Earlier Time to Remission Predicts Sustained Clinical Remission in Early Rheumatoid Arthritis — Results from the Canadian Early Arthritis Cohort (CATCH)

Bindee Kuriya, Juan Xiong, Gilles Boire, Boulos Haraoui, Carol Hitchon, Janet Pope, John Carter Thorne, Diane Tin, Edward C. Keystone, and Vivian Bykerk, for the CATCH Investigators

ABSTRACT. ***Objective.*** To evaluate the prevalence and predictive factors of sustained remission in an early rheumatoid arthritis (ERA) population. Predictive factors of sustained remission in ERA are unknown. We hypothesized that a short time to remission is an important predictor of sustained clinical remission.

Methods. Patients in the Canadian Early Arthritis Cohort were included. Remission was defined by Boolean-based American College of Rheumatology/European League Against Rheumatism clinical trial and clinical practice definitions and Simplified Disease Activity Index (SDAI). Logistic regression analysis identified predictors of sustained remission and influence of time to remission.

Results. Of 1840 patients, 633 (34%) achieved clinical trial remission, 759 (41%) clinical practice remission, and 727 (39%) SDAI remission. Over half of those meeting remission criteria achieved sustained remission based on clinical trial (55%), clinical practice (60%), and/or SDAI (58%). Corticosteroid use and lack of initial disease-modifying antirheumatic drug (DMARD) were associated with decreased probability of sustained remission, while initial combination DMARD increased this probability. Female sex, greater pain, and longer time to first remission made sustained remission less likely.

Conclusion. Female sex, greater pain, and lack of initial DMARD therapy reduced the probability of sustained remission. A shorter time to remission is related to sustainability and supports striving for early remission. (First Release Oct 1 2014; J Rheumatol 2014;41:2161–6; doi:10.3899/jrheum.140137)

Key Indexing Terms:
RHEUMATOID ARTHRITIS — REMISSION
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The management of rheumatoid arthritis (RA) strives to achieve the lowest possible disease activity state — clinical remission — which has consistently shown association with favorable outcomes[1,2].

A sustained good response, rather than a fluctuating disease course, would intuitively be the desired goal. Sustained remission provides longterm benefit by improving quality of life and physical function, and by reducing radiographic progression[3,4,5]. A shorter time to remission influences the sustainability of remission, suggesting that a "window of opportunity" for intervention does exist[6,7].

There are limited data on predictors of sustained remission, especially in the context of stringent remission definitions[8]. Our objective was to evaluate the prevalence and predictive factors of sustained remission in an early RA

From the Rheumatology Department, Mount Sinai Hospital, University of Toronto, Toronto, Ontario; Université de Sherbrooke, Sherbrooke; Rheumatic Disease Unit, Institut de Rhumatologie, Montreal, Quebec; Arthritis Centre, University of Manitoba, Winnipeg, Manitoba; Rheumatology Department, St. Joseph's Health Care, Western University, London; Southlake Regional Health Centre, Newmarket, Ontario, Canada; Hospital for Special Surgery, Cornell University, New York, New York, USA.

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B. Kuriya, MD, MS, FRCPC; J. Xiong, MSc, PhD, Rheumatology Department, Mount Sinai Hospital, University of Toronto; G. Boire, MD, MSc, FRCPC, Université de Sherbrooke; B. Haraoui, MD, FRCPC, Rheumatic Disease Unit, Institut de Rhumatologie; C. Hitchon, MD, MSc, FRCPC, Arthritis Centre, University of Manitoba; J. Pope, MD, MPH, FRCPC, Rheumatology Department, St. Joseph's Health Care, Western University; J.C. Thorne, MD, FRCP, FACP; D. Tin, BSc PHm, RPh, CDE, CGP, Southlake Regional Health Centre; E.C. Keystone, MD, FRCPC, Rheumatology Department, Mount Sinai Hospital, University of Toronto; V. Bykerk, MD, FRCPC, Rheumatology Department, Mount Sinai Hospital, University of Toronto, and Hospital for Special Surgery, Cornell University.

Address correspondence to Dr. B. Kuriya, Mount Sinai Hospital, University of Toronto, 60 Murray St., Room 2-008, Toronto, Ontario M5T 3L9, Canada. E-mail: bkuriya@mtsinai.on.ca

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(ERA) population. We hypothesized that a short time to remission is an important predictor of sustained clinical remission.

