

Supplemental Material:

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Supplemental Figure 2. Cumulative incidence of composite kidney failure outcome by hypertension and proteinuria for sensitivity analysis eGFR less than 60.

Supplemental Figure 3. Cumulative incidence of composite kidney failure outcome by hypertension and proteinuria for sensitivity analysis stricter proteinuria.

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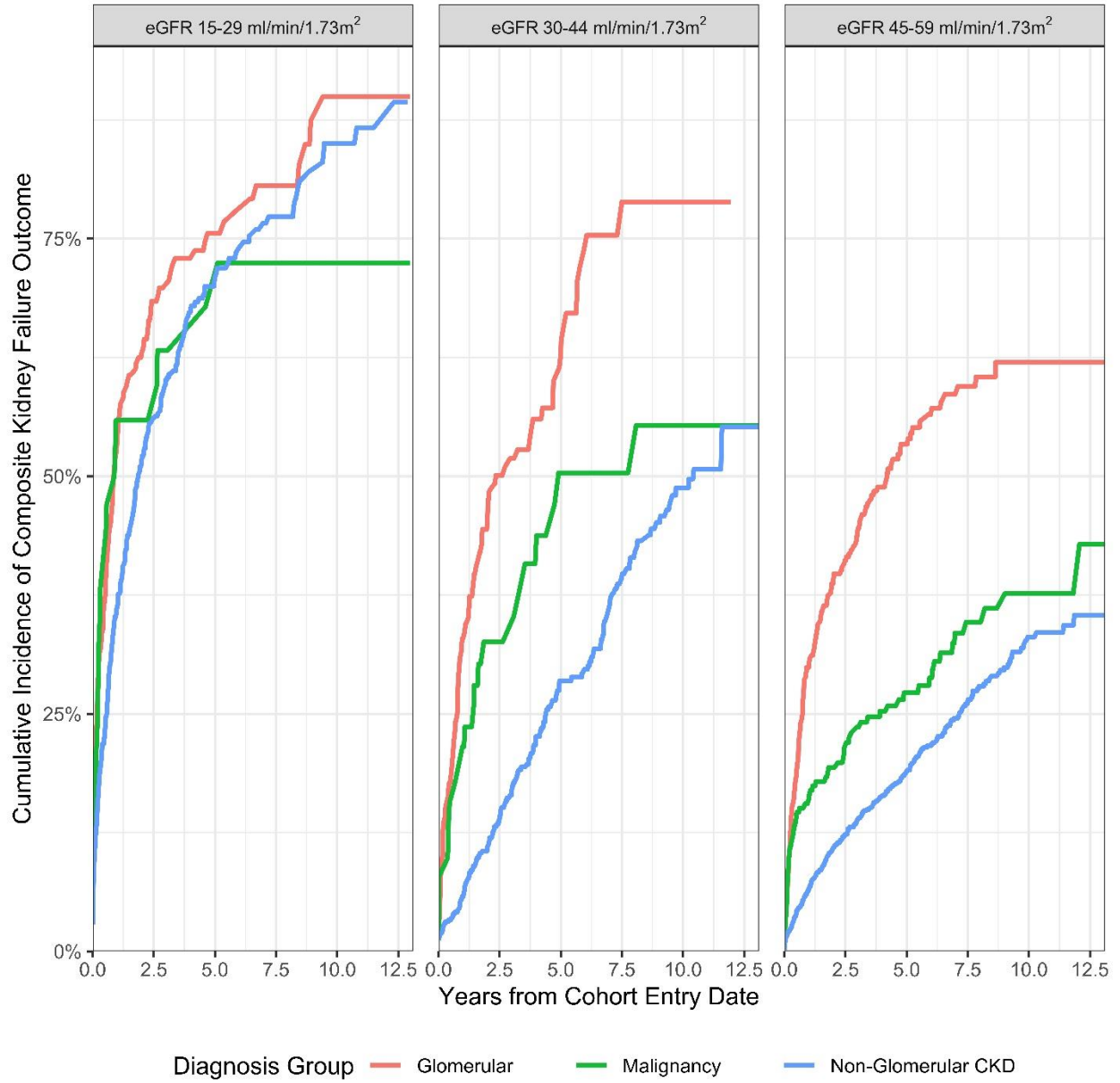
Supplemental Table 5. Composite kidney failure outcome and component outcomes overall and by sub-cohort of chronic kidney disease.

Supplemental Table 6. Frequency of composite kidney failure outcome by starting eGFR category at cohort entrance and proteinuria.

