Multimorbid Rheumatoid Arthritis

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Disclosures

Consulting to Boehringer Ingelheim
Royalties from UpToDate
Rheumatoid Arthritis

What’s missing?
Patient with RA (#1)

For adults with moderate to severe RA

From a RA commercial
Patient with RA (#2)
Quiz: Match Description to Picture

A. “TV RA”
B. “Real RA”

Patient with RA #1  Patient with RA #2
What does “Real RA” really look like?

**Veterans Affairs Rheumatoid Arthritis Registry**

- **RA alone**
  - 25%

- **Multimorbid**
  - 75%

**FORWARD**

- **RA alone**
  - 24%

- **Multimorbid**
  - 76%

*Defined as ≥1 condition in Rheumatic Disease Comorbidity Index*
Comorbidity vs. Multimorbidity in RA

- Osteoporosis
- Lung
- Cancer
- Obesity
- CVD

- Osteoporosis
- Lung
- Cancer
- Obesity
- CVD

RA
Comorbidity vs. Multimorbidity in RA

- Osteoporosis
- Lung
- CVD
- Obesity
- Cancer

RA
Comorbidity vs. Multimorbidity in RA

- Osteoporosis
- Lung Cancer
- Obesity
- CVD

RA is linked to all these conditions, indicating a complex interplay of diseases.
Multimorbidity: For Specialists Too!

1. Drive onset & progression of multimorbidity
   - Shortened lifespan
   - Reduced quality of life
   - Increased healthcare use
   - Expensive

2. Poor long-term outcomes (e.g. MM-related outcomes)
   - Shortened lifespan
   - Reduced quality of life
   - Increased healthcare use
   - Expensive

3. MM Changes disease management
Burden & Trajectory of Multimorbidity in RA

MarketScan database 2006-2015

- Overall cohort (n=277k)
  Matched 1:1 RA:Non-RA
- Multimorbidity (≥2 / 44 conditions)
  RA: 34% (51% at 1yr)
  Non-RA: 21%
  OR: 2.29 (2.25-2.34)

Incident cohort (n=61k)

Primary approach (n=44 conditions)

RA/non-RA: $\beta 1.13 (1.10, 1.17), P < 0.001$
RA x time: $\beta 0.21 (0.20, 0.21), P < 0.001$

Multimorbidity Trajectory in RA

Excluding RA-related conditions (n=36 conditions)

RA/non-RA: $\beta = 0.62$ (0.59, 0.64), $P < 0.001$
RA x time: $\beta = 0.12$ (0.11, 0.13), $P < 0.001$

Excluded: anemia, osteoarthritis, fibromyalgia, interstitial lung disease, chronic back pain, gout, osteoporosis, inflammatory skin disorders

2 years pre-index date (n=44 conditions)

RA/non-RA: $\beta = 0.29$ (0.27, 0.31), $P < 0.001$
RA x time: $\beta = 0.33$ (0.32, 0.35), $P < 0.001$

Multimorbidity Trajectory in RA

- Ontario, Canada (1995-2016)
- N=27 Johns Hopkins EDC conditions
- Year of diagnosis: 131% increase vs. control
  67% increase vs. medical history matched
Identifying Multimorbidity Patterns with Factor Analysis

N=226,850 (1:1 RA, non-RA)
76% female
Mean age: F53, M58
MTX, 62%
b/tsDMARDs, 32%

N=120,780 (1:1 RA, non-RA)
89% male
Mean age: F53, M64
MTX, 57%
b/tsDMARDs, 14%

Assessed n=44 chronic conditions

MarketScan

VA

# Identifying Multimorbidity Patterns with Factor Analysis

**MarketScan**

<table>
<thead>
<tr>
<th></th>
<th>RA</th>
<th>Non-RA</th>
<th>RA</th>
<th>Non-RA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Females</strong></td>
<td>Cardiopulmonary (0.47) Mental Health &amp; Chronic Pain (0.17) Cardiometabolic (0.07)</td>
<td>Cardiopulmonary &amp; metabolic (0.46) Mental Health &amp; Chronic Pain (0.19) Vascular (0.07)</td>
<td>Mental Health &amp; Chronic Pain (0.52) Cardiovascular (0.17) Metabolic (0.07)</td>
<td>Mental Health &amp; Chronic Pain (0.59) Cardiovascular (0.15) Metabolic (0.06) Mental Health &amp; Substance Abuse (0.06)</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td>Cardiometabolic (0.44) Mental Health &amp; Chronic Pain (0.18) Cardiopulmonary (0.07) Mental Health &amp; Substance Abuse (0.07)</td>
<td>Cardiovascular (0.50) Mental Health &amp; Chronic Pain (0.14) Metabolic (0.07)</td>
<td>Mental Health &amp; Substance Abuse (0.48) Cardiovascular (0.15) Chronic Pain (0.07) Metabolic (0.07)</td>
<td>Chronic pain (0.51) Cardiovascular (0.14) Metabolic (0.07) Mental Health &amp; Substance Abuse (0.06) Cancer (0.05)</td>
</tr>
</tbody>
</table>