MATERIALS AND METHODS

Subjects. Data were collected from patients enrolled into the Canadian early ArThritis CoHort (CATCH) study. CATCH is a prospective cohort of patients with ERA that recruited 2178 patients at 19 sites between January 1, 2007, and May 6, 2013[9]. Therapy is left to the discretion of the treating rheumatologist and includes disease-modifying antirheumatic drug (DMARD) monotherapy or combination therapy, biologics, and options of bridging with corticosteroids. Patients are followed every 3 months during the first year and every 6 months thereafter.

We included all patients since inception with confirmed RA according to the 1987 or 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria who had complete baseline and followup data necessary to calculate remission indices. Single imputation methods (using the Month 3 observation to impute) were used for categorical variables missing at baseline: rheumatoid factor (RF), anticitrullinated protein antibodies (ACPA), and presence of radiographic erosions.

Remission definitions. Clinical remission was defined according to the 2011 ACR/EULAR Boolean and index-based remission criteria[8], which include (1) Boolean clinical trial definition [tender joint count (TJC) ≤ 1 using 28 joints, swollen joint count (SJC) ≤ 1 using 28 joints, C-reactive protein (CRP) ≤ 1 mg/dl, and patient global assessment (PtGA) ≤ 1 on a 0–10 scale]; (2) Boolean clinical practice definition that omits CRP (TJC ≤ 1, SJC ≤ 1, and PtGA ≤ 1); and (3) Simplified Disease Activity Index (SDAI) ≤ 3.3. Remission was considered sustained if patients satisfied any 1 definition for ≥ 6 months or ≥ 2 consecutive visits. A secondary definition evaluated sustained remission as ≥ 12 months.

Statistical analyses. First, we described the number of patients achieving remission according to at least 1 remission definition over the course of followup (up to 5 years for some patients). The occurrence of a first remission was used to calculate the median time to remission for each definition. Second, we examined the prevalence of sustained remission (among those who achieved remission).

Logistic regression analyses were used to assess the relationship between baseline variables and sustained remission. Separate regression models were run using each of the 3 sustained remission definitions as the dependent variable. Baseline variables included (1) demographic factors (age, sex, and smoking status); (2) clinical features [symptom duration, TJC28, SJC28, pain, fatigue, physician global assessment, PtGA, disease activity measured by 28-joint Disease Activity Score using erythrocyte sedimentation rate (DAS28-ESR), SDAI, disability, and presence of erosive disease]; (3) laboratory markers (ESR, CRP, RF, and ACPA); (4) initial treatment, defined as therapy instituted ≤ 4 weeks before baseline or ≤ 6 weeks after the baseline visit and categorized as DMARD monotherapy or combination therapy, oral corticosteroid with or without DMARD, and biologic use. Time to remission (in mos) was also included as a continuous covariate in all models.

Sensitivity analyses using the secondary outcome definition of sustained remission (≥ 12 mos) were conducted. Baseline variables with p value < 0.10 in univariate analyses were retained in multivariate models in addition to clinically important confounders that were selected *a priori* (age, sex, disease duration, and baseline DAS28 score). Full multivariate models were reduced by backward stepwise removal of variables with p value < 0.05. Multicollinearity was excluded using the variance inflation factor. Statistical analyses were performed using SAS software, version 9.3.

RESULTS

From the 2178 patients enrolled, 1840 were eligible for analysis (Figure 1). Mean age was 53.4 years (SD 15.3) and 73% were female (Table 1). Disease activity at cohort entry was indicative of moderate to severe disease. Combination DMARD was the most common initial treatment (46%), followed by methotrexate monotherapy (31%) and oral corticosteroids (31%). Corticosteroids were most frequently co-prescribed with combination DMARD (93%; Table 1). At baseline, corticosteroid users were significantly older (mean age 55.4 yrs vs 51.8 in nonusers), had higher numbers of tender/swollen joints, higher ESR and CRP values, greater pain, greater fatigue, and higher global health scores, mean DAS28, and HAQ scores (data not shown).

