Table S1. Results of randomized controlled trials (RCTs) of biologicals and small molecule JAK inhibitors compared to placebo in methotrexate inadequate responders

| Intervention     | MOA      | Follow-up (weeks) | ACR 50 (%) | Trial                                      |
|------------------|----------|-------------------|------------|--------------------------------------------|
| Adalimumab       | anti-TNF | 24                | 55%        | Weinblatt, ARMADA [61]                     |
| Adalimumab       | anti-TNF | 52                | 42%        | Keystone [62]                              |
| Certolizumab     | anti-TNF | 52                | 37%        | Keystone, RAPID 1 [63]                     |
| Certolizumab     | anti-TNF | 24                | 33%        | Smolen, RAPID 2 [64]                       |
| Etanercept       | anti-TNF | 24                | 40%        | Moreland [65]                              |
| Golimumab        | anti-TNF | 16                | 37%        | Kay [66]                                   |
| Golimumab        | anti-TNF | 14                | 35%        | Keystone, GO FORWARD [67]                  |
| Infliximab       | anti-TNF | 30                | 27%        | Maini, ATTRACT [68]                        |
| Infliximab       | anti-TNF | 14                | 31%        | Abe [69]                                   |
| Abatacept        | IL-6     | 52                | 40%        | Kremer, AIM [70]                           |
| Abatacept        | IL-6     | 52                | 42%        | Kremer [71]                                |
| Rituximab        | B-Cell   | 12                | 43%        | Edwards [72]                               |
| Rituximab        | B-Cell   | 24                | 34%        | Emery, DANCER [73]                         |
| Tocilizumab      | IL-6     | 24                | 44%        | Smolen, OPTION [74]                        |
| Tocilizumab      | IL-6     | 16                | 53%        | Maini, CHARISMA [75]                       |
| Tofacitinib      | JAKi     | 24                | 32%        | van der Heijde, ORAL SCAN [76]             |
| Baricitinib      | JAKi     | 12                | 35%        | Keystone [77]                              |
| **Average First line all MOA** |          | **27**            | **39%**    |                                            |
| **Average First line no anti-TNF** |          | **27**            | **40%**    |                                            |
Table S2. Results of randomized controlled trials of biologics and small molecule JAK inhibitors compared to placebo in TNF inadequate responders

| Intervention       | MOA   | Follow-up (weeks) | ACR 50 (%) | Trial                          |
|--------------------|-------|-------------------|------------|--------------------------------|
| Golimumab          | anti-TNF | 24               | 16%        | Smolen, GO AFTER [78]          |
| Abatacept          | IL-6  | 24                | 20%        | Genovese, ATTAIN [79]          |
| Rituximab          | B-Cell | 24               | 26%        | Emery, SERENE [80]             |
| Tocilizumab        | IL-6  | 24                | 29%        | Emery, RADIATE [81]            |
| Tofacitinib        | JAK   | 12                | 27%        | Burmester, ORAL Step [82]      |
| **Average Second line all MOA** |       | **22**           | **24%**   |                                |
| **Average Second line no anti-TNF** |       | **22**           | **26%**   |                                |
Table S3. Response rates for second line anti-TNF therapy cycling and other MOAs

| Intervention         | ACR50 (%) | Usage |
|----------------------|-----------|-------|
| anti-TNF             | 16%       | 60%   |
| Other MOA (average)  | 26%       | 40%   |
| Weighted average     | 20%       |       |

Table S4. Biologic drug pharmacy cost from the payer perspective. Total biologic costs include the total biologic drug and associated administration costs, based on the actual drug utilization and drug administrations.

| Biologic   | MOA      | Drug Cost | Usage  |
|------------|----------|-----------|--------|
| Abatacept  | T cell   | $42,306   | 38%    |
| Rituximab  | B cell   | $30,746   | 54%    |
| Tocilizumab| IL-6     | $27,627   | 8%     |
|            | MOA Weighted Average | $34,906.98 | 12 months |
|            |          |           | $17,453.49 | 6 months |
| etanercept | Anti-TNF | $40,422   | 50%    |
| adalimumab | Anti-TNF | $40,415   | 32%    |
| infliximab | Anti-TNF | $28,906   | 11%    |
| Golimumab  | Anti-TNF | $34,863   | 4%     |
| Certolizumab| Anti-TNF | $34,775   | 3%     |
|            | anti-TNF Weighted Average | $38,728.32 | 12 months |
|            |          |           | $19,364.16 | 6 months |

| Second Line |          |          |        |
|-------------|----------|----------|--------|
| anti-TNF    |          | $38,728  | 60%    |
| MOA         |          | $34,907  | 40%    |
| Weighted Average with TNF Cycling | $37,199.78 | 12 months |
|            |          |           | $18,599.89 | 6 months |
Table S5. Total Medical and Pharmacy Costs. Total medical cost include inpatient hospitalizations, joint replacement surgeries, infections, CV events, ED encounters, outpatient visits, physician office visits, rheumatologist office visits, physical/occupational therapy, durable medical equipment, and imaging such as radiographs, magnetic resonance imaging and other types of imaging. Non-biologic pharmacy costs include all-cause pharmacy costs include all costs related to outpatient pharmacy fills, with the exception of fills for biologic drugs.

