

## Supplementary Materials:

# Outcome Definition Influences the Relationship Between Genetic Polymorphisms of *ERCC1*, *ERCC2*, *SLC22A2* and Cisplatin Nephrotoxicity in Adult Testicular Cancer Patients

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**Table S1.** Genotyping details for adjusted-AKI outcome in patients with European proportion ancestry  $\geq 80\%$  (N=93).

| Gene-rsID               | SNP                      | Minor     | Minor Allele         |               | HWE <i>p</i> -value | Minor Allele      |               | HWE <i>p</i> -value |
|-------------------------|--------------------------|-----------|----------------------|---------------|---------------------|-------------------|---------------|---------------------|
|                         | Call                     | Allele    | Frequency            | Frequency     |                     | Frequency         | Frequency     |                     |
|                         | Rate                     | Frequency | Observed             | Observed      |                     | Observed          | Observed      |                     |
|                         | (%)                      | Observed  | (Expected)           |               |                     | (Expected)        |               |                     |
|                         | In Total Cohort (N = 93) |           | In Controls (N = 46) |               |                     | In Cases (N = 47) |               |                     |
| <i>ERCC1</i> rs11615    | 100                      | 0.392     | G                    | 0.337 (0.337) | 0.883               | G                 | 0.447 (0.447) | 0.414               |
| <i>ERCC1</i> rs3212986  | 99.5                     | 0.285     | A                    | 0.239 (0.238) | 0.609               | A                 | 0.330 (0.330) | 0.558               |
| <i>ERCC2</i> rs13181    | 99.5                     | 0.386     | C                    | 0.378 (0.378) | 0.317               | C                 | 0.394 (0.394) | 0.023*              |
| <i>ERCC2</i> rs1799793  | 100                      | 0.457     | C                    | 0.489 (0.424) | 0.077               | C                 | 0.423 (0.426) | 0.137               |
| <i>SLC22A2</i> rs316019 | 98.1                     | 0.110     | A                    | 0.057 (0.056) | 0.690               | A                 | 0.160 (0.160) | 0.049*              |

\* significant ( $p < 0.05$ ), a-AKI: adjusted acute kidney-injury, SNP: single nucleotide polymorphism, HWE: Hardy-Weinberg equilibrium.

**Table S2.** Genotyping details for AKI-CTCAE outcome in patients with European proportion ancestry  $\geq 80\%$  (N = 88).

| Gene–rsID               | SNP                      | Minor     | Minor Allele         |               | HWE <i>p</i> -value | Minor Allele      |               | HWE <i>p</i> -value |
|-------------------------|--------------------------|-----------|----------------------|---------------|---------------------|-------------------|---------------|---------------------|
|                         | Call                     | Allele    | Frequency            | Frequency     |                     | Frequency         | Frequency     |                     |
|                         | Rate                     | Frequency | Observed             | Observed      |                     | Observed          | Observed      |                     |
|                         | (%)                      | Observed  | (Expected)           |               |                     | (Expected)        |               |                     |
|                         | In Total Cohort (N = 93) |           | In Controls (N = 46) |               |                     | In Cases (N = 47) |               |                     |
| <i>ERCC1</i> rs11615    | 100                      | 0.369     | G                    | 0.359 (0.360) | 0.690               | G                 | 0.396 (0.398) | 0.133               |
| <i>ERCC1</i> rs3212986  | 100                      | 0.267     | A                    | 0.273 (0.273) | 0.445               | A                 | 0.250 (0.250) | 0.586               |
| <i>ERCC2</i> rs13181    | 99.4                     | 0.356     | C                    | 0.325 (0.326) | 0.181               | C                 | 0.438 (0.438) | 0.046*              |
| <i>ERCC2</i> rs1799793  | 100                      | 0.466     | C                    | 0.484 (0.484) | 0.013*              | C                 | 0.417 (0.419) | 0.889               |
| <i>SLC22A2</i> rs316019 | 97.5                     | 0.099     | A                    | 0.040 (0.040) | 0.740               | A                 | 0.250 (0.250) | 0.586               |

\* significant ( $p < 0.05$ ), a-AKI: adjusted acute kidney-injury, SNP: single nucleotide polymorphism, HWE: Hardy-Weinberg equilibrium.

