

# The Epidemiological, Clinical, and Healthcare System Implications of New Persistent Opioid Use Post-surgery in the United States

Stephan Frangakis<sup>1</sup>, Kim T Dangova<sup>2</sup>, Scott J Keating<sup>3</sup>, Konrad Pisarczyk<sup>2</sup>, Janice Stricker-Shaver<sup>2</sup>, Ann M Menzie<sup>3</sup>

<sup>1</sup>University of Michigan, Ann Arbor, MI, United States; <sup>2</sup>Maple Health Group LLC, New York, NY; United States; <sup>3</sup>Vertex Pharmaceuticals Incorporated, Boston, MA, United States



## BACKGROUND

- The adverse clinical and societal consequences of prescription opioid utilization remain a significant public health challenge in the United States.
- Surgical procedures are often patients' first exposure to opioids, prescribed for managing acute pain. Opioid use in opioid-naïve patients may be cause for concern as some experience inadequately managed acute pain and progress to persistent or even chronic opioid use.
- New persistent opioid use is an important and potentially underrecognized complication of perioperative care.

## OBJECTIVES

- To assess the incidence of new persistent opioid use in opioid-naïve patients stemming from post-surgical acute pain management in the United States and evaluate the associated risk factors and outcomes.

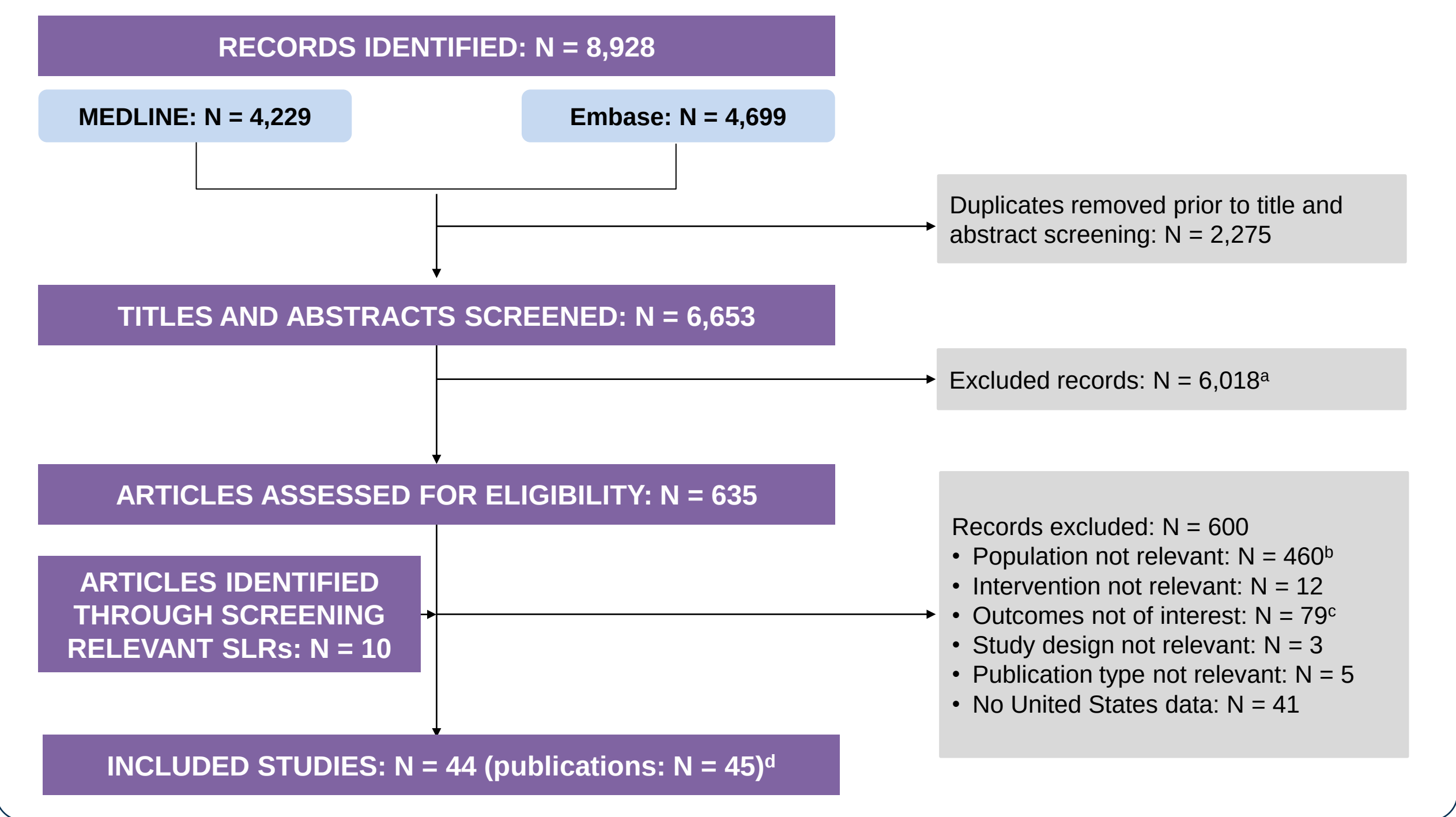
## METHODS

- A systematic literature review (SLR) was conducted utilizing the MEDLINE and Embase databases to identify observational studies published in the United States between 01 Jan 2013 and 26 Jun 2023. This review is registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42023446403).
- Selection criteria included adult, opioid-naïve patients who received prescription opioids for acute pain management following any surgery, excluding patients with cancer-related pain.
- The range of new persistent opioid use rates was reported for all studies with relevant data, as well as stratified by:
  - Surgery types: orthopedic, gynecologic, plastic/reconstructive, and cardiovascular (CV)/cardiothoracic procedures
  - Insurance types: Commercial, Medicare, Medicaid

