommended Rheumatoid Arthritis Disease Activity Measures. Arthritis Care Res. doi:10.1002/acr.24042

Clinical Role of MID

Minimally Important Difference (MID), (≥8 on the test report) in patients with moderate or high Vectra® scores is statistically meaningful

Vectra Scores Over Time



ROLE OF MID:

1. When therapy is changed or added
2. When a provider fells the patient is starting to lose response.

- A **decrease of the Vectra Score** of ≥8 points may be indicative of response to that therapy for those patients in moderate or high disease activity
- An **increase in the Vectra Score** of ≥8 points may be indicative of a therapeutic assessment and potential change in treatment

https://www.ncbi.nlm.nih.gov/pubmed/?term=England+BR+Tiong

Current Standard of Practice

Current Practice

- Patient diagnosed with RA
- Rheumatologist puts patient on methotrexate (MTX)
  Dose is variable across specialty
- If the therapy is deemed a failure by CDAI, SDAI, RAPID3 or DAS28, they are put on biologic DMARDs
  Current measures of disease activity all have one or more subjective components

Vectra® Guided Care

- Vectra is the only objective measure of disease activity
- Vectra is proven to provide superior stratification of patient risk
  - Patients identified as low risk may benefit from less aggressive therapy

The Adjusted Multi-biomarker Disease Activity Score as a Prognostic Test for Radiographic Progression in Rheumatoid Arthritis

ABSTRACT #466

W. Huizinga[1]; Michael E. Weinblatt[2]; Nancy A Shadick[2]; Cecille H. Brahe[3]; Mikkel Ostergaard[3]; Merete Lund Hetland[3]; Karen Hambardzumyan[4]; Saedis Saevarsdottir[4,5]; Megan Horton[6]; Brent Mabey[6]; Dari D. Flake II[6]; Rotem Ben-Shachar[6]; Eric H. Sasso[7]; Jeffrey R. Curtis[8]

[1]Leiden University Medical Center, Leiden, Netherlands, [2]Department of Rheumatology, Brigham and Women's Hospital, Boston, MA, USA; [3]Copenhagen Center Arthritis Research and DANBIO, Center for Rheumatology and Spine Diseases, Rigshospitalet, Glostrup, and Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark, [4]Rheumatology Unit, Department of Medicine, Solna, Karolinska Institute, Stockholm, Sweden, [5]Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden, [6]Myriad Genetics, Inc, Salt Lake City, UT, [7]Crescendo Bioscience, Inc, South San Francisco, CA, USA, [8]University of Alabama at Birmingham, Birmingham, AL

BACKGROUND

- The multi-biomarker disease activity (MBDA) blood test has been shown to bea predictor of risk for radiographic progression in patients with rheumatoid arthritis (RA).
- The MBDA score has disease activity categories of low (<30), moderate (30-44) and high (>44).
- Since December 2017, the MBDA score has been adjusted to account for the effects of age, sex and adiposity using leptin as a surrogate. In a study of two cohorts (OPERA, BRASS) it was shown to be better than conventional disease activity measures and than the original MBDA score for predicting risk for radiographic progression (Curtis JR, et al. Rheumatology 2018).
- We have now combined 4 cohorts to validate the adjusted MBDA score as a prognostic for radiographic progression over one year in the largest such analysis to date.
- We have also: 1) compared the prognostic ability of the adjusted MBDA score to conventional measures, and 2) developed a curve for predicting risk for radiographic progression over one year with the adjusted MBDA score as a continuous variable.

METHODS

- Four cohorts with requisite data were identified and combined (N=953):

- Leiden registry (N=163) (not previously evaluated)
- OPERA study (N=154) (previously evaluated)
- SWEFOT study (N=235) (not previously evaluated)
- BRASS registry (N=401) (previously evaluated)

- The associations of the adjusted MBDA score, seropositivity (RF and/or ACPA positive), CRP, baseline total TSS, DAS28-CRP, swollen jaunt count, sex, age, and CDAI with radiographic progression over one year as a continuous variable (ΔTSS) were evaluated using linear regression.
- Logistic regression was used to estimate risk of radiographic progression (Δ TSS >5), as a function of the continuous adjusted MBDA score.