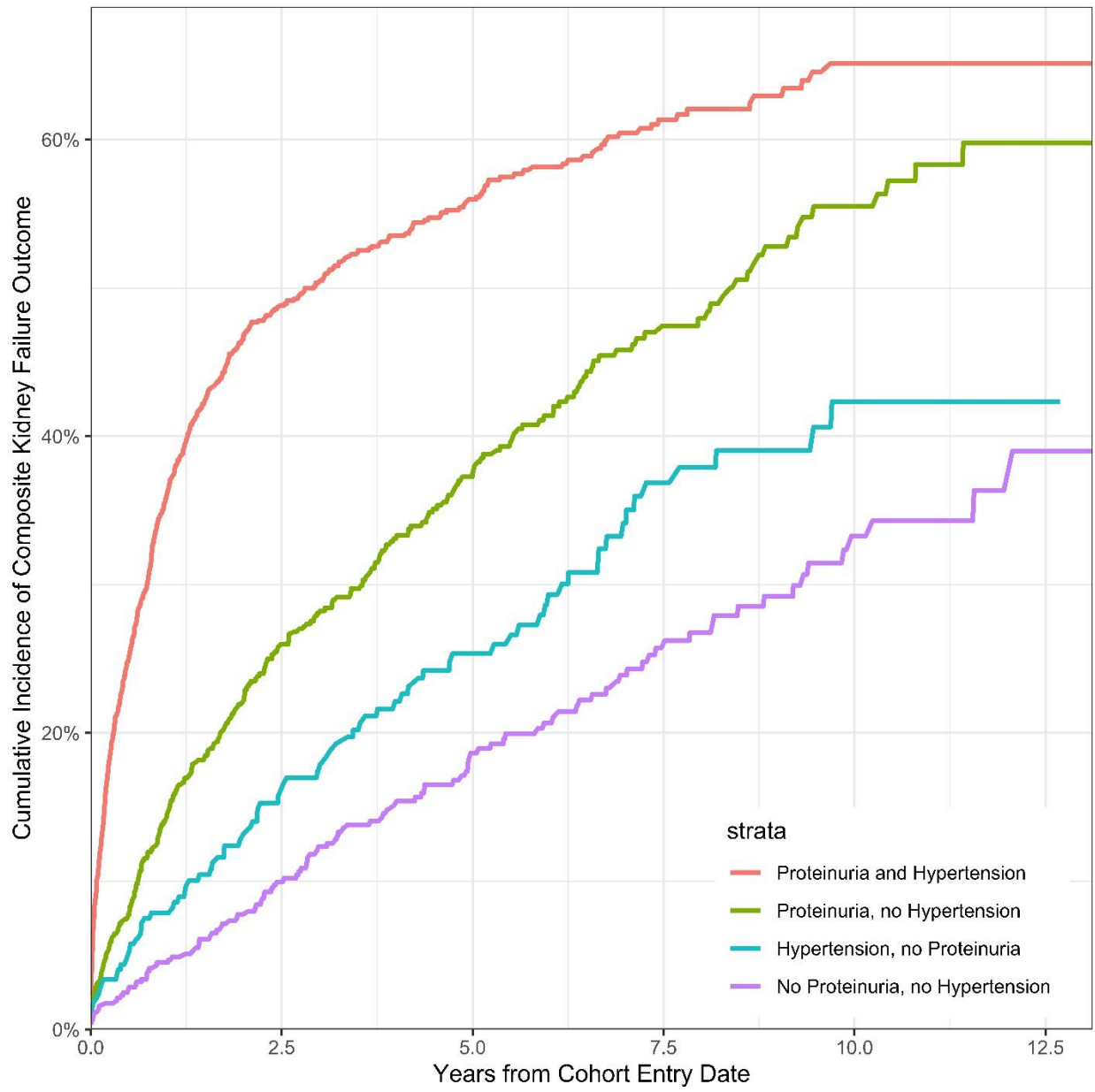
Supplemental Table 7. Multivariable Cox proportional hazards model and Weibull accelerated failure time model evaluating the association of clinical factors with progression to the composite kidney failure outcome for sensitivity analysis eGFR less than 60.

Supplemental Table 8. Multivariable Cox proportional hazards model and Weibull accelerated failure time model evaluating the association of clinical factors with progression to the composite kidney failure outcome for sensitivity analysis using stricter proteinuria definition.

