Genomic classifications of renal cell carcinoma: a critical step towards the future application of personalized kidney cancer care with pan-omics precision

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Abstract

Over the past 20 years, classifications of kidney cancer have undergone major revisions based on morphological refinements and molecular characterizations. The 2016 WHO classification of renal tumors recognizes more than ten different renal cell carcinoma (RCC) subtypes. Furthermore, the marked inter- and intra-tumor heterogeneity of RCC is now well appreciated. Nevertheless, contemporary multi-omics studies of RCC, encompassing genomics, transcriptomics, proteomics, and metabolomics, not only highlight apparent diversity but also showcase and underline commonality. Here, we wish to provide an integrated perspective concerning the future ‘functional’ classification of renal cancer by bridging gaps among morphology, biology, multi-omics, and therapeutics. This review focuses on recent progress and elaborates the potential value of contemporary pan-omics approaches with a special emphasis on cancer genomics unveiled through next-generation sequencing technology, and how an integrated multi-omics approach might impact precision-based personalized kidney cancer care in the near future.

Keywords: renal cell carcinoma; genomics; transcriptomics; proteomics; metabolomics; biomarkers; targeted therapy; precision therapeutics; personalized medicine

Introduction

Renal cell carcinoma (RCC) encompasses a large heterogeneous group of cancers derived from renal tubular epithelial cells and accounts for more than 90% of cancers detected in the kidney [1]. Among the ten most common cancers worldwide [1], RCC represents more than ten molecular and histopathological subtypes [2,3], the classification of which has undergone major revisions, due to recent advances in morphological and molecular characterizations of renal tumors [2–7]. RCC major subtypes (≥5%) include clear cell RCC (ccRCC) at ~75% [8], papillary RCC (pRCC) at ~15% [9], and chromophobe RCC (chRCC) at ~5% [1,3,10]. Clear cell papillary RCC (cpcRCC) is a newly defined entity that accounts for ~4% of RCCs and is a clinically more indolent disease [2]. The remaining subtypes are very rare at less than 1%, such as medullary RCC (mdRCC), collecting duct RCC (cdRCC), TFE-translocation RCC (tfeRCC) [11], FH-loss HLRCC [12], TSC-loss RCC angiomyolipoma (AML) [13,14], and SDH-loss RCC (sdRCC) [1,3,15]. RCCs that fail to be categorized based on updated histopathological/molecular criteria are grouped and denoted as unclassified RCC (uRCC) at ~4% and encompass heterogeneous RCC entities [1,3,16].

Treatment of localized RCC includes nephrectomy (partial or radical), ablation (radiofrequency or cryo), or active radiographic surveillance [1]. About 30% of patients present with metastatic disease at the time of diagnosis, and an additional 30% of patients with localized RCC, despite surgery with curative intent, eventually develop recurrence or metastasis [1]. Currently approved drugs for metastatic ccRCC include targeted therapies, i.e. bevacizumab, sorafenib, sunitinib, pazopanib, axitinib, tivozanib, cabozantinib, lenvatinib, temsirolimus, and everolimus, and immunotherapies, i.e. interferon-α, IL-2, and nivolumab [1]. With 13 approved agents rounding up six different mechanisms, i.e. inhibitors of VEGFR, mTORC1, c-MET and FGFR; cytokines; and anti-PD1/PDL1 immune checkpoint inhibitors, we have made marked strides against metastatic ccRCC over the past 10 years, doubling patient median survival from 15 months to 30 months [1]. However, treatment responses are highly variable among patients and agents, reflecting...
underlying heterogeneities stemming from drug action mechanisms, cancer biology, and host tumor–immune interactions [17]. Unfortunately, most metastatic ccRCC patients eventually succumb to their diseases and there have been no major therapeutic advances made against the other RCC subtypes (so-called non-clear cell RCC, nccRCC) [18,19].

Over the past 5 years, seminal omic studies performed on RCC by individual laboratories and consortiums including the Cancer Genome Atlas (TCGA) have presented an unprecedented, comprehensive molecular understanding of individual RCC pathobiology [8–10,20–26]. As molecular pathology supplants histopathology, invaluable insights can be drawn from integrated classifications, which could refine and impact the future application of precision-focused, personalized clinical management of RCC [6,27–30]. As a prelude to the pan-omics precision therapeutics era, this review concentrates on genomics/transcriptomics-based RCC stratifications and attempts to present a categorical view of RCC subtypes with most molecular advances.