| Costs                        | 12 months | 6 months |
|------------------------------|-----------|----------|
| Responders                   |           |          |
| Medical Costs                | $ 7,581   | $ 3,791  |
| Pharmacy excluding biologic  | $ 1,698   | $ 849    |
| Inadequate responders        |           |          |
| Medical Costs                | $ 13,318  | $ 6,659  |
| Pharmacy excluding biologic  | $ 2,052   | $ 1,026  |

Table S6. Definition of PrismRA result

| PrismRA result | Likelihood of inadequate response to anti-TNF therapy | Inadequate response signal detection |
|----------------|-------------------------------------------------------|-------------------------------------|
| ≥16.6          | ≥95%                                                  | Very high                           |
| ≥11.5          | ≥90%                                                  | High                                |
| ≥9.4           | ≥85%                                                  | Moderate                            |
| <9.4           | N/A                                                   | Not detected                        |

Table S7. Assessment of disease measures stratified by PrismRA signal of inadequate response to anti-TNF therapies

| Metric                  | Timepoint | PrismRA likelihood of non-response | N     | Mean | Standard deviation |
|-------------------------|-----------|-----------------------------------|-------|------|--------------------|
| DAS28-CRP               | Baseline  | Very High                          | 47    | 5.17 | 0.83               |
|                         |           | High                               | 26    | 4.87 | 0.92               |
|                         |           | Moderate                            | 9     | 5.18 | 0.88               |
|                         |           | Low                                | 93    | 4.91 | 1.04               |
|                         | 6 months  | Very High                          | 46    | 3.95 | 1.24               |
|                         |           | High                               | 22    | 3.48 | 1.40               |
|                         |           | Moderate                            | 8     | 2.96 | 1.26               |
|                         |           | Low                                | 88    | 3.05 | 1.31               |
| Tender joint count      | Baseline  | Very High                          | 47    | 13.32| 7.16               |
|                         |           | High                               | 26    | 12.40| 7.6                |
|                         |           | Moderate                            | 9     | 10.82| 7.18               |
|                         |           | Low                                | 93    | 11.40| 7.28               |
|                         | 6 months  | Very High                          | 47    | 8.09 | 7.16               |
|                         |           | High                               | 26    | 5.87 | 7.22               |
|                             | Moderate | Low       |
|-----------------------------|----------|-----------|
| Swollen joint count         |          |           |
| Baseline                    | 9        | 2.59      |
| High                        | 26       | 7.11      |
| Moderate                    | 9        | 10.43     |
| Low                         | 93       | 8.18      |
| 6 months                    | 47       | 4.72      |
| Very High                   | 26       | 3.53      |
| Moderate                    | 9        | 1.69      |
| Low                         | 93       | 2.57      |
| CDAI                        |          |           |
| Baseline                    | 47       | 33.68     |
| High                        | 26       | 30.51     |
| Moderate                    | 9        | 32.88     |
| Low                         | 93       | 29.65     |
| 6 months                    | 47       | 20.64     |
| Very High                   | 26       | 16.67     |
| Moderate                    | 9        | 9.33      |
| Low                         | 92       | 12.83     |
Table S8. Number of patients reaching endpoints stratified by PrismRA signal of inadequate response to anti-TNF therapies

| Clinical metric | Other | LDA | Remission |
|-----------------|-------|-----|-----------|
| DAS28-CRP       |       |     |           |
| Very High       | 35    | 5   | 6         |
| High            | 16    | 0   | 6         |
| Moderate        | 4     | 1   | 3         |
| Low             | 48    | 5   | 35        |

Table S9. Odds of inadequate response to anti-TNF therapies

| Clinical metric                                      | OR (95% CI) |
|------------------------------------------------------|-------------|
| PrismRA                                              | 6.58 (2.75, 15.6) |
| Female sex                                           | 2.42 (1.20, 4.88) |
| BMI ≥30 kg/m² (obese)                                | 2.01 (1.00, 4.04) |
| Number of swollen joints                             | 1.92 (0.98, 3.71) |
| CDAI                                                 | 1.45 (0.70, 3.01) |
| Any tobacco smoke (current or previous)              | 1.13 (0.59, 2.18) |
| Age > 50 years                                       | 0.84 (0.43, 1.68) |
| Number of tender joints                              | 0.75 (0.39, 1.45) |
| Clinical metrics algorithm                           | 1.34 (0.67, 2.34) |