

## Supplementary Appendix

Supplement to: Deputy NP, Deckert J, Chard AN, et al. Vaccine effectiveness of JYNNEOS against mpox disease in the United States. *N Engl J Med* 2023;388:2434-43. DOI: 10.1056/NEJMoa2215201

This appendix has been provided by the authors to give readers additional information about the work.

## Supplementary Appendix

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### Supplementary Methods:

Epic's Cosmos platform, an integrated electronic health care record (EHR) database, comprises data from health care organizations, including hospitals, clinics, academic medical centers, federally qualified health centers, and rural and critical access centers. These organizations voluntarily submit information to Cosmos through their Epic EHR. A Health Insurance Portability and Accountability Act (HIPAA)-defined limited data set is then created that includes demographic information, International Classification of Diseases, Tenth Revision codes (ICD-10), medications, and laboratory codes and values.

**Table S1: Definitions for Eligible Case and Control Patients and Associated International Classification of Diseases, Tenth Revision (ICD-10) Codes and Logical Observation Identifiers Names and Codes (LOINC)**

| <b>Monkeypox</b>  |   |
|---|---|
| <i>One or more of the following codes or positive results present between August 15, 2022 and November 19, 2022</i> |   |
| ICD-10 Code   | Description   |
| B04   | Monkeypox   |
| LOINC Code  | Long Common Name  |
| 41853-3   | Orthopoxvirus Deoxyribonucleic acid, or DNA [Presence] in Specimen by Nucleic Acid Amplification, or NAA with probe detection |
| 100434-0  | Orthopoxvirus non-variola DNA [Presence] in Specimen by NAA with probe detection  |
| 100383-9  | Monkeypox virus DNA [Presence] in Specimen by NAA with probe detection  |
| 100888-7  | West African monkeypox virus DNA [Presence] in Specimen by NAA with probe detection   |
| 100889-5  | Congo Basin monkeypox virus DNA [Presence] in Specimen by NAA with probe detection  |
| 100892-9  | Orthopoxvirus IgM Ab [Presence] in Serum or Plasma by Immunoassay   |
| Unmapped Laboratory test  | Laboratory test name  |
|   | BH AMB LAB ORTHOPOXVIRUS DNA, QL PCR  |
|   | CDC Monkeypox PCR   |
|   | EXT Monkeypox PCR   |
|   | External ORTHOPOXVIRUS DNA, PCR   |
|   | MONKEYPOX   |
|   | Monkeypox (Non-variola Orthopoxvirus) screen, PCR   |
|   | MONKEYPOX (ORTHOPOXVIRUS) BY PCR  |
|   | Monkeypox (Orthopoxvirus) DNA PCR   |
|   | Monkeypox (Orthopoxvirus) PCR   |
|   | Monkeypox (Orthopoxvirus), PCR  |
|   | Monkeypox CDC   |
|   | MonkeyPox DNA   |
|   | Monkeypox DNA PCR   |
|   | Monkeypox generic   |
|   | Monkeypox ISDH  |
|   | Monkeypox PCR   |
|   | Monkeypox Result  |
|   | Monkeypox Virus   |
|   | Monkeypox virus (Orthopoxvirus) PCR   |
|   | Monkeypox Virus by PCR  |
|   | Monkeypox virus Clade I   |
|   | Monkeypox virus Clade II  |

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|  |   |
|--|---|
|  | Monkeypox virus DNA                             |
|  | Monkeypox Virus DNA PCR                         |
|  | Monkeypox virus DNA QL PCR                      |
|  | Monkeypox Virus DNA Qual                        |
|  | Monkeypox Virus DNA, QL                         |
|  | MONKEYPOX VIRUS DNA, QL PCR                     |
|  | Monkeypox Virus DNA, QL-PCR                     |
|  | Monkeypox Virus DNA, Qual PCR                   |
|  | Monkeypox Virus DNA, Qualitative PCR            |
|  | Monkeypox Virus DNA, Qualitative, Real-time PCR |
|  | Monkeypox Virus DNA,QL PCR                      |
|  | Monkeypox Virus DNA,QL PCR Grady                |
|  | MONKEYPOX VIRUS NAAT EXTERNAL                   |
|  | Monkeypox Virus PCR                             |
|  | Monkeypox Virus, DNA PCR                        |
|  | Monkeypox Virus, DNA, PCR                       |
|  | Monkeypox Virus, PCR                            |
|  | Monkeypox WA specific                           |
|  | MONKEYPOX, PCR                                  |
|  | Monkeypox/Orthopox                              |
|  | Monkeypoxvirus DNA                              |
|  | Monkeypoxvirus DNA, qualitative PCR             |
|  | MPXDX, ORTHOPOXVIRUS DNA, PCR                   |
|  | Non-Variola Orthopox                            |
|  | Non-Variola Orthopox DNA                        |
|  | NON-VARIOLA ORTHOPOX EXTERNAL                   |
|  | Non-Variola Orthopox PCR (DOH)                  |
|  | Non-Variola Orthopox Virus                      |
|  | Non-Variola Orthopox Virus by RT-PCR            |
|  | NON-VARIOLA ORTHOPOXVIRUS DNA                   |
|  | Non-variola Orthopoxvirus DNA by PCR            |
|  | Non-variola Orthopoxvirus DNA PCR               |
|  | Non-variola orthopoxvirus Real-Time PCR         |
|  | Non-Variola Orthopoxvirus, Qualitative          |
|  | Note, Monkeypox                                 |
|  | ORTHOPOX  |
|  | Orthopox DNA, Qualitative PCR                   |
|  | Orthopox PCR                                    |
|  | Orthopox Virus                                  |
|  | Orthopox Virus DNA                              |
|  | Orthopox virus DNA QL PCR                       |

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|  |  |
|--|--|
|  | Orthopox Virus DNA, QL PCR                 |
|  | Orthopox Virus Nonvariola DNA, QL-PCR      |
|  | Orthopox Virus Sample Conclusion           |
|  | Orthopox, PCR Assay                        |
|  | Orthopoxirus DNA                           |
|  | Orthopoxvirus                              |
|  | Orthopoxvirus (Including Monkeypox) by PCR |
|  | Orthopoxvirus (Monkeypox Virus by PCR)     |
|  | Orthopoxvirus DNA                          |
|  | Orthopoxvirus Dna (Labcorp)                |
|  | ORTHOPOXVIRUS DNA LC                       |
|  | Orthopoxvirus DNA PCR                      |
|  | Orthopoxvirus DNA QL PCR                   |
|  | Orthopoxvirus DNA Qual                     |
|  | Orthopoxvirus DNA, PCR                     |
|  | ORTHOPOXVIRUS DNA, QL PCR                  |
|  | Orthopoxvirus DNA, QL PCR Grady            |
|  | Orthopoxvirus DNA, QL, PCR                 |
|  | Orthopoxvirus DNA, Qual PCR                |
|  | Orthopoxvirus DNA, qualitative PCR         |
|  | Orthopoxvirus DNA,QL PCR                   |
|  | Orthopoxvirus Non-Variola DNA              |
|  | Orthopoxvirus PCR                          |
|  | Orthopoxvirus, DNA                         |
|  | Orthopoxvirus, DNA QL                      |
|  | Orthopoxvirus, DNA, PCR                    |
|  | Orthopoxvirus.non-variola DNA              |
|  | PCR FOR NON-VARIOLA ORTHOPOX GROUP VIRUSES |
|  | Quest Orthopoxvirus DNA QL PCR (External)  |
|  | WEST AFRICAN MONKEYPOX                     |
|  | West African monkeypox virus DNA           |