**Category one classification: histopathology**

Major RCC morphological subtypes (≥5%) include ccRCC, pRCC, and chRCC, which are primarily distinguished by histologic characteristics [3,31].

**Clear cell RCC**

Clear cell RCC (ccRCC) is characterized by lipid-and glycogen-rich cytoplasm, which is lost in histologic processing, giving the distinguishing appearance of clear cytoplasm (Figure 1). Its architecture can vary with solid, alveolar, and/or acinar patterns, and frequently contains a network of thin-walled vasculature. High-grade tumors may contain cells with eosi

**Papillary cell RCC**

Papillary RCC (pRCC) typically contains malignant epithelial cells forming papillae and tubules and is further divided morphologically into type 1 and type 2 tumors (Figure 2). Type 1 pRCC (p1RCC) tends to present as multifocal tumors and the papillae are covered by small cells arranged in a single layer on the papillary basement membrane, often with scant cytoplasm; type 2 pRCC (p2RCC) often has pseudostratified nuclei of higher nuclear grade and abundant eosinophilic cytoplasm. Of note, RCC subtypes including clear cell papillary (ccp) RCC, tfeRCC, cdRCC, and uRCC can display various papillary histologies [32].

**Chromophobe RCC**

Chromophobe RCC (chRCC) generally consists of large polygonal cells with atypical nuclei, mixed with smaller, granular cells in a solid growth pattern (Figure 3). Thick-walled blood vessels, focal calcifications, and broad fibrotic septa are often present as well [33].

**Rare RCC**

The remaining rare RCC subtypes (Figure 4) are also categorized by histologic appearance but with emphasis on unique clinical features such as patient demographics, e.g. TFE-3 translocation RCC in young adults [11] and medullary RCC in sickle cell hemoglobinopathy patients [34].

**Sarcomatoid RCC**

Sarcomatoid dedifferentiation occurs in ~5% of RCCs [35] and can be observed in any RCC histological subtypes [7,36] but at higher incidences in ccRCC (~8%), chRCC (~9%), cdRCC (~29%), and uRCC (11%) [37]. Hence, sarcomatoid RCC (srRCC) does not represent a distinct subtype of RCC, and is classified according to underlying histology. When no epithelia component can be identified in srRCC, it is classified as unclassified RCC (uRCC). In general, srRCC foretells aggressive cancer behavior and poor clinical outcome [35,38,39].

**Category two classification: molecular pathology**

In fact, morphological characteristics of RCC likely denote the underlying molecular pathophysiology. For example, ccRCC cells are full of lipid and glycogen, which is likely due to the near universal inactivation of the tumor suppressor gene VHL that results in uncontrolled HIF activity, the ensuing inhibition of mitochondrial function, and the subsequent redirection of glucose and glutamine for glycogen and lipid synthesis [26]. Early investigations into the molecular pathology of RCC began with familial RCC syndromes, which revealed mutations in several genes such as VHL, MET, and FH [40,41]. Importantly, these mutations can also be detected in distinct subtypes of sporadic RCC but at varied incidences [1,40]. Over the past decade, the original concept of single-gene pathology underlying sporadic RCC has undergone rapid evolution, due to the adaptation of next-generation sequencing technologies for cancer classification [1].

**Clear cell RCC**

Large-scale genomic studies of ccRCC tumors have consistently demonstrated that the loss of heterozygosity of chromosome 3p occurs in more than 90% of ccRCC cases and the complete loss of the VHL tumor suppressor gene, located at 3p25, via genetic (point mutations, insertions, and deletions) and/or epigenetic (promoter methylation) mechanisms occurs in more than 80% of cases [42]. Thus, VHL loss constitutes the earliest and fundamental driving event in the development of ccRCC [43]. VHL, the mutated gene underlying von Hippel–Lindau disease, encodes pVHL, which
is a component of the E3 ligase complex responsible for the ubiquitination of hypoxia-inducible factors 1α and 2α (HIF1α and HIF2α) for proteasome-mediated degradation [44–46]. Of note, among VHL wild-type, chromosome 3 intact ccRCC tumors, recurrent hotspot mutations of TCEB1, a component of the VHL E3 ligase complex, have been identified [23,47]. Unregulated accumulation of HIF proteins, which are normally activated in response to low oxygen stress, promotes activation of HIF-target genes that regulate angiogenesis, metabolism, and cell death [45,48]. Thereby, the pathological loss of VHL underlies the highly vascular
Figure 2. Integrated analyses of papillary RCC (pRCC). The left side panels show the typical histology (top) and the indicated omic features (middle to bottom panels) associated with type 1 papillary RCC (adapted from refs 9 and 68). The right side panels show the typical histology (top) and the indicated omic features (middle to bottom panels) associated with type 2 papillary RCC (adapted from [9] and [68]).

