

## SUPPLEMENTARY MATERIAL

### Frequency, Severity, and Costs of Flares Increase With Disease Severity in Newly Diagnosed Systemic Lupus Erythematosus: A Real-World Cohort Study, United States, 2004–2015

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## SUPPLEMENTARY TABLES

**Table S1.** Claims-Based Algorithm Supplemented With EMR Data for Defining SLE Disease Severity<sup>a</sup>

Claims-Based Algorithm <sup>a</sup>	EMR Adaptation
<b>MILD DISEASE</b>	
<ul style="list-style-type: none"><li>• Did not meet criteria for moderate or severe disease</li><li>• Patients who died and had less than 1 month (30 days) of enrollment in the time period (follow-up, year 1, or year 2) were classified as having died with short enrollment rather than being assigned an SLE disease severity level</li></ul>	<ul style="list-style-type: none"><li>• Did not meet criteria for moderate or severe disease</li></ul>
<b>MODERATE DISEASE</b>	
<ul style="list-style-type: none"><li>○ Had no filled prescriptions for cyclophosphamide or rituximab or oral corticosteroid with <math>\geq 60</math> mg/day of prednisone equivalent dose and no claims with a diagnosis of a severe condition; AND</li><li>○ Met 1 or both of the following criteria at any time during the follow-up period:</li></ul>	<ul style="list-style-type: none"><li>• Had <math>\geq 1</math> EMR record with a diagnosis listed as moderate</li></ul>

- Had ≥1 nonlaboratory claim with
  - a diagnosis of a condition listed as “moderate,” where the diagnosis occurs in any position on the claim; OR
- Had ≥1 filled prescription for an oral corticosteroid with a prednisone equivalent dose of ≥7.5 mg/day and <60 mg/day or for an immunosuppressive agent (other than cyclophosphamide)
- Moderate conditions: acute pancreatitis, chorioretinitis, demyelinating syndrome/acute inflammatory demyelinating polyradiculoneuropathy, episcleritis/scleritis, hemolytic anemia, hepatitis (nonviral), ischemic necrosis of bone, nephritis, renal impairment other than nephritis or end-stage renal disease, lupus enteritis/colitis, mononeuropathy/polyneuropathy, myelopathy, myocarditis, pericarditis, pleurisy/pleural effusion, pseudotumor
- Moderate conditions: acute pancreatitis, chorioretinitis, demyelinating syndrome/acute inflammatory demyelinating polyradiculoneuropathy, episcleritis/scleritis, hemolytic anemia, hepatitis (nonviral), ischemic necrosis of bone, nephritis, renal impairment other than nephritis or end-stage renal disease, lupus enteritis/colitis, mononeuropathy/polyneuropathy, myelopathy, myocarditis, pericarditis, pleurisy/pleural effusion, pseudotumor

cerebri, seizure, uveitis vasculitis (excluding aortitis)	cerebri, seizure, uveitis vasculitis (excluding aortitis)
<b>SEVERE DISEASE</b>	
<ul style="list-style-type: none"> <li>Had <math>\geq 1</math> filled prescription for cyclophosphamide or rituximab or oral corticosteroid with a prednisone equivalent dose of <math>\geq 60</math> mg/day; OR</li> </ul>	<ul style="list-style-type: none"> <li>Had <math>\geq 1</math> EMR record with a diagnosis listed as severe</li> </ul>
<ul style="list-style-type: none"> <li>Had <math>\geq 1</math> nonlaboratory claim with a diagnosis listed as severe, where the diagnosis occurs in any position on the claim</li> <li>Severe conditions: acute confusional state/psychosis, aortitis, arterial/venous thrombosis, aseptic meningitis, cardiac tamponade, cranial neuropathy, intestinal pseudo-obstruction, end-stage renal disease, optic neuritis, pulmonary hemorrhage, stroke/transient ischemia attack</li> </ul>	<ul style="list-style-type: none"> <li>Had <math>\geq 1</math> EMR record with a diagnosis listed as severe</li> <li>Severe conditions: acute confusional state/psychosis, aortitis, arterial/venous thrombosis, aseptic meningitis, cardiac tamponade, cranial neuropathy, intestinal pseudo-obstruction, end-stage renal disease, optic neuritis, pulmonary hemorrhage, stroke/transient ischemia attack</li> </ul>

EMR = electronic medical records; SLE = systemic lupus erythematosus.