**HIV**

*One or more of the following codes present between August 15, 2022 and October 29, 2022 and no indication of these codes prior to November 19, 2022*

| ICD-10 Code | Description   |
|-------------|---|
| B20         | Human immunodeficiency virus [HIV] disease                          |
| LOINC Code  | Test  |
| 7917-8      | HIV 1 Ab [Presence] in Serum  |
| 7919-4      | HIV 2 Ab [Presence] in Serum  |
| 56888-1     | HIV 1+2 Ab+HIV1 p24 Ag [Presence] in Serum or Plasma by Immunoassay |

**PrEP**

*Medication order for Truvada® or Descovy® between August 15, 2022 and November 19, 2022 and no HIV ICD-10 or LOINC code*

**Table S2. List of Immunocompromising Conditions and Associated International Classification of Diseases, Tenth Revision (ICD-10) Codes and Immunosuppressive Medications**

|                                  |   |  |
|----------------------------------|---|--|
| <b>Immunocompromising codes*</b> | Organ Transplant  | T86.1, T86.2, T86.3, T86.4, T86.81, T86.85, Z48.2, Z94.0, Z94.1, Z94.2, Z94.3, Z94.4, Z94.82, Z94.83   |
|                                  | Stem Cell Transplant  | Z94.84, T86.0, T86.5   |
|                                  | Underlying Immunodeficiency   | D80, D81.0, D81.1, D81.2, D81.9, D82, D83, D84, D89.8, D89.9   |
|                                  | Chemotherapy or Radiation Therapy   | Z51.0, Z51.1   |
|                                  | Hematologic Conditions  | C95.00, C95.10, D61.0, D61.2, D61.9, D70 (except D70.9), D71, D72 (except D72.829 or D72.819), D73.0, C81, C82, C83, C84, C85, C86, C88, C90, C91, C92, C93, C94, C96, D46 |
|                                  | Chronic Use of Steroids   | Z79.5  |
|                                  | HIV   | B20, B97.35, O98.7, Z21  |
| <b>Pharmaceutical Class</b>      | <b>Medications</b>  |  |
| 5-Aminosalicylic Acid Derivative | Mesalamine, sulfasalazine   |  |
| Antihelminthic                   | Levamisole  |  |
| Antineoplastic Agent             | Adriamycin, aldesleukin, altretamine, amsacrine, arsenic trioxide, asparaginase, axicabtagene ciloleucel, azacitidine, bendamustine hydrochloride, bexarotene, bleomycin sulfate, bortezomib, brexucabtagene autoleucel, busulfan, cabazitaxel, capecitabine, carboplatin, carfilzomib, carmustine, chlorambucil, ciltacabtagene autoleucel, cisplatin, cladribine, clofarabine, cyclophosphamide, cytarabine, cytarabine liposome, dacarbazine, dactinomycin, dasatinib, daunorubicin, daunorubicin citrate liposome, decitabine, denileukin diftitox, docetaxel, doxorubicin, doxorubicin hydrochloride, doxorubicin hydrochloride liposome, epirubicin, eribulin mesylate, erlotinib, estramustine phosphate sodium, etoposide, everolimus, floxuridine, fludarabine, fluorouracil, gefitinib, gemcitabine, idarubicin, idecabtagene vicleucel, ifosfamide, ifosfamide / mesna, imatinib, irinotecan, ixabepilone, ixazomib, lapatinib, lenalidomide, lisocabtagene maraleucel, lomustine, mechlorethamine, melphalan, mercaptopurine, methotrexate, mitomycin, mitotane, mitoxantrone, nelarabine, nilotinib, osimertinib, oxaliplatin, paclitaxel, pazopanib, pegaspargase, pemetrexed, pentostatin, plicamycin, porfimer sodium, pralatrexate, procarbazine, romidepsin, selinexor, sirolimus, sorafenib, streptozocin, sunitinib, temozolomide, temsirolimus, teniposide, thalidomide, thioguanine, thiotepa, topotecan, tretinoin, uracil mustard, venetoclax, vinblastine, vincristine, vinorelbine, or vorinostat |  |
| Antirheumatic                    | Abatacept, auranofin, aurothioglucose, belatacept, gold sodium thiomalate, hydroxychloroquine, leflunomide, or tocilizumab  |  |
| Biological                       | Glatiramer acetate  |  |

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|  |  |
|--|--|
| Chemoprotective Agent                            | Amifostine, dextrazoxane, mesna, or palifermin   |
| Corticosteroid, Systemic                         | Betamethasone, budesonide, dexamethasone, methylprednisolone, methylprednisolone sodium succinate, prednisolone, prednisone, or triamcinolone  |
| Enzyme   | Pegademase bovine  |
| Hematopoietic Agent                              | Filgrastim, lenograstim, or lipegfilgrastim  |
| Immunosuppressant Agent                          | Alefacept, azathioprine, basiliximab, cyclosporine, mycophenolate, pimecrolimus, or tacrolimus   |
| Immunotherapy                                    | Sipuleucel-T or tisagenlecleucel   |
| Biological Response Modulator                    | Interferon alfa-2a, interferon alfa-2b, interferon alfacon-1, interferon alfa-3, interferon beta-1a, interferon beta-1b, interferon gamma-1b, peginterferon alfa-2a, or peginterferon alfa-2b  |
| Monoclonal Antibody                              | Adalimumab, alemtuzumab, anakinra, belimumab, benralizumab, bevacizumab, blinatumomab, brentuximab vedotin, canakinumab, certolizumab pegol, cetuximab, daclizumab, denosumab, eculizumab, efalizumab, emapalumab-lzsg, etanercept, gemtuzumab ozogamicin, golimumab, guselkumab, ibritumomab tiuxetan, infliximab, inotuzumab ozogamicin, ipilimumab, mepolizumab, muromonab-CD3, natalizumab, obinutuzumab, ocrelizumab, ofatumumab, palivizumab, panitumumab, pertuzumab, rilonacept, rituximab, trastuzumab, ustekinumab, or vedolizumab |
| Radiopharmaceutical                              | Iodine-131-tositumomab   |
| Sphingosine 1-Phosphate (S1P) Receptor Modulator | Fingolimod   |
| Thrombolytic Agent                               | Defibrotide  |

\*For parent codes that are listed, all sub-codes are included unless specified.

