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ABSTRACT

Background Opioid overdoses in the USA have increased to unprecedented levels. Administration of the opioid antagonist naloxone can prevent overdoses.

Objective This study was conducted to reveal the pharmacoepidemiologic patterns in naloxone prescribing to Medicaid patients from 2018 to 2021 as well as Medicare in 2019.

Design Observational pharmacoepidemiologic study

Setting US Medicare and Medicaid naloxone claims

Intervention The Medicaid State Drug Utilisation Data File was utilised to extract information on the number of prescriptions and the amount prescribed of naloxone at a national and state level. The Medicare Provider Utilisation and Payment was also utilised to analyse prescription data from 2019.

Outcome measures States with naloxone prescription rates that were outliers of quartile analysis were noted.

Results The number of generic naloxone prescriptions per 100 000 Medicaid enrollees decreased by 5.3%, whereas brand naloxone prescriptions increased by 245.1% from 2018 to 2021. There was a 33.1-fold difference in prescriptions between the highest (New Mexico=1809.5) and lowest (South Dakota=54.6) states in 2019. Medicare saw a 30.4-fold difference in prescriptions between the highest (New Mexico) and lowest states (also South Dakota) after correcting per 100 000 enrollees.

Conclusions This pronounced increase in the number of naloxone prescriptions to Medicaid patients from 2018 to 2021 indicates a national response to this widespread public health emergency. Further research into the origins of the pronounced state-level disparities is warranted.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study characterises national trends of naloxone prescribing and costs across the USA.
⇒ Investigation was not performed on naloxone trends in other countries or with private insurance.
⇒ Comparison was performed on naloxone prescribing between states for both Medicare and Medicaid.
⇒ The impact that state prescribing differences may have on mortality was not studied.

INTRODUCTION

Opioid overdoses have become a national epidemic in the USA. The Centres for Disease Control and Prevention reported 79 770 overdoses involving opioids from December 2021 to December 2022.[1] Within recent years, the rate appears to be increasing. One study looking at 491 counties found that between January of 2018 and March of 2022, there was a 4% average increase in non-fatal opioid overdoses each quarter encountered by emergency medical services.[2] The cost for opioid addiction and death in the USA totalled over one-trillion dollars in 2017 alone.[3] Clearly, this is a major national issue that needs to be addressed.

The opioid antagonist naloxone can be both easy to administer and immediate in its life-saving effects.[4] Naloxone comes in multiple formulations including injection and nasal spray.[5] It is ineffective against other drugs that can cause sedation such as benzodiazepines, alcohol or non-opioid analgesics.[5] However, naloxone is typically benign and does not cause adverse effects when administered in an unneeded situation.[5] Naloxone was first approved by the US Food and Drug Administration (FDA) in 1971.[6] Since then, it has been formulated with auto-injectors and nasal spray.

Many states have implemented legal mandates to coprescribe naloxone to individuals at increased risk of overdose.[7] A national evaluation of the number of prescriptions prescribed for naloxone from 2011 to 2017 in IQVIA's national prescription audit, which contains 90% of all retail pharmacies' prescription data determined that states with naloxone coprescription laws had an approximately 7.75-fold higher dispensing

rate of naloxone compared with states that did not have the requirement.[8] Nationally, naloxone dispensing to commercially insured patients increased by over 13-fold from 7229 prescriptions in 2015 to 99 917 prescriptions in 2018.[9]

Due to the continued escalation and potential preventability of opioid overdoses, this study investigated how naloxone prescribing patterns have changed from 2018 to 2021 among US Medicaid patients. A secondary objective was to characterise any state-level disparities among Medicaid and Medicare patients.

METHODS

Procedures

Data were collected from 16 March 2023 to 26 April 2023. This study was determined to be not human subject research by the Geisinger Institutional Review Board. Medicaid part D Prescriber Public Use File was accessed to review data collected on naloxone prescriptions from 2018 to 2021.[10] Enrollee data were also collected from the Centres for Medicare and Medicaid Services (CMS).[11] The year 2021 was selected as the most recent available at the time of analysis (16 March 2023–13 April 2023). Claims that were not filled are excluded and not found within the database. For simplicity, generic naloxone is subsequently designated as $Naloxone_G$ and brand name formulations as $Naloxone_B$. Cost of $Naloxone_B$ and $Naloxone_G$ per prescription over time was also obtained.

