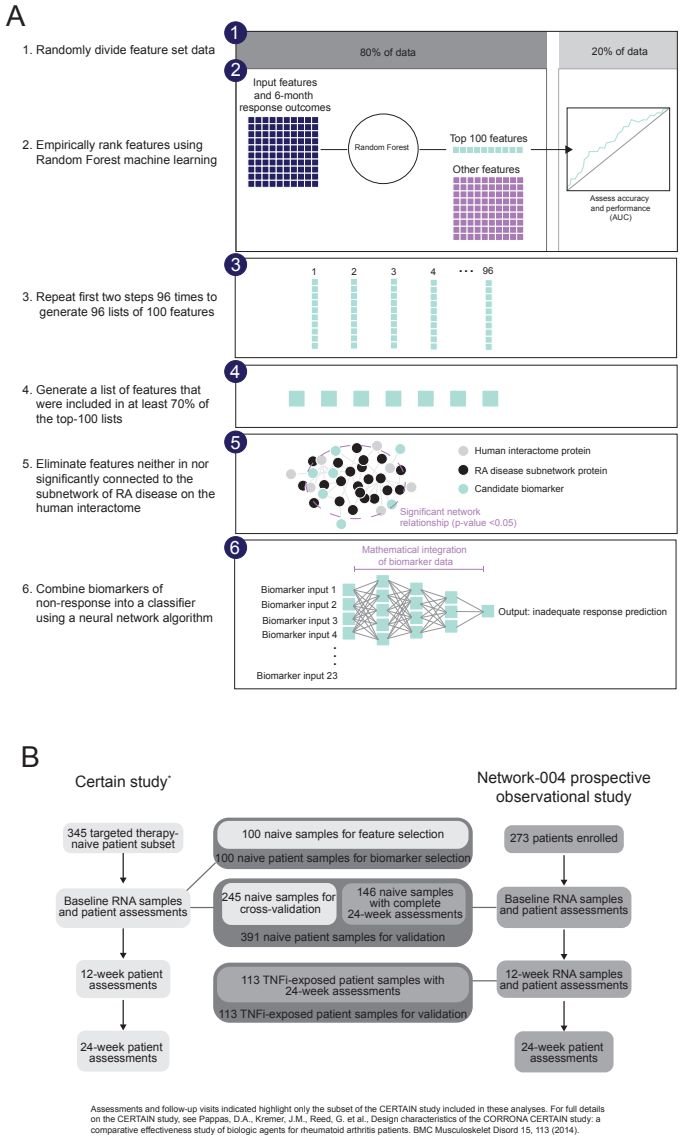
SUPPLEMENTARY MATERIAL

Supplementary Fig. S1. Flow chart of study design. **a**) Biomarker feature selection using machine learning and network-based methods as detailed in the methods section. **b**) A subset of 345 patients from the CERTAIN study were analyzed: 100 for identification of transcript biomarkers of non-response to TNFi therapies and 245 for cross-validation. 273 patients enrolled in the NETWORK-004 blinded prospective observational study; 244 passed initial enrollment screening, 194 completed the 3-month follow-up visit and 168 completed the 6-month follow-up visit. 87% (146/168) of patients who completed the study had complete molecular and clinical data required to perform validation analyses.



Assessments and follow-up visits indicated highlight only the subset of the CERTAIN study included in these analyses. For full details on the CERTAIN study, see Pappas, D.A., Kremer, J.M., Reed, G. et al., Design characteristics of the CORRONA CERTAIN study: a comparative effectiveness study of biologic agents for rheumatoid arthritis patients. BMC Musculoskelet Disord 15, 113 (2014).

Supplementary Table S1. Characteristics of patients who did not complete the NETWORK-004 prospective observational trial.

