SUPPLEMENTARY DATA

Prevalence of comorbidities and concomitant medication use in acromegaly: Analysis of real-world data from the United States

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**Supplementary Table 1 Prevalence of all concomitant medications by anatomic therapeutic class**

| Anatomical Therapeutic Chemical classification, n (% of patients)                              | Acromegaly cohort (N=1,175) | Control cohort (N=5,875) | p-value |
|--------------------------------------------------------------------------------------------|----------------------------|--------------------------|---------|
| Antibacterials for systemic use                                                              | 822 (70.0)                 | 3267 (55.6)              | <0.0001 |
| Analgesics                                                                                  | 661 (56.3)                 | 2239 (38.1)              | <0.0001 |
| Cough and cold preparations                                                                 | 545 (46.4)                 | 2084 (35.5)              | <0.0001 |
| Psycholeptics                                                                               | 501 (42.6)                 | 1455 (24.8)              | <0.0001 |
| Sex hormones and modulators of the genital system                                           | 438 (37.3)                 | 746 (12.7)               | <0.0001 |
| Thyroid therapy                                                                             | 410 (34.9)                 | 520 (8.9)                | <0.0001 |
| Corticosteroids for systemic use                                                             | 408 (34.7)                 | 842 (14.3)               | <0.0001 |
| Lipid modifying agents                                                                      | 402 (34.2)                 | 1547 (26.3)              | <0.0001 |
| Anti-inflammatory and antirheumatic products                                                 | 400 (34.0)                 | 1575 (26.8)              | <0.0001 |
| Psychoanaleptics                                                                            | 395 (33.6)                 | 1343 (22.9)              | <0.0001 |
| Agents acting on the renin-angiotensin system                                               | 391 (33.3)                 | 1440 (24.5)              | <0.0001 |
| Diuretics                                                                                   | 326 (27.7)                 | 1050 (17.9)              | <0.0001 |
| Drugs for acid related disorders                                                             | 320 (27.2)                 | 1097 (18.7)              | <0.0001 |
| Antiemetics and antinauseants                                                               | 304 (25.9)                 | 819 (13.9)               | <0.0001 |
| Drugs used in diabetes                                                                      | 287 (24.4)                 | 624 (10.6)               | <0.0001 |
| Muscle relaxants                                                                            | 277 (23.6)                 | 839 (14.3)               | <0.0001 |
| Contrast media                                                                              | 257 (21.9)                 | 89 (1.5)                 | <0.0001 |
| Anti-epileptics                                                                             | 251 (21.4)                 | 629 (10.7)               | <0.0001 |
| Beta blocking agents                                                                        | 246 (20.9)                 | 827 (14.1)               | <0.0001 |
| Calcium channel blockers                                                                    | 196 (16.7)                 | 674 (11.5)               | <0.0001 |
| Antihistamines for systemic use                                                              | 195 (16.6)                 | 662 (11.3)               | <0.0001 |
| Urologicals                                                                                 | 190 (16.2)                 | 682 (11.6)               | <0.0001 |
| Vitamins                                                                                    | 188 (16.0)                 | 435 (7.4)                | <0.0001 |
| Antivirals for systemic use                                                                  | 157 (13.4)                 | 594 (10.1)               | 0.0012  |
| Ophthalmologicals                                                                           | 157 (13.4)                 | 576 (9.8)                | 0.0003  |
| Drugs for obstructive airway diseases                                                        | 132 (11.2)                 | 441 (7.5)                | <0.0001 |
| Pituitary and hypothalamic hormones and analogs                                              | 130 (11.1)                 | 15 (0.3)                 | <0.0001 |
| Anesthetics                                                                                 | 129 (11.0)                 | 298 (5.1)                | <0.0001 |
| Antibiotics and chemotherapeutics for dermatological use                                     | 127 (10.8)                 | 406 (6.9)                | <0.0001 |
| Antithrombotic agents                                                                       | 118 (10.0)                 | 406 (6.9)                | 0.0002  |
| Drugs for functional gastrointestinal disorders                                              | 115 (9.8)                  | 291 (5.0)                | <0.0001 |
Supplementary Table 2 Prevalence of all concomitant medications by ingredient