Table 1. Study outcomes

| Outcome           | Definition                                                                                                                                                                                            |
|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Primary Outcome   | Incidence of new persistent opioid use, defined as evidence of opioid use 90 to 180 days after surgery. Studies reporting opioid use within only the first 90 days, or beyond 180 days were excluded. |
| Secondary Outcome | Risk factors, negative clinical outcomes, healthcare resource utilization and costs related to new persistent opioid use.                                                                             |

Figure 1. Search Results



<sup>a</sup> Titles and abstracts were screened based on pre-defined selection criteria; those not meeting Population, Intervention, Comparison and Outcomes (PICOS) criteria were excluded  
<sup>b</sup> Definitions of opioid-naïve patients were not aligned with PICOS criteria  
<sup>c</sup> Definitions of post-operative opioid use or pain were not aligned with PICOS criteria  
<sup>d</sup> 45 publications corresponded to 44 unique studies, including one cohort of opioid-naïve patients that was described in two publications

## RESULTS

### Study and patient characteristics

- Among the 44 included studies, the majority were retrospective analyses of large claims databases (n=40; 91%) that included between 438 and >4 million patients. These studies analyzed datasets spanning from 2002 to 2021. The remaining four studies (9%) were prospective, observational in design, and enrolled between 81 and 407 patients.
- The mean or median ages reported in the literature ranged from 31.8 to 75.9 years. Most patients were female (61.2%), and Caucasian/white (67.4%) or African American/black (11.9%).
- Most patients included in these studies had commercial insurance (75.2%), followed by Medicare (19.7%), and Medicaid (4.5%), and the frequency of surgeries included gynecologic (12.1%), orthopedic (6.9%), plastic (2.6%), and CV/cardiothoracic (0.7%).