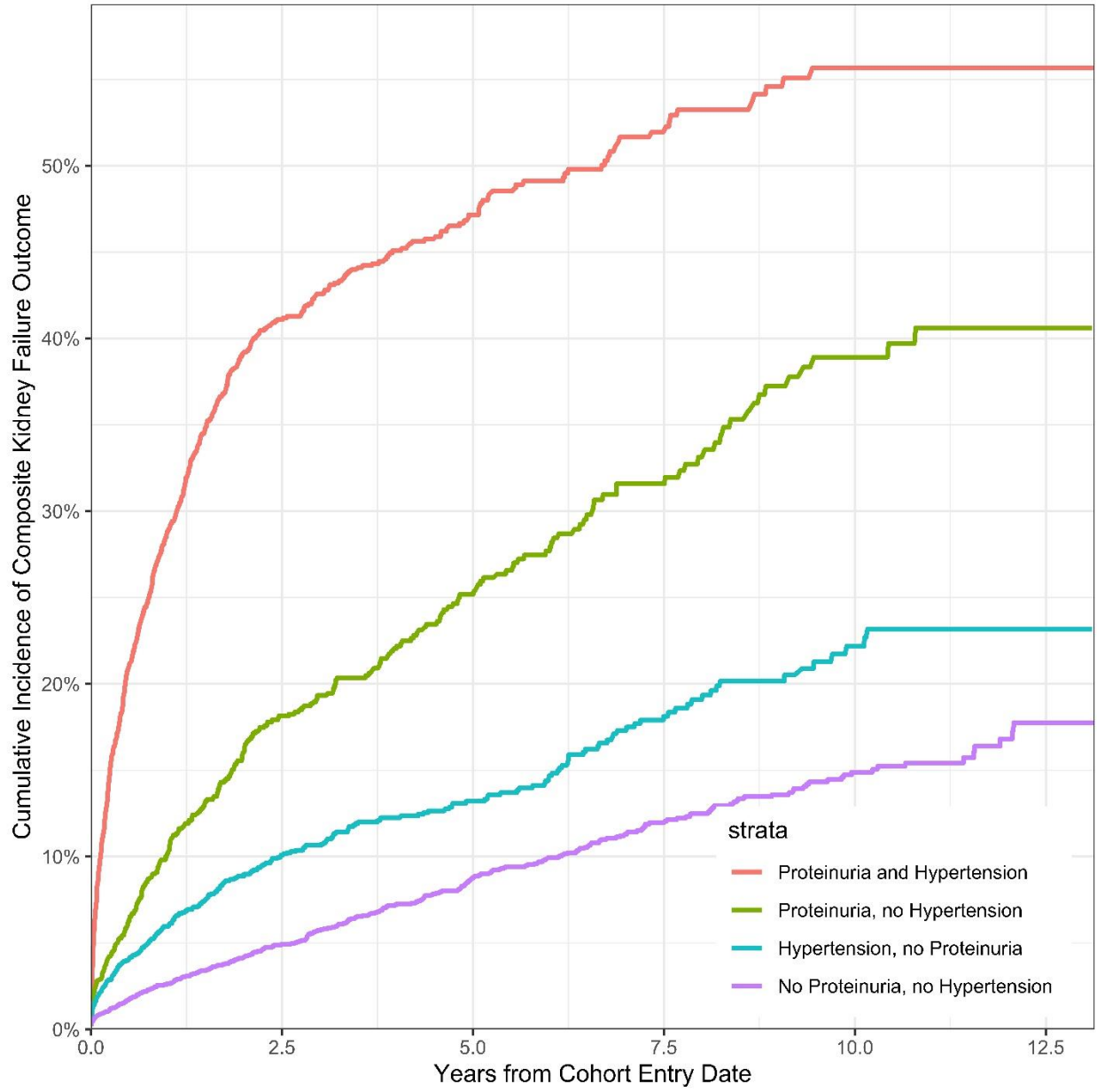
Supplemental Figure 1. Cumulative incidence of composite kidney failure outcome by entry eGFR category and sub-cohort for sensitivity analysis eGFR less than 60.