The Medicare Provider Utilisation and Payment database was used to extract drug prescription claims as well as locations for the year 2019.[12] This Medicare database extracts information from finalised prescription drug claims, which excludes any claims that have not been resolved or need adjustments that have not been completed. In addition, the database suppresses any provider and claim data for less than or equal to 11 total claims for that year and is represented by a blank value. Enrollees for that year were also collected from The Henry J. Kaiser Family Foundation's data set.[13]

Data analysis

For both Medicaid and Medicare databases, only outpatient data are available, and as such was the only setting analysed. The prescriptions of naloxone per state were corrected for Medicaid enrolment which was pulled from the first month of each quarter from the database.[11] National distribution was plotted versus time using GraphPad Prism. A box and whisker plot and waterfall graph were also made via GraphPad Prism to visualise disparities in distribution. States that were found to be outliers were also noted. Outliers are defined as above the value of quartile 3+1.5 multiplied by the interquartile range (IQR), or below the value of quartile 1–1.5 multiplied by the IQR. Medicare's data were also corrected for the number of enrollees.

Patient and public involvement

No patient or public involvement.

RESULTS

Medicaid

Figure 1 shows an overall increase in quarterly prescriptions after correcting for Medicaid enrollees. When comparing corrected national prescriptions of $Naloxone_B$ and $Naloxone_G$, a distinct difference was noted. Q1 of 2018 (93.5) to Q4 2021 (322.7) for $Naloxone_B$ showed a large increase (+245.1%). For $Naloxone_G$, it decreased from 15 to 14.2 (−5.3%). When combined, Q1 of 2018 was calculated as 108.5 and Q4 of 2021 was 336.9. Thus, a 3.1-fold increase was seen in those 4 years.

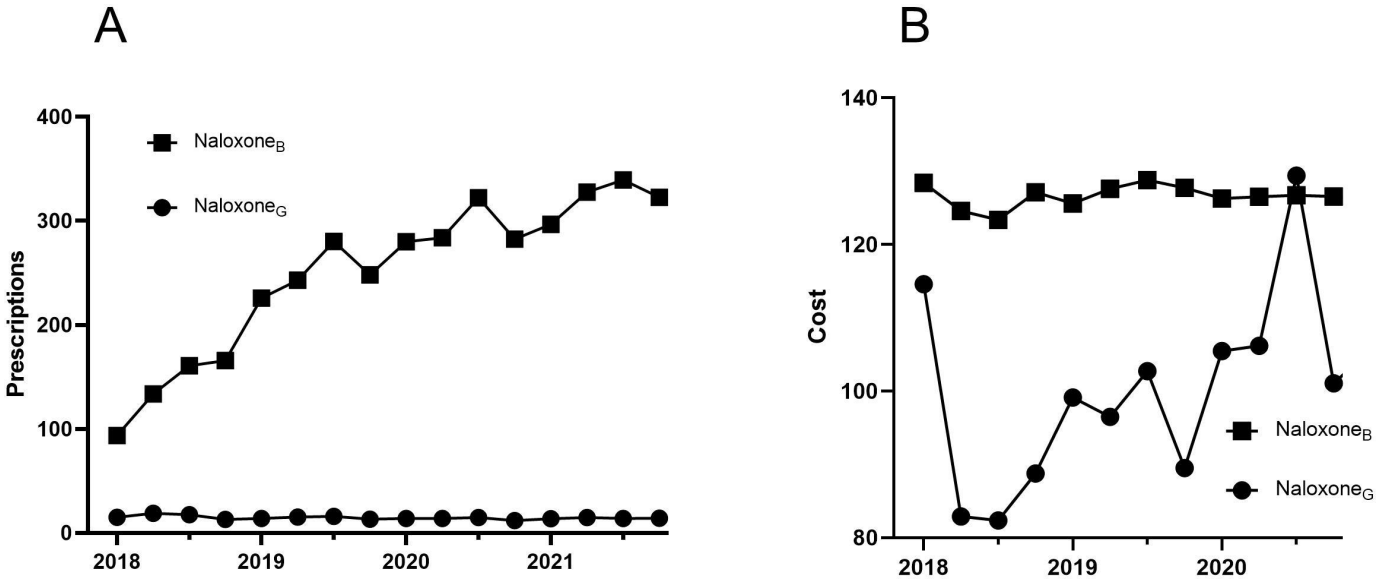

Figure 1 (A) Total naloxone prescriptions in Medicaid by formulation per quarter corrected for number of enrollees. (B) Cost per prescription (US$) of generic ($Naloxone_G$) and brand ($Naloxone_B$) formulations for 2018 to 2021.

