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Emerging Reclassification Schemes of RCC: How Identifying New Molecular Entities Among Non-Clear Cell RCC Signifies an Evolution in Managing the Disease

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This is the first of a two-part series on reclassification of renal cell carcinomas (RCCs), many of which are considered non-clear cell RCC (nccRCC). The first part will outline most clinically relevant classifications that should be taken into consideration in treatment planning, and the second part will detail the contemporary genomics information on individual subtypes of kidney cancer. With the evolution of RCC classification, some tumors have an atypical morphology and these tumors often are difficult to categorize in any specific subtype. This report highlights these issues, focuses on how the field is evolving, and what factors need to be considered as part of identifying and characterizing new subtypes. Most importantly, the information emerging from new reports not only crystallizes our understanding of pathologic variants but points toward therapeutic and prognostic opportunities as well.

When each subtype of a tumor harbors a unique biology and responds differently to available treatment strategies, integrated pathologic and molecular classification becomes an all-important consideration. Classification is highly important in RCC for a number of reasons, not the least of which is the implication for selecting appropriate therapies in an era when the spectrum of choices has expanded dramatically. Kidney cancer care has been remarkably reshaped by a series of advances—development of minimally invasive techniques for surgery in the retroperitoneum, emergence of focal therapy, reemergence of percutaneous renal biopsy, introduction of active surveillance strategies, renewed interest in immunotherapy, and the introduction of targeted therapies for patients with advanced disease.[1] The appropriate choice of these can depend on the identification of a variant or phenotype amenable to an evidence-based decision. These more clearly defined subtypes not only allow for a common descriptive language, they help to crystallize the understanding of RCC's molecular origins and its clinical behavior. A robust classification scheme for kidney cancer is important for other reasons: for example, up to 20% of enhancing small renal masses are benign and may not need treatment.[2] Tumors such as papillary adenomas, pure oncocytomas, and angiomyolipomas (except a rare epithelioid variant) do not metastasize.[1] Local symptoms, such as pain or hemorrhage, are rarely associated with these tumors unless they are large, such as >4 cm with angiomyolipomas.

While most of the attention in the clinical literature tends to focus on the evolution of these management approaches in the past, pathobiology-based treatment stratification is at center stage and promises better, effective, personalized care, i.e. tailored treatment plan of individual cancer patients based on tumor morphology, biology, and genetics. This will move current wholesale type clinical trials to smaller yet more targeted trials. Arguably one of the most significant paradigm shifts in the clinical constructs that shape kidney cancer care is the advance in molecular characterization of most kidney cancer subtypes. Current efforts first morphologically group kidney cancer into major subtypes and then perform molecularly characterization for subclassification.[2]

A History Lesson on Classification: Rapid Change, Better Characterization

There has been a rapid evolution in thinking in the pathology community with some of the terms first used in the early 20th century still occasionally used in modern pathology reports. In brief, here is how the knowledge base has grown since the 1980s until now, and within the next few years we are likely to see a new characterization of tumor types that could represent another sea change in our classification schemes.

- Clear cell RCC has long been recognized as the predominant histologic subtype.
- Papillary RCC was better characterized in the 1980s.

Keywords: tumor heterogeneity; reclassification; WHO renal cell carcinoma classification; clear cell renal cell carcinoma; non-clear cell renal cell carcinoma; histological subtypes.

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Table. Common Histologic Renal Cell Carcinoma Subtypes and Their Appearance and Associated Molecular Alterations