Over the course of followup, 633 (34%) achieved Boolean clinical trial remission, 759 (41%) achieved Boolean clinical practice remission, and 727 (39%) achieved SDAI remission. More than half of patients meeting clinical remission went on to satisfy sustained remission according to the Boolean clinical trial (345; 55%), Boolean clinical practice (453; 60%), and/or SDAI definitions (422; 58%). The number meeting all 3 sustained definitions was 316; 65 met 2 definitions, and 142 achieved sustained remission by fulfilling only 1 definition. For all definitions considered, patients were more likely to achieve sustained remission during followup (Table 2).

Factors associated with sustained remission are shown in Table 3. Initial use of oral corticosteroids and longer time to first remission were independently associated with decreased probability of sustained remission. Initial combination DMARD therapy increased the probability of sustained remission and overall had the largest effect estimate (OR 1.51–1.58, 95% CI 1.07–2.28). Female sex, higher baseline pain score, and lack of DMARD use at baseline were negatively associated with sustained remission, according to the Boolean clinical practice definition. A secondary analysis changing the definition of sustained remission to ≥ 12 months revealed fewer patients reaching this outcome, according to the Boolean clinical trial (33%), Boolean clinical practice (37%), and SDAI definitions (37%). Time to remission was found to be an independent predictor of sustained remission by all 3 definitions (data not shown).

DISCUSSION

This is the first study, to our knowledge, to examine the prevalence and baseline predictors of sustained remission using the stringent ACR/EULAR Boolean remission criteria in an ERA cohort. Our results showed that sustained remission occurs frequently once clinical remission is achieved and increases over time. We identified that female sex, higher pain score, lack of DMARD use, and need for oral corticosteroids at cohort entry reduced the probability of sustained remission. In contrast, the use of initial combination DMARD was positively associated with sustainability, and a quicker time to remission was a consistent and