and lipid- and glycogen-laden nature of human ccRCC [49]. However, given the latency of ccRCC development in human VHL syndrome and the inability to induce ccRCC in Vhl-deficient mice [50], VHL loss alone is inadequate for ccRCC formation and additional genetic or epigenetic events are required [51]. Indeed, large-scale cancer genomics sequencing efforts have discovered several novel prevalent gene mutations in ccRCC, including the tumor suppressor genes PBRM1 (40%), SETD2 (15%), BAP1 (15%), KDM5C (7%), and TP53 (5%) [6], and the oncogene MTOR (5–6%) [52]. Furthermore, SQSTM1 was demonstrated as the key oncogene aberration resulting from a common (~70%) chromosome 5q gain event [53]. The importance of such mutations in pathogenesis, clinical outcome, and targeted therapy response of ccRCC will be discussed in the ‘Category three classification’ section below.

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Figure 3. Integrated analyses of chromophobe RCC (chRCC). The left side panels show the typical histology (top) and the indicated omic features (middle to bottom panels) associated with non-metastatic chRCC (adapted from [63]). The right side panels show the more aggressive histology (top) and the indicated omic features (middle to bottom panels) associated with metastatic chRCC (adapted from [63] and [64]).
Figure 4. Histologic and genomic analyses of the indicated rare RCC subtypes.

Papillary cell RCC

Papillary cell RCC (pRCC) accounts for ~15% of RCCs [1], is subdivided into type 1 (p1RCC) and type 2 (p2RCC) based on histologic characteristics [3], and commonly exhibits multifocal tumors (8–41%) [33,54]. p1RCC is typically smaller, lower grade, more indolent, and less metastatic than p2RCC [55]. Sporadic p1RCC is associated with MET gene alteration, whereas sporadic p2RCC is characterized by CDKN2A silencing, SETD2 mutations, NF2 mutations, CUL3 mutations, TERT promoter mutations, increased expression of the NRF2-antioxidant pathway, and gains of chromosomes 7, 12, 16, and 17 [9,56–60]. Hereditary p1RCC is characterized by bilateral, multifocal tumors and germline MET activation mutations [61,62]. The MET gene encodes the receptor tyrosine kinase c-MET for hepatocyte growth factor (HGF), the alterations of which either through activating mutation or through gene amplification in renal epithelial cells promote oncogenic pathways that confer cancer cell growth, survival, and invasion advantages [62]. p2RCC can occur in the hereditary leiomyomatous and RCC syndrome (HLRCC) patients, which is linked to a germline mutation in the fumarate hydratase (FH) gene [12], a key enzyme of the tricarboxylic acid (TCA) cycle [62].

Chromophobe RCC

Chromophobe RCC (chRCC) originates from distal convoluted tubule cells of the nephron [63] and comprises ~5% of RCC tumors [1]. chRCC grows slowly, seldom metastasizes (5–10%) [64], and portends a relatively better survival except for those with sarcomatoid changes [18,65,66]. Most chRCCs display a nonrandom pathognomonic loss of approximately seven chromosomes, i.e. chromosomes 1, 2, 6, 10, 13, 17, and 21 [63,67]. Whole-genome sequencing of 66 chRCCs by KICH TCGA reported the low (~31) exonic somatic mutations, and TP53 and PTEN were the only two genes mutated at more than 10% incidence [63]. Combined mitochondrion DNA and RNA analysis indicated oxidative phosphorylation defects, explaining the commonly observed overabundance of mitochondria in chRCC cells [63,68]. Of note, chRCC can also be detected in patients with Birt–Hogg–Dubé (BHD) syndrome, characterized by mutations in the folliculin (FLCN) gene, residing on chromosome 17. Additional clinical manifestations of BHD include cutaneous fibrofolliculomas, renal oncocytoma, and renal hybrid oncocytic tumors [69].