Reason for leaving trial	**Percent of patients**
Lost to follow up	9%
Screen failure	13%
Other	27%
Adverse Event	4%
Withdrawal by subject	17%
Study terminated by sponsor	1%
Death	1%
Physician decision	2%
Non-compliance with treatment	8%
Protocol violation	2%
Failed final data review; incomplete molecular or clinical data	17%
Other events (N = 29)	**Percentage of other events**
Financial problem	32%
Switched targeted therapy	13%
Protocol violation	26%
TNFi not initiated during study period	19%
Not reported	10%

Supplementary Table S2. Odds of a patient with a molecular signature of non-response having an inadequate response according to different criteria and follow-up assessment timepoints during cross-validation.

	AUC	Odds ratio (95% CI; p-value)
Cross-validation, naive		
ACR50, 6 months	0.66	3.0 (1.6-5.5; 0.0002)
ACR70, 6 months	0.66	3.4 (1.6-7.1; 0.0008)
CDAI LDA, 6 months	0.67	3.7 (2.2-6.4; <0.0001)
CDAI remission, 6 months	0.67	3.4 (1.6-7.6; 0.0014)
DAS28-CRP LDA, 6 months	0.64	2.5 (1.5-4.3; 0.0005)
DAS28-CRP remission, 6 months	0.65	2.7 (1.6-4.7; 0.0003)

AUC = area under the curve, CI = confidence interval, ACR = American college of rheumatology, CDAI = clinical disease activity index, LDA = low disease activity, DAS28-CRP = disease activity score 28-joint count with C-Reactive protein, TNFi = tumor necrosis factor-α inhibitor

Supplementary Table S3. Comparison of baseline demographic characteristics between patients who did or did not respond to TNFi treatment according to ACR50 non-responder (NR) and responder (R) status at 6 months. Total-cohort demographic information is reported in Table 2.

	CERTAIN study feature selection (N = 100)			CERTAIN study cross-validation (N = 245)			NETWORK-004 study targeted therapy-naïve (N = 146)		
Characteristic	**NR (n = 69)**	**R (n = 31)**	**p-value**	**NR (n = 170)**	**R (n = 75)**	**p-value**	**NR (n = 81)**	**R (n = 65)**	**p-value**
Age (year), mean (SD)	54 (10.8)	55 (15.4)	0.82	56 (11.8)	52 (13.2)	0.07	59 (12.5)	55 (15.7)	0.11
Female, n (%)	55 (79.7)	17 (54.8)	0.02	132 (77.6)	47 (62.7)	0.02	62 (76.5)	53 (81.5)	0.60
Duration of disease (year), median (IQR)	1 (1,4)	1 (1, 7.5)	0.63	2 (1, 6)	2 (1, 5.5)	0.76	1 (1,5)	1 (0, 4)	0.61
Race, n (%)			0.36			0.47			0.69
White	55	28		145	68		63 (77.8)	54 (83.1)	
African American	8	1		11	2		12 (14.8)	4 (6.2)	
Other	20	2		30	5		6 (7.4)	7 (10.8)	
Anti-CCP positive, n (%)	38 (55.1)	24 (77.4)	0.01	99 (58.2)	55 (73.3)	0.01	36 (44.4)	36 (55.4)	0.26
RF positive, n (%)	51 (73.9)	25 (80.6)	0.61	117 (68.8)	55 (73.3)	0.71	22 (38.6)	33 (70.2)	0.005
Prednisone at baseline, n (%)	19 (27.5)	11 (35.5)	0.57	51 (30.0)	13 (17.3)	0.06	12 (14.8)	25 (38.5)	0.02
Prednisone dosage, median (IQR)	5 (5,10)	5 (5, 8.75)	0.61	5 (5,10)	5 (5,10)	0.95	5 (5,10)	5 (4, 5)	0.10
Current csDMARD, n (%)			ND*						ND*
Methotrexate	35 (50.7)	21 (67.7)		97 (57.1)	41 (54.7)	N/A*	64 (79.0)	56 (86.2)	
≥2 csDMARDs	5 (7.2)	2 (6.5)		27 (15.9)	15 (20.0)	N/A*	6 (7.4)	6 (9.2)	
None	11 (15.9)	4 (12.9)		29 (17.1)	8 (10.7)	N/A*	16 (19.8)	9 (13.8)	
TNFi use, n (%)			0.92			0.28			0.22
Adalimumab	26 (37.7)	10 (32.3)		67 (39.4)	31 (41.3)		22 (27.2)	26 (40.0)	
Etanercept	23 (33.3)	12 (38.7)		52 (30.6)	24 (32.0)		19 (23.5)	12 (18.5)	
Infliximab	11 (15.9)	4 (12.9)		27 (21.8)	11 (14.7)		9 (11.1)	9 (13.8)	
Certolizumab pegol	6 (8.7)	4 (12.9)		12 (7.1)	5 (6.7)		6 (7.4)	7 (10.8)	
Golimumab	3 (4.3)	1 (3.2)		2 (1.2)	4 (5.3)		25 (30.9)	11 (16.9)	