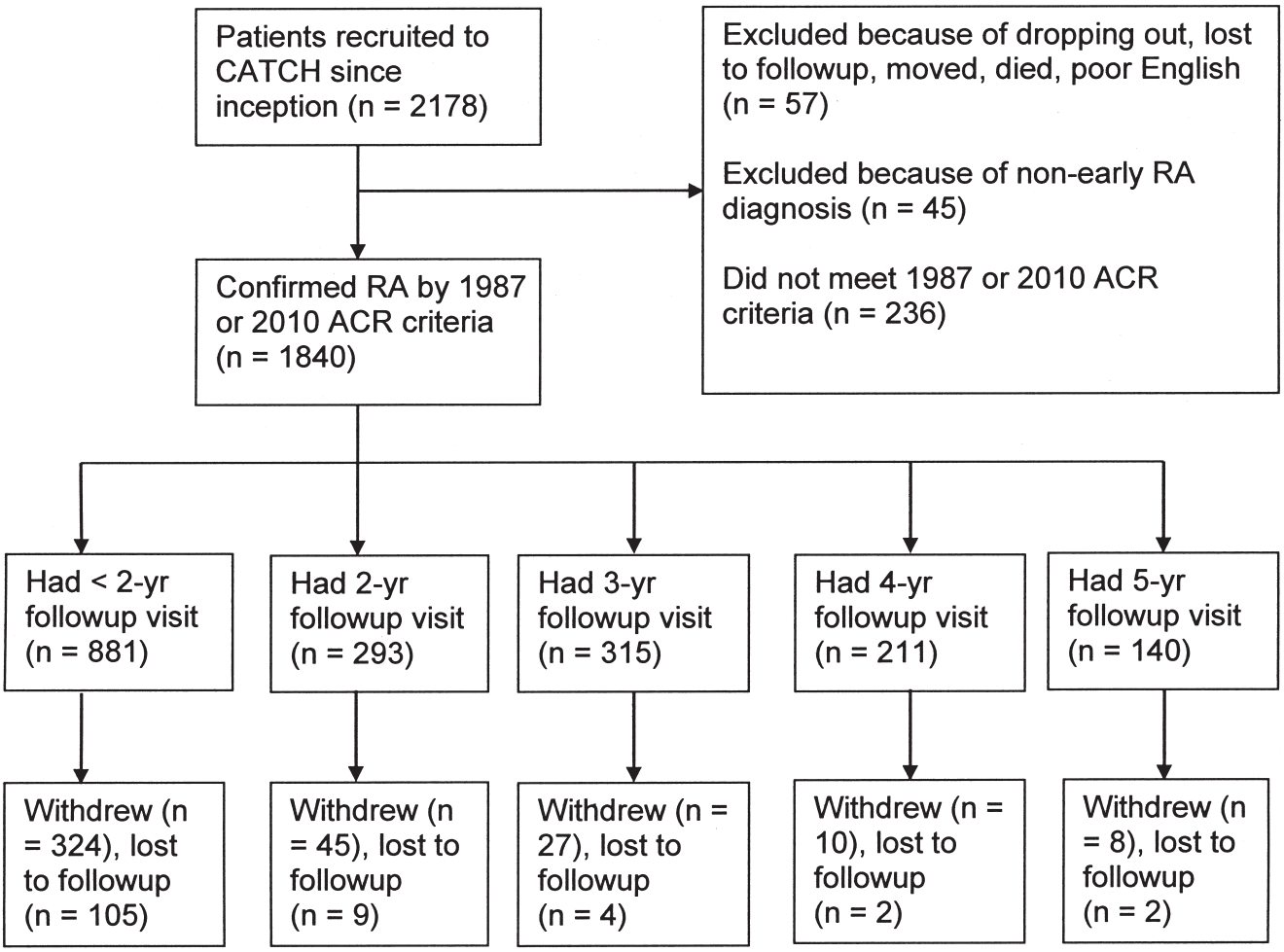

Figure 1. Study sample size and reasons for exclusion. CATCH: Canadian Early Arthritis Cohort; RA: rheumatoid arthritis; ACR: American College of Rheumatology.

strong determinant of sustained remission across all outcome definitions.

Our study included a large number of patients and we demonstrate that stringently defined sustained clinical remission is possible in a real-world setting where initial combination DMARD is the most common therapy. Our findings were strengthened by testing several remission definitions and by performing a sensitivity analysis that extended the duration of sustained remission. We studied a wide number of candidate predictors and show for the first time, to our knowledge, the influence of patient-reported outcomes (e.g., pain) on achieving sustained remission.

These data can be compared to other studies evaluating sustained clinical remission. Our prevalence of sustained remission ranging from 55% to 60% is higher than the range of 8% to 38% cited by others[10,11,12,13,14,15]. This discrepancy may arise because of differences in patient characteristics (e.g., patients meeting the 2010 ACR criteria, which may reflect milder disease or illness of shorter duration), secular trends and treatment strategies (e.g., treat-to-target), or the remission criterion used, which affects results[16]. To date, there is no consensus on how to define sustained remission. Studies vary in the type of disease activity score/index used and some have incorporated "drug-free" remission into the concept of sustained outcome[11]. We chose to test the stringent Boolean and index-based ACR/EULAR criteria for clinical remission because they are more apt to detect the essence of remission (no synovitis), not simply low disease activity.

The predictors of response we identified are comparable to those in previous studies. Men are more likely to achieve sustained remission in ERA[12,13,14]. The biological mechanism (e.g., genetic or immunologic differences) for this finding has yet to be elucidated. A potential explanation suggested by others is that "gender" perceptions (e.g., ability to interpret/report pain) play a greater role in creating this difference[13]. Higher pain may in turn affect PtGA, and we are aware from previous work that high PtGA are often

Table 1. Baseline characteristics of CATCH patients with ERA (n = 1840). Values are number (%) unless otherwise indicated.