Rare RCC

Collecting duct RCC (cdRCC) originates from the renal collecting system, exhibits a prominent stromal reaction, and is associated with a very poor clinical outcome. Genomics of 17 cdRCC patients identified recurrent mutations in NF2 (5/17), SETD2 (4/17), SMARCB1 (3/17), FH (2/17), and CDKN2A (2/17) [70]. Medullary RCC (mdRCC) occurs in patients with sickle cell hemoglobinopathy [34]. mdRCC is diagnosed with the loss of nuclear staining for the SMARCB1/INI1 tumor suppressor protein [71], resulting from either loss of heterozygosity (LOH) and balanced translocations [72] or biallelic loss [73]. TFE-3 or TEF-B translocation-associated RCCs (tfeRCCs) exhibit varied histology from clear cell morphology to papillary architecture [74]. Various TFE-3 RCC translocation partners have been identified including SFPQ, ASPSCR1, PRCC, NONO, CLTC, KSHRP, and LUC7L3 [11,75].

| Collecting Duct | Medullary | SDHB-Deficient | TFE Translocation |
|----------------|-----------|----------------|------------------|
| Morphology     |           |                |                  |
| Genotypic Alterations | Losses of 1p, 8p, 9p, 16p | Poorly described, likely have normal karyotype | Loss of 1p | Recurrent translocations involving TFE3 (Xp11.2) or TFEB (6p21) |
| Significantly Mutated Genes | NF2, SETD2, SMARCB1, FH | Sickle cell trait | SMARCB1/INI1 | SDHB | TFE3 | TFEB |

*Figure 4. Histologic and genomic analyses of the indicated rare RCC subtypes.*
Molecular classification of unclassified RCC
RCCs that cannot be categorized as any specific subtype based on contemporary morphological and molecular definitions are aggregated as unclassified RCC (uRCC) [1,3,16]. Hence, uRCC encompasses a ‘lost-and-found’ bag of low-frequency, mixed-characteristics, heterogeneous clinical outcome, yet-to-be-determined/recognized renal cancers [76,77]. To address this knowledge gap and fill the unmet need in the diagnosis of uRCC, Chen et al performed comprehensive molecular characterizations of 62 aggressive uRCCs (Figure 5). They demonstrated recurrent mutations in NF2 (18%), SETD2 (18%), BAP1 (13%), KMT2C (10%), and MTOR (8%), and pathway alterations in NF2/Hippo (26%), MOTRC1 (21%), and chromatin/DNA damage (21%). Furthermore, within this 62-patient aggressive uRCC series, three FH-loss and one ALK-translocation RCCs were identified and thereby reclassified [16].

Sarcomatoid RCC
Sarcomatoid transformation of RCC displays spindle cell morphology through an epithelial–mesenchymal transition (EMT) process that arises from the adjacent epithelial carcinoma [37,78], and this carries significant prognostic values in all subtypes of RCC [35,79–81]. Early studies comparing sarcomatoid RCC (sRCC) with the adjacent epithelial RCC demonstrated TP53 inactivation as the only recurrent genetic event [39,82]. Two recent elegant genomic studies shone more light on the genetic aberrations underlying sarcomatoid transformation in RCC [83,84]. Combined recurrent somatic events found in their reports include mutations in TP53, BAP1, ARID1A, PTEN, CDKN2a, and NF2 [39,83,84]. Of note, Casuscelli et al reported a high incidence of whole-genome duplication events in sarcomatoid chRCC [64], which could also represent a common driver event underlying sarcomatoid dedifferentiation in other RCC subtypes.

Category three classification: genomic correlates with clinical outcome
The term ‘translation oncology’ emphasizes ‘the application of learned research knowledge for the improvement of human cancer care’. Facing the ever-increasing complexity of treatment modalities [1] and the demonstrated marked tumor heterogeneity [60,85–87] in RCC, the notion of applying molecular pathology to future patient management is exciting yet challenging [6]. Here, we illustrate some recent human RCC cancer genomic advances that might have translational values through which they could complement current histological subtypes [65,88] and refine prevalent risk-stratification schemes [89–91].