<sup>a</sup>Claims-based algorithm previously published in Garris C, Jhingran P, Bass D, Engel-Nitz NM, Riedel A, Dennis G. Healthcare utilization and cost of systemic lupus erythematosus in a US managed care health plan. *J Med Econ* 2013;16:667–77.

**Table S2.** Claims-Based Algorithm Supplemented With EMR Data for Defining SLE Flare Severity<sup>a,b</sup>

Claims-Based Algorithm <sup>a</sup>	EMR Adaptation
<b>MILD FLARE</b>	
Initiation of any of the following:	
<ul style="list-style-type: none"> <li>• Hydroxychloroquine or another antimalarial</li> <li>• An oral corticosteroid with prednisone-equivalent dose of <math>\leq 7.5</math> mg/day</li> <li>• Nonimmunosuppressive therapy (NSAIDs, androgens)</li> </ul>	
Treatment was considered to be initiated if there were no filled prescriptions for that class of medication in the 60 days prior to the medication fill	
<p><i>Length of flare:</i> 30 days. However, if a flare of higher severity (moderate or severe) occurs during that 30 days, the length of the flare was limited to the time between the start of the mild flare and the start of the higher-severity flare</p>	
<b>MODERATE FLARE</b>	

a. Initiation of any of the following:

- An oral corticosteroid with prednisone-equivalent dose  
 $>7.5 \text{ mg/day}$  but  $\leq 40 \text{ mg/day}$
- Immunosuppressive therapy, with the exception of cyclophosphamide

Treatment was considered to be initiated if

there were no filled prescriptions for that class of medication in the 60 days prior to the medication fill. For oral corticosteroids, if the patient had a prior fill within 60 days, treatment was considered initiated if the prior fill was for a prednisone-equivalent dose

$\leq 7.5 \text{ mg/day}$

## OR

b. A claim for an emergency room visit with a primary diagnosis of SLE (710.0x) with no inpatient admission within 1 day

## OR

c. A claim for an emergency room or office visit with a primary or secondary diagnosis for a specified SLE-related condition.<sup>c</sup> If An office visit with a primary or secondary diagnosis for a specified SLE-related condition. If the diagnosis occurred during an

the diagnosis occurred during an office visit, the condition was required to be new, defined as no claims with this diagnosis during the previous 60 days. If the condition occurred in an emergency room visit, no inpatient admission within 1 day following the emergency room visit was allowed

*Length of flare:* 30 days. However, if a severe flare occurred during those 30 days, the length of the flare was limited to the time from the start of the moderate flare to the start of the higher-severity flare. If the flare was initiated by a hospitalization, or a hospitalization occurred during the middle of the flare, and the hospitalization lasted beyond the 30 days, the length of the flare was still set at 30 days

office visit, the condition was required to be new, defined as no office visits with this diagnosis during the previous 60 days

*Length of flare:* 30 days. However, if a severe flare occurred during those 30 days, the length of the flare was limited to the time from the start of the moderate flare to the start of the higher-severity flare. If the flare was initiated by a hospitalization, or a hospitalization occurred during the middle of the flare, and the hospitalization lasted beyond the 30 days, the length of the flare was still set at 30 days

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## SEVERE FLARE

- a. Initiation of any of the following:
  - An oral corticosteroid with prednisone-equivalent dose >40 mg/day

- Cyclophosphamide

For corticosteroids, if the patient had a prior fill within 60 days, treatment was considered initiated if the prior fill was for a dose  $\leq 40$  mg/day. For cyclophosphamide, each prescription was counted as a new prescription if the prior fill or administration was more than 100 days earlier

**OR**

b. Admission for an inpatient hospital stay with a primary diagnosis of SLE (710.0x)

**OR**

c. Admission for an inpatient hospital stay with a primary diagnosis for a specified SLE-related condition<sup>c</sup>

For flares based upon a hospitalization, the start date of the flare was the date that the patient was admitted to the hospital, unless the patient was admitted to the emergency room (with any diagnosis) during the previous day; if patients had an emergency room admission the day prior to the

hospitalization, the date of the emergency room admission was considered to be the start date of the flare. Note that only visits to an emergency room site were considered under this definition; visits to urgent care or outpatient clinics were not included

*Length of flare:* 30 days

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EMR = electronic medical records; NSAIDs = nonsteroidal anti-inflammatory drugs;  
SLE = systemic lupus erythematosus.