**Table S3: Associations Between Selected Patient Characteristics and Case or Control Patient Status – United States, August 15 – November 19, 2022**

|  | No. of case patients | No. of control patients | Unadjusted Odds Ratio (95% CI) | Adjusted* Odds Ratio (95% CI) |
|--|----------------------|-------------------------|--------------------------------|-------------------------------|
| <b>Age</b>                                   |                      |                         |                                |                               |
| 18-35 (ref)                                  | 1216                 | 4054                    |                                |                               |
| 36-49  | 679                  | 2347                    | 1.0 (0.9 - 1.1)                | 1.0 (0.8 - 1.1)               |
| 50+  | 298                  | 1918                    | 0.5 (0.5 - 0.6)                | 0.5 (0.4 - 0.5)               |
| <b>Race/ethnicity</b>                        |                      |                         |                                |                               |
| White, Non-Hispanic (ref)                    | 764                  | 4605                    |                                |                               |
| Black, Non-Hispanic                          | 797                  | 1516                    | 3.3 (3.0 - 3.8)                | 2.1 (1.9 - 2.4)               |
| Hispanic/Latino                              | 480                  | 1450                    | 2.0 (1.7 - 2.2)                | 1.5 (1.3 - 1.8)               |
| Other, Non-Hispanic (including AN/AI, Asian) | 152                  | 748                     | 1.2 (1.0 - 1.5)                | 1.1 (0.9 - 1.4)               |
| <b>Social Vulnerability Index</b>            |                      |                         |                                |                               |
| Q1 [0,.24] (ref)                             | 254                  | 1353                    |                                |                               |
| Q2 [.25,.49]                                 | 362                  | 1947                    | 1.0 (0.9 - 1.2)                | 0.9 (0.8 - 1.1)               |
| Q3 [.50,.74]                                 | 489                  | 2139                    | 1.3 (1.1 - 1.5)                | 1.1 (0.9 - 1.3)               |
| Q4 [.75,1]                                   | 1071                 | 2847                    | 2.1 (1.8 - 2.4)                | 1.4 (1.2 - 1.6)               |
| <b>Immunocompromising condition</b>          |                      |                         |                                |                               |
| No (ref)                                     | 1267                 | 6612                    |                                |                               |
| Yes  | 926                  | 1707                    | 2.9 (2.6 - 3.2)                | 2.5 (2.3 - 2.9)               |

\*Adjusted for vaccination status, age group, race/ethnicity, Social Vulnerability Index, and presence or absence of immunocompromising conditions defined in Table S2.

**Table S4: Characteristics of Case Patients and Control Patients by Vaccination Status – United States, August 15 – November 19, 2022**

|   | Unvaccinated* |          | Partially vaccinated† |          | Fully vaccinated‡ |          |
|---|---------------|----------|-----------------------|----------|-------------------|----------|
|   | n             | column % | n                     | column % | n                 | column % |
| <b>Total</b>  | 9006          | 100      | 1146                  | 100      | 360               | 100      |
| <b>Age in years</b>   |               |          |                       |          |                   |          |
| 18-35   | 4548          | 50.5     | 576                   | 50.3     | 146               | 40.6     |
| 36-49   | 2547          | 28.3     | 353                   | 30.8     | 126               | 35.0     |
| 50-64   | 1553          | 17.2     | 186                   | 16.2     | 78                | 21.7     |
| 65+   | 358           | 4.0      | 31                    | 2.7      | 10                | 2.8      |
| <b>Sex (legal)</b>  |               |          |                       |          |                   |          |
| Male  | 7988          | 88.7     | 1134                  | 99.0     | 358               | 99.4     |
| Female  | 1003          | 11.1     | 11                    | 1.0      | 2                 | 0.6      |
| Other   | 5             | 0.1      | 1                     | 0.1      | 0                 | 0        |
| Unknown   | 10            | 0.1      | 0                     | 0        | 0                 | 0        |
| <b>Gender Identity</b>  |               |          |                       |          |                   |          |
| Male  | 7867          | 87.4     | 1119                  | 97.6     | 360               | 100      |
| Female  | 981           | 10.9     | 5                     | 0.4      | 0                 | 0        |
| Transgender Male  | 5             | 0.1      | 1                     | 0.1      | 0                 | 0        |
| Transgender Female  | 87            | 1.0      | 10                    | 0.9      | 0                 | 0        |
| Other   | 65            | 0.7      | 11                    | 1        | 0                 | 0        |
| Chose not to disclose   | 1             | 0.01     | 0                     | 0        | 0                 | 0        |
| <b>Race/Ethnicity</b>   |               |          |                       |          |                   |          |
| White Non-Hispanic  | 4422          | 49.1     | 697                   | 60.8     | 250               | 69.4     |
| Black Non-Hispanic  | 2180          | 24.2     | 110                   | 9.6      | 23                | 6.4      |
| Hispanic/Latino   | 1657          | 18.4     | 211                   | 18.4     | 62                | 17.2     |
| Asian Non-Hispanic  | 353           | 3.9      | 87                    | 7.6      | 12                | 3.3      |
| Alaska Native/American Indian, Non-Hispanic                       | 31            | 0.3      | 1                     | 0.1      | 0                 | 0        |
| Other, Non-Hispanic   | 363           | 4.0      | 40                    | 3.5      | 13                | 3.6      |
| <b>Social Vulnerability Index Quartile†</b>                       |               |          |                       |          |                   |          |
| [0, 0.24]   | 1242          | 13.8     | 258                   | 22.5     | 107               | 29.7     |
| [0.25, 0.49]  | 1946          | 21.6     | 289                   | 25.2     | 74                | 20.6     |
| [0.50, 0.74]  | 2213          | 24.6     | 319                   | 27.8     | 96                | 26.7     |
| [0.75, 1]   | 3558          | 39.5     | 278                   | 24.3     | 82                | 22.8     |
| Unknown   | 47            | 0.5      | 2                     | 0.2      | 1                 | 0.3      |
| <b>U.S. Census Region</b>   |               |          |                       |          |                   |          |
| South   | 3697          | 41.1     | 215                   | 18.8     | 99                | 27.5     |
| Northeast   | 1292          | 14.4     | 228                   | 19.9     | 32                | 8.9      |
| West  | 2535          | 28.2     | 537                   | 46.9     | 148               | 41.1     |
| Midwest   | 1482          | 16.5     | 166                   | 14.5     | 81                | 22.5     |
| <b>U.S. Department of Health and Human Services Census Region</b> |               |          |                       |          |                   |          |
| Region 1 (CT, ME, MA, NH, RI, VT)                                 | 218           | 2.4      | 51                    | 4.5      | 14                | 3.9      |