Characteristic	Missing, n (%)	
Demographic		
Age, mean ± SD yrs	0	53.4 ± 15.3
White	0	1504 (81.7)
Female sex	0	1342 (72.9)
Smoker, n = 1834	6 (0.3)	
Current	—	337 (18.4)
Ex-smoker	—	691 (37.7)
Never	—	806 (43.9)
Clinical		
Symptom duration, mos, mean ± SD	6 (0.3)	5.94 ± 3.53
TJC in 28 joints, mean ± SD	4 (0.2)	8.80 ± 6.62
SJC in 28 joints, mean ± SD	4 (0.2)	7.90 ± 6.07
Duration AM stiffness, h, mean ± SD	16 (0.9)	0.62 ± 0.48
VAS pain, mm, mean ± SD (0–100 mm scale)	69 (3.8)	56.17 ± 28.20
VAS fatigue, mm, mean ± SD (0–100 mm scale)	36 (1.9)	53.13 ± 30.27
PtGA, mm, mean ± SD (0–100 mm scale)	36 (1.9)	58.64 ± 29.22
MDGA, mean ± SD mm (0–100 mm scale)	34 (1.8)	49.26 ± 24.37
DAS28-ESR score, mean ± SD	170 (9.2)	5.09 ± 1.44
SDAI score, mean ± SD	226 (12.3)	28.83 ± 14.80
SDAI low disease status	226 (12.3)	162 (10)
M-HAQ score, mean ± SD	53 (2.9)	1.04 ± 0.71
Presence of erosions **	342 (18.5)	399 (26.6)
Laboratory		
ESR, mm/h, mean ± SD	133 (7.2)	27.90 ± 23.18
CRP, mg/l, mean ± SD	164 (8.9)	1.47 ± 1.82
RF-positive **	186 (10.1)	1038 (62.8)
ACPA-positive**	584 (31.6)	693 (55.2)
Initial treatment during first 3 mos		
Combination therapy (MTX or LEF ± SSZ ± HCQ)	109 (5.9)	793 (45.8)
MTX alone	109 (5.9)	549 (31.7)
Oral corticosteroid (alone or with DMARD)*	109 (5.9)	537 (31.0)
No DMARD	109 (5.9)	162 (9.4)
Biologic agent	109 (5.9)	39 (2.3)

* Ninety-three percent of oral corticosteroid was used with combination DMARD therapy. ** Data for RF, ACPA, and erosions are based on nonimputed data. CATCH: Canadian Early Arthritis Cohort; ERA: early rheumatoid arthritis; ACPA: anticitrullinated protein antibodies; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS28-ESR: 28-joint Disease Activity Score using ESR; DMARD: disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; HCQ: hydroxychloroquine; LEF: leflunomide; MDGA: physician global assessment of disease; M-HAQ: modified Health Assessment Questionnaire; MTX: methotrexate; PtGA: patient global assessment of disease; RA: rheumatoid arthritis; RF: rheumatoid factor; SDAI: Simplified Disease Activity Index; SJC: swollen joint count; SSZ: sulfasalazine; TJC: tender joint count; VAS: visual analog scale.

Table 2. Patients achieving sustained remission by various definitions, according to length of followup. Data are n (%).

	Duration of Followup				
	< 2 Yrs	2 Yrs	3 Yrs	4 Yrs	≥ 5 Yrs
Remission definition					
Clinical trial	75 (8.5)	68 (23.2)	83 (26.3)	54 (25.6)	65 (46.4)
Clinical practice	103 (11.7)	93 (31.7)	104 (33.0)	74 (35.1)	79 (56.4)
SDAI	93 (10.6)	84 (28.7)	96 (30.5)	69 (32.7)	80 (57.1)

SDAI: Simplified Disease Activity Index.

a limiting factor for reaching remission[17]. In keeping with this hypothesis, our study is the first, to our knowledge, to report pain as making sustained remission less likely. The OR for pain was very close to 1; therefore, future research needs to confirm this finding.

To our knowledge, only 1 other large observational study has examined the association of time to remission with sustained remission. Our findings are consistent with those of Schipper, *et al*, who demonstrated that earlier time to first remission was the strongest predictor of sustained remission[6]. They found this relationship to be constant over a 20-year period when treatment paradigms were highly variable, suggesting that rapid entry into clinical remission — and not necessarily the type of treatment selected — is a key to sustaining the response.

In addition to time to remission, our results support previous findings that use of combination DMARD therapy increases the chance of remission while delays in treatment reduce the probability of response[18,19]. Interestingly, combination DMARD was positively associated with achieving Boolean clinical trial and SDAI sustained remission but not the Boolean clinical practice definition. A possible explanation is that DMARD lower CRP levels more rapidly, resulting in lower scores, but have less influence on the clinical practice definition, where CRP is omitted[17]. Almost all initial corticosteroids (93%) were used in conjunction with combination DMARD, yet this variable made remission less likely across all definitions. This likely reflects channeling bias — a tendency of physicians to prescribe corticosteroids to "sicker" patients who are less likely to enter remission[20]. Even though we adjusted for poor prognostic markers, unmeasured confounders that are differentially distributed among patients receiving corticosteroids may partially explain the weak link between this treatment and sustained remission. Therefore, the optimal initial treatment approach that will lead to sustained remission is difficult to determine from these data alone.