| Ingredient, n (% of patients) | Form | Acromegaly cohort (N=1,175) | Control cohort (N=5,875) | p-value |
|-------------------------------|------|----------------------------|---------------------------|---------|
| Acetaminophen                 | Oral | 541 (46.0)                 | 1824 (31.0)               | <0.0001 |
| Amoxicillin                   | Oral | 457 (38.9)                 | 1616 (27.5)               | <0.0001 |
| Hydrocodone                   | Oral | 428 (36.4)                 | 1445 (24.6)               | <0.0001 |
| Levothyroxine                 | Oral | 400 (34.0)                 | 514 (8.7)                 | <0.0001 |
| Azithromycin                  | Neither oral nor injection | 304 (25.9)               | 1262 (21.5)               | 0.0011  |
| Clavulanate                   | Oral | 282 (24.0)                 | 862 (14.7)                | <0.0001 |
| Prednisone                    | Oral | 263 (22.4)                 | 938 (16.0)                | <0.0001 |
| Oxycodone                     | Oral | 251 (21.4)                 | 695 (11.8)                | <0.0001 |
| Fluticasone                   | Neither oral nor injection | 246 (20.9)               | 938 (16.0)                | <0.0001 |
| Ciprofloxacin                 | Oral | 236 (20.1)                 | 692 (11.8)                | <0.0001 |
| Gadobutrol                    | Injection | 236 (20.1) | 77 (1.3) | <0.0001 |
| Hydrochlorothiazide           | Oral | 235 (20.0)                 | 804 (13.7)                | <0.0001 |
| Metformin                     | Oral | 234 (19.9)                 | 514 (8.7)                 | <0.0001 |
| Potassium chloride            | Oral | 215 (18.3)                 | 497 (8.5)                 | <0.0001 |
| Dexamethasone                 | Neither oral nor injection | 213 (18.1)               | 744 (12.7)                | <0.0001 |
| Hydrocortisone                | Oral | 211 (18.0)                 | 4 (0.1)                   | <0.0001 |
| Triamcinolone                 | Neither oral nor injection | 210 (17.9)               | 815 (13.9)               | 0.0005  |
| Fentanyl                      | Neither oral nor injection | 193 (16.4)               | 495 (8.4)                | <0.0001 |
| Ondansetron                   | Injection | 192 (16.3) | 491 (8.4) | <0.0001 |
| Ondansetron                   | Oral | 187 (15.9)                 | 445 (7.6)                 | <0.0001 |
| Cephalexin                    | Oral | 185 (15.7)                 | 675 (11.5)                | 0.0001  |
| Polyethylene glycol 3350      | Oral | 181 (15.4)                 | 367 (6.2)                 | <0.0001 |
| Cyclobenzaprine               | Oral | 180 (15.3)                 | 559 (9.5)                 | <0.0001 |
| Ibuprofen                     | Oral | 178 (15.1)                 | 704 (12.0)                | 0.0032  |
| Midazolam                     | Injection | 177 (15.1) | 488 (8.3) | <0.0001 |
| Testosterone                  | Neither oral nor injection | 177 (15.1)               | 73 (1.2)                | <0.0001 |
| Albuterol                     | Neither oral nor injection | 177 (15.1)               | 743 (12.6)              | 0.0280  |
| Gadopentetate dimeglumine     | Injection | 177 (15.1) | 55 (0.9) | <0.0001 |
| Atorvastatin                  | Oral | 176 (15.0)                 | 685 (11.7)                | 0.0018  |
| Trimethoprim                  | Oral | 175 (14.9)                 | 566 (9.6)                 | <0.0001 |
| Sulfamethoxazole              | Oral | 174 (14.8)                 | 561 (9.5)                 | <0.0001 |
| Lisinopril                    | Oral | 173 (14.7)                 | 754 (12.8)                | 0.0887  |
| Tramadol                      | Oral | 170 (14.5)                 | 497 (8.5)                 | <0.0001 |
| Sodium chloride               | Injection | 170 (14.5) | 419 (7.1) | <0.0001 |
| Doxycycline                   | Oral | 170 (14.5)                 | 592 (10.1)                | <0.0001 |
| Ingredient, n (% of patients) | Form                        | Acromegaly cohort (N=1,175) | Control cohort (N=5,875) | p-value |
|------------------------------|-----------------------------|-----------------------------|--------------------------|---------|
| Codeine                      | Oral                        | 168 (14.3)                  | 692 (11.8)               | 0.0183  |
| Methylprednisolone           | Neither oral nor injection  | 167 (14.2)                  | 683 (11.6)               | 0.0148  |
| Omeprazole                   | Oral                        | 162 (13.8)                  | 555 (9.4)                | <0.0001 |
| Amlodipine                   | Oral                        | 161 (13.7)                  | 544 (9.3)                | <0.0001 |
| Sodium chloride              | Oral                        | 161 (13.7)                  | 328 (5.6)                | <0.0001 |
| Methylprednisolone           | Injection                   | 141 (12.0)                  | 557 (9.5)                | 0.0097  |
| Gabapentin                   | Oral                        | 140 (11.9)                  | 351 (6.0)                | <0.0001 |
| Lidocaine                    | Neither oral nor injection  | 137 (11.7)                  | 304 (5.2)                | <0.0001 |
| Levofoxacin                  | Oral                        | 137 (11.7)                  | 420 (7.1)                | <0.0001 |
| Ketorolac                    | Injection                   | 134 (11.4)                  | 420 (7.1)                | <0.0001 |
| Ergocalciferol               | Oral                        | 132 (11.2)                  | 295 (5.0)                | <0.0001 |
| Simvastatin                  | Oral                        | 132 (11.2)                  | 512 (8.7)                | 0.0073  |
| Promethazine                 | Oral                        | 129 (11.0)                  | 473 (8.1)                | 0.0013  |
| Meloxicam                    | Oral                        | 126 (10.7)                  | 477 (8.1)                | 0.0043  |
| Sodium bicarbonate           | Oral                        | 124 (10.6)                  | 240 (4.1)                | <0.0001 |
| Metoprolol                   | Oral                        | 124 (10.6)                  | 454 (7.7)                | 0.0016  |
| Testosterone                 | Injection                   | 121 (10.3)                  | 57 (1.0)                 | <0.0001 |
| Alprazolam                   | Oral                        | 119 (10.1)                  | 320 (5.4)                | <0.0001 |
### Supplementary Table 3: Number of medication ingredients by comorbidity