<sup>a</sup>Claims-based algorithm previously published in Garris C, Jhingran P, Bass D, et al. Healthcare utilization and cost of systemic lupus erythematosus in a US managed care health plan. *J Med Econ* 2013;16:667–77.

<sup>b</sup>Additional rules were applied to the algorithm to determine flare durations, including start and end dates. The rules were based on timing of utilizations and use of different classes of medication. The expected duration of a flare was 30 days; if a service type changed (eg, office visit to emergency room visit, or a subsequent office visit with a different diagnosis) more than 30 days after the start of a flare, the new record was considered a new flare. Within each service type (defined by medications of the same class, office visits with the same diagnosis, emergency room visits, or hospitalizations regardless of the diagnosis), if there were at least 60 days (100 for cyclophosphamide) between adjacent records, then a new flare was considered to be initiated. Otherwise, it was recorded as a continuation of the previous flare. Rules were also created for cases in which the service type changed within 30 days. If the flare severity of the new record

remained the same or decreased from the previous record, it was recorded to be a part of the same flare. If the flare severity of the new record increased, the more severe flare was considered a new flare, regardless of the number of days between this record and the previous record.

<sup>c</sup>Specified SLE-related conditions include those listed for the disease severity algorithm under moderate and severe conditions (Supplementary Table 1), plus the following conditions: arthritis/arthralgia, dry eye/tear film insufficiency, rash, low white blood cell count (leukopenia, neutropenia, lymphocytopenia), lymph node enlargement, myalgia/myositis, urticaria.

**Table S3.** Corticosteroid Dose Equivalents for the Calculation of Prednisone Equivalent Dose in Patients With Newly Diagnosed SLE<sup>a</sup>

Equivalent dose	Steroid	Conversion factor
1.2 mg	Betamethasone (long-acting)	8.33
1.5 mg	Dexamethasone (long-acting)	6.67
8.0 mg	Methylprednisolone (intermediate-acting)	1.25
8.0 mg	Triamcinolone (intermediate-acting)	1.25
<b>10.0 mg</b>	<b>Prednisone (intermediate-acting)</b>	<b>1.00</b>
10.0 mg	Prednisolone (intermediate-acting)	1.00
40.0 mg	Hydrocortisone (short-acting)	0.25
50.0 mg	Cortisone (short-acting)	0.20
Not used for anti-inflammatory effect	Fludrocortisone	NA

SLE = systemic lupus erythematosus.

<sup>a</sup>Prednisone equivalent dose = (strength \* quantity dispensed \* conversion factor) / days supply.

**Table S4.** Mean Costs Per Flare for Patients With Newly Diagnosed SLE Who Had a Flare During the 1-Year Postdiagnosis Period at 30, 60, and 90 Days After Flare by Flare Severity and Setting of Care

All-cause cost, <sup>b</sup> mean (SD)	Flare severity <sup>a</sup>			<i>P</i> -value
	Mild (n=2232)	Moderate (n=4923)	Severe (n=418)	
30 days after flare				
Total cost	\$1672 (\$4566)	\$3831 (\$11,552)	\$16,856 (\$29,001)	<0.0001
By setting				
Inpatient	\$289 (\$2939)	\$995 (\$9839)	\$12,181 (\$25,944)	<0.0001
ED	\$44 (\$388)	\$182 (\$955)	\$272 (\$786)	<0.0001
Outpatient <sup>c</sup>	\$683 (\$2736)	\$1456 (\$4374)	\$2922 (\$9014)	<0.0001
Office	\$132 (\$174)	\$277 (\$253)	\$312 (\$294)	<0.0001
Laboratory	\$87 (\$581)	\$187 (\$616)	\$400 (\$1668)	<0.0001
Pharmacy	\$437 (\$927)	\$733 (\$1980)	\$769 (\$1954)	<0.0001
60 days after flare				
Total cost	\$2639 (\$6894)	\$6225 (\$14,641)	\$22,252 (\$35,807)	<0.0001
By setting				
Inpatient	\$448 (\$4142)	\$1479 (\$11,416)	\$14,024 (\$29,763)	<0.0001
ED	\$60 (\$445)	\$288 (\$1365)	\$458 (\$1480)	<0.0001
Outpatient <sup>c</sup>	\$1134 (\$4326)	\$2522 (\$6859)	\$5160 (\$13,486)	<0.0001
Office	\$209 (\$270)	\$434 (\$383)	\$573 (\$497)	<0.0001
Laboratory	\$122 (\$621)	\$284 (\$762)	\$613 (\$1887)	<0.0001
Pharmacy	\$667 (\$1557)	\$1219 (\$2785)	\$1425 (\$3469)	<0.0001
90 days after flare				
Total cost	\$3312 (\$8048)	\$8582 (\$18,278)	\$27,468 (\$40,332)	<0.0001
By setting				
Inpatient	\$564 (\$4647)	\$2040 (\$13,288)	\$15,517 (\$31,179)	<0.0001
ED	\$71 (\$464)	\$373 (\$1666)	\$721 (\$3170)	<0.0001
Outpatient <sup>c</sup>	\$1413 (\$4957)	\$3515 (\$9152)	\$7620 (\$18,263)	<0.0001
Office	\$267 (\$315)	\$576 (\$507)	\$803 (\$658)	<0.0001
Laboratory	\$151 (\$648)	\$382 (\$937)	\$794 (\$2106)	<0.0001
Pharmacy	\$847 (\$1773)	\$1699 (\$3984)	\$2015 (\$4361)	<0.0001