*ND: not determined; patients receiving methotrexate and a second csDMARD are included in both categories. SD = standard deviation, IQR = interquartile range, csDMARD = conventional synthetic disease modifying antirheumatic drug, TNFI = tumor necrosis factor-α inhibitor, Anti-CCP = anti-cyclic citrullinated protein

Supplementary Table S4. Confusion matrix indicating the number of targeted therapy naïve RA patients who achieved remission at 6 months according to CDAI (≤2.8) and DAS28-CRP (<2.4) who also had a molecular signature of non-response detected at baseline.

CDAI remission	**Non-responder**	**Responder**
Signal detected	74	4
Signal not detected	46	22
DAS28-CRP remission	**Non-responder**	**Responder**
Signal detected	64	11
Signal not detected	33	33

CDAI = clinical disease activity index, DAS28-CRP = disease activity score 28-joint count with C-Reactive protein

SUPPLEMENTARY DISCUSSION: BIOLOGY OF BIOMARKERS

TNF-α and cytokine biosynthesis

TNF-α is synthesized as a transmembrane precursor (pro-TNF-α) and then proteolytically cleaved to a soluble, mature homotrimer [1, 2]. Release is primarily regulated at the transcriptional level after a stimulus triggers biosynthesis [3]. Newly formed pro-TNF-α is continuously secreted without the need for a second stimulus, by constitutive trafficking through the endoplasmic reticulum, Golgi and endosomal network to the cell surface where pro-TNF-α can be cleaved or endocytosed. Secretory and endocytic pathways modulate the number and availability of biologically active TNF-α molecules [4]. Secondly, binding of TNFi to transmembrane TNF-α results in internalization of the TNFi/TNF complex first into early endosomes [5, 6].

GOLGA1 encodes golgin-97, which is an autoantigen [7] and is essential for endosome-to-trans-Golgi network trafficking [8].

COMMD5 is localized on early endosomes and recycling endosomes, [5] colocalizing with common endosomal markers to those of TNF-α [9]. Recycling endosomes are specialized secretory compartments with functions that include trafficking of cytokines to cell surfaces. Furthermore, COMMD5 depletion results in re-organization of actin filaments and microtubules distribution, which impacts directional cell migration and junctions [5].

T and B cell homeostasis

T cells are crucial to the pathophysiology of rheumatoid synovitis, and previous studies of the molecular pathways that identify patients who will not respond to TNFi therapies demonstrated a connection between T cell signaling and RA disease biology [10-15]. Large numbers of activated T cells can be detected in the joints of RA patients and synovial inflammation includes natural killer cells, $CD4^+$, and $CD8^+$ T cells [16-20]. During T cell-dependent inflammatory responses, B cells can differentiate into antibody-producing plasma cells or enter follicles to form germinal centers. Dysregulation of germinal center response has been implicated in development of systemic autoimmunity [21-23]. TNF-α is required for germinal center organization and development in mice during normal homeostatic conditions and infections [24-27]. Germinal centers are common in inflamed synovia of RA patients and modulation of synovial inflammation by TNFi is associated with a reversal of synovial lymphoid neogenesis [28-31].