Tumor type	Subtype	Gross appearance	Microscopic appearance		Known somatic alterations	Cytogenetic alterations
Clear cell	–	Yellow, well circumscribed, and can possess distinct areas of hemorrhage and necrosis	Abundant clear cytoplasm due to deposition of lipid and glycogen		VHL, PBRM1, SETD2, BAP1, JARID1A, mTOR, PI3K	3p (90%), 14q, 8p, and 9p and gains at 5q and 12q
Papillary	1 2	Mixed cystic/solid consistency. Papillary RCC lesions are often reddish-brown and frequently have a well-demarcated pseudocapsule	Papillary or tubulopapillary architecture. Calcifications, necrosis, and foamy macrophage infiltration.	Type 1: thin, basophilic papillaewith clear cytoplasm Type 2: heterogenous, thicker papillae andeosinophilic cytoplasm.	MET NRF2, CUL3	Gains of 7, 8q, 12q, 16p, 17, 20, and loss of 9p. Papillary type 2 with gains of 8q, loss of 1p and 9p.
Chromophobe	Classic Eosinophilic	Large, well circumscribed, tan-brown tumor with occasional central scar	Distinct cell borders and voluminous cytoplasm, nuclear morphology with perinuclear halos, binucleation	Pale cytoplasm Large tumor cells with fine eosinophilic granules	TP53	Loss of chromosomes 1, 2, 6, 10, 13, and 17
Oncocytoma	–	Mahogany color, well circumscribed, occasional central scar, and rarely with necrosis	Polygonal cell with abundant eosinophilic cytoplasm and uniform, round nuclei		Mitochondrial complex I genes	Loss of 1 p, loss of Y, often normal karyotype
Collecting duct	–	Partially cystic, white-gray appearance and often exhibit invasion into the renal sinus	Tubulopapillary pattern, often with cells taking columnar pattern with hobnail appearance, presence of mucinous material, desmoplastic stroma		Unknown	Losses at 8p, 16p, 1p, 9p, and gains at 13q
Medullary	–	Tan/white, poorly defined capsule, extensive hemorrhage and necrosis	Poorly differentiated, eosinophilic cells; inflammatory infiltative cells; sheet-like or reticular pattern common		Unknown	Poorly described, but believed normal karyotype
MiT family	–	Yellowish tissue often studded by hemorrhage and necrosis	Papillary or nested architecture, granular and eosinophilic cells with voluminous, cytoplasm		–	Recurrent translocations involving Xp11.2 (TFE3) or 6p21(TFEB)

*See Table 1 for known genes/germline mutations associated with each pathologic subtype.
Adapted from: Shuch B, Amin A, Armstrong AJ, et al. Understanding pathologic variants of renal cell carcinoma: distilling therapeutic opportunities from biologic complexity. *Eur Urol*. 2014;http://dx.doi.org/10.1016/j.eururo.2014.04.029.

Kovacs et al[3] reported that these tumors contained more than 75% of papillary features and did not have characteristic 3p chromosomal loss on karyotype analysis. Since that report, two different classes of papillary tumors have been verified.[4]

- Chromophobe RCC, the third most common subtype, was described in the mid-1980s.[5]
- In the 1990s, reports further delineated rare, histologic subtypes, including collecting duct, medullary RCC, translocation RCC, and mucinous tubular and spindle-cell RCC.[6]

Along the way, the widely recognized World Health Organization (WHO) classification of adult renal epithelial neoplasms was introduced in 1998 and then updated in 2004, based on pathology and genetic abnormalities.[7] These classification schemes served as benchmarks for further elucidation of pathological variants. Ten years after the introduction of the 2004 WHO criteria, new efforts seek to redefine the descriptions in this document.

New Initiatives to Revamp the WHO Classification

Until the results of this initiative are presented [*Editor's note: see related article.*], it is useful to examine how far the classification schemes currently applied have clarified various entities and what insights can be gained from modifications proposed in the WHO classification by other groups organized for that purpose. One group providing new direction in the field is the classification working group of the International Society of Urological Pathology (ISUP) with its Vancouver Classification of Renal Neoplasia.[8] Although not yet officially incorporated as part of the WHO scheme, the ISUP produced a consensus that offers a framework for reconsidering existing criteria and how the field is evolving and what new epithelial neoplasms should be recognized. After an exhaustive literature review and a survey of members from numerous international centers such as Johns Hopkins Medical Institutions, Memorial Sloan-Kettering Cancer Center and New York University Medical Center, the working group suggested that 5 entities should be recognized as new distinct epithelial tumors within the WHO classification scheme: (1) tubulocystic RCC; (2) acquired cystic diseae-associated RCC; (3) clear cell (tubule) papillary RCC; (4) the MiT family translocation RCCs (in particular t(6;11), and (5) hereditary leiomyomatosis RCC syndrome-associated RCC. The group also identified 3 rare carcinomas, including Succinate Dehydrogenase B (SDHB) associated RCC, ALK translocation RCC, and on which further study is needed because they are emerging entities.

Overall, some new concepts and modifications were

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proposed by the working group with regard to existing entities already widely recognized. These concepts included the following:

- In clear cell RCC, multicystic clear cell RCC is best considered as a neoplasm of low malignant potential.
- Subtyping of papillary RCC is worthwhile and the oncocystic variant of papillary RCC should not be considered a distinct entity.
- The chromophobe RCC category has at least for now, gained another subtype. This is the hybrid oncocyte chromophobe tumor. This tumor occurs in 3 settings—Birt-Hogg-Dube Syndrome, renal oncocytosis and as a sporadic neoplasm.