**Table S3.** Clinical characteristics of cases and controls in adjusted-AKI outcome (N = 163).

| Characteristics                                           |                 | Cases (N = 75) <sup>a</sup> | Controls (N = 88) <sup>a</sup> | p-value <sup>b</sup> |
|-----------------------------------------------------------|-----------------|-----------------------------|--------------------------------|----------------------|
| Age at start treatment, median (IQR), years               |                 | 31 (24–40)                  | 30 (24–37)                     | 0.091                |
| Ancestry, median (IQR), proportion                        | European        | 0.84 (0.75–0.88)            | 0.81 (0.65–0.87)               | 0.267                |
|                                                           | East-Asian      | 0.01 (0–0.05)               | 0.02 (0–0.08)                  | 0.348                |
|                                                           | American        | 0.02 (0–0.05)               | 0.02 (0–0.04)                  | 0.581                |
|                                                           | African         | 0.03 (0.01–0.05)            | 0.03 (0.01–0.05)               | 0.819                |
|                                                           | South-Asian     | 0.08 (0.03–0.14)            | 0.07 (0.02–0.13)               | 0.641                |
| Cardiovascular disease, no. (%), yes (vs. no)             |                 | 3 (4.0)                     | 2 (2.3)                        | 0.662                |
| Diabetes, no. (%), yes (vs. no)                           |                 | 2 (2.7)                     | 0 (0)                          | 0.210                |
| Concomitant nephrotoxic medication, no. (%), yes (vs. no) | ACEIs           | 2 (2.7)                     | 0 (0)                          | 0.210                |
|                                                           | Aminoglycosides | 3 (4.0)                     | 1 (1.1)                        | 0.335                |
|                                                           | ARBs            | 1 (1.3)                     | 0 (0)                          | 0.460                |
|                                                           | Benzodiazepines | 8 (10.7)                    | 11 (12.5)                      | 0.809                |
|                                                           | NSAIDs          | 3 (4.0)                     | 3 (3.4)                        | 1.000                |
|                                                           | Betalactams     | 9 (12.0)                    | 11 (12.5)                      | 1.000                |
|                                                           | PPIs            | 11 (14.7)                   | 8 (9.1)                        | 0.330                |
|                                                           | Quinolones      | 18 (24.0)                   | 5 (5.7)                        | 0.001*               |
|                                                           | Statins         | 1 (1.3)                     | 1 (1.1)                        | 1.000                |
|                                                           | Acetaminophen   | 13 (17.3)                   | 6 (6.8)                        | 0.050                |
|                                                           | Other           | 44 (58.7)                   | 44 (50)                        | 0.275                |
| Baseline [SCr], median (IQR), umol/L                      |                 | 83.5 (72–92)                | 82.5 (74–90)                   | 0.713                |
| Baseline [K], median (IQR), mmol/L                        |                 | 4.1 (3.9–4.4)               | 4.1 (3.9–4.3)                  | 0.707                |
| Baseline [Mg], median (IQR), mmol/L                       |                 | 0.83 (0.77–0.90)            | 0.88 (0.82–0.94)               | 0.008*               |
| Baseline [Na <sup>+</sup> ], median (IQR), mmol/L         |                 | 139 (137–140)               | 138 (137–141)                  | 0.480                |
| Cumulative platinum dose, median (IQR), mg/m <sup>2</sup> |                 | 400 (300–400)               | 300 (300–400)                  | 0.001*               |
| Duration cisplatin treatment, median (IQR)                | weeks           | 9.6 (6.6–9.75)              | 6.7 (6.6–9.6)                  | 0.151                |
|                                                           | cycles          | 4 (3–4)                     | 3 (3–4)                        | 0.001*               |
| Chemotherapy protocol, no. (%), BEP (vs. other)           |                 | 46 (61.3)                   | 65 (73.9)                      | 0.095                |
| Chemotherapy hydration, median (IQR), L/cycle             |                 | 10.75 (10.70–10.75)         | 10.75 (10.75–10.75)            | 0.129                |
| ERCC1 rs11615, no. (%)                                    | GG              | 16 (21.33)                  | 18 (20.45)                     |                      |
|                                                           | GA              | 39 (52)                     | 42 (47.73)                     |                      |
|                                                           | AA              | 20 (26.67)                  | 28 (31.82)                     |                      |
| ERCC1 rs3212986 (N=1 failed genotyping), no. (%)          | AA              | 6 (8)                       | 6 (6.90)                       |                      |
|                                                           | AC              | 30 (40)                     | 42 (48.28)                     |                      |
|                                                           | CC              | 39 (52)                     | 39 (44.83)                     |                      |
| ERCC2 rs13181 (N=1 failed genotyping), no. (%)            | CC              | 15 (20)                     | 11 (12.64)                     |                      |
|                                                           | CA              | 25 (33.33)                  | 35 (40.23)                     |                      |
|                                                           | AA              | 35 (46.67)                  | 41 (47.13)                     |                      |
| ERCC2 rs1799793, no. (%)                                  | CC              | 13 (17.33)                  | 26 (29.55)                     |                      |
|                                                           | CA              | 35 (46.67)                  | 35 (39.77)                     |                      |
|                                                           | AA              | 27 (36)                     | 27 (30.68)                     |                      |
| SLC22A2 rs316019 (N=4 failed genotyping), no. (%)         | AA              | 2 (2.74)                    | 1 (1.16)                       |                      |
|                                                           | AC              | 14 (19.18)                  | 15 (17.44)                     |                      |
|                                                           | CC              | 57 (78.08)                  | 70 (81.40)                     |                      |