RESULTS

Table 1. Cohort designs

Study/ Registry	Leiden	OPERA	SWEFOT	BRASS
Patients, N	163	154	235	401
Type of study	Registry	RT	RT	Registry
Inclusion criteria and treatment				
Previous treatment	Non-biologic DMARDs (biologic-naïve)	DMARD-naive	Treatment - naive	DMARDs (non-biologic & biologic)
Symptom duration	Variable[a]	Early RA (<6 months)	Early RA (<1 year)	Variable
Treatment during year of radiographic evaluation	Ongoing non-biologic DMARDs (alone or in combination)	MTX monotherapy, MTX+ADA; each with IA CS for swollen joints	MTX monotherapy, MTX+SSZ+HCQ, MTX + infliximab	DMARDs any non-biologic 89.3%, MTX 50.6%; any biologic 38.7%, anti-TNF 38.4%

Abbreviations: ADA, adalimumab; CS, corticosteroid; DMARD, Disease-modifying anti-rheumatic drug; HCQ hydroxychloroquine; IA, intra-articular; MTX, methotrexate; n/a, not available; RA rheumatoid arthritis; RT randomized trial; SSZ, sulfasalazine.
[a]Parent study or registry that provided the cohorts analyzed for the relationship between MBDA score and radiographic progression.
[b]Upon enrollment in the Leiden Early Arthritis Clinic (EAC), all patients had recent onset RA (<2 years); time between EAC enrollment and inclusion in the cohort used here was variable.

- Patients in the OPERA and SWEFOT cohorts had early onset RA (mean durations 87 days and 6.1 months, respectively). Patients in the BRASS and Leiden cohorts tended to have established RA (mean duration 13.8 years, median duration 4.6 years, respectively).
- The four cohorts combined (N=953) included patients receiving biologic and non-biologic DMARDS (Table 1), with mean values of DAS28-CRP 4.5, SJC 8, and CRP 20 mg/L The mean adjusted MBDA score, 51.2, was high (>44) (Table 2).
- In continuous and binary analyses, the MBDA score was the most significant predictor of radiographic progression over one year compared to eight other variables (Table 3).
- The frequency of radiographic progression agreed more with the adjusted MBDA score than with DAS28- CRP, CRP, SJC or CDAI, both overall and when they were discordant (Figure 1).

Figure 1. Radiographic progression (RP; TSS >5) by category of adjusted MBDA score cross-classified with conventional disease activity measures

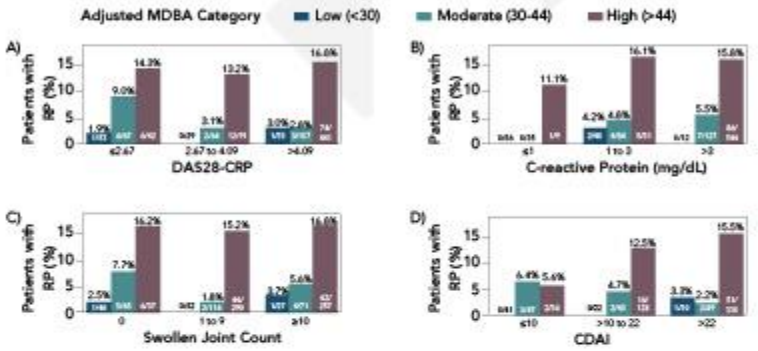


Table 2. Demographics & disease measures

4 cohorts combined (N=953)	
Patient characteristics, mean or %	
Age, years (SD)	55.4 (13.4)
Female, %	74.5%
Seropositive, %	75.5%
Symptom duration[a]	6.8 years
Baseline disease activity or radiographic progression, mean (SD)	
DAS28-CRP	4.5 (1.6)
Swollen Joing Count[b]	8.0 (6.6)
CRP, mgL	20.0 (31.1)
Adjusted MBDA score	51.2 (18.2)
TSS	29.1 (58.9)

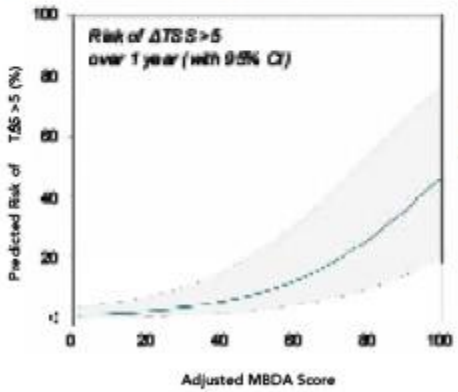
Abbreviations: SD, standard deviation;
[a]Median value used from Leiden
[b]Swollen Joint Count is based on 28-joint counts.