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|   |      |      |      |      |     |      |
|---|------|------|------|------|-----|------|
| Region 2 (NJ, NY)   | 442  | 4.9  | 26   | 2.3  | 7   | 1.9  |
| Region 3 (DE, DC, MD, PA, VA, WV)                                       | 1404 | 15.6 | 177  | 15.5 | 22  | 6.1  |
| Region 4 (AL, FL, GA, KY, MS, NC, SC, TN)                               | 1808 | 20.1 | 126  | 11.0 | 52  | 14.4 |
| Region 5 (IL, IN, MI, MN, OH, WI)                                       | 1376 | 15.3 | 159  | 13.9 | 74  | 20.6 |
| Region 6 (AR, LA, NM, OK, TX)   | 1130 | 12.6 | 64   | 5.6  | 37  | 10.3 |
| Region 7 (IA, KS, MO, NE)   | 87   | 1.0  | 6    | 0.5  | 6   | 1.7  |
| Region 8 (CO, MT, ND, SD, UT, WY)                                       | 479  | 5.3  | 130  | 11.3 | 78  | 21.7 |
| Region 9 (AZ, CA, HI, NV)   | 1422 | 15.8 | 339  | 29.6 | 67  | 18.6 |
| Region 10 (AK, ID, OR, WA)  | 640  | 7.1  | 68   | 5.9  | 3   | 0.8  |
| <b>Index Encounter Type (assoc. w/dx or lab)</b>                        |      |      |      |      |     |      |
| In-person outpatient  | 7026 | 78.0 | 1105 | 96.4 | 352 | 97.8 |
| Emergency department  | 1458 | 16.2 | 25   | 2.2  | 5   | 1.4  |
| Urgent care   | 19   | 0.2  | 0    | 0    | 0   | 0    |
| Hospital admission  | 424  | 4.7  | 15   | 1.3  | 2   | 0.6  |
| ICU admission   | 79   | 0.9  | 1    | 0.1  | 1   | 0.3  |
| <b>Source of index encounter event</b>                                  |      |      |      |      |     |      |
| Diagnosis code  | 1610 | 17.9 | 111  | 9.7  | 17  | 4.7  |
| Laboratory confirmed result   | 1030 | 11.4 | 53   | 4.6  | 10  | 2.8  |
| Diagnosis code + laboratory confirmed                                   | 726  | 8.1  | 24   | 2.1  | 10  | 2.8  |
| Prescription medication   | 5640 | 62.6 | 958  | 83.6 | 323 | 89.7 |
| <b>Number of underlying medical conditions   </b>                       |      |      |      |      |     |      |
| 0   | 2625 | 29.2 | 437  | 38.1 | 126 | 35.0 |
| 1   | 2744 | 30.5 | 347  | 30.3 | 105 | 29.2 |
| 2   | 1805 | 20.0 | 196  | 17.1 | 70  | 19.4 |
| 3   | 986  | 11.0 | 101  | 8.8  | 34  | 9.4  |
| 4   | 455  | 5.1  | 43   | 3.8  | 16  | 4.4  |
| 5+  | 391  | 4.3  | 22   | 1.9  | 9   | 2.5  |
| <b>Number of face-to-face encounters in past year</b>                   |      |      |      |      |     |      |
| 0   | 565  | 6.3  | 46   | 4.0  | 6   | 1.7  |
| 1   | 1653 | 18.4 | 161  | 14.1 | 34  | 9.4  |
| 2   | 1287 | 14.3 | 141  | 12.3 | 44  | 12.2 |
| 3   | 1062 | 11.8 | 137  | 12.0 | 38  | 10.6 |
| 4   | 893  | 9.9  | 124  | 10.8 | 48  | 13.3 |
| 5+  | 3546 | 39.4 | 537  | 46.9 | 190 | 52.8 |
| <b>Immunocompromising condition ¶</b>                                   |      |      |      |      |     |      |
| No  | 6519 | 72.4 | 1034 | 90.2 | 326 | 90.6 |
| Yes   | 2487 | 27.6 | 112  | 9.8  | 34  | 9.4  |
| <b>Living with HIV</b>  |      |      |      |      |     |      |
| No  | 6889 | 76.5 | 1063 | 92.8 | 338 | 93.9 |
| Yes   | 2117 | 23.5 | 83   | 7.2  | 22  | 6.1  |
| <b>Newly diagnosed with HIV **</b>                                      |      |      |      |      |     |      |
| No  | 6889 | 82.6 | 1063 | 95.9 | 338 | 96.3 |
| Yes   | 1456 | 17.5 | 46   | 4.2  | 13  | 3.7  |
| <b>Has active PrEP prescription (among persons not living with HIV)</b> |      |      |      |      |     |      |

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|   |      |      |     |      |     |      |
|---|------|------|-----|------|-----|------|
| No  | 1116 | 16.2 | 64  | 6.0  | 7   | 2.1  |
| Yes   | 5773 | 83.8 | 999 | 94.0 | 331 | 97.9 |
| <b>Vaccinated with ACAM2000 prior to index date</b> | 81   | 0.9  | 11  | 1.0  | 2   | 0.6  |

\*Patients were considered unvaccinated if there were no documented doses before the index event.

†Patients were considered partially vaccinated if they received one dose  $\geq$  14 days before the index event, or the second dose was  $<14$  days before the index event; patients who received one dose  $<14$  days before the index event were excluded as vaccination might represent post-exposure prophylaxis (n=73 for case patients and n=323 for control patients).

‡Patients were considered fully vaccinated if they received two doses of JYNNEOS vaccine  $\geq$  24 days apart and the second dose was  $\geq$  14 days before the index event. Patients were excluded if they received two doses  $<$  24 days apart (n=0 for case patients and n=7 for control patients).

§Social Vulnerability Index is an indicator of community-level vulnerability that ranges from 0 to 1.0, with higher scores indicating greater vulnerability.

||Medical conditions are defined in Table S7.

¶Includes selected conditions defined by presence of selected conditions identified by ICD-10 codes or immunosuppressive medication prescribed in the past 6 months defined in Table S2.

\*\*Denominator excludes patients who are not at risk for a new HIV diagnosis (due to an existing HIV diagnosis).

**Table S5: Characteristics of Case Patients with Mpox and Control Patients with an HIV Diagnosis or HIV Pre-Exposure Prophylaxis (PrEP) Prescription, among Individuals Seeking Health Care – United States, August 15 – November 19, 2022\***

| Characteristics   | Mpox<br>Case patients |       | Control patients<br>(PrEP or HIV) |       |
|---|-----------------------|-------|-----------------------------------|-------|
|   | N                     | Col % | N                                 | Col % |
| <b>Total</b>  | 2,266                 | 100.0 | 8,649                             | 100.0 |
| <b>Age in years</b>   |                       |       |                                   |       |
| 18-35   | 1,252                 | 55.3  | 4,221                             | 48.8  |
| 36-49   | 707                   | 31.2  | 2,434                             | 28.1  |
| 50-64   | 273                   | 12.1  | 1,619                             | 18.7  |
| 65+   | 34                    | 1.5   | 375                               | 4.3   |
| <b>Sex (legal)</b>  |                       |       |                                   |       |
| Male  | 2,059                 | 90.9  | 7,821                             | 90.4  |
| Female  | 204                   | 9.0   | 815                               | 9.4   |
| Other   | 1                     | 0.0   | 5                                 | 0.1   |
| Unknown   | 2                     | 0.1   | 8                                 | 0.1   |
| <b>Gender Identity</b>  |                       |       |                                   |       |
| Male  | 2,022                 | 89.2  | 7,717                             | 89.2  |
| Female  | 199                   | 8.8   | 790                               | 9.1   |
| Transgender Male  | 2                     | 0.1   | 4                                 | 0.1   |
| Transgender Female  | 23                    | 1.0   | 75                                | 0.9   |
| Other   | 19                    | 0.8   | 62                                | 0.7   |
| Chose not to disclose   | 1                     | 0.0   | 1                                 | 0.0   |
| <b>Race/Ethnicity</b>   |                       |       |                                   |       |
| White, Non-Hispanic   | 792                   | 35.0  | 4,800                             | 55.5  |
| Black, Non-Hispanic   | 816                   | 36.0  | 1,545                             | 17.9  |
| Hispanic/Latino   | 500                   | 22.1  | 1,519                             | 17.6  |
| Asian Non-Hispanic  | 71                    | 3.1   | 413                               | 4.8   |
| Alaska Native/American Indian, Non-Hispanic                           | 8                     | 0.4   | 24                                | 0.3   |
| Other, Non-Hispanic   | 79                    | 3.5   | 348                               | 4.0   |
| <b>Social Vulnerability Index Quartile†</b>                           |                       |       |                                   |       |
| [0, 0.24]   | 268                   | 11.8  | 1,423                             | 16.5  |
| [0.25, 0.49]  | 374                   | 16.5  | 2,030                             | 23.5  |
| [0.50, 0.74]  | 501                   | 22.1  | 2,209                             | 25.5  |
| [0.75, 1]   | 1,106                 | 48.8  | 2,954                             | 34.2  |
| Unknown   | 17                    | 0.8   | 33                                | 0.4   |
| <b>U.S. Census Region</b>   |                       |       |                                   |       |
| South   | 879                   | 38.8  | 3,235                             | 37.4  |
| Northeast   | 322                   | 14.2  | 1,273                             | 14.7  |
| West  | 708                   | 31.2  | 2,693                             | 31.1  |
| Midwest   | 357                   | 15.8  | 1,448                             | 16.7  |
| <b>U.S. Department of Health and Human Services<br/>Census Region</b> |                       |       |                                   |       |