**VA**

Factors selected based on Eigenvalue $\geq 1$

Multimorbidity patterns were considered present if at least two conditions from that pattern were present. Patterns depicted are those identified from RA patients in each dataset.
Multimorbidity: For Specialists Too!

1. Drive onset & progression of multimorbidity
   - Shortened lifespan
   - Reduced quality of life
   - Increased healthcare use
   - Expensive

2. Poor long-term outcomes (e.g. MM-related outcomes)
   - Shortened lifespan
   - Reduced quality of life
   - Increased healthcare use
   - Expensive

3. MM Changes disease management
Increased Mortality Rates in RA

95% of Deaths *Not* Attributed Directly to RA

### Cause of Death Among Men with RA (n = 332 deaths)

<table>
<thead>
<tr>
<th>Cause</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td></td>
</tr>
<tr>
<td>Coronary atherosclerosis</td>
<td>28</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>17</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>13</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>13</td>
</tr>
<tr>
<td>Other heart disease</td>
<td>9</td>
</tr>
<tr>
<td>Aortic &amp; peripheral artery</td>
<td>5</td>
</tr>
<tr>
<td>disease</td>
<td></td>
</tr>
<tr>
<td>Heart valve disorder</td>
<td>4</td>
</tr>
<tr>
<td>Pulmonary heart disease</td>
<td>4</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3</td>
</tr>
<tr>
<td>Cardiac dysrhythmia</td>
<td>2</td>
</tr>
<tr>
<td>Other circulatory disease</td>
<td>2</td>
</tr>
<tr>
<td>Conduction disorder</td>
<td>1</td>
</tr>
<tr>
<td>Cardiomyopathy, endo/myocarditis</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>105</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cause</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>34</td>
</tr>
<tr>
<td>Leukemia</td>
<td>7</td>
</tr>
<tr>
<td>Non-Hodgkins lymphoma</td>
<td>6</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>6</td>
</tr>
<tr>
<td>Pancreas</td>
<td>4</td>
</tr>
<tr>
<td>Not specified</td>
<td>4</td>
</tr>
<tr>
<td>Colon</td>
<td>3</td>
</tr>
<tr>
<td>Esophagus</td>
<td>3</td>
</tr>
<tr>
<td>Head and neck</td>
<td>2</td>
</tr>
<tr>
<td>Liver and bile duct</td>
<td>2</td>
</tr>
<tr>
<td>Skin</td>
<td>2</td>
</tr>
<tr>
<td>Bladder</td>
<td>1</td>
</tr>
<tr>
<td>Brain and nervous system</td>
<td>1</td>
</tr>
<tr>
<td>Stomach</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>76</td>
</tr>
</tbody>
</table>

### Respiratory

<table>
<thead>
<tr>
<th>Cause</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>28</td>
</tr>
<tr>
<td>Other lower respiratory</td>
<td>12</td>
</tr>
<tr>
<td><em>Respiratory failure</em></td>
<td>3</td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
</tr>
</tbody>
</table>

*Interstitial lung disease, n=11

1700 men
>6,000 PY f/u
Registry linked to NDI

Mortality Gap Narrowed, But Still Persists

2000-2005
2006-2011
2012-2017

**All-cause**

- 2000-2005: 1.31 (1.26-1.36)
- 2006-2011: 1.22 (1.18-1.27)
- 2012-2017: 1.09 (1.03-1.16)

**Cardiovascular**

- 2000-2005: 1.23 (1.15-1.32)
- 2006-2011: 1.19 (1.11-1.27)
- 2012-2017: 1.13 (1.01-1.26)

**Cancer**

- 2000-2005: 1.26 (1.16-1.36)
- 2006-2011: 1.17 (1.08-1.26)
- 2012-2017: 1.11 (0.99-1.25)

**Respiratory**

- 2000-2005: 1.45 (1.31-1.60)
- 2006-2011: 1.56 (1.42-1.71)
- 2012-2017: 1.29 (1.11-1.52)