Table 3. Univariate analyses of association of baseline measures with radiographic progression

	4 Cohorts Combined				
Variable	N*	Δ TSS (continuous)		Δ TSS >5	
		Coefficient[a] (95% CI)	p-value	Odds Ratio	p-value
Adjusted MBDA score	953	0.061 (0.044, 0.076)	$2.5x10^{-12}$	1.05 (1.03, 1.06)	$2.5x10^{-11}$
Seropositivity[b]	719/952	1.47 (0.89, 2.06)	$9.9x10^{-7}$	6.20 (2.90, 16.1)	$7.0x10^{-6}$
log (CRP +1)	946	0.58 (0.33, 0.83)	$4.7x10^{-6}$	1.57 (1.29, 1.91)	$6.8x10^{-6}$
Baseline Tss	953	0.0074 (0.0028, 0.012)	0.0018	1.01 (1.00, 1.01)	0.0072
DAS28-CRP	927	0.31 (0.11, 0.50)	0.0026	1.24 (1.05, 1.46)	0.0096
Swollen Joint Count	953	0.062 (0.020, 0.100)	0.004	1.04 (1.00, 1.07)	0.05
Male Sex	243/953	-0.45 (-1.04, 0.14)	0.14	0.78 (0.47, 1.26)	0.32
Age	953	-0.0043 (-0.024, 0.015)	0.66	1.00 (0.98, 1.01)	0.67
CDAI	766	0.014 (-0.0053, 0.034)	0.15	1.01 (0.99, 1.02)	0.47

Abbreviations: aCRP, C-reactive protein; DAS28-CRP, Disease Activity Score using 28-joing count and CRP; MBDA, multi-biomarker disease activity; TSS, total Sharp score.
*Patients within total group that had suitable radiographic data and for whom baselin data were available for indicated variable. Ratios indicate number of patients in indicated category and total number with data available for that variable.
[a]Coefficients for continuous variables (all except seropositivity, male & smoking status) represent slope of linear regression line, expressed as units of Δ mTSS per one-unit change in indicated variable.
[b]Seropositivity defined as having tested positive for rheumatoid factor and/or anti-CCP antibodies

Figure 2. Risk curve for radiographic progression



- Risk for radiographic progression over one year increased continuously with the MBDA score, ranging from 1 % to 3% in the low (1-30) adjusted MBDA category to 7% to 47% in the high (45-100) adjusted MBDA category (Figure 2).

CONCLUSIONS

- The adjusted MBDA score was validated in four cohorts combined as a superior prognostic of radiographic progression, compared with conventional measures.
- Progression risk increased continuously with the adjusted MBDA score, exceeding 40% for the highest scores.

Abstract 466: Predicting Risk of Radiographic Progression for Patients with Rheumatoid Arthritis

Objective:

The MBDA score was adjusted to account for the effects of age, sex and adiposity and was shown in two cohorts to be better than conventional disease activity measures or predicting risk for radiographic progression.

Methods:

Four cohorts with requisite data were identified and combined: the BRASS registry (N=401) and OPERA study (N=154), and the SWEFOT study (N=235) and Leiden registry (N=163), which are new to these analyses.

The associations of radiographic progression (change per year in total Sharp score [ΔTSS]) with the adjusted MBDA score, seropositivity (RF and/or ACPA positive), DAS28-CRP, SDAI, CDAI, CRP, baseline total TSS, age, and sex, were evaluated using linear regression.

Logistic regression was used to estimate risk of radiographic progression (TSS >5)

Abstract 466: Predicting Risk of Radiographic Progression for Patients with Rheumatoid Arthritis