JYNNEOS Vaccine Effectiveness Against Monkeypox Disease in the U.S

|  |          |      |          |      |
|--|----------|------|----------|------|
| Region 1 (CT, ME, MA, NH, RI, VT)                              | 60       | 2.7  | 237      | 2.7  |
| Region 2 (NJ, NY)  | 97       | 4.3  | 383      | 4.4  |
| Region 3 (DE, DC, MD, PA, VA, WV)                              | 329      | 14.5 | 1,307    | 15.1 |
| Region 4 (AL, FL, GA, KY, MS, NC, SC, TN)                      | 462      | 20.4 | 1,594    | 18.4 |
| Region 5 (IL, IN, MI, MN, OH, WI)                              | 336      | 14.8 | 1,343    | 15.5 |
| Region 6 (AR, LA, NM, OK, TX)                                  | 253      | 11.2 | 1,002    | 11.6 |
| Region 7 (IA, KS, MO, NE)                                      | 21       | 0.9  | 83       | 1.0  |
| Region 8 (CO, MT, ND, SD, UT, WY)                              | 146      | 6.4  | 584      | 6.8  |
| Region 9 (AZ, CA, HI, NV)                                      | 413      | 18.2 | 1,525    | 17.6 |
| Region 10 (AK, ID, OR, WA)                                     | 149      | 6.6  | 591      | 6.8  |
| <b>Index Event Type</b>  |          |      |          |      |
| In-person outpatient   | 1,308    | 57.7 | 7,555    | 87.4 |
| Emergency department   | 787      | 34.7 | 717      | 8.3  |
| Urgent care  | 12       | 0.5  | 10       | 0.1  |
| Hospital admission   | 142      | 6.3  | 302      | 3.5  |
| ICU admission  | 17       | 0.8  | 65       | 0.8  |
| <b>Source of index event</b>                                   |          |      |          |      |
| Diagnosis code   | 729      | 32.2 | 1028     | 11.9 |
| Laboratory confirmed result                                    | 874      | 38.6 | 252      | 2.9  |
| Diagnosis code + laboratory confirmed                          | 663      | 29.3 | 128      | 1.5  |
| Prescription medication  | 0        | 0.0  | 7,241    | 83.7 |
| <b>Hospital admission duration (median days, IQR)‡</b>         | 5.0, 5.5 |      | 5.0, 5.0 |      |
| <b>Number of underlying medical conditions §</b>               |          |      |          |      |
| 0  | 740      | 32.7 | 2,597    | 30.0 |
| 1  | 727      | 32.1 | 2,583    | 29.9 |
| 2  | 436      | 19.2 | 1,704    | 19.7 |
| 3  | 221      | 9.8  | 941      | 10.9 |
| 4  | 84       | 3.7  | 448      | 5.2  |
| 5+   | 58       | 2.6  | 376      | 4.4  |
| <b>Number of face-to-face encounters in past year</b>          |          |      |          |      |
| 0  | 118      | 5.2  | 508      | 5.9  |
| 1  | 517      | 22.8 | 1,389    | 16.1 |
| 2  | 342      | 15.1 | 1191     | 13.8 |
| 3  | 253      | 11.2 | 1026     | 11.9 |
| 4  | 167      | 7.4  | 945      | 10.9 |
| 5+   | 869      | 38.4 | 3,590    | 41.5 |
| <b>Immunocompromising condition   </b>                         |          |      |          |      |
| No   | 1,304    | 57.6 | 6,924    | 80.1 |
| Yes  | 962      | 42.5 | 1,725    | 19.9 |
| <b>Persons with HIV</b>  |          |      |          |      |
| No   | 1,407    | 62.1 | 7,241    | 83.7 |
| Yes  | 859      | 37.9 | 1,408    | 16.3 |
| <b>Persons with HIV and CD4 count &lt;200 in last 6 months</b> |          |      |          |      |
| No   | 2,052    | 90.6 | 8,394    | 97.1 |

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|   |       |      |       |       |
|---|-------|------|-------|-------|
| Yes   | 214   | 9.4  | 255   | 3.0   |
| <b>Newly diagnosed with HIV¶</b>                                    |       |      |       |       |
| No  | 1,407 | 92.2 | 7,241 | 83.7  |
| Yes   | 119   | 7.8  | 1,408 | 16.3  |
| <b>Has active HIV PrEP prescription (among persons without HIV)</b> |       |      |       |       |
| No  | 1,217 | 86.5 | 0     | 0.0   |
| Yes   | 190   | 13.5 | 7,241 | 100.0 |
| <b>Tecovirimat (TPOXX) prescription**</b>                           |       |      |       |       |
| No  | 1,816 | 80.1 | 8,649 | 100.0 |
| Yes   | 450   | 19.9 | 0     | 0.0   |
| <b>Pain medication††</b>  |       |      |       |       |
| None  | 1,811 | 79.9 | 7,942 | 91.8  |
| Prescription medication (oral or topical)                           | 302   | 13.3 | 408   | 4.7   |
| Intravenous medication  | 153   | 6.8  | 299   | 3.5   |
| <b>Vaccinated with ACAM2000 prior to 2022</b>                       |       |      |       |       |
| No  | 2,258 | 99.7 | 8,562 | 99.0  |
| Yes   | 8     | 0.4  | 87    | 1.0   |
| <b>Calendar week of diagnosis</b>                                   |       |      |       |       |
| 8/14  | 367   | 16.2 | 1,275 | 14.7  |
| 8/21  | 375   | 16.6 | 1,406 | 16.3  |
| 8/28  | 339   | 15.0 | 1,285 | 14.9  |
| 9/4   | 257   | 11.3 | 988   | 11.4  |
| 9/11  | 223   | 9.8  | 885   | 10.2  |
| 9/18  | 167   | 7.4  | 662   | 7.7   |
| 9/25  | 112   | 4.9  | 447   | 5.2   |
| 10/2  | 102   | 4.5  | 406   | 4.7   |
| 10/9  | 82    | 3.6  | 328   | 3.8   |
| 10/16   | 61    | 2.7  | 243   | 2.8   |
| 10/23   | 63    | 2.8  | 252   | 2.9   |
| 10/30   | 46    | 2.0  | 184   | 2.1   |
| 11/06   | 51    | 2.3  | 204   | 2.4   |
| 11/13   | 21    | 0.9  | 84    | 1.0   |
| <b>Vaccination Status</b>   |       |      |       |       |
| <b>Fully Vaccinated‡‡</b>   |       |      |       |       |
| Overall   | 25    | 1.1  | 335   | 4.0   |
| <i>Administration Timing Relative to Index Event (IE)</i>           |       |      |       |       |
| Dose 2 24-28 day interval and ≥ 14 days before IE                   | 11    | 44.0 | 133   | 39.7  |
| Dose 2 29-45 day interval and ≥ 14 days before IE                   | 11    | 44.0 | 164   | 49.0  |
| Dose 2 ≥46 day interval and ≥ 14 days before IE                     | 3     | 12.0 | 38    | 11.3  |
| <b>Administration Route</b>   |       |      |       |       |
| Both administrations subcutaneous                                   | 6     | 24.0 | 63    | 18.8  |
| Both administrations intradermal                                    | 5     | 20.0 | 42    | 12.5  |
| Heterologous administration   | 8     | 32.0 | 150   | 44.8  |
| Other/Missing   | 6     | 24.0 | 80    | 23.9  |