Table 2. Definitions of new persistent opioid use

| Definition                                                                                                                                   | Number of studies, N (%) |
|----------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| Evidence of opioid use between 90 and 180 days after surgery                                                                                 | 34 (77%)                 |
| Evidence of an opioid prescription within two consecutive time periods, including the first 90 days and 91 to 180 days following the surgery | 6 (14%)                  |
| Opioid use at 180 days after surgery                                                                                                         | 2 (5%)                   |

### Rates of new persistent opioid use by subgroup

- 42 studies reported incidence of transition to new persistent opioid use in opioid-naïve patients, including 39 retrospective analyses of real-world databases, and 3 prospective studies. Estimates of new persistent opioid use incidence ranged from 0.7% to 18.5%, with approximately half of estimates (n=21, 47.7%) being between 6% and 11%.
- The incidence rates of new persistent opioid use in opioid-naïve patients undergoing orthopedic, gynecologic, plastic/reconstructive, and CV/cardiothoracic surgeries were similar (**Table 3**).
- The rate of new persistent opioid use was the highest among Medicaid-insured patients (**Table 4**).

Table 3. Incidence of new persistent opioid use among studies reporting rates by surgery type

| Surgery Type           | Studies (N) | Patients (N) | Range of New Persistent Opioid Use Estimates (%) |
|------------------------|-------------|--------------|--------------------------------------------------|
| Orthopedic             | 12          | 716,206      | 1.5%–15.6%                                       |
| Gynecologic            | 8           | 1,280,032    | 1.9%–14.3%                                       |
| Plastic/Reconstructive | 6           | 273,090      | 3.1%–13.0%                                       |
| CV/Cardiothoracic      | 6           | 75,389       | 1.3%–19.5%                                       |

CV: cardiovascular

Table 4. Incidence of new persistent opioid use among studies reporting rates by insurance type

| Insurance Type         | Studies (N) | Patients (N) | Range of New Persistent Opioid Use Estimates (%) |
|------------------------|-------------|--------------|--------------------------------------------------|
| Commercial             | 22          | 4,410,288    | 1.5%–14.0%                                       |
| Commercial or Medicare | 2           | 50,750       | 7.0%–13.9%                                       |
| Medicare               | 7           | 1,055,837    | 0.7%–18.5%                                       |
| Medicaid               | 5           | 265,155      | 5.4%–34.4%                                       |

| Table 5. Risk factors associated with new persistent opioid use |                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-----------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Risk Factors                                                    | Description                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Age                                                             | Studies found that patients aged 64 years and younger had significantly higher risk of new persistent opioid use than patients 65 years and older (OR=1.28, <i>P</i> =0.028) <sup>1</sup> and that patients 65 years and older had a lower risk compared to patients aged 18 to 34 years (OR range: 0.50 to 0.80, <i>P</i> <0.05). <sup>2,3</sup>                                                                                         |
| Comorbidity burden                                              | Studies showed that higher burden of comorbidities (Charlson Comorbidity Index or Elixhauser score) were significantly associated with increased risk of new persistent opioid use. For each increase in Charlson comorbidity index score, the risk of new persistent opioid use was shown to increase by 6% to 16% (OR/RR range: 1.06 to 1.16, <i>P</i> <0.05 in most comparisons). <sup>4,5-8</sup>                                     |
| Substance abuse                                                 | Statistically significant associations between substance use-related risk factors and risk of transition to new persistent opioid use were observed, including tobacco use and drug or substance use disorder, with OR/RR estimate ranges of 1.10 to 2.09 <sup>3,6,8-11</sup> and 1.31 to 1.79, <sup>10,12</sup> respectively ( <i>P</i> <0.05 in most comparisons).                                                                      |
| Psychological comorbidities                                     | Mental health disorders or illnesses increased the likelihood of new persistent opioid use by 10% <sup>13</sup> to 20%, <sup>14</sup> compared to patients without those conditions (OR=1.10, <i>P</i> =0.006; <sup>13</sup> OR=1.20, <i>P</i> <0.001, <sup>14</sup> respectively) with the highest risk increase reported for anxiety, depression, and mood disorder.                                                                    |
| Pre-existing pain conditions                                    | Patients with pre-existing arthritis, back pain, and neck pain had a 9% to 57% higher risk for developing persistent opioid use after surgery, compared to patients without these pain conditions (OR/RR range: 1.09 to 1.57, <i>P</i> <0.05 in most comparisons). <sup>4,8-10,12,15,16</sup>                                                                                                                                             |
| Pre-operative opioid use                                        | A first opioid prescription within 30 days prior to surgery was consistently shown as a risk factor of transition to new persistent opioid use, <sup>5,8,17-20</sup> with one analysis suggesting that patients may have 4.3-times higher risk of becoming persistent opioid users after the surgery, compared to subjects who did not fill opioid prescription during this pre-operative period (OR=4.34, <i>P</i> <0.001). <sup>5</sup> |
| Polypharmacy                                                    | Patients who filled prescriptions for both benzodiazepine (with or without other agents) and an opioid had a higher risk of transition to new persistent opioid use compared to patients who did not fill these two prescriptions concurrently in the peri-operative period (OR=1.24 to 1.35, <i>P</i> <0.001). <sup>14,15</sup>                                                                                                          |