SPON2 is secreted into the extracellular matrix that is essential for initiation of immune responses, acts as an integrin ligand for inflammatory cell recruitment and T cell priming, and SPON2 knockout mice display impaired humoral responses to T cell-dependent antigens [32-34].
STOML2 is upregulated in T cell upon effector responses while down-regulation of STOML2 expression correlates with loss of sustained TCR signaling and decreased T cell activation [35, 36]. Furthermore, IL-2 production by activated T cells is reduced in STOML2 knockout mice [37]. Interleukin-2 (IL-2) is a cytokine predominantly produced by $CD4^+$ T cells and has numerous functions including promoting cell survival, activation, growth and differentiation [38]. IL-2 is a key regulator that controls the balance between regulatory and effector T cell function [38]. Peripheral blood mononuclear cells from RA patients, particularly from those with extra-articular disease, exhibit lower levels of IL-2 production [39, 40]. Treatment with low dose recombinant human IL-2 protein is being explored as a therapy in RA (NCT02467504).
BCL6 encodes a transcription factor that is the master regulator of germinal center creation and functions by recruiting co-repressor complexes to induce epigenetic changes and suppression of >1000 genes [41-43]. IL-21 signaling through STAT3 induces expression of BCL6 and mice deficient in IL21, IL21R, or STAT3 have defects in antibody responses and germinal center formation [44].

Response to methotrexate

The American College of Rheumatology (ACR) treatment guidelines states the methotrexate is the preferred initial DMARD for most early RA patients [45]. Methotrexate is the most common csDMARD prescribed concurrently with TNFi therapies and, compared to TNFi therapy alone, therapy persistence is longer and development of anti-drug antibodies is reduced [46-49]. Furthermore, methotrexate may impact the biological response to TNFi therapies by altering the immunobiology of the cellular targets of TNFi inhibitors [50].
IMPDH2 is upregulated in and increases the sensitivity to methotrexate of human cancer cells [51, 52]. Furthermore, IMPDH2 expression changes occur upon methotrexate treatment of cell lines in culture [53] and methotrexate treatment induces IMPDH filament formation in cell culture [54]. Taken together, this suggests that IMPDH2 may be acting as a molecular marker that assesses methotrexate use among RA patients. Efforts to investigate IMPDH2 polymorphisms with respect to methotrexate response RA have been limited by insufficient data [55].

Alternatively, IMPDH2 has been shown to form filaments during antigen-specific T cell activation in healthy mouse spleen, thymus and pancreas [56-58]. IMPDH inhibitors (eg. azathioprine, mycophenolic acid) limit lymphocyte proliferation and are used clinically as immunosuppressants [59, 60].

Bone destruction

Elevated osteoclast activity, impaired osteoblast function and osteoblast differentiation contribute to focal bone erosion development in RA [61-64]. TNF-α is one of the several pro-inflammatory cytokines involved in regulation of bone homeostasis by stimulating osteoclastogenesis and inhibiting osteoblast function. Treatment with TNFi therapies reduces radiographic progression [65-73]. However, disease activity correlates with radiographic progression, even among patients treated with TNFi therapies [74].

SPINT2 is upregulated in RA synovial fibroblasts compared with healthy synovial fibroblasts [75]. SPINT2 encodes the transmembrane protein HAI-2 that inhibits the hepatocyte growth factor activator (HGFA). HGFA proteolytically cleaves hepatocyte growth factor (HGF) into its active form, which regulates various physiological functions including immune regulation and viability of osteoblasts and osteoclasts [76]. Furthermore, HGF decreased circulating TNF-α, MCP-1, IL-1 and IL-6 levels in the serum of mice [76]. Among RA patients, elevated levels of HGF predicted more severe radiographic joint damage [77].

ATRAID is induced by the ligand all-trans retinoic acid that binds NELL-1 [78], a secreted protein that promotes bone mineralization in mice and potentiates osteoblast differentiation in an ATRAID-dependent manner [79, 80]. Furthermore, loss of ATRAID function limits therapeutic responses to widely used medications for bone diseases [81].