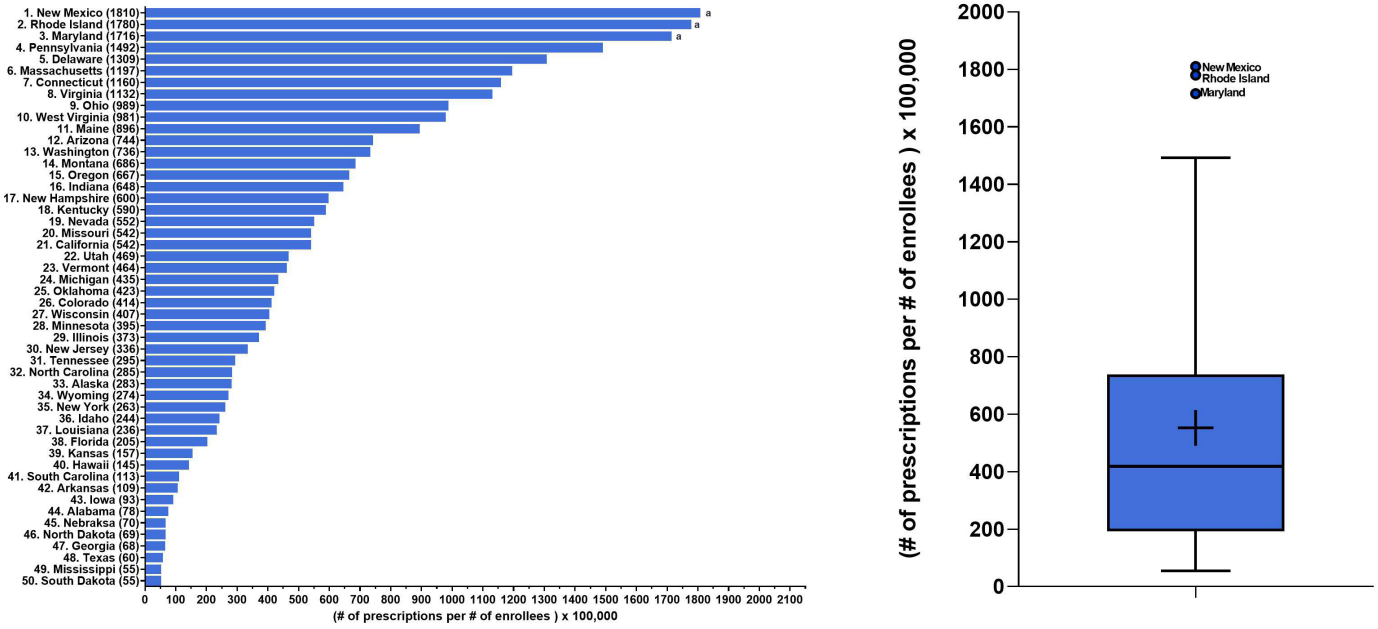

Figure 2 Naloxone prescriptions per 100 000 Medicaid enrollees by state in 2019 as a waterfall (A) and box and whisker plot (B). The outliers to the data are marked with the letter 'a' on the waterfall graph.

Cost of prescription was also assessed. $Naloxone_B$ showed a slight (−1.6%) decrease, while $Naloxone_G$ decreased by 14.6% from 2018 to 2021. The cost per prescription of $Naloxone_G$ decreased from $114.59 at the beginning of 2018 to $97.82 at the end of 2021. $Naloxone_B$ slightly decreased from $128.41 to $126.38.

Examination of prescription rates by state in 2019 was also completed (figure 2). Quartile ranges were calculated, with New Mexico, Rhode Island and Maryland being outliers past the upper limit (1555.7). No outliers were found below the calculated lower limit (−625.1). The median was 418.7 with the first quartile being 192.7 and the third quartile being 737.9. There was a 33.1-fold greater prescribing rate in New Mexico (1809.5) prescriptions per 100k enrollees relative to South Dakota (54.6).

Medicare

Quartile range analysis was also performed for Medicare data (figure 3). New Mexico, California, Tennessee and Rhode Island were outliers past the upper limit (528.8). No outliers were found past the lower limit (−70.3). The median was 214.2 with the first quartile being 154.3 and the third quartile being 304.1. There was a 30.4-fold difference between New Mexico (2061.7) and South Dakota (67.8).