\* significant, IQR: Interquartile Range, <sup>a</sup> Percentages given are percentages within cases and controls,

<sup>b</sup> Categorical variables were analyzed using a 2-sided Fisher's exact test. Continuous variables were analyzed using Mann-Whitney U Test.

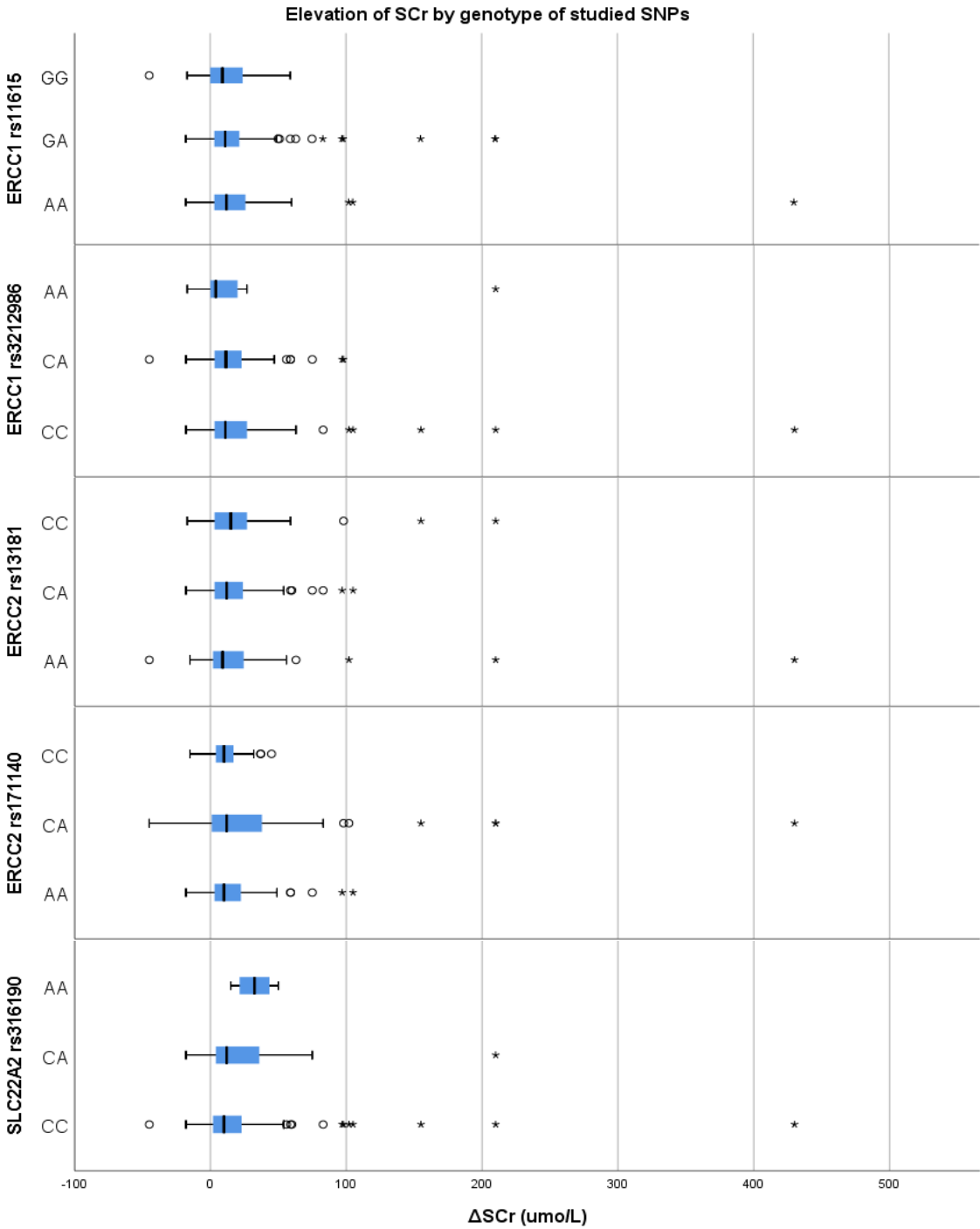
**Table S4.** Clinical characteristics of cases and controls in AKI-CTCAE outcome (N = 159).

| Characteristics                                           |             | Cases (N = 36) <sup>a</sup><br>CTCAE grade ≥ 1 | Controls (N = 123) <sup>a</sup><br>CTCAE grade 0 | p-value <sup>b</sup> |
|-----------------------------------------------------------|-------------|------------------------------------------------|--------------------------------------------------|----------------------|
| Age at start treatment, median (IQR), years               |             | 35 (28–46)                                     | 29 (23–37)                                       | 0.002*               |
| Ancestry, median (IQR), proportion                        | European    | 0.853 (0.768–0.889)                            | 0.811 (0.637–0.862)                              | 0.017*               |
|                                                           | East-Asian  | 0 (0–0.034)                                    | 0.023 (0.072)                                    | 0.041*               |
|                                                           | American    | 0.024 (0–0.054)                                | 0.022 (0–0.048)                                  | 0.878                |
|                                                           | African     | 0.033 (0.008–0.053)                            | 0.031 (0.01–0.048)                               | 0.895                |
|                                                           | South-Asian | 0.06 (0.024–0.095)                             | 0.077 (0.025–0.139)                              | 0.415                |
| Cardiovascular disease, no. (%), yes (vs. no)             |             | 3 (8.3)                                        | 2 (1.6)                                          | 0.077                |
| Diabetes, no. (%), yes (vs. no)                           |             | 1 (2.8)                                        | 1 (0.8)                                          | 0.403                |
| Concomitant nephrotoxic medication, no. (%), yes (vs. no) |             |                                                |                                                  |                      |
| ACEIs                                                     |             | 2 (5.6)                                        | 0 (0)                                            | 0.05                 |