	4 Cohorts Combined				
Variable	N[e]	ΔTSS (continuous)		ΔTSS >5	
		Coefficient[f] (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Adjusted MBDA Score	953	0.061 (0.044, 0.076)	$2.5x10^{-13}$	1.05 (1.03, 1.06)	$2.5x10^{-}$
Seropositivity[g]	719/952	1.47 (0.89, 2.06)	$9.9x10^{-7}$	6.20 (2.90, 16.1)	$7.0x10^{-8}$
log (CRP + 1)	946	0.58 (0.33, 0.83)	$4.7x10^{-6}$	1.57 (1.29, 1.91)	$6.8x10^{-6}$
Baseline TSS	953	0.0074 (0.0028, 0.012)	0.0018	1.01 (1.00, 1.01)	0.0072
DAS28-CRP	927	0.31 (0.11, 0.50)	0.0026	1.24 (1.05, 1.46)	0.0096
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Male sex	243/953	-0.45 (-1.04, 0.14)	0.14	0.78 (0.47, 1.26)	0.32
Age	953	-0.0043 (-0.024, 0.015)	0.66	1.00 (0.98, 1.01)	0.67
CDAI	766	0.014 (-0.0053, 0.034)	0.15	1.01 (0.99, 1.02)	0.47

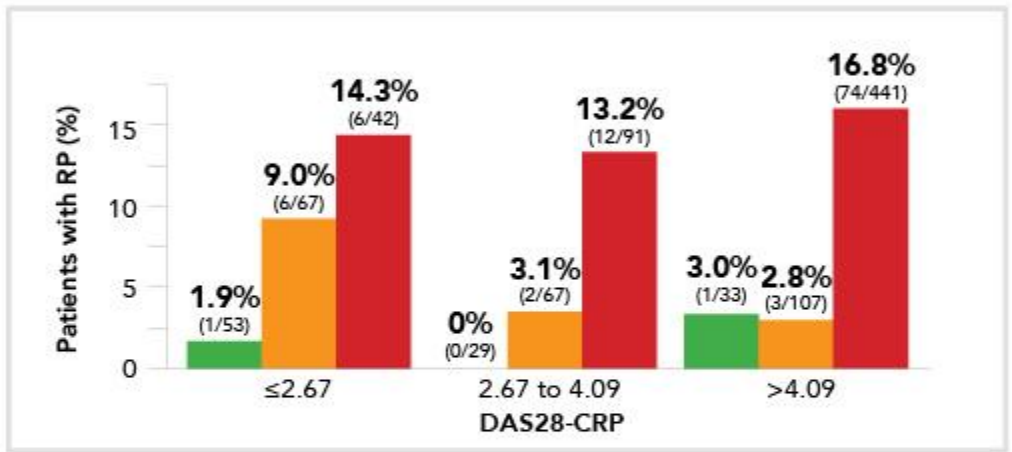
Conclusion:

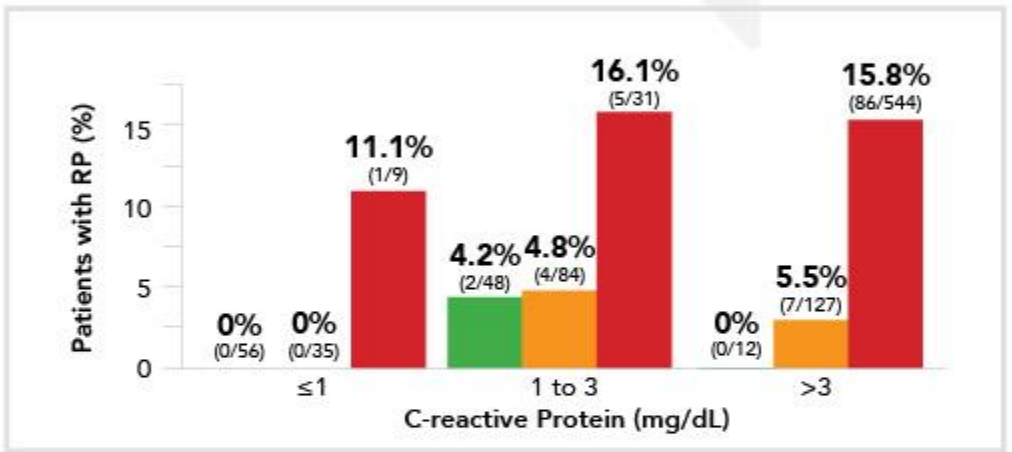
In a combined analysis of four cohorts of patients with RA, risk of radiographic progression (ΔTSS >5) was nearly absent when the adjusted MBDA score, as a continuous variable, was low, and exceeded 40% for patients with the highest MBDA scores.