Finally, a scatterplot was created to examine the association of the Medicaid and Medicare prescribing (figure 4). The Spearman correlation calculation was performed with a calculated r(48) value of 0.4676, with a two-tailed p-value=0.0006. When NM and CA were removed, the Spearman correlation was found to be r(46) = 0.4408, p=0.0017.

DISCUSSION

Overall, there was a substantial increase in naloxone prescriptions. This 210.5% elevation in Medicaid should come as no surprise for a few reasons. Past work has similarly described increases in naloxone prescriptions within Medicaid during an earlier (2013–2017) period.[14] The increase in prescriptions may be due to Medicaid expansion and the updates in standing orders/laws individual states issue. Medicaid expansion previously accounted for an 8.3% increase in naloxone units from 2009 to 2016.[15] Further review of the literature has only continued to solidify the weight of Medicaid's influence over naloxone access.[16] Individuals insured by Medicaid may face financial and housing insecurity.[17] As such, coverage of naloxone may be a major factor for accessibility. State interventions such as standing orders show conflicting evidence over their efficacy in increasing accessibility to naloxone.[18 19] Internationally, we see increased naloxone accessibility with the implementation of programmes such as in Ontario.[20] However, while there are studies in favour of state intervention, other studies have argued otherwise. For example, in North Carolina, one report showed evidence that even with the implementation of a standing order, only three-fifths of retail pharmacies carried naloxone.[21] Another report from Philadelphia revealed that communities with higher rates of opioid

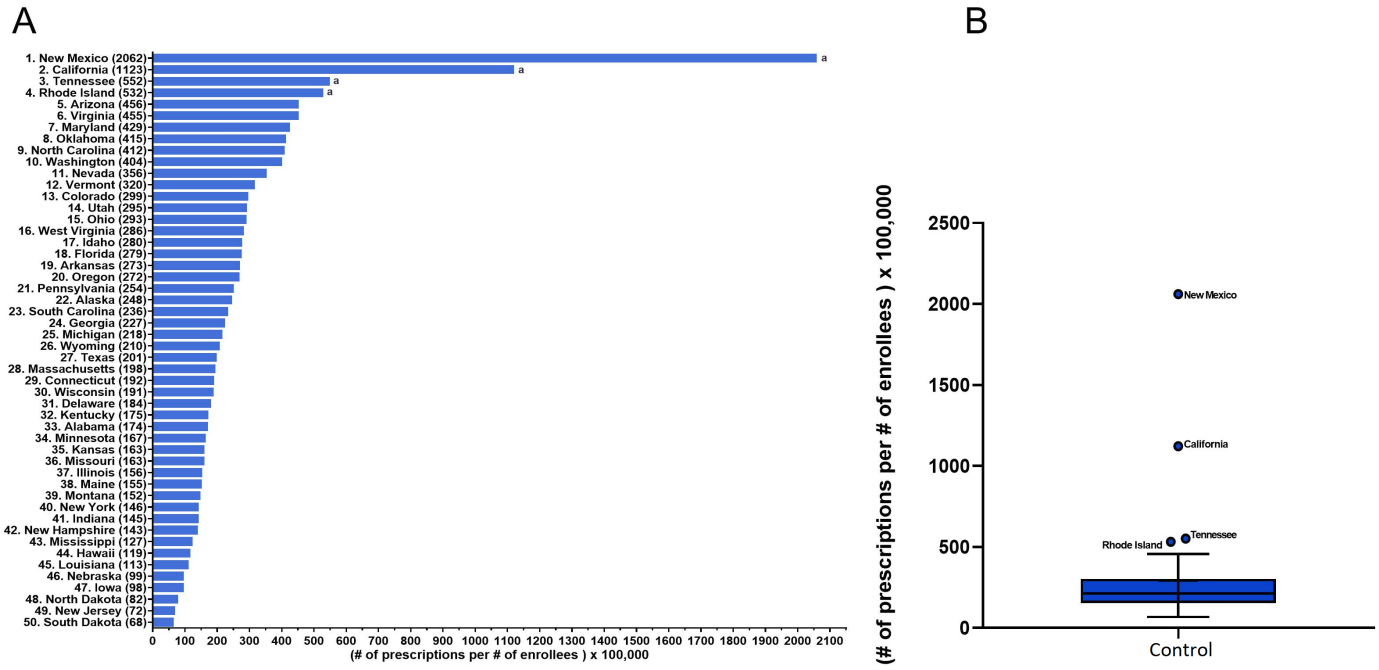

Figure 3 Naloxone prescriptions per 100 000 Medicare enrollees per state in 2019 as a waterfall (A) and box and whisker plot (B). The outliers to the data are marked with the letter 'a' on the waterfall graph.