<sup>a</sup>Flare severity classified based on a previously published claims-based algorithm supplemented with electronic medical records; from Garris et al.<sup>3</sup>

<sup>b</sup>2017 US\$.

<sup>c</sup>Outpatient services included all nonpharmacy claims not categorized as inpatient, ER, office, or laboratory services.

ED, emergency department; SD, standard deviation; SLE, systemic lupus erythematosus.

**Table S5.** Median Costs Per Flare for Patients With Newly Diagnosed SLE Who Had a Flare During the 1-Year Postdiagnosis Period at 30, 60, and 90 Days After Flare by Flare Severity and Setting of Care

All-cause cost, <sup>a</sup> median (IQR)	Flare severity <sup>b</sup>		
	Mild (n=2232)	Moderate (n=4923)	Severe (n=418)
<b>30 days after flare</b>			
Total cost	\$536 (196–1387)	\$1256 (512–3272)	\$5914 (1,194–18862)
By setting			
Inpatient	\$0 (0–0)	\$0 (0–0)	\$0 (0–13,325)
ED	\$0 (0–0)	\$0 (0–0)	\$0 (0–77)
Outpatient <sup>c</sup>	\$19 (0–300)	\$233 (10–1107)	\$634 (79–2372)
Office	\$92 (0–189)	\$223 (117–371)	\$251 (120–412)
Laboratory	\$0 (0–25)	\$0 (0–118)	\$23 (0–217)
Pharmacy	\$167 (54–500)	\$203 (37–655)	\$258 (72–651)
<b>60 days after flare</b>			
Total cost	\$880 (322–2232)	\$2391 (920–6109)	\$9518 (2564–25,899)
By setting			
Inpatient	\$0 (0–0)	\$0 (0–0)	\$0 (0–14,716)
ED	\$0 (0–0)	\$0 (0–0)	\$0 (0–264)
Outpatient <sup>c</sup>	\$101 (0–559)	\$549 (91–2334)	\$1436 (289–4577)
Office	\$133 (0–299)	\$343 (178–574)	\$472 (259–783)
Laboratory	\$0 (0–72)	\$36 (0–245)	\$98 (0–443)
Pharmacy	\$265 (79–778)	\$411 (84–1236)	\$558 (161–1255)
<b>90 days after flare</b>			
Total cost	\$1198 (404–2971)	\$3432 (1311–8802)	\$12,443 (3870–33,415)
By setting			
Inpatient	\$0 (0–0)	\$0 (0–0)	\$0 (0–16,571)
ED	\$0 (0–0)	\$0 (0–0)	\$0 (0–446)
Outpatient <sup>c</sup>	\$159 (0–808)	\$868 (161–3390)	\$2158 (543–7147)
Office	\$173 (55–376)	\$458 (237–756)	\$681 (371–1056)
Laboratory	\$0 (0–108)	\$74 (0–349)	\$183 (16–694)
Pharmacy	\$341 (102–980)	\$592 (125–1752)	\$829 (280–2037)

<sup>a</sup>2017 US\$.