The limitations of our work should be mentioned. We evaluated baseline variables and so cannot comment on whether time-varying changes such as treatment modifications (e.g., biologic use beyond the initial 3 mos) influence sustained remission. Patient withdrawal over the study period was low but a higher initial dropout rate may have arisen among patients less likely to achieve remission, which would lead to an overestimation of the prevalence of sustained remission in our study. We also took the first occurrence of sustained remission and did not quantify the duration of time spent in remission thereafter, which has

Table 3. Multivariate analysis of predictors for achieving sustained remission (OR and 95% CI). Significant data are given in bold face.

Variable	Boolean Clinical Trial Definition	Boolean Clinical Practice Definition	SDAI
Age, yrs	0.99 (0.98, 1.00)	0.99 (0.98, 1.00)	0.99 (0.98, 1.00)
Sex (female vs male)	0.74 (0.49, 1.11)	**0.58 (0.40, 0.86)**	0.96 (0.66, 1.4)
Smoker (current vs never)	0.63 (0.37, 1.06)	1.02 (0.85, 1.23)	0.84 (0.50, 1.38)
Smoker (ex-smoker vs never)	0.97 (0.65, 1.44)	—	1.08 (0.74, 1.58)
Symptom duration, mos	1.05 (0.99, 1.12)	1.04 (0.98, 1.09)	1.03 (0.97, 1.09)
Baseline DAS28-ESR, mean score	1.03 (0.91, 1.16)	1.13 (0.97, 1.32)	1.02 (0.89, 1.16)
Baseline pain, mean score	—	**0.99 (0.98, 0.99)**	—
Baseline fatigue, mean score	—	—	0.99 (0.99, 1.00)
No initial DMARD use (yes vs no)	—	**0.41 (0.22, 0.76)**	—
Initial use of oral corticosteroids (yes vs no)	**0.48 (0.32, 0.73)**	**0.64 (0.44, 0.92)**	**0.54 (0.37, 0.80)**
Initial use of combination DMARD (yes vs no)	**1.58 (1.09, 2.28)**	—	**1.51 (1.07, 2.13)**
Time to remission, mos	**0.94 (0.92, 0.96)**	**0.94 (0.92, 0.96)**	**0.94 (0.92, 0.95)**

All variables significant in univariate analyses according to selection rule $p < 0.10$ were entered into multivariate logistic regression analyses. DAS28-ESR: 28-joint Disease Activity Score using erythrocyte sedimentation rate; DMARD: disease-modifying antirheumatic drug; SDAI: Simplified Disease Activity Index.

previously been reported as low[15]. Lastly, the observational nature of our study means we had to contend with possible bias from residual confounding.

We identified several predictors of sustained clinical remission in ERA and reveal earlier time to remission as a key determinant of sustaining this response. Future research aimed at comparing patients who gained remission but did not sustain it will help determine whether differential predictors identify the odds of clinical remission versus sustained remission or whether the rapidity of response, as we have shown, is the most important. Along those lines, determining how "early" remission should be sought and when this window of opportunity optimally opens and closes will be of great clinical value.

APPENDIX 1.

List of study collaborators: CATCH investigators: Vandana Ahluwalia, Pooneh Akhavan, Hector Arbillaga, Murray Baron, Mary Bell, William Bensen, Gilles Boire, Vivian Bykerk, Alf Cividino, Ines Colmegna, Paul Haraoui, Carol Hitchon, Shahin Jamal, Ed Keystone, Alice Klinkhoff, Majed Kraishi, Maggie Larche, Chris Lyddell, Henri Ménard, Dianne Mosher, Bindu Nair, Erin Norris, Chris Penney, Janet Pope, Laurence Rubin, Emily Shaw, Evelyn Sutton, John Carter Thorne, and Michel Zummer.

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