ALPL encodes a tissue-nonspecific alkaline phosphatase. Alkaline phosphatase is an osteoblastic marker and a predictor of bone mineral density in osteoporosis [82, 83]. ALPL is necessary for postnatal bone formation and bone deformities are related to the extent of ALPL deficiency [84, 85]. Ablation of ALPL in mice induced premature bone aging [86].

Unfolded protein response

The unfolded protein response protects the cell from stresses that impact protein folding and quality and has been implicated in a growing number of inflammatory and autoimmune conditions [87, 88]. RA synovial fibroblasts are under ER stress that is further increased by TNF-α [89], and ER stress is buffered by activation of the unfolded protein response during

which misfolded proteins are transported from the ER to the cytosol for proteasomal degradation [90]. Furthermore, in response to TNF-α, autophagy stimulation increases dependence on the proteasome for RA synovial fibroblast cell viability [89].
KLHDC3 binds to and is an adaptor for the E3 ubiquitin ligase CUL2, thus targeting glycine-ended peptides for proteasomal degradation [91, 92]. The majority of proteins targeted for degradation by the KLHDC3/CUL2 are aberrant proteins with molecular characteristics that direct them for elimination [93].
NOD2 has also been linked to activation of the unfolded protein response through TRAF2 and RIP2 [94, 95].

Synovitis and pleiotropic pro-inflammatory signaling, including NFkB signaling
Synovitis, when the joint becomes inflamed, is a hallmark of RA. Six features are master regulators of pro-inflammatory processes including transcription factors, regulators of NF-κB signaling, pro-inflammatory cytokines and key components of the JAK-STAT pathway. These features transmit intracellular signals that drive inflammation in RA patient synovia. These proteins also impact many of the other aspects of RA disease biology discussed above including innate immune pathways, adaptive immune cell activation, endoplasmic reticulum stress and autophagy.
NOTCH1 encodes is a ubiquitous signaling receptor involved in nearly all aspects of the cellular life cycle [96]. Additionally, it regulates inflammatory responses [97]. In RA, Notch1 signaling proteins are over-expressed in synovial tissues and Notch expression in RA synoviocytes contributes to TNF-α-induced proliferation [98, 99]. Furthermore, suppression of Notch signaling suppresses inflammatory arthritis and NF-kB proinflammatory cytokines, including TNF-α, IL-6, IL-12 and IFN-ɣ [100-102].
NOD2, belonging to the intracellular NOD-like receptor family, detects conserved motifs in bacterial peptidoglycan and promotes their clearance through activation of a proinflammatory transcriptional program and other innate immune pathways, including autophagy and endoplasmic reticulum stress [94, 103]. In murine autoimmune arthritis, Nod2 deficiency augments Th17 responses and exacerbates arthritis symptoms [104]. Nod2 activates NF-κB, which requires IKKɣ and is inhibited by dominant negative mutants of IκBα, IKKα, IKKβ, and IKKɣ [105].
LIMK2 encodes a serine/threonine/tyrosine kinase that is phosphorylated by Rho-associated protein serine/threonine kinase (ROCK1) [106]. Treatment of cells in culture with TNF-α activates ROCK1 signaling [107] and LIMK2 has been identified as a potential response marker

to TNFi therapy in psoriasis [108, 109]. Enhanced ROCK activity has been reported in PBMCs and synovium from RA patients [110, 111]. Furthermore, inhibition of ROCK signaling reduced synovial inflammation in rats with collagen-induced arthritis and inhibited NFkB signaling ex vivo in PBMCs from RA patients [111].

The Janus kinases (JAK) family of intracellular tyrosine kinases (JAK1, JAK2, JAK3, and TYK2) are key components of the JAK-STAT pathway that transmit signals of many cytokines involved in the pathogenesis of numerous immune-mediated diseases [112]. The importance of JAK-STAT signaling is typified by the inhibition of JAKs for treatment of RA [113, 114].