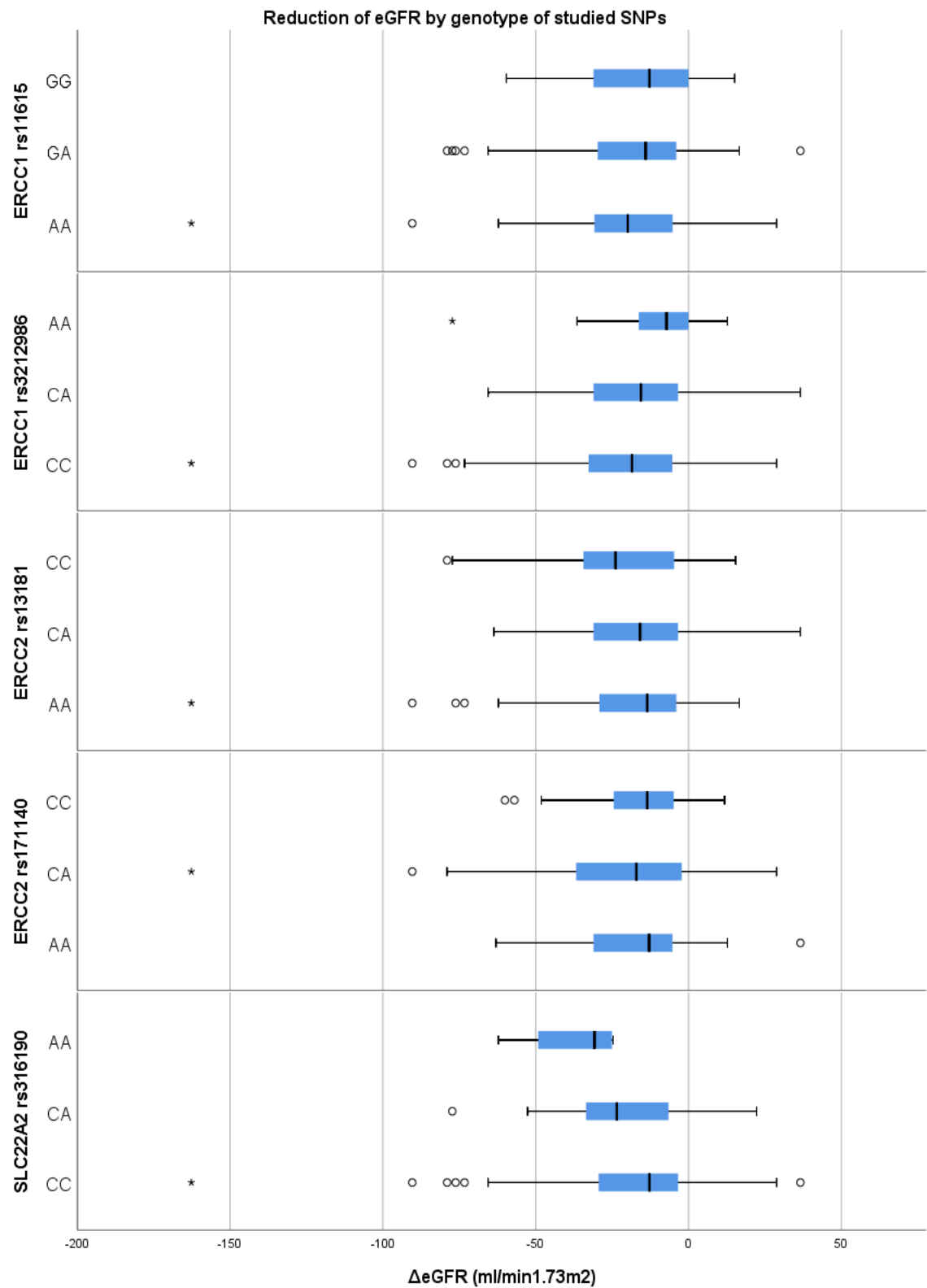
|                                                           |        |                    |                 |        |
|-----------------------------------------------------------|--------|--------------------|-----------------|--------|
| Aminoglycosides                                           |        | 1 (2.8)            | 3 (2.4)         | 1.000  |
| ARBs                                                      |        | 1 (2.8)            | 0 (0)           | 0.226  |
| Benzodiazepines                                           |        | 6 (16.7)           | 13 (10.6)       | 0.380  |
| NSAIDs                                                    |        | 2 (5.6)            | 4 (3.3)         | 0.619  |
| Betalactams                                               |        | 4 (11.1)           | 14 (11.4)       | 1.000  |
| PPIs                                                      |        | 9 (25)             | 10 (8.1)        | 0.015* |
| Quinolones                                                |        | 9 (25)             | 13 (10.6)       | 0.051  |
| Statins                                                   |        | 1 (2.8)            | 1 (0.8)         | 0.403  |
| Acetaminophen                                             |        | 9 (25)             | 13 (10.6)       | 0.051  |
| Other                                                     |        | 23 (63.9)          | 63 (51.2)       | 0.19   |
| Baseline [SCr], median (IQR), umol/L                      |        | 82 (72–95)         | 83 (74–90)      | 0.789  |
| Baseline [K], median (IQR), mmol/L                        |        | 4.1 (3.9–4.3)      | 4.1 (3.9–4.3)   | 0.970  |
| Baseline [Mg], median (IQR), mmol/L                       |        | 0.81 (0.75–0.9)    | 0.86 (0.8–0.93) | 0.054  |
| Baseline [Na+], median (IQR), mmol/L                      |        | 139 (136–141)      | 139 (137–140)   | 0.792  |
| Cumulative platinum dose, median (IQR), mg/m <sup>2</sup> |        | 400 (300–437)      | 300 (300–400)   | 0.005* |
| Duration cisplatin treatment, median (IQR)                | weeks  | 10 (7–10)          | 10 (7–10)       | 0.639  |
|                                                           | cycles | 4 (3–4)            | 3 (3–4)         | 0.007* |
| Chemotherapy protocol, no. (%), BEP (vs. other)           |        | 19 (52.8)          | 89 (72.4)       | 0.041* |