Clear cell RCC
One of the striking discoveries in ccRCC genomics was the close genomic localization of four prevalent tumor suppressor genes, VHL, PBRM1, SETD2, and BAP1, spanning chromosome 3p21–3p25 that is lost in more than 90% of ccRCCs [8]. Hence, the near universal singular chromosome 3 short arm loss in ccRCC results in a simultaneous one-copy loss of four tumor suppressors, which is unprecedented [42,60]. Furthermore, the fact that PBRM1, SETD2, and BAP1 encode chromatin- and histone-regulating tumor suppressor proteins suggests epigenetic dysregulation as a convergent pathogenic theme in ccRCC [17]. As VHL loss is the truncal event during ccRCC development, its mutation status has no impact on clinical outcome [1], whereas PBRM1 [24], SETD2 [92], BAP1 [22,92–94], KDM5C [95], TP53 [96], and TERT promoter [97] mutations are associated with more aggressive clinical features when all stages of ccRCC are considered, which is consistent with a notion that their loss occurs as a second, third or further downstream driver event [98]. Of note, mouse modeling demonstrated that PBRM1, a key component of the PBAF SWI/SNF chromatin remodeling complex, functions as a tumor suppressor by preventing self-perpetuating, feed-forward amplification of HIF oncogenic signals [51,99,100], and this may explain why its mutation in small renal masses is associated with tumor invasiveness [24]. Taken together, these pieces of information are likely of value in prognosticating ccRCC patients who present with non-metastatic clinical stage I–III diseases [1,6,96].

When evaluating the impact of these prevalent mutations on the clinical outcome of metastatic ccRCC patients in the targeted therapy era, distinct clinical outcomes have been observed, which is likely of value for precision therapeutics that emphasizes mechanism-based selection of treatment remedies [1]. Of note, in the primary tumors of both localized and metastatic ccRCC patients, PBRM1 and BAP1 mutations occur in a statistically significant mutually exclusive manner [22,30]. In a large randomized phase II clinical trial (RECORD-3) in which RCC patients received a first-line treatment of either sunitinib (anti-VEGFR) or everolimus (mTORC1 inhibitor) [101], a genomic biomarker study demonstrated, with first-line sunitinib, that KDM5C, PBRM1, and BAP1 mutations were associated with a PFS of 20.6, 11.0, and 8.1 months, respectively; and that mutations in VHL, SETD2, and PTEN had no statistically significant impact on outcome [30]. Although mTORC1 inhibition is inferior to anti-VEGFR inhibition for the majority of ccRCC patients, a small percentage of patients carrying mutations in the mTORC1 signaling pathway (including PIK3CA, TSC1, TSC2, and MTOR) derived prolonged disease control [27,28,52,102,103]. All these findings
Figure 5. Integrated analyses of uRCC. The top panel shows the histology of an unclassified RCC case. The middle panel shows the genomic classification of aggressive uRCC (adapted from ref 16). The bottom graphs show (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$) the distinct clinical outcomes associated with the indicated genomic subtypes of uRCC (adapted from [16]).

were further evaluated using independent cohorts [29,104] and warrant prospective validations.

Non-clear cell RCC: papillary cell RCC and unclassified RCC with papillary features
Despite major therapeutic and survival progresses made in metastatic ccRCC, patients with non-clear cell histology (nccRCC) continued to fare poorly despite administering targeted therapeutic agents [18,19,66,105], e.g. sunitinib (6.1–8.3 months) and everolimus (4.1–5.6 months) [106,107]. Nevertheless, studies on papillary RCC (pRCC) and uRCC with papillary features showed promising clinical benefits with the dual MET/VEGFR2 inhibitor foretinib (PFS of 9.3 months) [108] or the combination of everolimus and bevacizumab (anti-VEGF-A antibody) (PFS of 12.9 months) [109]. The molecular basis underlying such varied treatment responses warrants urgent investigation through cooperative group or consortium efforts [19].

Metastatic chromophobe RCC
Among RCC subtypes, chromophobe RCC (chRCC) is relatively indolent and occasionally (5–10%) metastasizes [19,64]. However, due to its rarity, all chRCC patients after nephrectomy were monitored based on guidelines established for ccRCC patients [110–112].
To investigate how chromophobe RCC cells typified by a classical approximately seven chromosome loss (1, 2, 6, 10, 13, 17, and 21) and low somatic exonic mutations could develop lethal metastasis [113], Casuicelli et al performed integrated analyses consisting of whole-genome sequencing, targeted exome sequencing, OncoScan, FACETS, and FISH on a cohort of 79 chRCC patients among whom 38 had metastatic disease [64]. Remarkably, this study recognized high-risk genomic features associated with chRCC metastasis besides the known high-risk sarcomatoid morphological feature. They showed that chRCC patients whose primary tumors carried any of the three high-risk genomic features, i.e. TP53 (chromosome 17) mutation, PTEN (chromosome 10) mutation, and imbalanced chromosome duplication (ICD; a chromosome duplication feature reminiscent of whole-genome duplication demonstrated in other cancer types), are more prone to develop metastasis than those with none; this was also validated using an independent KICH TCGA cohort [64]. Importantly, among metastatic chRCC patients, these high-risk features further foretell worse clinical outcome [64]. Accordingly, a personalized post-nephrectomy follow-up scheme based on genomics might be feasible in the future for chRCC patients, once these high-risk features are validated in prospective studies.