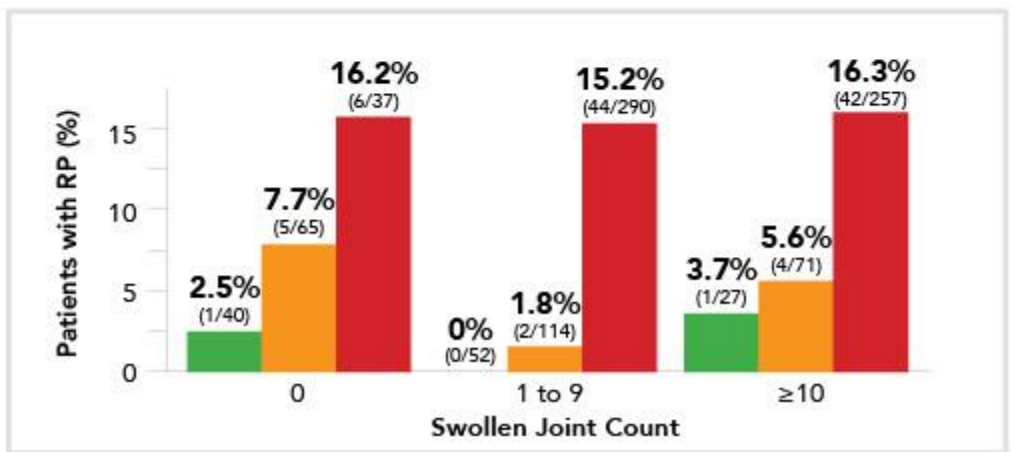
Abbreviations: ADA, adalimumab; CS, corticosteroids; DMARD, Disease-modifying anti-rheumatic drug; HCQ, hydroxychloroquine; IA, intra-articular; MTX, methotrexate; n/a, not available; RA, rheumatoid arthritis; RT randomized trial; SSZ, sulfasalazine; SD, standard deviation; aCRP, C-reactive protein; DAS28-CRP, Disease Activity Score using 28-joint count and CRP; MBDA, multi-biomarker disease activity; TSS, total Sharp score. **Table Notes: a.** Parent study or registry that provided the cohorts analyzed for the relationship between MBDA score and radiographic progression. **b.** Upon enrollment in the Leiden Early Arthritis Clinic (EAC), all patients had recent onset RA (<2 years); time between EAC enrollment and inclusion in the cohort used here was variable. **c.** Median value used from Leiden. **d.** Swollen Joint Count is based on 28-joint counts. **e.** Patients within total group that had suitable radiographic data and for whom baseline data were available for indicated variable. Ratios indicate number of patients in indicated category and total number with data available for that variable. **f.** Coefficients for continuous variables (all except seropositivity, male & smoking status) represent slope of linear regression line, expressed as units of ΔmTSS per one-unit change in indicated variable. **g.** Seropositivity defined as having tested positive for rheumatoid factor and/or anti-CCP antibodies. **References: 1.** Curtis JR, et al. Rheumatology 2018. **2.** Huizinga T, et al. Predicting Risk of Radiographic Progression for Patients with Rheumatoid Arthritis [abstract]. Arthritis Rheumatol. 2019; 71 (suppl 10). https://acrabstracts.org/abstract/predicting-risk-of-radiographic-progression-for-patients-with-rheumatoid-arthritis/. Accessed October 24, 2019.

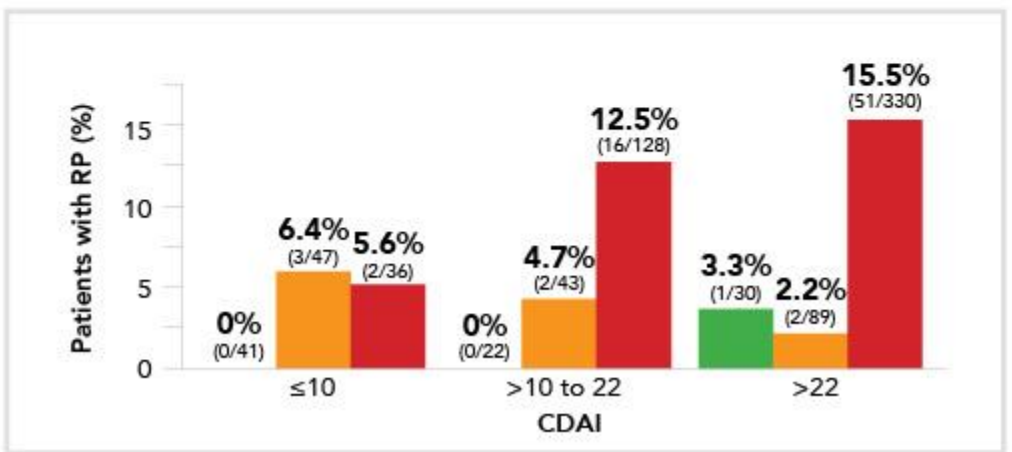
Adjusted Vectra Score Predicted Rapid Radiographic Progression Better than Conventional Clinical Measures