OR: odds ratio; RR: relative risk

Table 6. Negative clinical outcomes associated with new persistent opioid use

| Risk Factors                           | Description                                                                                                                                                                                                                                                                                                                                                                                                |
|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mortality                              | Patients with new persistent opioid use had a significantly higher odds of mortality within 6 to 12 months following surgery compared to patients without new persistent opioid use (adjusted HR=3.44, 95% CI: 2.99, 3.96). <sup>21</sup>                                                                                                                                                                  |
| Opioid use disorder                    | Patients who developed new persistent opioid use after surgery had a more than 6-times higher risk of opioid dependence, abuse, or overdose compared to patients without new persistent opioid use (OR=6.39, <i>P</i> <0.0001). <sup>22</sup>                                                                                                                                                              |
| Serious falls or fall-related injuries | Patients who transitioned to new persistent opioid use after surgery had a significantly higher risk of serious falls or fall-related injuries resulting in rehospitalizations or ED visits within 6 to 12 months after surgery, compared to patients without new persistent opioid use (3.0% vs 2.5%, respectively; adjusted OR=1.21, <i>P</i> <0.001). <sup>21</sup>                                     |
| Respiratory complications              | Transition to new persistent opioid use was associated with significantly higher frequency of respiratory complications during the index hospitalization (6.4% vs 3.5%, respectively, <i>P</i> =0.042), <sup>23</sup> within the first 6 months after discharge (14.4% vs 6.8%, <i>P</i> <0.001) <sup>24</sup> and within 6 and 12 months (5.2% vs 3.3%, adjusted OR=1.67, <i>P</i> <0.001). <sup>21</sup> |

CI: confidence interval; ED: emergency department; HR: hazard ratio; OR: odds ratio

Table 7. Healthcare resource utilization observed in the literature

| Outcome       | Findings                                                                                                                                                                                                                                                                                                                                                                        |
|---------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Inpatient LOS | A hospital LOS of over 5 days after cancer surgery* was found to be more common among patients who transitioned to new persistent opioid use (44.3%) than those who did not (32.7%) ( <i>P</i> <0.001). <sup>10</sup>                                                                                                                                                           |
| ED visits     | At 6 months of post-operative follow-up, ED visits were reported by 40.4% to 45.6% of patient groups with new persistent opioid use and 22.8% to 25.4% of patient groups without new persistent opioid use ( <i>P</i> <0.001 for all comparisons). <sup>9,23,24</sup>                                                                                                           |
| Readmissions  | The rate of readmissions in the 12 months following index surgery in patients with new persistent opioid use were significantly higher compared to those who did not transition to new persistent opioid use (9.5% to 24.4% vs 3.3% to 13.8%, <i>P</i> <0.001 for all comparisons), and differences were consistent across insurance status and surgical setting. <sup>25</sup> |

ED: emergency department; LOS: length of stay  
\*While studies reporting cancer-related pain were excluded, studies of patients undergoing surgery for the treatment of cancer were eligible for inclusion provided the pain being treated was post-surgical pain.