IL1B is a proinflammatory cytokine that contributes to RA pathogenesis [115, 116]. IL-1 cytokine levels are elevated in plasma and synovial fluid of RA patients, correlate to aspects of disease activity and IL-1 receptor is the target of a targeted therapy for treatment of RA [117, 118].

ZFP36 encodes tristatraprolin (TTP), which is a negative regulatory of proinflammatory gene expression by binding to and promoting degradation of specific RNA transcripts [119]. TTP expression is elevated in RA patient synovium [120]. Transgenic mice lacking TTP displayed characteristics of erosive arthritis, phenocopying chronic administration of TNF-α, which was prevented through treatment with anti-TNF antibodies [121].

Apoptosis and autophagy

Apoptosis is regulated cell death. In conjunction with FasL, TNF-α contributes to protection against apoptosis in the RA joint and promotes apoptosis of bone marrow progenitor cells that can cause anemia in chronic disease [122]. FasL or TNF-α can stimulate Fas (CD95) on fibroblasts and lymphocytes to activate an intracellular cascade of caspases that lead to apoptosis [123]. However, despite the expression of Fas in a variety of cells in RA synovial tissue, synovial cells rarely undergo apoptosis in vivo [124].

Autophagy is the regulated destruction of soluble macromolecules and organelles via lysosomes. This cellular process is critical to cellular homeostasis and contributes to inflammation in RA by controlling cell development, survival and proliferation [125, 126]. Furthermore, autophagy has implicated in generation of citrullinated peptides in RA [127] and autophagy influences resistance to TNFi therapy [128].

CFLAR encodes FLICE-inhibitory protein (FLIP) that prevents the association of caspase 8 with FADD and thus exerts an antiapoptotic effect through inhibition of Fas-mediated apoptosis. Furthermore, constitutive activation of murine FLIP causes autoimmunity in mice [129].

CDK11A encodes a cyclin dependent kinase that not only has a role in cell cycle regulation but is also required to induce autophagy [130].

Innate immunity

Innate immune cells – monocytes, macrophages and dendritic cells – are involved in inflammatory responses of RA patients and drive activation of the adaptive immune system [131]. Furthermore, the continual expression of macrophage-derived cytokines in RA (TNF-α, IL-1 and IL-6) suggests that the innate immune system is persistently activated [132].
TRIM25 encodes a ubiquitin E3 ligase active in innate immunity and cell fate decisions [133]. TRIM25-mediated ubiquitination of the cytosolic pattern recognition receptor RIG-I has roles in early innate immunity, including negative regulation of RIG-I and modulation of p53 [134-136]. Furthermore, TRIM25 has been implicated in mediating response to ER stress, as discussed in the context of RA above in “Unfolded protein response” [137].

Clinical features in the MSRC

Clinical features included among the biomarkers are sex, BMI, anti-CCP antibody seropositivity and patient global assessment. The increased risk of RA in females has been associated with pregnancy, hormonal contraceptive use, and lower levels of testosterone [138, 139]. Men may respond better to TNFi treatment than women in early, but not established RA [140-143]. Seropositive RA is characterized by abnormally elevated levels of circulating autoantibodies including anti-CCP. Measurement of anti-CCP is highly specific (98%) and sensitive (80%) for RA and anti-CCP titer correlates with erosive disease and worse prognosis [144, 145]. However, many studies have reported conflicting results regarding the association of antibody titer and response to TNFi therapy [141, 146-157], suggesting that the transcript features in the MSRC may deconvolute additional variables that give rise to these conflicting results. The patient global assessment is one of the most widely used patient reported outcomes and is a key component of many validated disease assessments. It captures complex underlying factors such as pain, depression and anxiety, inability to participate in daily activities and fibromyalgia [158]. The patient global assessment may be a better indicator of improvement after treatment than other disease measures, such as the tender and swollen joint counts [159]. Independently, each clinical feature may be poorly predictive of response to TNFi therapy when considered in a diverse patient population but help to maximize predictive power when assessed in conjunction with the unique molecular disease biology of each patient.

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