JYNNEOS Vaccine Effectiveness Against Monkeypox Disease in the U.S

| <i>Partially Vaccinated</i> §§                          |       |      |       |      |
|---|-------|------|-------|------|
| Overall   | 146   | 6.7  | 1,000 | 12.0 |
| <i>Administration Timing Relative to IE</i>             |       |      |       |      |
| Dose 1 $\geq$ 14 days before IE                         | 80    | 54.8 | 366   | 36.6 |
| Dose 2 $\geq$ 24-day interval and $<$ 14 days before IE | 53    | 36.3 | 269   | 26.9 |
| Dose 2 after IE   | 13    | 8.9  | 365   | 36.5 |
| <i>Administration Route</i>                             |       |      |       |      |
| Subcutaneous administration                             | 106   | 72.6 | 704   | 70.4 |
| Intradermal administration                              | 27    | 18.5 | 186   | 18.6 |
| Other/Missing   | 13    | 8.9  | 110   | 11.0 |
| <i>Unvaccinated</i> ¶¶                                  |       |      |       |      |
| Overall   | 2,022 | 92.2 | 6,984 | 84.0 |
| <i>Administration Timing Relative to IE</i>             |       |      |       |      |
| No documented doses                                     | 1,922 | 95.1 | 6,406 | 91.7 |
| Dose 1 on same day as IE                                | 70    | 3.5  | 171   | 2.4  |
| Dose 1 after IE   | 30    | 1.5  | 407   | 5.8  |

\*Percentages may not sum to 100% due to rounding.

†Social Vulnerability Index is an indicator of community-level vulnerability that ranges from 0 to 1.0, with higher scores indicating greater vulnerability.

‡Hospital admission duration was defined as the first hospital admission within 28 days of the index event and may not have been specifically linked to the index event.

§Medical conditions are listed in Table S7.

¶Includes selected conditions defined by presence of selected conditions identified by ICD-10 codes or immunosuppressive medication prescribed in the past 6 months defined in Table S2.

||Denominator excludes patients who are not at risk for a new HIV diagnosis (due to an existing HIV diagnosis).

\*\*Prescribed within 14 days prior to diagnosis or any time after diagnosis during the study period.

††Pain medications are listed in Table S8.

‡‡Patients were considered fully vaccinated if they received two doses of JYNNEOS vaccine  $\geq$  24 days apart and the second dose was  $\geq$  14 days before the index event. Patients were excluded if they received two doses  $<$  24 days apart (n=0 for case patients and n=7 for control patients).

§§Patients were considered partially vaccinated if they received one dose  $\geq$  14 days before the index event, or if the second dose was  $<$  14 days before the index event; patients who received one dose  $<$  14 days before the index event were excluded as vaccination might represent post-exposure prophylaxis (n=73 for case patients and n=323 for control patients).

**Table S6: E-Values for Point Estimates and Upper 95% Confidence Intervals for Association Between Vaccination Status and Case or Control Patient Status, Overall and By Subpopulations of Interest**

| Model<br>(Table Where<br>Presented)   | Vaccination<br>Status   | aOR<br>(95% CI)*         | Adjusted Vaccine<br>Effectiveness<br>(95% CI)† | E-Value<br>for Point<br>Estimate | E-value<br>for Upper<br>95% CI |
|---|-------------------------|--------------------------|--|----------------------------------|--------------------------------|
| <b>Overall<br/>(Table 2)</b>  | Partially<br>Vaccinated | 0.642<br>(0.529 – 0.779) | 35.8<br>(22.1 - 47.1)                          | 2.49                             | 1.89                           |
|   | Fully<br>Vaccinated     | 0.340<br>(0.219 – 0.526) | 66.0<br>(47.4 - 78.1)                          | 5.33                             | 3.21                           |
| <b>Males Only<br/>(Table 3)</b>   | Partially<br>Vaccinated | 0.641<br>(0.524 - 0.784) | 35.9<br>(21.6 - 47.6)                          | 2.49                             | 1.87                           |
|   | Fully<br>Vaccinated     | 0.352<br>(0.227 - 0.548) | 64.8<br>(45.2 - 77.3)                          | 5.13                             | 3.05                           |
| <b>Males only,<br/>18-49 years and<br/>without ACAM2000<br/>vaccination (Table 3)</b> | Partially<br>Vaccinated | 0.645<br>(0.514 - 0.809) | 35.5<br>(19.1 - 48.6)                          | 2.47                             | 1.78                           |
|   | Fully<br>Vaccinated     | 0.413<br>(0.257 - 0.661) | 58.7<br>(33.9 - 74.3)                          | 4.28                             | 2.39                           |
| <b>Immunocompetent<br/>(Table 3)</b>  | Partially<br>Vaccinated | 0.592<br>(0.466 - 0.752) | 40.8<br>(24.8 - 53.4)                          | 2.77                             | 1.99                           |
|   | Fully<br>Vaccinated     | 0.237<br>(0.132 - 0.423) | 76.3<br>(57.7 - 86.8)                          | 7.91                             | 4.16                           |

\*Adjusted odds ratio and 95% CI from conditional logistic regression models used to evaluate associations between vaccination status and case or control patient status.

†Adjusted vaccine effectiveness was calculated as  $(1 - aOR) \times 100$ .

‡ The E-value is the minimum strength of association that an unmeasured confounder would need to have with both the exposure (vaccination status) and the outcome (case or control patient status), beyond the covariates included in the model, to explain the observed association (i.e., to move the point estimate, or the upper bound of the 95% CI, to the null).