Main Subtypes of RCC

Renal cancers encompass many distinctive subtypes of neoplasms that arise in the kidney parenchyma. The most common subtype is clear cell renal cell carcinoma (ccRCC) summing up ~75% (**Figure 1**) kidney cancers, and the remaining 25% are aggregates of rare kidney cancers and commonly referred to as non-clear cell RCC (nccRCC). Within nccRCC, papillary type I (pIRCC) is at 5-10%, papillary type II (pIIRCC) at 5%, chromophobe type (chRCC) at 5%, unclassified type (ucRCC) at 5%, TFE-fusion type (tfeRCC) at 1%, collecting duct type (cdRCC) at 1%, me-dullary type (mdRCC) at 1%, and several <1% morphologically distinct types. Each of these different types of kidney cancer can be characterized by different histologies, clinical courses, and responses to therapies, and are associated with alterations of different tumor suppressors and/or oncogenes. With the technical advance in next-generation sequencing, efforts led by kidney cancer TCGA (the cancer genome atlas) working groups (KIRC, clear cell; KICH, chromophobe; KIRP, papillary) have begun to provide a better genomics picture on major subtypes of RCC. However, those 1% rare subtypes are poorly studied. Furthermore, how many disease entities are currently aggregated under the "unclassified" subtype is unknown. The molecular determinants of individual RCC subtypes will be discussed in the second half of this two-part series.

Clinical Difficulties that nccRCC Patients and Their Physicians Encounter

Over the past decade, we kidney cancer clinicians have conducted multiple international phase III trials, leading to the approval of new effective drugs for metastatic clear cell type kidney cancer (ccRCC), including sunitinib, sorefenib, pazopanib, axitinib, bevacizumab, everolimus, and temsirolimus. Current treatment has greatly extended the life expectancy of metastatic ccRCC patients from 12-18 months to 30-36 months. Despite these marked strides against ccRCC, the remaining 25% of kidney cancer patients with so-called non-clear cell renal cell cancer (nccRCC) who develop metastasis are left with no standard of care option and now fare worse than ccRCC patients (**Figure 2**).[9]

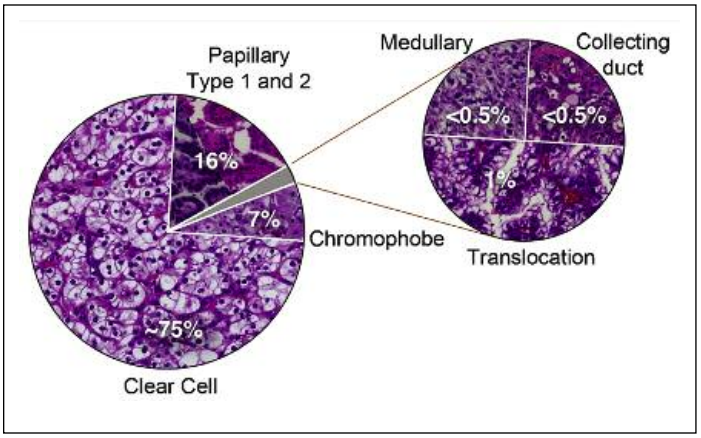

Figure 1. Pie chart showing distribution of the most common histologic subtypes of renal cell carcinoma. Medullary, collecting duct, and translocation renal tumors make up approximately 2% renal cell carcinomas.

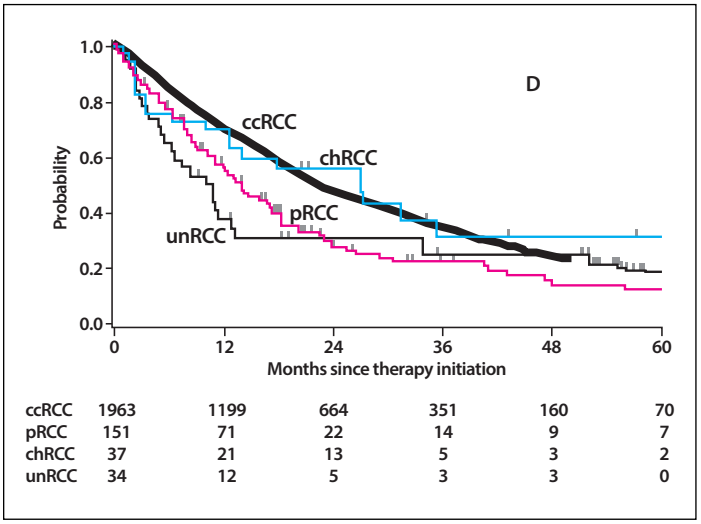

Figure 2. Probability of survival in different tumors shows worse prognosis in non-clear cell RCC.