HR = 1

N=29,779 incident RA
N=245,285 non-RA

Outcomes from Multimorbidity in RA

- Multimorbidity accounted some of the excess all-cause and cardiovascular morality in RA
  - Nurses Health Study (1k RA, 10k matched non-RA)
  - Multimorbidity weighted index (n=61 conditions)
  - HR 1.5 -> 1.2 with adjustment for multimorbidity burden
- Multimorbidity associated with poor HRQOL
  - Derived in BRASS, validated in COMORA cohort
  - Multimorbidity index (MMI; n=40 conditions)
  - Weighted and unweighted MMI outperformed Charlson for predicting EQ-5D

Assess 42 chronic conditions
1. Hypertension
2. Diabetes mellitus
3. Heart failure

RA Cohort

Factor analysis

MarketScan® MM Patterns
1. Mental health & chronic pain
2. Cardiopulmonary
3. Vascular
4. Metabolic

VA MM Patterns
1. Mental health or substance abuse
2. Metabolic
3. Cardiovascular
4. Chronic pain

Assess 42 chronic conditions
1. Hypertension
2. Diabetes mellitus
3. Heart failure

K-means clustering of RA patients based on multimorbidity patterns

Clusters of RA Patients

<table>
<thead>
<tr>
<th>Pt</th>
<th>MHCP</th>
<th>CP</th>
<th>Vasc</th>
<th>Met</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>3</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>36</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>3</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>
Multimorbidity Patterns & Health Care Utilization

MarketScan (n=113,425)

VA (n=32,640)
Multimorbidity & RA Disease Course

Disease Activity

N=2941 veterans with RA

Multimorbidity patterns applied at enrollment
Followed up to 5 years

Number of VHA Patterns

- One VHA Pattern (p = 0.10)
  - 0.10 [-0.02, 0.21]
- Two VHA Patterns (p < 0.001)
  - 0.21 [0.10, 0.32]
- Three VHA Patterns (p < 0.001)
  - 0.39 [0.26, 0.52]
- Four VHA Patterns (p < 0.001)
  - 0.60 [0.36, 0.84]

Multimorbidity: For Specialists Too!

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   - Shortened lifespan
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   - Expensive

2. Poor long-term outcomes (e.g. MM-related outcomes)
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   - Increased healthcare use
   - Expensive

3. MM Changes disease management

Diagram showing relationships among conditions like CVD, Lung, RA, Obesity, and Osteoporosis.
Not All Doom & Gloom: RA Advancements

**THEN**
- NSAIDs
- Glucocorticoids
- Methotrexate
- Sulfasalazine
- Hydroxychloroquine
- Minocycline
- Gold
- Penicillamine
- Azathioprine
- Cyclosporine
- Cyclophosphamide
- Combination DMARDs

**NOW**
- Glucocorticoids
- Methotrexate
- Sulfasalazine
- Hydroxychloroquine
- Minocycline
- Azathioprine
- Combination DMARDs
- Leflunomide
- Etanercept
- Infliximab
- Adalimumab
- Golimumab
- Certolizumab
- Anakinra
- Abatacept
- Rituximab
- Tocilizumab
- Sarilumab
- Tofacitinib
- Baricitinib
- Upadicitinib
- Biosimilars
# 2021 ACR RA Treatment Guidelines