**Table S7. List of Underlying Conditions and Associated International Classification of Diseases, Tenth Revision (ICD-10) Codes**

| <b>Underlying condition*</b> | <b>ICD-10 Code</b>   |
|------------------------------|--|
| Asthma                       | J45 or J82.83  |
| Bronchiectasis               | J47.0, J47.1, or J47.9   |
| Cancer                       | C00-26, C30-34, C37-41, C43, C45-58, C60-79, C7A, C7B, C80, C81, D09.0, Z85.038, Z85.040, Z85.048, Z85.110, Z85.118, Z85.3, Z85.42, Z85.46, or Z85.79  |
| Cerebrovascular Disease      | G45.0, G45.1, G45.2, G45.8, G45.9, G46.0-8, G97.31, G97.32, I60-63, I65-66, I67.2, I67.81-5, I69, I97.810, I97.811, I97.820, I97.821, or Z86.73  |
| Chronic Kidney Disease       | D59.3, E08.2, E09.2, E10.2, E11.2, E13.2, I12, I13.0, I13.1, I13.2, I70.1, I72.2, K76.7, M10.3, M32.14, M32.15, M35.04, N02-08, N11, N12, N13.1, N13.2, N13.30, N13.39, N14-16, N18-19, N25, N26.1, N26.9, O26.83, P96.0, Q61.1-4, Q62.0, Q62.10-12, Q62.2, Q62.31, Q62.32, Q62.39, R94.4, or Z99.2  |
| Chronic Liver Disease        | K70, K74, K75.4, K75.81, or K76.0  |
| COPD                         | J40, J41.0, J41.1, J41.8, J42, J43.0, J43.1, J43.2, J43.8, J43.9, or J44   |
| Cystic Fibrosis              | E84  |
| Diabetes                     | E10, E11.0-6, E11.8, E11.9, E13.01, E13.10, E13.21, E13.22, E13.29, E13.311, E13.319, E13.321, E13.329, E13.331, E13.339, E13.341, E13.3491-3, E13.3499, E13.351, E13.3521, E13.3522, E13.3523, E13.3529, E13.3531, E13.3532, E13.3539, E13.3541, E13.3542, E13.3542, E13.3543, E13.3549, E13.3551, E13.3552, E13.3559, E13.359, E13.36, E13.40-44, E13.49, E13.51, E13.52, E13.59, E13.618, E13.620, E13.621, E13.622, E13.628, E13.630, E13.638, E13.641, E13.65, E13.69, E13.8, E13.9, Z79.4, or Z79.84   |
| Disabilities                 | E13.69, E13.8, E75.22, E78.71, E78.72, E88.41, E88.42, E88.49, F07.0, F07.81, F07.89, F48.2, F70-F73, F78, F79, F80.0, F80.1, F80.2, F80.4, F80.81, F80.82, F80.89, F80.9, F81.0, F81.2, F81.81, F81.89, F81.9, F82, F84, F88, F89, F90.0, F90.1, F90.2, F90.8, F90.9, F95.2, G04.1, G10, G11.4, G12, G13, G20, G21, G23.1, G23.8, G31.82, G36.0, G70, G71.11, G71.3, G73, G80.0-4, G80.8, G80.9, G81-83, H47.22, H54.0X33-35, H54.0X43-45, H54.0X53-55, H54.10-12, H54.2, H54.3, H54.8, H90.3, H90.41, H90.42, H90.5, H90.6, H90.71, H90.72, H90.8, H90.A21, H90.A22, H90.A31, H90.A32, H91.01-03, H91.09, H91.8X1-3, H91.8X9, H91.90-93, H93.25, I69.031, I69.032, I69.034, I69.039, I69.041-4, I69.049, I69.051-4, I69.059, I69.061-5, I69.069, I69.131-4, I69.139, I69.141-4, I60.149, I69.151-4, I69.159, I69.161-5, I69.169, I69.231-4, I69.239, I69.241-4, I69.249, I69.251-4, I69.259, I69.261-5, I69.269, I69.331-4, I69.339, I69.341-4, I69.349, I69.351-4, I69.359, I69.361-5, I69.369, I69.831-4, I69.839, I69.841-4, I69.849, I69.851-4, I69.859, I69.861-5, I69.869, I69.931-4, I69.939, I69.941-4, I69.949, I69.951-4, I69.959, I69.961-5, I69.969, M14.67, P04.3, Q00.0-2, Q01.0-2, Q01.8, Q01.9, Q02, Q03.0, Q03.1, Q03.8, Q03.9, Q04.1-6, Q04.8, Q04.9, Q05.0-9, Q06.1-4, Q06.8, Q06.9, Q07, Q10-Q45, Q50-Q56, Q60-Q85, Q86.0, Q86.1, Q86.2, Q86.8, Q87.0-5, Q87.81, Q87.82, Q87.89, Q89-Q92, Q93.0-5, Q93.7-9, Q95.2, Q95.3, Q95.5, Q95.8, Q95.9, Q96.6, Q96x, Q97x, Q98, Q99.0, Q99.1, Q99.2, Q99.8, Q99.9, R48.0, S06.0X0S, S06.0X1S, |

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S06.0X2S, S06.0X3S, S06.0X4S, S06.0X5S, S06.0X6S, S06.0X9S, S06.1X0S, S06.1X1S, S06.1X2S, S06.1X3S, S06.1X4S, S06.1X5S, S06.1X6S, S06.1X9S, S06.2X0S, S06.2X1S, S06.2X2S, S06.2X3S, S06.2X4S, S06.2X5S, S06.2X6S, S06.2X9S, S06.300S, S06.301S, S06.302S, S06.303S, S06.304S, S06.305S, S06.306S, S06.309S, S06.310S, S06.311S, S06.312S, S06.313S, S06.314S, S06.315S, S06.316S, S06.319S, S06.320S, S06.321S, S06.322S, S06.323S, S06.324S, S06.325S, S06.326S, S06.329S, S06.330S, S06.331S, S06.332S, S06.333S, S06.334S, S06.335S, S06.339S, S06.340S, S06.341S, S06.342S, S06.343S, S06.344S, S06.345S, S06.346S, S06.349S, S05.350S, S05.351S, S06.352S, S06.353S, S06.354S, S06.355S, S05.356S, S06.359S, S06.360S, S06.361S, S06.362S, S06.363S, S06.364S, S06.365S, S06.366S, S06.369S, S06.370S, S06.371S, S06.372S, S06.373S, S06.374S, S06.375S, S06.376S, S06.379S, S06.380S, S06.381S, S01.382S, S01.383S, S06.384S, S06.385S, S06.386S, S06.389S, S06.4X0S, S06.4X1S, S06.4X2S, S06.4X3S, S06.4X4S, S06.4X5S, S06.4X6S, S06.4X9S, S06.5X0S, S06.5X1S, S06.5X2S, S06.5X3S, S06.5X4S, S06.5X5S, S06.5X6S, S06.5X9S, S06.6X0S, S06.6X1S, S06.6X2S, S06.6X3S, S06.6X4S, S06.6X5S, S06.6X6S, S06.6X9S, S06.810S, S06.811S, S06.812S, S06.813S, S06.814S, S06.815S, S06.816S, S06.819S, S06.820S, S06.821S, S06.822S, S06.823S, S06.824S, S06.825S, S06.826S, S06.829S, S06.890S, S06.891S, S01.892S, S06.893S, S06.894S, S06.895S, S06.896S, S06.899S, S06.9X0S, S06.9X1S, S06.9X2S, S06.9X3S, S06.9X4S, S06.9X5S, S06.9X6S, X06.9X9S, S14.0XXA, S14.0XXS, S14.101A, S14.102A, S14.103A, S14.104A, S14.105A, S14.106A, S14.107A, S14.108A, S14.109A, S14.111A, S14.111S, S14.112A, S14.112S, S14.113A, S14.113S, S14.114A, S14.114S, S14.115A, S14.115S, S14.116A, S14.116S, S14.117A, S14.117S, S14.118A, S14.118S, S14.119A, S14.119S, S14.121A, S14.121S, S14.122A, S14.122S, S14.123A, S14.123S, S14.124A, S14.124S, S14.125A, S14.125S, S14.126A, S14.126S, S14.127A, S14.127S, S14.128A, S14.128S, S14.129A, S14.129S, S14.131A, S14.131S, S14.132A, S14.132S, S14.133A, S14.133S, S14.134A, S14.134S, S14.135A, S14.135S, S14.136A, S14.136S, S14.137A, S14.137S, S14.138A, S14.138S, S14.139A, S14.139S, S14.141A, S14.141S, S14.142A, S14.142S, S14.143A, S14.143S, S14.144A, S14.144S, S14.145A, S14.145S, S14.146A, S14.146S, S14.147A, S14.147S, S14.148A, S14.148S, S14.149A, S14.149S, S24.0XXA, S24.0XXS, S24.101A, S24.101S, S24.102A, S24.102S, S24.103A, S24.103S, S24.104A, S24.104S, S24.109A, S24.109S, S24.111A, S24.111S, S24.112A, S24.112S, S24.113A, S24.113S, S24.114A, S24.114S, S24.119A, S24.119S, S24.131A, S24.131S, S24.132A, S24.132S, S24.133A, S24.133S, S24.134A, S24.134S, S24.139A, S24.139S, S24.141A, S24.141S, S24.142A, S24.142S, S24.143A, S24.143S, S24.144A, S24.144S, S24.149A, S24.149S, S34.01XA, S34.01XS, S34.02XA, S34.02XS, S34.101A, S34.101S, S34.102A, S34.102S, S34.103A, S34.103S, S24.104A, S34.104S, S34.105A, S34.105S, S34.109A, S34.109S, S34.111A, S34.111S, S34.112A, S34.112S, S34.113A, S34.113S, S34.114A, S34.114S, S34.115A, S34.115S, S34.119A, S34.119S, S34.121A, S34.121S, S34.122A, S34.122S, S34.123A, S34.123S, S34.124A, S34.124S, S34.125A, S34.125S, S34.129A, S34.129S, S34.131A, S34.131S, S34.132A, S34.132S, S34.139A, S34.139S, S34.3XXA, Z73.6, Z74.0-3, Z74.8, Z74.9, or Z99.3