Working Toward a Prognostic Model in Non-clear Cell RCC

One of the goals of efforts to further characterize variations of RCC is to propose models of different phenotypes that could be useful in treatment situations among patients whose disease has been relatively undifferentiated. A case in point is the subgroup with non-clear cell RCC. In these patients the goal of one international group was to reliably predict overall survival (OS) and time to treatment failure (TTF). For example, the 20% of kidney cancer patients with non-clear cell RCC served as a study population for the International mRCC Database Cosortium (IMDC)(13). The IMDC, or Heng model, has been a useful prognostic model in major clinical trials of targeted therapies.[14] In two reports on development of the Heng model, the criteria (essentially 6 independent predictors of poor survival) were validated without consideration of the histological subtypes.[11,12] Heng et al assumed that the results they obtained were largely affected by the clear-

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Dynamic New Initiatives in RCC Target Elusive Issues, Including Tumor Heterogeneity, Metabolic Derangements and Genomics

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The concept of renal cell carcinoma (RCC) as a uniform malignant phenotype has been reengineered so many times that it bears no resemblance to later classification schemes. In some ways, even the WHO 2004 classification system is losing its relevance as well. Remarkable advances in the understanding of basic morphology, immunohistochemistry, cytogenetics, and molecular pathology have ushered in a new era of classification of RCC. And much more is on the horizon, as consensus conferences and study groups introduce new models of RCC subtypes that only recently have been integrated into our understanding of pathologic variants of the disease.

Whether we refer to them as "non clear cell" or "non-conventional" RCC, such tumors histologically are not as elusive as previously thought and new reports are revealing more of the characteristics that enable our identification of them as emerging entities. Over the last decade there have been refinements in many existing categories within the 2004 WHO classification system. More refinements are in the preliminary stages as research initiatives, such as those under study at the Memorial Sloan-Kettering Cancer Center, point toward new directions. Although the research initiatives are only now being launched, they serve as an important reminder of gaps in our knowledge base with regard to the understanding of:

- The mechanisms and therapeutics of anti-angiogenic resistant clear cell RCC.
- The need for an integrated molecular and imaging approach of kidney cancer as a metabolic disease.
- Tumor heterogeneity of kidney cancer and its impact on clinical/pathologic outcomes and treatment response.
- The genomics and therapeutics of rare kidney cancers.

The ideas and focus behind these initiatives are still in development at MSKCC, but their aims and objectives suggest the line of thinking to further characterize approaches to RCC.

One of the directions to be pursued is to investigate the mechanisms and therapeutics of anti-angiogenic resistant clear cell RCC. The goals of this proposed initiative are to:

(1) Discover biomarkers of response and resistance to anti-angiogenic TKI in human ccRCC tumors.
(2) Establish additional PDX models of ccRCC that recapitulate primary resistance to anti-angiogenic TKIs and molecularly dissect the underlying resistance mechanisms.
(3) Identify therapeutic strategies for ccRCC patients with primary resistance to anti-angiogenic TKIs.

A second initiative at MSKCC focuses on an integrated molecular and imaging approach of kidney cancer as a metabolic disease. Among the aims of researchers are the following objectives. To investigate the molecular basis of metabolic derangements in RCC, MSKCC investigators would:

(1) Perform multidimensional integrated genomics on distinct metabolic clusters of ccRCC.
(2) Determine the role of elevated 2-HG in ccRCC.
(3) Investigate metabolic pathways that associated tumor aggressiveness

Novel metabolic imaging of RCC would be utilized to:

(1) Characterize cancer metabolism utilizing a combination of isotope tracing Mass Spectroscopy (MS) and hyperpolarized Magnetic Resonance (MR) derived flux
(2) Image RCC mouse models using hyperpolarization (HP) MR imaging.
(3) Perform HP MR imaging on human kidney cancer patients.