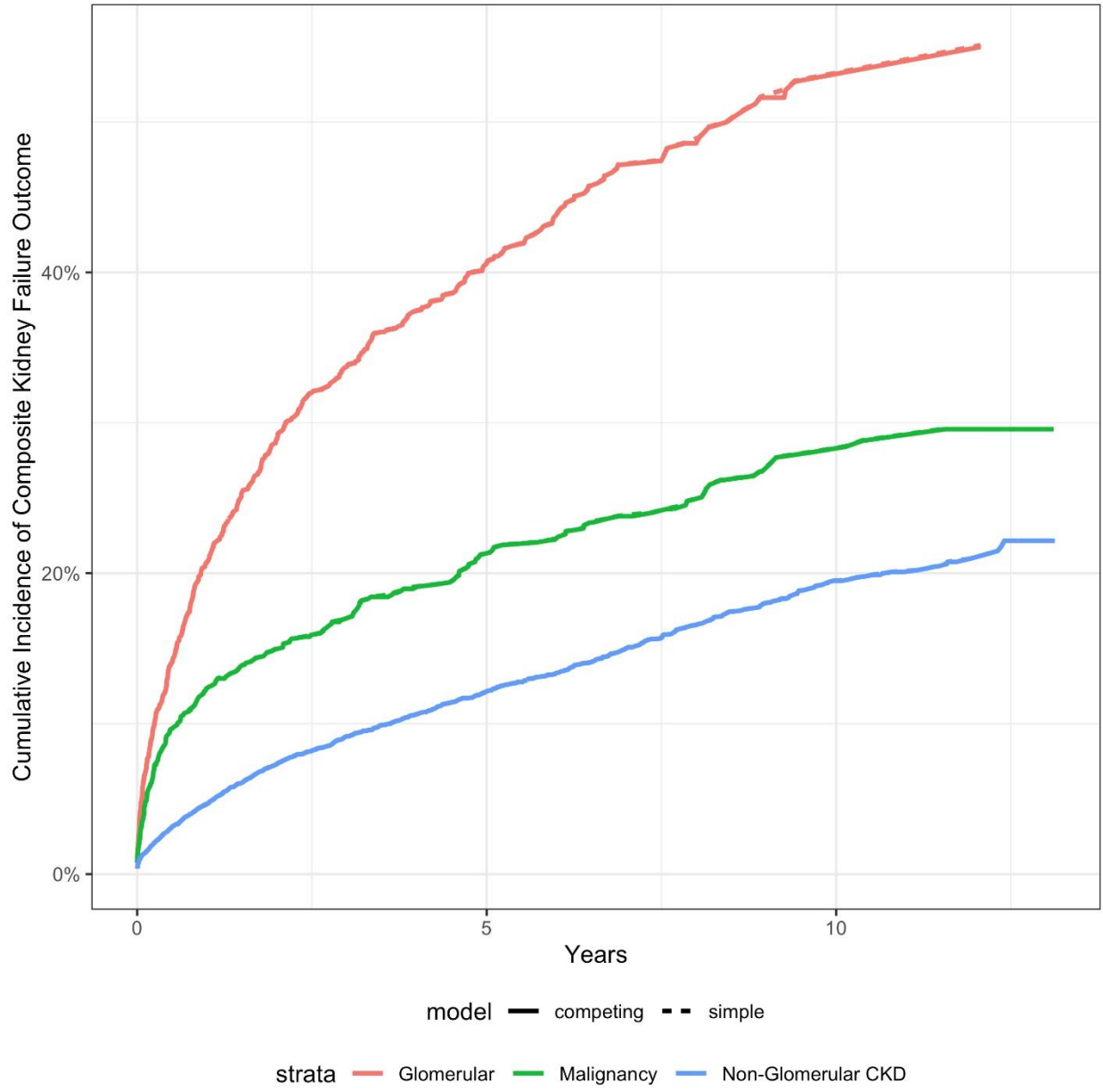
Supplemental Figure 2. Cumulative incidence of composite kidney failure outcome by hypertension and proteinuria for sensitivity analysis eGFR less than 60.



Supplemental Figure 3. Cumulative incidence of composite kidney failure outcome by hypertension and proteinuria for sensitivity analysis stricter proteinuria.



Supplemental Figure 4. Cumulative incidence of composite kidney failure outcome by cohort with competing risk of death.



Supplemental Table 1. Top 25 most frequent kidney and genitourinary diagnoses (from PMCA) CKD non-glomerular sub-cohort at or after cohort entry.

| Icd | Concept code | Concept name                                                                                                                   | Number of children |
|-----|--------------|--------------------------------------------------------------------------------------------------------------------------------|--------------------|
| 10  | N18.2        | Chronic kidney disease, stage 2 (mild)                                                                                         | 2250               |
| 10  | N18.9        | Chronic kidney disease, unspecified                                                                                            | 1883               |
| 10  | N28.89       | Other specified disorders of kidney and ureter                                                                                 | 1481               |
| 10  | N18.1        | Chronic kidney disease, stage 1                                                                                                | 1418               |
| 10  | N13.30       | Unspecified hydronephrosis                                                                                                     | 1271               |
| 10  | N18.3        | Chronic kidney disease, stage 3 (moderate)                                                                                     | 1137               |
| 9   | 591          | Hydronephrosis                                                                                                                 | 1005               |
| 10  | Q61.4        | Renal dysplasia                                                                                                                | 1004               |
| 10  | I12.9        | Hypertensive chronic kidney disease with stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease | 877                |
| 10  | N31.9        | Neuromuscular dysfunction of bladder, unspecified                                                                              | 711                |
| 10  | Q60.0        | Renal agenesis, unilateral                                                                                                     | 584                |
| 9   | 753.0        | Renal agenesis and dysgenesis                                                                                                  | 560                |
| 10  | I15.8        | Other secondary hypertension                                                                                                   | 547                |
| 10  | N18.4        | Chronic kidney disease, stage 4 (severe)                                                                                       | 534                |
| 10  | Z94.0        | Kidney transplant status                                                                                                       | 506                |
| 9   | 788.30       | Urinary incontinence, unspecified                                                                                              | 458                |
| 9   | 596.54       | Neurogenic bladder NOS                                                                                                         | 442                |
| 9   | V42.0        | Kidney replaced by transplant                                                                                                  | 406                |
| 10  | N18.6        | End stage renal disease                                                                                                        | 387                |
| 10  | N13.39       | Other hydronephrosis                                                                                                           | 360                |
| 9   | 753.6        | Atresia and stenosis of urethra and bladder neck                                                                               | 334                |
| 10  | I15.0        | Renovascular hypertension                                                                                                      | 332                |
| 10  | N18.5        | Chronic kidney disease, stage 5                                                                                                | 321                |
| 10  | N13.729      | Vesicoureteral-reflux with reflux nephropathy without hydroureter, unspecified                                                 | 248                |
| 10  | I12.0        | Hypertensive chronic kidney disease with stage 5 chronic kidney disease or end stage renal disease                             | 235                |