overdose were less likely to have pharmacy accessibility to naloxone.[22]

This study also showed the price of generic and brand naloxone decreased overall. However, throughout the 4 years, there were both increases and decreases in price. Multiple variables can account for rises in price, including increases in demand, drug shortages and limited competition.[23]

Finally, when looking at state-by-state naloxone prescription rates, disparities were clearly seen throughout the USA. There was a 33.1-fold difference between the highest and lowest states when correcting for enrollees in 2019 for Medicaid. Similarly, Medicare showed a 30.4-fold difference. Literature investigating naloxone patterns in the past have provided many arguments as to why. Some major themes highlighted which may be present here

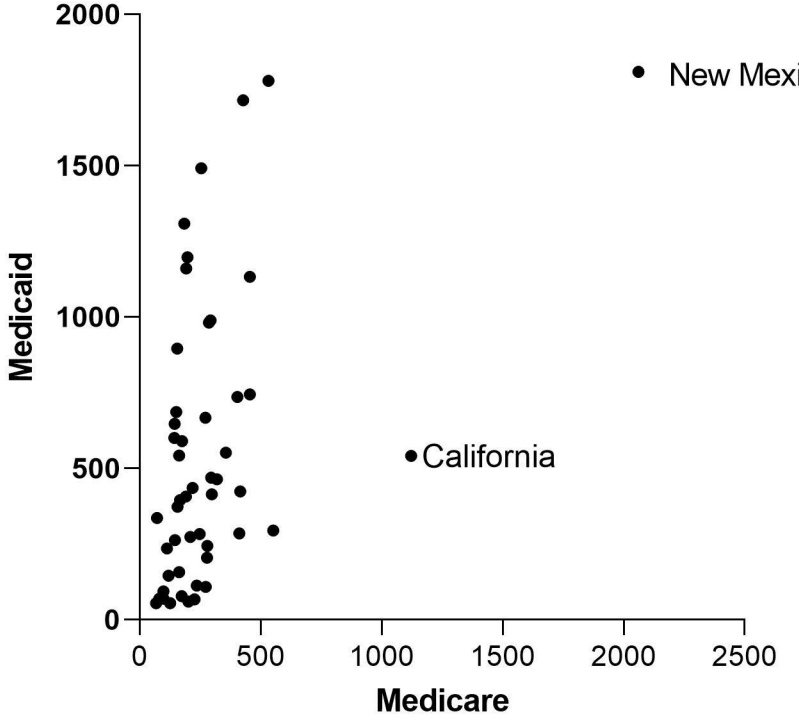

Figure 4 Medicare and Medicaid naloxone claims per state correcting for the number of enrollees. Spearman correlation reveals an r=0.4676 with a two-tailed p-value=0.0006.

include financial barriers, standing orders/state intervention and the stigma/guidance providers are exposed to. As mentioned previously, the population insured by Medicaid may face a variety of issues such as financial insecurity.[15] Thus, the actual coverage and expansion Medicaid provides carries appreciable influence. If we assume each state has its own funded programmes to assist community members, along with differing levels of efficacy in education on such resources, we can already begin to identify discrepancies between states. One study provided evidence that even within a specific area, community, pharmacy and prescription-based access to naloxone have differing levels of effectiveness at increasing accessibility.[24] Finally, stigma and guidance can have a profound effect on naloxone accessibility. For example, pharmacies in Texas not only differ on naloxone access but also on reasons for why they are not or will not be available.[25] For the consumer, this can make accessing naloxone very challenging, and reasons for such barriers may be rooted in stigma. One pharmacist stated, 'being that kind of medication, we are going to pass.'[25] States may provide legal access for consumers, but if stigma runs rampant, people who need naloxone will face major challenges getting it. Influence can have an opposite impact too. For example, one report noted how a recommendation by the American Society of Anesthesiologists led to an increase in prescriptions of naloxone.[19] Hence, state-by-state levels of stigma contribute to the differing levels of naloxone prescription, and this is further affected by different professional association recommendations and guidelines for healthcare providers.