Adjusted MBDA Category LOW (<30) MODERATE (30-44) HIGH (>44)





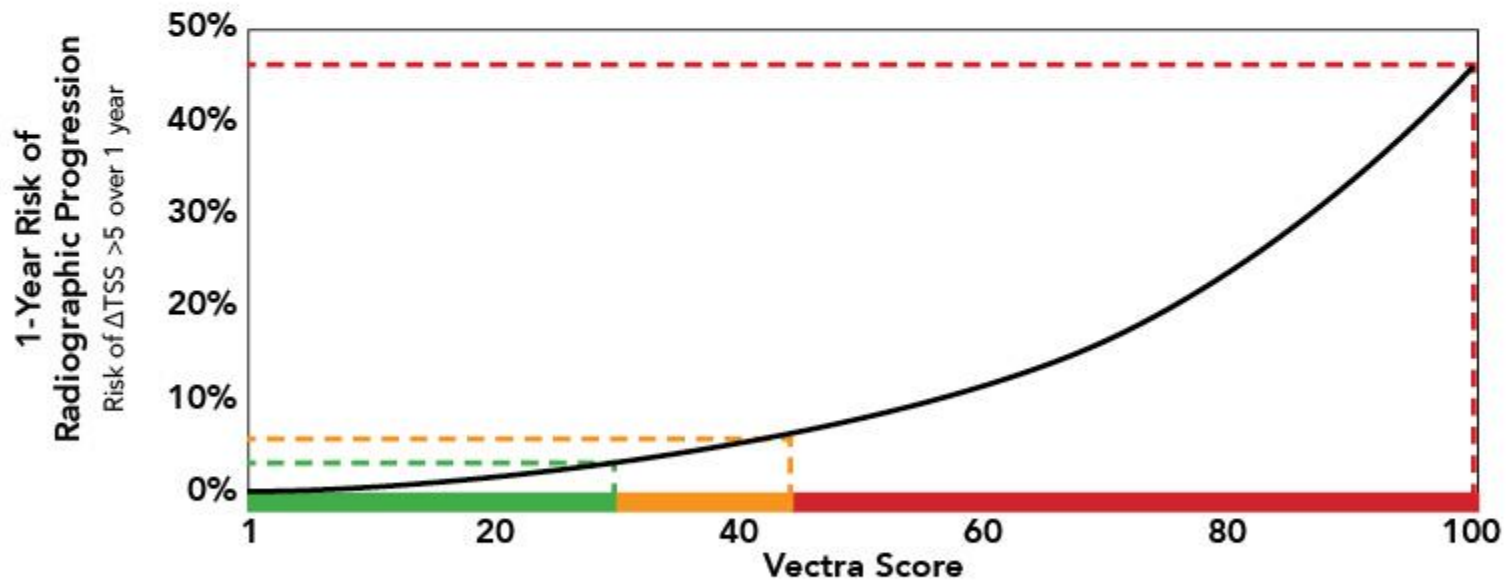




References: 1. Curtis JR, et al. Rheumatology 2018. 2. Huizinga T, et al. Predicting Risk of Radiographic Progression for Patients with Rheumatoid Arthritis [abstract]. Arthritis Rheumatol. 2019; 71 (suppl 10). https://acrabstracts.org/abstract/predicting-risk-of-radiographic-progression-for-patients-with-rheumatoid-arthritis/. Accessed October 24, 2019.

A High Vectra® Score Correlates with a Risk of Future Irreversible Joint Damage[1,2]

The risk for radiographic progression over one year increases continuously with an increasing Vectra Score.