SDH-loss RCC

SDH-loss RCC (sdlRCC) is the newest recognized RCC subtype that is defined by the loss of the enzyme succinate dehydrogenase (SDH) and is extremely rare [114]. The SDH enzyme consists of A, B, C, and D subunits [115]; germline mutations of SDH genes are common in patients with hereditary paraganglioma and phaeochromocytoma [116]; only ~50 patients of sdlRCC cases have been reported thus far; most (83%) carry SDHB mutations and they account for 0.05–0.2% of RCCs [15,117]. Due to its rarity and pleomorphic clinical and pathological features, sdlRCC is likely underdiagnosed [15]. Molecular characterizations of three young, lethal SDHB-loss RCC patients demonstrated that germline SDHB mutations followed by the LOH of the remaining wild-type allele through deletion of chromosome 1p where the SDHB gene resides are truncal driver events, and the extreme Warburg effect manifesting with persistent hyperlactatemia despite normal tissue oxygenation and very high FDG-PET avidity are associated late-stage clinical features [15].

Cancer of unknown primary RCC

Cancer of unknown primary origin (CUP) comprises 3–5% of new cancer diagnoses in the United States [118], and presents extreme therapeutic challenges. Genomics profiling of two CUP patients whose metastatic tumors showed clear cell histology favoring renal origin by Wei et al showed 3p loss, PBRM1 mutation, and SETD2 mutation in one patient, and NF2 mutation, SETD2 mutation, and TSC1 mutation in the other patient [119]. As the genomic and histologic features of these two CUP patients were consistent with cancer of unknown primary RCC (cupRCC) and because RCC is known to be refractory to conventional chemotherapy, both patients received front-line treatment with standard-of-care targeted therapies for RCC instead of chemotherapy for CUP, and derived clinical benefits [119].

Category four classification: integrated multi-omics across RCC subtypes

Multi-omics performed on cancers of various tissue origins has enabled pan-cancer analyses, such as cluster of clusters analysis (COCA), and has revealed shared oncogenic pathways or mutations beyond histologic boundaries [120]. To understand whether there is any common pathogenetic thread behind different RCC subtypes, multi-platform analyses of a larger TCGA cohort of 894 RCC cases beyond the initially reported KIRC (446), KIRP (161), and KICH (66) have been reported [68]. By consolidating five genomic data platforms (DNA methylation, DNA copy alteration, mRNA expression, microRNA expression, and protein expression), Chen et al demonstrated that differences in patient survival and in alteration of specific pathways including hypoxia, metabolism, NRF2-ARE, Hippo, immune checkpoint, and PI3K/AKT/mTOR could further distinguish subtypes [68]. These findings inspired the subsequent discovery of pan-urologic cancer genomic subtypes that transcend the tissue of origin [121].

Conclusion remarks and future perspectives

Over the past 10 years, the treatment of metastatic ccRCC came out of ‘the Dark age’ in 2005, when only two ineffective drugs were available; passed through ‘the Modern age’, with nine drugs, and marched into ‘the Golden age’ in 2015, with 12 drugs approved and counting (Figure 1) [1]. Sadly, this marked improvement in clinical outcome is limited to ccRCC [19]. Therefore, more preclinical and clinical research is urgently needed for the other RCC subtypes. In addition to modern therapeutics, the employment of contemporary molecular technologies to study human kidney cancer has blossomed in recent years, and includes transcriptomics [122–125], metabolomics [26,49,126–128], multi-omics [68], radiogenomics [129], and immunogenomics [130–132]. All these advancements herald the promise of an upcoming pan-omics era for RCC when a confident assessment of clinically applicable predictive biomarkers becomes routine clinical practice in guiding choices of mechanism-based combination therapies to avoid treatment resistance and overcome tumor heterogeneity [1,17,133].
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Author contributions statement

JHH conceived the project, wrote the manuscript, and finalized the figures. VL prepared the manuscript and figures. DC provided pathological pictures and reviewed the manuscript. EHC discussed and reviewed the manuscript. CJC provided high resolution figures and reviewed the manuscript.

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