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|   |   |
|---|---|
| Heart Conditions (such as heart failure, coronary artery disease, or cardiomyopathies)                        | I05-I09, I11.0, I13.0, I13.2, I20.0, I20.1, I20.8, I20.9, I22-25, I30-I52, or P29, Z95  |
| Interstitial Lung Disease   | D86.0, D86.2, J60-67, J68.4, J70.1, J70.3, J70.4, J82.81, J84.0, J84.1, J84.2, J84.8, J84.9, J85.06-09, M30.1, M31.0, or M32.13   |
| Mental Health Conditions (such as mood disorders, including depression, and schizophrenia spectrum disorders) | F20.0-20.3, F20.5, F20.81, F20.89, F20.9, F21, F25.0, F25.1, F25.8, F25.9, F30.10-13, F30.2, F30.3, F30.8, F30.9, F31.0, F31.10-13, F31.2-6, F31.70, F31.71, F31.73, F31.75, F31.77, F31.81, F31.89, F31.9, F32.0-4, F32.81, F32.89, F32.9, F32.A, F33.0-3, F33.40, F33.41, F33.8, F33.9, F34.0, F34.1, F34.9, F39, F43.21, or F43.23 |
| Neurologic Conditions (Dementia)  | F01-03, G30, G31.0, or G31.83   |
| Physical Inactivity   | Z71.82 or Z72.3   |
| Pulmonary Embolism or Pulmonary Hypertension  | I26, I27.0, or I27.2  |
| Tuberculosis  | A15-19, J65, O98.01-03, or P37.0  |
| Current or Former Smoker  | Patient smoking status of “light smoker”, “heavy tobacco smoker”, “every day”, “current every day smoker”, “heavy smoker”, “light tobacco smoker”, “current some day smoker”, “smoker, current status unknown”, “some days”, “former”, or “former smoker”   |
| Obesity   | Patients whose most recent BMI documentation on or before the index date $\geq 30$  |
| Pregnancy and Recent Pregnancy  | Patients who had an actively tracked pregnancy on the index encounter or on an encounter in the 42 days prior to the index date   |

\*Includes the following medical conditions mapped to the following ICD-10 codes or their children codes.

**Table S8. List of Pain Medication Prescribed Within 14 Days Prior to Diagnosis or Any Time After Diagnosis During the Study Period**

| Pain medication category*       | Pain medication name  |
|---------------------------------|---|
| General Analgesics              | Acetaminophen with codeine, alfentanil HCl, benzhydrocodone/acetaminophen, buprenorphine, buprenorphine HCl, butorphanol tartrate, codeine sulfate, fentanyl, fentanyl citrat/dextrose 5%/PF, fentanyl citrate, fentanyl citrate/PF, fentanyl citrate-0.9 % NaCl/PF, fentanyl/bupivacaine/NS/PF, fentanyl/ropivacaine/NS/PF, hydrocodone bitartrate, hydrocodone/acetaminophen, hydrocodone/ibuprofen, hydromorphone HCl, hydromorphone HCl in 0.9% NaCl, hydromorphone HCl in D5W/PF, hydromorphone HCl in water/PF, hydromorphone HCl/0.9% NaCl/PF, hydromorphone HCl/PF, hydromorphone/bupiv/0.9NaCl/PF, hydromorphone/ropiv/sod chl/PF, hydromorphone/sod chlor,iso/PF, ibuprofen/oxycodone HCl, levorphanol tartrate, meperidine HCl, meperidine HCl in 0.9 % NaCl, meperidine HCl in 0.9% NaCl/PF, meperidine HCl/PF, methadone HCl, methadone in 0.9 % sod.chlorid, morphine sulfate, morphine sulfate in 0.9 % NaCl, morphine sulfate/0.9% NaCl/PF, morphine sulfate/D5W, morphine sulfate/D5W/PF, morphine sulfate/naltrexone, morphine sulfate/PF, nalbuphine HCl, oliceridine fumarate, oxycodone HCl, oxycodone HCl/acetaminophen, oxycodone HCl/aspirin, oxycodone myristate, oxymorphone HCl, pentazocine HCl/naloxone HCl, pentazocine lactate, remifentanil HCl, remifentanil in 0.9 % NaCl/PF, sufentanil citrate, sufentanil/bupivacaine/NS/PF, tapentadol HCl, tramadol HCl, or tramadol HCl/acetaminophen |
| Non-Opioid Analgesics           | Acetaminophen, celecoxib, choline salicyl/mag salicylate, diclofenac potassium, diclofenac sodium, diclofenac submicronized, diflunisal, etodolac, fenoprofen calcium, flurbiprofen, gabapentin, ibuprofen, ibuprofen/glycerin, indomethacin, indomethacin, submicronized, ketoprofen, ketorolac tromethamine, magnesium salicylate, meclofenamate sodium, mefenamic acid, meloxicam, meloxicam, submicronized, nabumetone, naproxen, naproxen sodium, oxaprozin, piroxicam, salsalate, or sulindac   |
| Topical/Mouth-Throat Analgesics | Lidocaine or lidocaine HCl and a default route of topical (top), mucous membrane, transmucosal, laryngotracheal, or Mouth/Throat or categorized to a simple generic name of benzocaine, benzocaine/menthol, lidocaine HCl, diphenhydramine HCl, or magnesium, aluminum hydroxide  |

\*Prescription or administration routes of intrathecal, epidural, intra-articular, or intraspinal were excluded.