VECTRA SCORE	RISK OF RAPID RP
HIGH (45-100)	7-47%
MODERATE (30-44)	4-6%
LOW (1-29)	1-3%

1. Curtis JR, et al. Validation of a novel multibiomarker test to assess rheumatoid arthritis disease activity. Arthritis Care Res. 2012; 64 (12): 1794-1803. 2. Huizinga T, et al. Predicting Risk of Radiographic Progression for Patients with Rheumatoid Arthritis [abstract]. Arthritis Rheumatol. 2019; 71 (suppl 10). https://acrabstracts.org/abstract/predicting-risk-of-radiographic-progression-for-patients-with-rheumatoid-arthritis/. Accessed October 24, 2019.

Vectra® Score Interpretation

VECTRA SCORE	MEDICAL MANAGEMENT RECOMMENDATION‡
Low (<30)	CONSIDER ONE OF THE FOLLOWING: • **No treatment change** (re-test in 6-12 months or sooner if indicated) • **Reduce treatment if the Vectra Score is low at two consecutive measures** (re-test in 6-12 months or sooner if indicated)* *See ACR Guidelines for therapy reduction in clinically well controlled patients

Moderate (30-44)	CONSIDER ONE OF THE FOLLOWING:
	• **Change or intensify treatment**
	  • If the Vectra Score has increased by ≥ 8 units since previous Vectra (re-test in 3 months)
	  • If the Vectra Score has decreased by <8 units since the most recent RA treatment change use clinical judgment (re-test when indicated)
	• **No treatment change**
	  • If the Vectra Score has decreased by >8 units since baseline or the most recent RA treatment change (re-test when indicated)
	  • If therapy was recently changed but no previous Vectra Score is available (re-test in 3 months)

High (>44)	CONSIDER ONE OF THE FOLLOWING: • **Change or intensify treatment** (re-test in 3 months) • **No treatment change if the Vectra Score has decreased by >8 units when a change in therapy has recently occurred** (re-test in 3 months)

This medical management guidance provides recommendations only. The treatment management decisions can only be done by a medical professional with the full information of patients medical status and medical history. These recommendations are currently being tested in clinical trial "VIVID" listed on clintrials.gov (NCT03810144).

‡ Chernoff D, (February 2019). Determination of the Minimally Important Difference (MID) in Multi-biomarker Disease Activity (MBDA) Test Scores. Clinical Rheumatology.
Curtis, JR, et al. November 2018. Uptake and Clinical Utility of the Multi-Biomarker Disease Activity Testing in the U.S. The Journal of Rheumatology.
Li, et al. August 2015. Relationship of Multi-Biomarker Disease Activity Score and Other Risk Factors with Radiographic Progression in an Observational Study of Patients with Rheumatoid Arthritis. Oxford Journals.

RETRO study design

PURPOSE: To evaluate the role of Vectra in predicting disease relapses in RA sustained remission, tapering DMARD therapy.

ENTRY CRITERIA:

- RA ≥ 1 year
- DAS28 <2.6 for ≥6 mo.
- cDMARD(s) +/- biologics therapy.

CONTINUATION → **No modification** of treatment (0-12 months)

TAPERING → **Reduction** of all conventional and/or biologic DMARDs by **50% (0-12 months)**