Table 8. Total additional direct healthcare costs for patients with new persistent opioid use compared to patients without new persistent opioid use by setting of care and time horizon

| Insurance Type                 | Inpatient (6 months)*  | Outpatient (6 months)*  |
|--------------------------------|------------------------|-------------------------|
| Commercial <sup>23,24,26</sup> | \$2,439 to \$5,422     | \$952                   |
| Insurance Type                 | Inpatient (12 months)* | Outpatient (12 months)* |
| Commercial <sup>25</sup>       | \$17,702               | \$11,234                |
| Medicare <sup>25</sup>         | \$13,142               | \$12,834                |
| Medicaid <sup>25</sup>         | \$7,944                | \$5,598                 |

\*All cost differences are statistically significant at *P*<0.001 compared to patients without new persistent opioid use.

## CONCLUSIONS

- New persistent opioid use is a common complication of perioperative acute pain management that contributes to poor patient outcomes, increased healthcare resource utilization, and higher healthcare costs.
- These findings underscore the need for novel non-opioid therapeutics and comprehensive strategies to manage acute surgery-related pain.

## REFERENCES

- Brescia et al. Ann. Thorac. Surg. 2019; 107(2).
- Marcusa et al. Plas. Recon. Surg. 2017; 140(6).
- Johnson et al. J. Hand Surg. 2016; 41(10).
- Bennett et al. Plas. Recon. Surg. 2019; 143(1).
- Howard et al. Ann. Surg. 2022; 276(5).
- Bicket et al. Am. J. Surg. 2019; 218(5).
- Gil et al. Am. J. Sport. Med. 2019; 47(5).
- Brummett et al. JAMA Surg. 2017; 152(6).
- Clement et al. J. Thorac. Cardiovasc. Surg. 2020; 160(4).
- Brescia et al. Ann Thorac. Surg. 2019; 108(4).
- Olds et al. JAMA Facial Plast Surg 2019; 21(4).
- Finney et al. J Bone Joint Surg Am 2019; 101(8).
- Sakamoto et al. J Natl Compr Canc Netw 2021; 19(1).
- Lan et al. J Arthroplasty 2023; 38(1).
- Santosa et al. Surgery (United States) 2020; 167(4).
- Tam et al. Urology 2019; 134.
- Kluger et al. HPB (Oxford) 2022; 24(6).
- Huang et al. Obs. and Gyn. 2020; 136(3).
- Kuo et al. Ann. Surg. 2021; 274(6).
- Wright et al. Obs. and Gyn. 2019; 134(2).
- Santosa et al. Ann. Surg 2022; 278(3).
- Wylie et al. Ann. Surg. 2022; 276(3).
- Clement et al. Ann Thorac Surg 2020; 110(3).
- Clement et al. Ann Thorac Surg 2021; 112(6).
- Brummett et al. J. Manag. Care Spec. Pharm. 2021; 27(6).
- Lee et al. Ann. Surg. 2020; 272(1).

## AUTHOR DISCLOSURES

SF is a consultant to Vertex Pharmaceuticals  
KD, KP, and JS-S are consultants to Maple Health Group  
SK and AM are employees of Vertex Pharmaceuticals and may own stock/stock options in the company

## ACKNOWLEDGEMENTS

Editorial coordination and support was provided by Allison Lord, PhD and Zara Petzoldt, PharmD of Vertex Pharmaceuticals who hold stock and/or stock options at the company. Graphic support was provided by Nucleus Global, funded by Vertex Pharmaceuticals.