Supplemental Table 2. Antihypertensive treatment exposure within the first 2 years of cohort entry for children with hypertension and/or proteinuria.

|                                             | <b>No<br/>Hypertension<br/>OR<br/>Proteinuria<br/><br/>(N=3114)</b> | <b>Hypertension<br/><br/>(N=1458)</b> | <b>Proteinuria<br/><br/>(N=2118)</b> | <b>Hypertension<br/>AND<br/>Proteinuria<br/><br/>(N=1978)</b> | <b>Missing<br/>Proteinuria<br/><br/>(N=2341)</b> |
|---------------------------------------------|---------------------------------------------------------------------|---------------------------------------|--------------------------------------|---------------------------------------------------------------|--------------------------------------------------|
| <b><i>Antihypertensive<br/>Exposure</i></b> |                                                                     |                                       |                                      |                                                               |                                                  |
| Any Anti-Hypertensive,<br>n(%)              | 524 (17)                                                            | 915 (61)                              | 745 (35)                             | 1,671 (83)                                                    | 621 (26)                                         |
| ACE Inhibitor, n(%)                         | 128 (4)                                                             | 514 (34)                              | 344 (16)                             | 1,032 (52)                                                    | 278 (12)                                         |
| Angiotensin II Receptor<br>Blocker, n(%)    | 19 (1)                                                              | 110 (7)                               | 91 (4)                               | 295 (15)                                                      | 81 (3)                                           |
| Any RAAS Blocker,<br>n(%)                   | 145 (5)                                                             | 598 (40)                              | 395 (18)                             | 1,176 (59)                                                    | 322 (13)                                         |
| Beta Blocker, n(%)                          | 46 (2)                                                              | 145 (10)                              | 43 (2)                               | 457 (23)                                                      | 95 (4)                                           |
| Calcium Channel<br>Blocker , n(%)           | 53 (2)                                                              | 356 (24)                              | 108 (5)                              | 1,047 (52)                                                    | 162 (7)                                          |
| Loop Diuretic, n(%)                         | 159 (5)                                                             | 123 (8)                               | 223 (10)                             | 710 (35)                                                      | 162 (7)                                          |
| Thiazide Diuretic, n(%)                     | 94 (3)                                                              | 112 (8)                               | 112 (5)                              | 370 (19)                                                      | 103 (4)                                          |
| Other Anti-<br>Hypertensive, n(%)           | 153 (5)                                                             | 178 (12)                              | 124 (6)                              | 477 (24)                                                      | 126 (5)                                          |

Supplemental Table 3. Characteristics of children with chronic kidney disease in PEDSnet at the time of cohort entry for sensitivity analysis eGFR less than 60.

|                                                      | Non-Glomerular  | Glomerular      | Malignancy      | Overall         |
|------------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| N                                                    | 2242            | 655             | 313             | 3210            |
| Age at cohort entrance (years)                       | 9 [4 - 14]      | 13 [9 - 16]     | 9 [5 - 13]      | 10 [5 - 14]     |
| Follow-up (years)                                    | 5.4 [2.8 - 8.9] | 5.1 [3.1 - 7.9] | 6.1 [3.6 - 9.4] | 5.4 [2.9 - 8.7] |
| Sex, n(%)                                            |                 |                 |                 |                 |
| Female                                               | 988 (44)        | 316 (48)        | 154 (49)        | 1,458 (45)      |
| Male                                                 | 1,254 (56)      | 339 (52)        | 159 (51)        | 1,752 (55)      |
| Race/Ethnicity <sup>1</sup> , n(%)                   |                 |                 |                 |                 |
| Hispanic or Latino                                   | 310 (14)        | 129 (20)        | 39 (13)         | 478 (15)        |
| Non-Hispanic Asian or Pacific Islander               | 91 (4)          | 29 (4)          | 12 (4)          | 132 (4)         |
| Non-Hispanic Black or African American               | 348 (16)        | 142 (22)        | 44 (14)         | 534 (17)        |
| Non-Hispanic White                                   | 1,290 (58)      | 304 (46)        | 196 (63)        | 1,790 (56)      |
| Multiple/Other/Missing                               | 203 (9)         | 51 (8)          | 22 (7)          | 276 (9)         |
| eGFR at cohort entrance (ml/min/1.73m <sup>2</sup> ) | 48 [34 - 55]    | 45 [28 - 54]    | 53.1 [44 - 57]  | 48 [34 - 56]    |
| eGFR category at cohort entrance, n(%)               |                 |                 |                 |                 |
| eGFR 45-59 ml/min/1.73m <sup>2</sup>                 | 1,267 (57)      | 332 (51)        | 226 (72)        | 1,825 (57)      |
| eGFR 30-44 ml/min/1.73m <sup>2</sup>                 | 515 (23)        | 143 (22)        | 51 (16)         | 709 (22)        |
| eGFR 15-29 ml/min/1.73m <sup>2</sup>                 | 460 (21)        | 180 (28)        | 36 (12)         | 676 (21)        |
| No Proteinuria <sup>2</sup> , n(%)                   | 722 (32)        | 41 (6)          | 100 (32)        | 863 (27)        |
| Proteinuria, n(%)                                    | 1,109 (50)      | 572 (87)        | 162 (52)        | 1,843 (57)      |
| Missing , n(%)                                       | 411 (18)        | 42 (6)          | 51 (16)         | 504 (16)        |
| Hypertension <sup>3</sup> , n(%)                     | 877 (39)        | 497 (76)        | 172 (55)        | 1,546 (48)      |
| History of cardiac disease <sup>4</sup> , n(%)       | 535 (24)        | 128 (20)        | 107 (34)        | 770 (24)        |