| Comorbidity                            | Oral medications | Injectable medications |
|----------------------------------------|-------------------|------------------------|
| **Number of different ingredients, n (%) of patients** | **p-value*** | **p-value*** |
| **Cardiovascular disorder**            | **Acromegaly Cohort (N=794)** | **Control Cohort (N=2,844)** | **Acromegaly Cohort (N=794)** | **Control Cohort (N=2,844)** |
| 0                                      | 14 (1.8)          | 118 (4.1)              | 191 (24.1)                     | 1244 (43.7)                     | <0.0001 |
| 1                                      | 18 (2.3)          | 103 (3.6)              | 147 (18.5)                     | 480 (16.9)                      | 0.3048  |
| 2–3                                    | 55 (6.9)          | 311 (10.9)             | 170 (21.4)                     | 519 (18.2)                      | 0.0501  |
| >3                                     | 707 (89.0)        | 2312 (81.3)            | 286 (36.0)                     | 601 (21.1)                      | <0.0001 |
| **Type 2 diabetes and hyperglycemia**  | **Acromegaly Cohort (N=223)** | **Control Cohort (N=524)** | **Acromegaly Cohort (N=233)** | **Control Cohort (N=524)** |
| 0                                      | 1 (0.45)          | 10 (1.9)               | 24 (10.8)                      | 149 (28.4)                      | <0.0001 |
| 1                                      | 3 (1.3)           | 6 (1.1)                | 38 (17.0)                      | 90 (17.2)                       | 0.9512  |
| 2–3                                    | 11 (4.9)          | 29 (5.5)               | 59 (26.5)                      | 120 (22.9)                      | 0.3429  |
| >3                                     | 208 (93.3)        | 479 (91.4)             | 102 (45.7)                     | 165 (31.5)                      | 0.0003  |
| **Sleep apnea**                        | **Acromegaly Cohort (N=293)** | **Control Cohort (N=460)** | **Acromegaly Cohort (N=293)** | **Control Cohort (N=460)** |
| 0                                      | 5 (1.7)           | 9 (2.0)                | 45 (15.4)                      | 154 (33.5)                      | <0.0001 |
| 1                                      | 6 (2.0)           | 16 (3.5)               | 46 (15.7)                      | 74 (16.1)                       | 0.9685  |
| 2–3                                    | 23 (7.8)          | 34 (7.4)               | 63 (21.5)                      | 100 (21.7)                      | 0.9891  |
| >3                                     | 259 (88.4)        | 401 (87.2)             | 139 (47.4)                     | 132 (28.7)                      | <0.0001 |
| **Arthritis and musculoskeletal disorders** | **Acromegaly Cohort (N=234)** | **Control Cohort (N=748)** | **Acromegaly Cohort (N=234)** | **Control Cohort (N=748)** |
| 0                                      | 5 (2.1)           | 20 (2.7)               | 33 (14.1)                      | 177 (23.7)                      | 0.0025  |
| 1                                      | 2 (0.85)          | 23 (3.1)               | 33 (14.1)                      | 134 (17.9)                      | 0.2095  |
| 2–3                                    | 9 (3.8)           | 51 (6.8)               | 46 (19.7)                      | 190 (25.4)                      | 0.0879  |
| >3                                     | 218 (93.2)        | 654 (87.4)             | 122 (52.1)                     | 247 (33.0)                      | <0.0001 |
## Prevalence of Comorbidities in Acromegaly