<table>
<thead>
<tr>
<th>Table 6. Specific patient populations*</th>
<th>Certainty of evidence</th>
<th>Based on the evidence report(s) of the following PICOs</th>
<th>Evidence table(s) in Supp. App. 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous nodules</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate is conditionally recommended over alternative DMARDs for patients with subcutaneous nodules who have moderate-to-high disease activity.</td>
<td>Very low</td>
<td>PICO 64</td>
<td>p. 427</td>
</tr>
<tr>
<td>Switching to a non-methotrexate DMARD is conditionally recommended over continuation of methotrexate for patients taking methotrexate with progressive subcutaneous nodules.</td>
<td>Very low</td>
<td>PICO 65</td>
<td>p. 428</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate is conditionally recommended over alternative DMARDs for the treatment of inflammatory arthritis for patients with clinically diagnosed mild and stable airflow or parenchymal lung disease who have moderate-to-high disease activity.</td>
<td>Very low</td>
<td>PICO 67</td>
<td>p. 430</td>
</tr>
<tr>
<td>Heart Failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Addition of a non-TNF inhibitor biDMARD or tocDMARD is conditionally recommended over addition of a TNF inhibitor for patients with NYHA class III or IV heart failure and an inadequate response to DMARDs.</td>
<td>Very low</td>
<td>PICO 70</td>
<td>p. 435</td>
</tr>
<tr>
<td>Switching to a non-TNF inhibitor biDMARD or tocDMARD is conditionally recommended over continuation of a TNF inhibitor for patients seeking a TNF inhibitor who develop heart failure.</td>
<td>Very low</td>
<td>PICO 71</td>
<td>p. 436</td>
</tr>
<tr>
<td>Lymphoproliferative disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab is conditionally recommended over other DMARDs for patients who have a previous lymphoproliferative disorder for which rituximab is an approved treatment and who have moderate-to-high disease activity.</td>
<td>Very low</td>
<td>PICO 75 and PICO 76</td>
<td>p. 446–7</td>
</tr>
<tr>
<td>Hepatitis B infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylactic antiviral therapy is strongly recommended over frequent monitoring alone for patients infected who are hepatitis B core antibody positive (regardless of hepatitis B surface antigen status).</td>
<td>Very low</td>
<td>PICO 82</td>
<td>p. 499</td>
</tr>
<tr>
<td>Prophylactic antiviral therapy is strongly recommended over frequent monitoring alone for patients infected who are hepatitis B core antibody positive and hepatitis B surface antigen positive.</td>
<td>Very low</td>
<td>PICO 83</td>
<td>p. 494</td>
</tr>
<tr>
<td>Prophylactic antiviral therapy is strongly recommended over prophylactic antiviral therapy for patients initiating a biDMARD other than rituximab or a tocDMARD who are hepatitis B core antibody positive and hepatitis B surface antigen negative.</td>
<td>Very low</td>
<td>PICO 84</td>
<td>p. 471</td>
</tr>
<tr>
<td>Noninfectious fatty liver disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate is conditionally recommended over alternative DMARDs for DMARD-naive patients with nonalcohol fatty liver disease, normal liver enzymes, and liver function tests, and no evidence of advanced liver fibrosis who have moderate-to-high disease activity.</td>
<td>Very low</td>
<td>PICO 87</td>
<td>p. 489</td>
</tr>
<tr>
<td>Persistent hyperammonemia without infection in the setting of persistent hyperammonemia without infection, continuation of rituximab therapy for patients at risk is conditionally recommended over switching to a different biDMARD or tocDMARD.</td>
<td>Very low</td>
<td>PICO 66</td>
<td>p. 429</td>
</tr>
<tr>
<td>Previous serious infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Addition of tocDMARDs is conditionally recommended over addition of a biDMARD or tocDMARD for patients with a serious infection within the previous 12 months who have moderate-to-high disease activity despite tocDMARD monotherapy.</td>
<td>Very low</td>
<td>PICO 88</td>
<td>p. 490</td>
</tr>
<tr>
<td>Addition of tocDMARDs is conditionally recommended over initiation of escalation of glucocorticoids for patients with a serious infection within the previous 12 months who have moderate-to-high disease activity.</td>
<td>Very low</td>
<td>PICO 90 and PICO 95</td>
<td>p. 466–7</td>
</tr>
<tr>
<td>Nontuberculous mycobacterial lung disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of the lower possible dose of glucocorticoids ( discontinuation if possible) is conditionally recommended over continuation of glucocorticoids for patients with nontuberculous mycobacterial lung disease.</td>
<td>Very low</td>
<td>No relevant PICO</td>
<td></td>
</tr>
<tr>
<td>Addition of tocDMARDs is conditionally recommended over addition of a biDMARD or tocDMARD for patients with nontuberculous mycobacterial lung disease who have moderate-to-high disease activity despite tocDMARD monotherapy.</td>
<td>Very low</td>
<td>PICO 92</td>
<td>p. 498</td>
</tr>
<tr>
<td>Addition of tocDMARDs is conditionally recommended over initiation of escalation of glucocorticoids for patients with nontuberculous mycobacterial lung disease who have moderate-to-high disease activity despite tocDMARD monotherapy.</td>
<td>Very low</td>
<td>PICO 93</td>
<td>p. 499</td>
</tr>
</tbody>
</table>

What if a patient has multiple chronic conditions?

Certainty of evidence: Very Low
Or Paradox?