Continuous data presented as median and inter-quartile range and categorical data as N (%). eGFR – estimated glomerular filtration rate

1. Race/Ethnicity based on self-report in EHR
2. Proteinuria defined as  $\geq 1$  urinalysis with  $\geq 1+$  protein within 2 years of cohort entrance
3. Hypertension defined as  $\geq 2$  visits with hypertension diagnosis code within 2 years of cohort entrance
4. Cardiac diagnosis within 3 years prior to cohort entrance determined using ICD9/10 codes provided by PMCA<sup>23</sup>



Supplemental Table 4. Characteristics of children with chronic kidney disease in PEDSnet at the time of cohort entry for sensitivity analysis stricter proteinuria definition.

|                                                      | Non-Glomerular  | Glomerular      | Malignancy       | Overall         |
|------------------------------------------------------|-----------------|-----------------|------------------|-----------------|
| N                                                    | 8987            | 1314            | 939              | 11240           |
| Age at cohort entrance (years)                       | 10 [5 - 14]     | 13 [9 - 15]     | 8 [4 - 13]       | 11 [5 - 15]     |
| Follow-up (years)                                    | 5.0 [2.7 - 8.2] | 4.9 [2.8 - 7.7] | 6.7 [4.2 - 10.2] | 5.1 [2.8 - 8.3] |
| Sex, n(%)                                            |                 |                 |                  |                 |
| Female                                               | 4,408 (49)      | 689 (52)        | 492 (52)         | 5,589 (50)      |
| Male                                                 | 4,579 (51)      | 625 (48)        | 447 (48)         | 5,651 (50)      |
| Race/Ethnicity <sup>1</sup> , n(%)                   |                 |                 |                  |                 |
| Hispanic or Latino                                   | 1,139 (13)      | 250 (19)        | 104 (11)         | 1,493 (13)      |
| Non-Hispanic Asian or Pacific Islander               | 299 (3)         | 65 (5)          | 39 (4)           | 403 (4)         |
| Non-Hispanic Black or African American               | 1,899 (21)      | 306 (23)        | 133 (14)         | 2,338 (21)      |
| Non-Hispanic White                                   | 4,934 (55)      | 591 (45)        | 593 (63)         | 6,118 (54)      |
| Multiple/Other/Missing                               | 716 (8)         | 102 (8)         | 70 (7)           | 888 (8)         |
| eGFR at cohort entrance (ml/min/1.73m <sup>2</sup> ) | 76 [63 - 83]    | 69 [45 - 81]    | 77 [66 - 84]     | 75 [61 - 83]    |
| eGFR category at cohort entrance, n(%)               |                 |                 |                  |                 |
| eGFR 60-89 ml/min/1.73m <sup>2</sup>                 | 7,011 (78)      | 813 (62)        | 780 (83)         | 8,604 (77)      |
| eGFR 45-59 ml/min/1.73m <sup>2</sup>                 | 960 (11)        | 171 (13)        | 88 (9)           | 1,219 (11)      |
| eGFR 30-44 ml/min/1.73m <sup>2</sup>                 | 514 (6)         | 134 (10)        | 39 (4)           | 687 (6)         |
| eGFR 15-29 ml/min/1.73m <sup>2</sup>                 | 502 (6)         | 196 (15)        | 32 (3)           | 730 (7)         |
| No Proteinuria <sup>2</sup> , n(%)                   | 5,447 (61)      | 296 (23)        | 539 (57)         | 6,282 (56)      |
| Proteinuria, n(%)                                    | 1,479 (17)      | 900 (69)        | 171 (18)         | 2,550 (23)      |
| Missing , n(%)                                       | 2061 (23)       | 118 (9)         | 229 (24)         | 2408 (21)       |
| Hypertension <sup>3</sup> , n(%)                     | 2,854 (32)      | 783 (60)        | 347 (37)         | 3,984 (35)      |
| History of cardiac disease <sup>4</sup> , n(%)       | 1,728 (19)      | 206 (16)        | 241 (26)         | 2,175 (19)      |