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| Comorbidity Number of different ingredients, n (% of patients) | Oral medications | Injectable medications |
|---------------------------------------------------------------|-------------------|------------------------|
|                                                               | p-value*          | p-value*               |
| Bone disorder                                                |                   |                        |
| Acromegaly Cohort (N=96)                                     |                   |                        |
| Control Cohort (N=218)                                      |                   |                        |
| 0                                                             | 0 (0.00)          | 15 (15.6)              |
| 1                                                             | 3 (3.1)           | 15 (15.6)              |
| 2–3                                                           | 2 (2.1)           | 20 (20.8)              |
| >3                                                            | 91 (94.8)         | 46 (47.9)              |
| Malignancy                                                   |                   |                        |
| Acromegaly Cohort (N=265)                                    |                   |                        |
| Control Cohort (N=505)                                      |                   |                        |
| 0                                                             | 4 (1.5)           | 47 (17.7)              |
| 1                                                             | 5 (1.9)           | 50 (18.9)              |
| 2–3                                                           | 17 (6.4)          | 51 (19.2)              |
| >3                                                            | 239 (90.2)        | 117 (44.2)             |
| Hypopituitarism and disorder of hypothalamus                 |                   |                        |
| Acromegaly Cohort (N=309)                                    |                   |                        |
| Control Cohort (N=10)                                       |                   |                        |
| 0                                                             | 7 (2.3)           | 61 (19.7)              |
| 1                                                             | 10 (3.2)          | 57 (18.4)              |
| 2–3                                                           | 25 (8.1)          | 72 (23.3)              |
| >3                                                            | 267 (86.4)        | 119 (38.5)             |

*p-values calculated using an unpaired t-test.