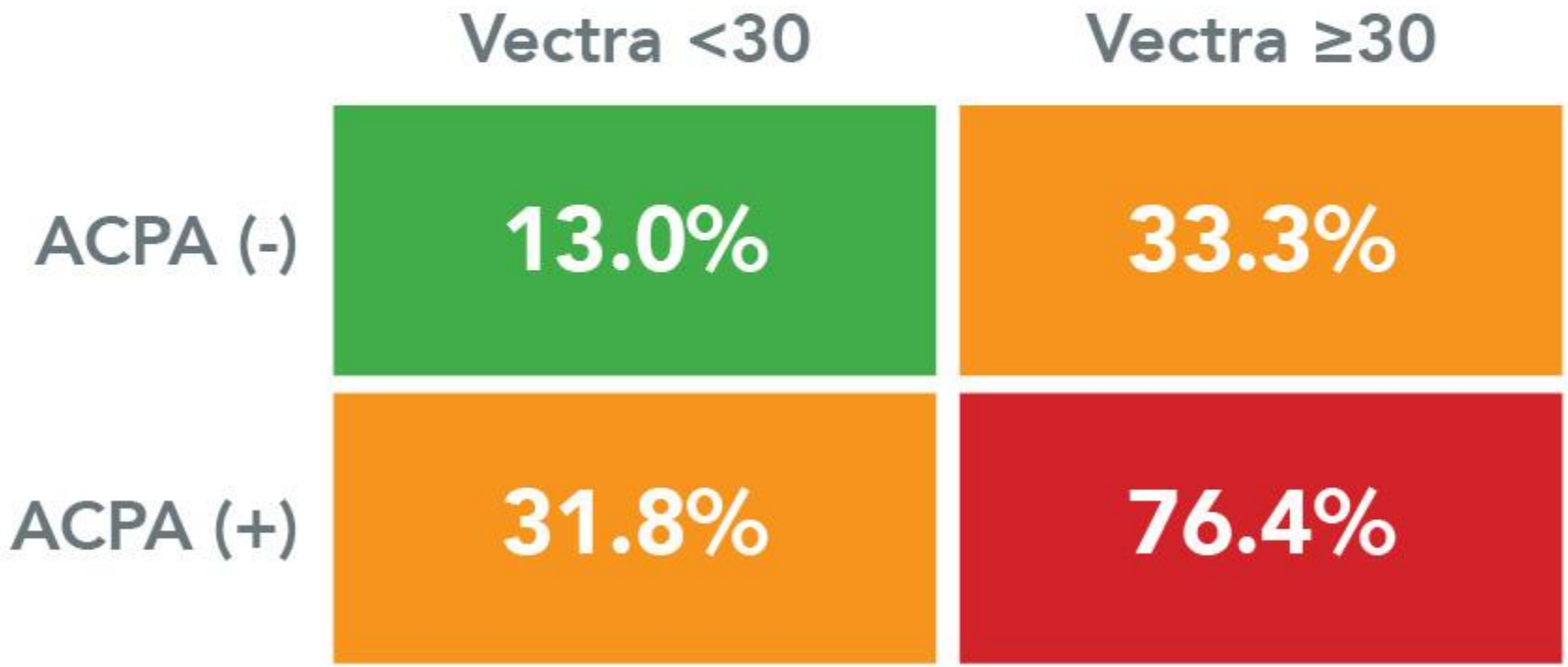
STOP → **Reduction** of all conventional and/or biologic DMARDs by **50% (0-6 months)** → **Withdrawal** of all conventional and/or biologic DMARDs **(6-12 months)**

N = 94, Continuation n = 35, Tapering n = 32, Stop n = 27.

Adapted from Rech J, et al. Ann Rheum Dis. 2015;0:1–7. doi:10.1136/annrheumdis-2015-207900.

Patients in Stable Remission with Vectra Score <30 and ACPA (-) Had Little Relapse when Undergoing Tapering

Frequency of relapse at 12 months based on ACPA status and Vectra Score



ACPA , anticitrullinated protein antibody. N = 94.

Rech J, et al. Ann Rheum Dis. 2015;0:1–7. doi:10.1136/annrheumdis-2015-207900.

Vectra Score Combined with ACPA Status Informs Cost-Savings Driven by Tapering Therapy

	ACPA (-) Vectra <30	ACPA (-) Vectra ≥30	ACPA (+) Vectra <30	ACPA (+) Vectra ≥30	TOTAL
CONTINUATION	No cost reduction	No cost reduction	No cost reduction	No cost reduction	No cost reduction
TAPERING	- $49,323	- $21,872	- $112,370	No cost reduction	**- $183,566**
STOP	- $37,388	No cost reduction	- $29,782	No cost reduction	**- $67,171**

Cost savings shown by subtracting month 12 direct treatment costs from baseline treatment costs
Cost savings converted into U.S. dollars

Hagen M, et al. J Rheumatol. 2018 Dec 1. pii:jrheum.180028. doi:10.3899jrheum.180028. [Epub ahead of print]

Vectra Informs Successful Tapering: Conclusions

- **Vectra improved the prediction of relapses** in patients with RA in stable remission undergoing DMARD tapering[1]
- If combined with ACPA testing, **Vectra informed prediction** of relapse in **more than 80% of patients**[1]
- Combining Vectra score and ACPA status may allow risk stratification for **cost-effective use of bDMARDs** in patients in deep remission[2]

1. Rech J, et al. Ann Rheum Dis. 2015;0:1–7. doi:10.1136/annrheumdis-2015-207900.
2. Hagen M, et al. J Rheumatol. 2018 Dec 1. pii:jrheum.180028. doi:10.3899jrheum.180028. [Epub ahead of print]

Vectra Product Lifecycle