Continuous data presented as median and inter-quartile range and categorical data as N (%). eGFR – estimated glomerular filtration rate

1. Race/Ethnicity based on self-report in EHR
2. Proteinuria defined as  $\geq 2$  urinalysis with  $\geq 1+$  protein within 2 years of cohort entrance
3. Hypertension defined as  $\geq 2$  visits with hypertension diagnosis code within 2 years of cohort entrance
4. Cardiac diagnosis within 3 years prior to cohort entrance determined using ICD9/10 codes provided by PMCA<sup>23</sup>

Supplemental Table 5. Composite kidney failure outcome and component outcomes overall and by sub-cohort of chronic kidney disease.

|                                                     | Non-<br>Glomerular | Glomerular | Malignancy | Overall    |
|-----------------------------------------------------|--------------------|------------|------------|------------|
| N                                                   | 8987               | 1314       | 939        | 11240      |
| Composite Outcome reached (Any of the below) , n(%) | 1,133 (13)         | 522 (40)   | 219 (23)   | 1,874 (17) |
| 50% eGFR decline, n(%)                              | 964 (11)           | 462 (35)   | 207 (22)   | 1,633 (15) |
| eGFR <15 mL/min/1.73m, n(%) <sup>2</sup>            | 680 (8)            | 362 (28)   | 93 (10)    | 1,135 (10) |
| Kidney Transplant, n(%)                             | 269 (3)            | 165 (13)   | 31 (3)     | 465 (4)    |
| Chronic Dialysis, n(%)                              | 167 (2)            | 243 (19)   | 38 (4)     | 448 (4)    |

Supplemental Table 6. Frequency of composite kidney failure outcome by starting eGFR category at cohort entrance and proteinuria.

| eGFR Category                        | No Proteinuria  | Proteinuria      | Missing Proteinuria |
|--------------------------------------|-----------------|------------------|---------------------|
| eGFR 15-29 ml/min/1.73m <sup>2</sup> | 50 / 113 (44%)  | 369 / 528 (70%)  | 55 / 89 (62%)       |
| eGFR 30-44 ml/min/1.73m <sup>2</sup> | 51 / 195 (26%)  | 142 / 369 (39%)  | 44 / 123 (36%)      |
| eGFR 45-59 ml/min/1.73m <sup>2</sup> | 54 / 439 (12%)  | 148 / 546 (27%)  | 38 / 234 (16%)      |
| eGFR 60-89 ml/min/1.73m <sup>2</sup> | 253 / 3919 (7%) | 514 / 2723 (19%) | 156 / 1962 (8%)     |

1. Data presented as frequency of patients reaching kidney failure per eGFR and proteinuria (%)

Supplemental Table 7. Multivariable Cox proportional hazards model and Weibull accelerated failure time model evaluating the association of clinical factors with progression to the composite kidney failure outcome for sensitivity analysis eGFR less than 60.

|                                 | N (%) of children with event | Cox Model (adjusted Hazard Ratio) |             | Weibull Accelerated Failure Time Model (log) (Ratio of survival times) |             |
|---------------------------------|------------------------------|-----------------------------------|-------------|------------------------------------------------------------------------|-------------|
|                                 |                              | Estimates                         | CI          | Ratios                                                                 | CI          |
| <i>Exposure</i> <sup>1</sup>    |                              |                                   |             |                                                                        |             |
| Age at Cohort Entrance (years)  | NA                           | 0.97                              | 0.96 – 0.99 | 1.05                                                                   | 1.03 – 1.08 |
| Sex                             |                              |                                   |             |                                                                        |             |
| Female                          | 470 (38)                     |                                   | Reference   |                                                                        | Reference   |
| Male                            | 612 (42)                     | 1.14                              | 1.01 – 1.28 | 0.86                                                                   | 0.69 – 1.07 |
| Proteinuria/Hypertension        |                              |                                   |             |                                                                        |             |
| No Proteinuria, No Hypertension | 116 (21)                     |                                   | Reference   |                                                                        | Reference   |
| Hypertension, No Proteinuria    | 82 (28)                      | 1.35                              | 1.01 - 1.79 | 0.60                                                                   | 0.38 - 0.95 |
| Proteinuria, No Hypertension    | 283 (39)                     | 1.92                              | 1.54 - 2.39 | 0.38                                                                   | 0.26 - 0.54 |
| Proteinuria, Hypertension       | 601 (55)                     | 2.98                              | 2.40 – 3.69 | 0.13                                                                   | 0.09 - 0.19 |
| CKD etiology                    |                              |                                   |             |                                                                        |             |
| Non-Glomerular                  | 621 (34)                     |                                   | Reference   |                                                                        | Reference   |
| Glomerular                      | 361 (60)                     | 1.72                              | 1.49 – 1.98 | 0.32                                                                   | 0.25 – 0.42 |
| Malignancy                      | 100 (38)                     | 1.22                              | 0.98 – 1.51 | 0.60                                                                   | 0.41 – 0.87 |
| eGFR category                   |                              |                                   |             |                                                                        |             |
| 45-59 ml/min/1.73m <sup>2</sup> | 454 (30)                     |                                   | Reference   |                                                                        | Reference   |
| 30-44 ml/min/1.73m <sup>2</sup> | 222 (38)                     | 1.34                              | 1.14 – 1.57 | 0.66                                                                   | 0.50 – 0.87 |
| 15-29 ml/min/1.73m <sup>2</sup> | 406 (70)                     | 3.35                              | 2.92 – 3.85 | 0.10                                                                   | 0.08 – 0.13 |
| Medical complexity <sup>2</sup> | NA                           | 1.03                              | 1.00 – 1.07 | 0.91                                                                   | 0.86 – 0.96 |