The Process of Evidence Based Medicine

“TV” RA

“Real” RA

DBRCT

Guidelines
Multimorbidity & RA Treatment: Real-World Data

- N=15,626 (RAPID3)
- N=5,733 (CDAI)
- Multimorbidity by RxRisk (n=46 categories)
- Mean RxRisk 6-7

Field guidance:

- Outcome assessment period
  Visits on or after initiation + 90d
  with valid RADAMx, up to 12
  months after anchor visit

- Baseline data
  365d prior to index

- Index Visit -1
  Mod/High disease activity
  by valid RADAMx

- Index Visit
  Mod/High disease activity
  by valid RADAMx

- Follow-up Visit #1
  at day 183 to 365
  (prior visits ignored
  between Index+1 to Index + 182)

- Valid RADAMx

- Follow-up Visit #Y

- Valid RADAMx

- Initiation as an exposure
  (subgroup)
  Index to (index + 90d)

- Initiation as an outcome
  Index + 365d

Multimorbidity & Initiating RA Treatment

RAPID3 cohort (n=15,626) 23% initiated new therapy

- OR (95% CI)
  - Ref: 1.00 (0.89, 1.13)
  - 1.00 (0.88, 1.14)
  - 0.97 (0.85, 1.11)

- RxRisk
  - 0-2
  - 3-6
  - 7-9
  - ≥10

CDAI cohort (n=5,733) 31% initiated new therapy

- OR (95% CI)
  - Ref: 1.03 (0.87, 1.22)
  - 1.08 (0.89, 1.31)
  - 0.96 (0.80, 1.16)

Adjusted for age, sex, race, U.S. region, insurance status, seropositivity, number of visits, csDMARDs, bDMARDs, and oral steroids

Multimorbidity & Achieving RA Target

RAPID3 cohort (n=1,558)

<table>
<thead>
<tr>
<th>OR (95% CI)</th>
<th>RxARisk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ref 1.00</td>
<td>0-2</td>
</tr>
<tr>
<td>0.69 (0.47, 0.99)</td>
<td>3-6</td>
</tr>
<tr>
<td>0.75 (0.50, 1.13)</td>
<td>7-9</td>
</tr>
<tr>
<td>0.54 (0.34, 0.85)</td>
<td>≥10</td>
</tr>
</tbody>
</table>

CDAI cohort (n=834)

<table>
<thead>
<tr>
<th>OR (95% CI)</th>
<th>RxARisk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ref 1.00</td>
<td>0-2</td>
</tr>
<tr>
<td>1.00 (0.63, 1.58)</td>
<td>3-6</td>
</tr>
<tr>
<td>0.70 (0.41, 1.18)</td>
<td>7-9</td>
</tr>
<tr>
<td>0.65 (0.37, 1.15)</td>
<td>≥10</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, race, U.S. region, insurance status, seropositivity, number of visits, oral steroids, number of prior csDMARDs, number of prior bDMARDs, number of prior tsDMARDs, baseline disease activity category, treatment being initiated (cDMARD, TNFi, non-TNFi bDMARD, tsDMARD)

• RCT of RAPID3 vs. CDAI assessment of certolizumab response
• SCP = use of concomitant medications indicated for the treatment of depression, anxiety, or neuropathic pain –OR- baseline medical diagnosis of depression, chronic pain, fibromyalgia, or myalgias

Multimorbidity & Shared Decision Making

- Treat-to-target, still the best option?
  - Are measures valid in multimorbid individuals?
  - Lower effectiveness of medications?
  - Higher risk of medications?
  - Will I meet quality metrics for reimbursement?
- Other health conditions may be the priority
- Are their arthritis symptoms limiting their function/QOL?
- Polypharmacy
- Expensive medications/healthcare
Example 1: RA and CVD prevention

58 y/o female with RA has lipid panel drawn:
• LDL 92 mg/dL
• ASCVD risk 4%
• Low risk, no statin initiated

High RA disease activity at last rheumatology visit:
• RA associated with 1.5-fold increased risk of CVD (risk calculators underestimate risk)
• Lipid paradox (LDL low during active inflammation)
• Taking prednisone 7.5 mg daily

Who runs the CVD prevention show?
PCP – understands CVD prevention, but ? RA impact
Rheum – understands RA impact, but? CVD prevention
Cardiology? Both?
Example 2: RA and ILD

67 y/o male with RA reports mild, non-productive cough:

- CT shows reticulation in subpleural region, bilateral lung bases
- PFT reveals normal FVC, DLCO
- Disease activity moderate
- Regimen: methotrexate, etanercept

Who runs the show?
- Rheum – change etanercept to rituximab, see pulm
- Pulm – stop methotrexate and enbrel, start nintedanib, see rheum
- PCP - ?
Multimorbid RA

• “Real RA” patients are multimorbid
• RA drives multimorbidity onset and progression early in the disease course
• Multimorbidity causes bad things to happen and changes the RA treatment landscape
• Understanding the patterns/networks of RA multimorbidity may allow for targeted intervention
• Research needs: A LOT – identification, assessment, pathophysiology, management, patient preferences, care delivery models
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