| Chemotherapy hydration, median (IQR), L/cycle             |        | 10.75 (10.5–10.75) | 10.75 (0)       | 0.004* |
| <i>ERCC1</i> rs11615, no. (%)                             | AA     | 11 (30.6)          | 38 (30.9)       |        |
|                                                           | GA     | 21 (58.3)          | 56 (45.5)       |        |
|                                                           | GG     | 4 (11.1)           | 29 (23.6)       |        |
| <i>ERCC1</i> rs3212986, no. (%)                           | CC     | 23 (63.9)          | 55 (44.7)       |        |
|                                                           | CA     | 11 (30.6)          | 58 (47.2)       |        |
|                                                           | AA     | 2 (5.6)            | 10 (8.1)        |        |
| <i>ERCC2</i> rs13181, no. (%)                             | AA     | 14 (38.9)          | 62 (50.8)       |        |
|                                                           | CA     | 12 (33.3)          | 46 (37.7)       |        |
|                                                           | CC     | 10 (27.8)          | 14 (11.5)       |        |
| <i>ERCC2</i> rs171140, no. (%)                            | AA     | 11 (30.6)          | 41 (33.3)       |        |
|                                                           | CA     | 20 (55.6)          | 49 (39.8)       |        |
|                                                           | CC     | 5 (13.9)           | 33 (26.8)       |        |
| <i>SLC22A2</i> rs316019, no. (%)                          | CC     | 22 (61.1)          | 101 (84.9)      |        |
|                                                           | CA     | 12 (33.3)          | 17 (14.3)       |        |
|                                                           | AA     | 2 (5.6)            | 1 (0.8)         |        |

\* significant, IQR: Interquartile Range, <sup>a</sup> Percentages given are percentages within cases and controls,

<sup>b</sup> Categorical variables were analyzed using a 2-sided Fisher's exact test. Continuous variables were analyzed using Mann-Whitney U Test.



**Figure S1.** Boxplot chart of SCr elevation ( $\Delta$ SCr) by genotype of studied SNPs.



**Figure S2.** Boxplot chart of eGFR reduction ( $\Delta eGFR$ ) by genotype of studied SNPs.