1. Exposures evaluated but not shown: Clinical sites
2. Numerical count of PMCA diagnosis categories (excluding kidney and genitourinary categories)

Supplemental Table 8. Multivariable Cox proportional hazards model and Weibull accelerated failure time model evaluating the association of clinical factors with progression to the composite kidney failure outcome for sensitivity analysis using stricter proteinuria definition.

|                                   | N (%) of children with event | Cox Model (adjusted Hazard Ratio) |             | Weibull Accelerated Failure Time Model (log) (Ratio of survival times) |             |
|-----------------------------------|------------------------------|-----------------------------------|-------------|------------------------------------------------------------------------|-------------|
|                                   |                              | Estimates                         | CI          | Ratios                                                                 | CI          |
| <i>Exposure</i> <sup>1</sup>      |                              |                                   |             |                                                                        |             |
| Age at Cohort Entrance (years)    | NA                           | 0.95                              | 0.94 – 0.96 | 1.10                                                                   | 1.07 – 1.12 |
| Sex                               |                              |                                   |             |                                                                        |             |
| Female                            | 729 (16)                     |                                   | Reference   |                                                                        | Reference   |
| Male                              | 837 (19)                     | 1.15                              | 1.04 – 1.27 | 0.81                                                                   | 0.68 – 0.97 |
| Proteinuria/Hypertension          |                              |                                   |             |                                                                        |             |
| No Proteinuria, No Hypertension   | 377 (9)                      |                                   | Reference   |                                                                        | Reference   |
| Hypertension, No Proteinuria      | 275 (13)                     | 1.59                              | 1.36 - 1.87 | 0.45                                                                   | 0.35 - 0.59 |
| Proteinuria, No Hypertension      | 285 (25)                     | 2.63                              | 2.24 – 3.09 | 0.22                                                                   | 0.17 - 0.29 |
| Proteinuria, Hypertension         | 629 (45)                     | 4.45                              | 3.83 – 5.18 | 0.07                                                                   | 0.05 - 0.09 |
| CKD etiology                      |                              |                                   |             |                                                                        |             |
| Non-Glomerular                    | 918 (13)                     |                                   | Reference   |                                                                        | Reference   |
| Glomerular                        | 467 (39)                     | 1.80                              | 1.58 – 2.04 | 0.29                                                                   | 0.23 – 0.37 |
| Malignancy                        | 181 (26)                     | 1.74                              | 1.48 – 2.05 | 0.35                                                                   | 0.26 – 0.47 |
| eGFR category                     |                              |                                   |             |                                                                        |             |
| 60-89 ml/min/1.73m <sup>2</sup> ) | 767 (12)                     |                                   | Reference   |                                                                        | Reference   |
| 45-59 ml/min/1.73m <sup>2</sup>   | 201 (20)                     | 1.43                              | 1.22 – 1.67 | 0.53                                                                   | 0.40 – 0.69 |
| 30-44 ml/min/1.73m <sup>2</sup>   | 192 (34)                     | 2.30                              | 1.95 – 2.70 | 0.25                                                                   | 0.19 – 0.34 |
| 15-29 ml/min/1.73m <sup>2</sup>   | 406 (65)                     | 5.48                              | 4.80 – 6.25 | 0.04                                                                   | 0.03 – 0.05 |
| Medical complexity <sup>2</sup>   | NA                           | 1.07                              | 1.05 – 1.10 | 0.85                                                                   | 0.82 – 0.89 |

1. Exposures evaluated but not shown: Clinical sites
2. Numerical count of PMCA diagnosis categories (excluding kidney and genitourinary categories)