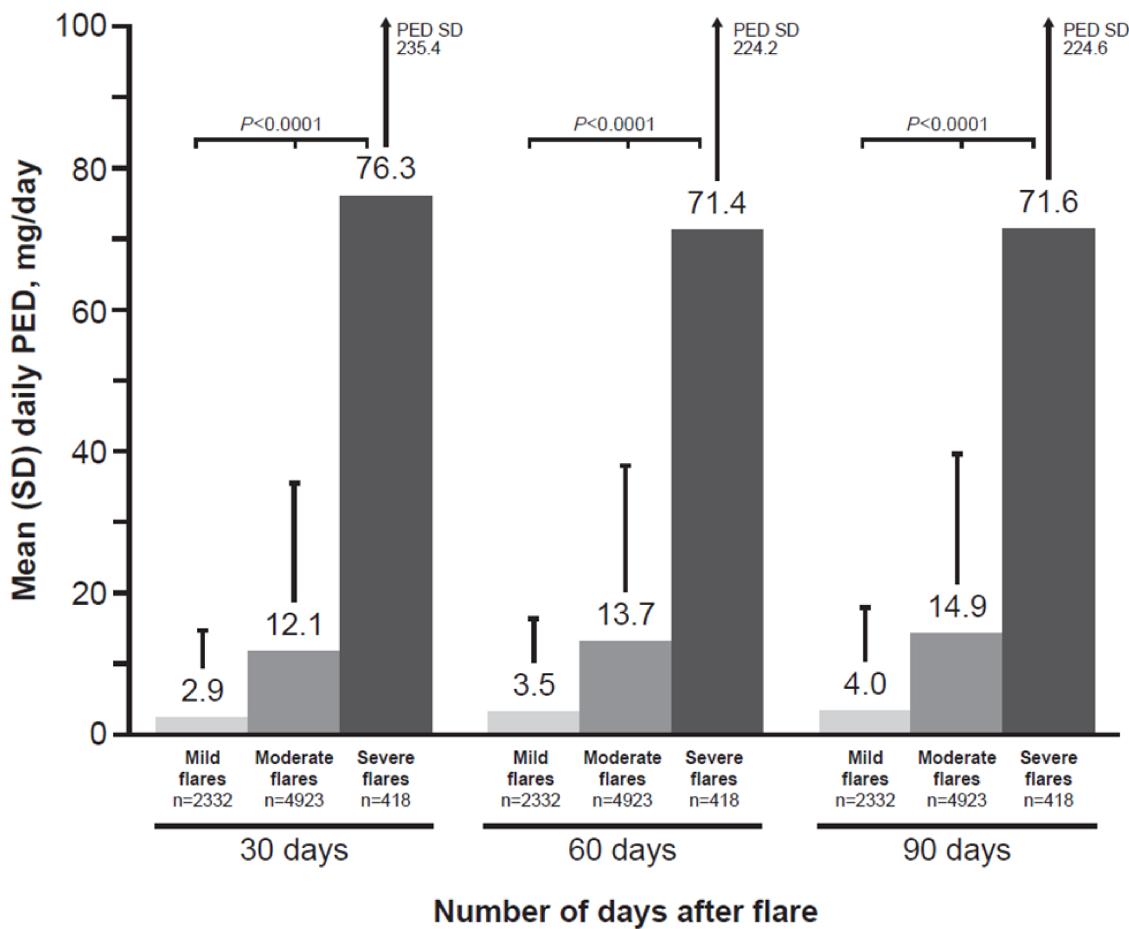
<sup>b</sup>Flare severity classified based on a previously published claims-based algorithm supplemented with electronic medical records; from Garris et al.<sup>3</sup>

<sup>c</sup>Outpatient services included all nonpharmacy claims not categorized as inpatient, ER, office, or laboratory services.

ED, emergency department; IQR, interquartile range; SD, standard deviation; SLE, systemic lupus erythematosus.

## SUPPLEMENTARY FIGURES

**Figure S1.** Mean Daily PEDs of Corticosteroids for All Patients With Newly Diagnosed SLE Who Had a Flare During the 1-Year Postdiagnosis Period at 30, 60, and 90 Days After Flare, by Flare Severity



*P*-values are for differences between the 3 flare severity groups at each time point.

PED, prednisone equivalent dosage; SD, standard deviation; SLE, systemic lupus erythematosus.