**Supplementary Methods**

**Study Centres**

Patients were recruited to the study from the following centres: St James’s University Hospital, Leeds, UK; Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK; Stockport NHS Foundation Trust, Stockport, UK; Nottingham University Hospitals NHS Trust, Nottingham, UK; NHS Lothian, Edinburgh, UK; Charing Cross Hospital, London, UK; Oxford University Hospitals NHS Foundation Trust, Oxford UK; Northwick Park Hospital, Harrow, UK; University Hospital Motol, Prague, Czech Republic; General University Hospital, Prague, Czech Republic; Masaryk Memorial Cancer Institute, Brno, Czech Republic; Palacký University Hospital, Olomouc, Czech Republic; České Budějovice Regional Hospital, České Budějovice, Czech Republic; Th. Burghele Hospital, Bucharest, Romania; N. N. Blokhin Cancer Research Centre, Moscow, Russia; Clinical Center of Serbia (KCS), Belgrade, Serbia; Military Medical Academy, Belgrade, Serbia. All were recruited to the study after obtaining informed consent. Recruitment in Central and Eastern Europe was coordinated by the International Agency for Research on Cancer. Ethical approvals were obtained from the Leeds (East) Local Research Ethics Committee, the International Agency for Research on Cancer Ethics Committee, as well as from local ethics committee for recruiting centres in Czech Republic, Romania, Russia, Serbia and Bosnia & Herzegovina.

**Study overview**

Cohort 1 (C1) consisted of 93 patient samples subject to whole genome sequencing, previously reported in a descriptive study1. C2 consisted of an additional 376 patient samples, of which 24 were analysed by exome sequencing and 352 underwent targeted sequencing of 42 genes, identified as being most frequently mutated in C1 (Supplementary Table 2). C3 consisted of an additional 474 patient samples, all of which were analysed by targeted sequencing of 12 genes (*ATM, ATP9B, BAP1, COL11A1, DMD, KDM5C, PBRM1, PTK7, SETD2, TP53, TRRAP*, and *VHL*), included in an RCC-focused gene panel2. These genes were selected on the basis of their known role in ccRCC biology, previously reported clinical associations, and/or our preliminary observed potential associations with outcome or other clinical parameters in C1 and C2.

**References**

1. Scelo G, Riazalhosseini Y, Greger L, et al. Variation in genomic landscape of clear cell renal cell carcinoma across Europe. *Nature Communications* **2014**;5: 5135.

2. Glennon KI, Maralani M, Abdian N, et al. Rational Development of Liquid Biopsy Analysis in Renal Cell Carcinoma. *Cancers (Basel)* **2021**;13:5825.