Our distinction between brand and generic versions of naloxone showed major differences in both prescriptions and cost. Given the population of Medicaid patients and the financial struggles they may face, financial barriers imposed by pharmaceutical companies can bar patients from accessing this life-saving drug. For deaths from opioid overdose, 30% of patients are uninsured, thus making up an important subpopulation where finances can make a large impact.[26] In comparison, for the buprenorphine market, it was found that multiple factors inhibited the release of generic sublingual buprenorphine.[27] Additionally, when examining insured patients specifically, the cost of buprenorphine decreased over time.[28] This interesting pattern follows naloxone, which, for insured patients decreased by 26.15%.[26] However, for the uninsured patient desiring naloxone, they instead saw a staggering 606.33% increase in cost.[26] As such, future work should be done to both encourage generic formulations of products that can combat the opioid epidemic and should also work to make prices more affordable to uninsured patients including for over-the-counter formulations.

Some caveats and future directions are noteworthy. Importantly, differences are noted between the Medicaid and Medicare databases utilised.[10 12] The Medicare data fields were created by Medicare part D plans and submitted to CMS for billing purposes rather than research. The data set includes prescription drugs prescribed to Medicare beneficiaries enrolled in part D by physicians and other healthcare providers. This data set contains the total number of prescription fills that were dispensed and the total drug cost paid organised by prescribing National Provider Identifier (NPI), drug brand name (if applicable) and drug generic name. Medicaid drug utilisation data are reported by states for covered outpatient drugs paid for by state Medicaid agencies. This data set contains the total number of prescriptions that were dispensed organised by state, drug name, National Drug Code, year and quarter of year. The data set includes the number of prescriptions, units reimbursed and total amount reimbursed for each covered drug by state and quarter of year. Additionally, the most recent date of Medicaid data differs from Medicare data available.[10 12] Given the differences in data availability, analysis was confined to the results presented here.

This study characterised the increases in prescriptions and pronounced state-level variation in Medicaid patients. As naloxone is prescribed for those at risk of opioid overdose and patients with opioid use disorder, the denominator in the analyses was the number of patients in each programme (Medicaid or Medicare). Future research should further examine the sources of naloxone (eg, primary care vs specialists) and specific patient populations (those with a history of emergency room visits for overdoses). As there are regional differences (East vs West) in overdoses and fentanyl seizures,[29] further investigations of how naloxone prescribing has impacted opioid mortality, with or without xylazine, are needed. Additionally, this study does not compare private versus public insurance, focuses only on the USA, and investigates broad trends over time, as opposed to patient-specific data. Future research should include a scope that includes these study ideas. One specific future study the authors recommend is analysing opioid overdose as well as opioid prescribing in relation to naloxone prescriptions via the electronic health record.

CONCLUSION

Overall, the opioid epidemic is a persistent but escalating challenge for the USA. While naloxone prescriptions to Medicaid patients have increased, more work should clearly be done to target this crisis including identifying the origins for the 33.1-fold disparities in prescribing between states and maximising the availability of evidence-based treatments to resource-limited populations. Education, preparedness to respond to an overdose and increased coprescription are different avenues worth further exploration.

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Contributors Conceptualisation: CDM, MSA, LRH and BJP. Methodology: CDM, MSA, LRH, SAK, NL, JOK, FK, CAM, TKS, MEA and CNM. Software: LRH and CDM. Formal analysis: CDM and MSA. Investigation: CDM, MSA, LRH, SAK, NL, JOK, FK, CAM, TKS, MEA and CNM. Resources: LRH and BJP. Data curation: CDM, MSA and SAK. Writing—original draft writing: CDM, MSA, LRH, SAK, NL, JOK, FK, CAM, TKS, MEA, CNM, KLM, JBF and BJP. Writing—review and editing: CDM, MSA, LRH and JOK. Visualisation: CDM, LRH and MSA. Supervision: BJP. Project administration: CDM. All authors have read and agreed to the submission of the manuscript for publication. CDM takes full responsibility for the work and/or conduct of the study, had access to the data, and controlled the decision to publish as guarantor.

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Competing interests BJP was (2019–2021) part of an osteoarthritis research team supported by Pfizer and Eli Lilly. He is also a principal investigator with the Pennsylvania Academic Clinical Research Centre (2022–2023 and 2023–2025). The other authors have no disclosures.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This research was designated by the Geisinger Institutional Review Board (IRB) as not human subject research. The IRB number is 2022-0533.

Provenance and peer review Not commissioned; externally peer reviewed.

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