One of the most timely areas to be addressed concerns tumor heterogeneity and treatment responses. The research initiatives in this regard will:

(1) Assess the impact of intratumoral heterogeneity (ITH) on clinical and pathologic outcomes across the disease spectrum of ccRCC and on the development of biopsy-based prognostic models.
(2) Study the effect of ITH on tumor immune microenvironment and its impact on therapeutic response.
(3) Investigate the spectrum of ITH and its implications in metastatic disease utilizing a Research Medical Donation (Rapid Autopsy) Program.

Still another area to be addressed covers the genomics and therapeutics of rare kidney cancers. The goals of an initiative on this topic will:

(1) Delineate the genomic landscape of aggressive renal cell carcinoma with unclassified histology to develop a molecular classification scheme.
(2) Dissect the molecular mechanism underlying a novel subset of unclassified RCC and develop genetically engineered mouse models for preclinical studies.
(3) Develop therapeutic strategies for unclassified RCC.

As these ideas coalesce and a protocol for investigative work takes shape, teams of researchers at MSKCC will report on their findings and their possible translational impact for clinical practice and future trials.

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cell RCC subtype because it was the predominant histological subtype in the development and validation cohort. The key question left unanswered by these earlier reports, however, is whether the IMDC prognostic model can be applied in the non-clear cell subtype. Another question addressed by the IMDC was whether outcomes tended to be worse among the nccRCC group.

Kroeger et al[9] and the Consortium determined whether the IMDC prognostic model could be applied to survival outcomes of patients with nccRCC treated with first-line VEGF and mTOR inhibitors. By assessing the applicability to this subtype, Kroeger et al could differentiate responses to such therapy in nccRCC vs the ccRCC cohort in the study. Tumors with nccRCC histology included papillary RCC (n=5151, 59.9%), chromophobe RCC (n=537, 14.7%), collecting duct RCC (n=57, 2.8%), unclassified RCC (n=534, 13.5%), and RCC with Xp11 translocation (n=54,1.6%).The 6 independent predictors of poor survival evaluated included:

(1) Karnofsky performance status <80%.
(2) Time from diagnosis to treatment interval <1 year.
(3) Anemia
(4) Hypercalcemia
(5) Neutrophilia
(6) Thrombocytosis

The two conclusions emerging from this report, based on data gathered from 2215 patients with ccRCC and 252 with nccRCC, were (1) the risk model based on independent predictors of poor survival was reliable as a prognostic tool in the nccRCC group; and (2) even in the era of targeted therapy, the majority of nccRCC patients still had inferior clinical outcomes compared with patients with ccRCC. OS (12.8 vs 22.3 months) and TTF (4.2 vs 7.8 months) were worse in the nccRCC group compared to the ccRCC cohort. The prognostic model reliably discriminated 3 risk groups in the nccRCC patients: favorable, intermediate, and poor prognosis. The OS of these groups was 31.4, 16.1, and 5.1 months in these risk groups and TTF was 9.6, 4.9, and 2.1 months. Kroeger et al[9] suggest that the prognostic model could be useful in counseling patients and in clinical trial design. According to the authors, there is no other prognostic model that has been assessed exclusively in advanced nccRCC.

The prognostic model from the IMDC is important because it reflects similar efforts to further characterize not only nccRCC but other non-conventional RCCs. As Voss et al (17) point out, despite recent advances in the treatment of metastatic ccRCC, the optimal therapy for patients with advanced RCC with less common histologies has not been established. Most pivotal trials with targeted agents have exclusively enrolled patients with clear-cell histology, one exception being the Advanced Renal Cell Carcinoma (ARCC) trial demonstrating benefits of temsirolimus in patients with non-clear histology. Yet this study did not provide insight into the distinct nccRCC subtypes. This is why the report by Voss et al is of interest: it retrospectively analyzed outcomes of patients with nccRCC and sarcomatoid clear-cell and non-clear cell subtypes previously treated with mTOR inhibitors at Memorial Sloan-Kettering Cancer center. The aim was to explore the efficacy of these agents across various RCC variants.

The results were somewhat disappointing and Voss et al reached the following conclusions:

- Patients with metastatic ncRCC and sarcomatoid ccRCC can benefit from mTOR-targeted therapy, but the majority of patients respond poorly with these agents.
- Therapeutic effect varies greatly between individual patients, even within the same subgroups of disease.
- Importantly, objective responses or prolonged disease stabilization can be seen fora subset of patients across several of these rare cancers without clear association with any particular histologic phenotype.

Perhaps the message emerging from this report is that we can only speculate at this point as to why there is this variability in response to treatment exists. Voss et al postulate that differences in underlying tumor genetics, rather than the histopathologic phenotype alone, may be the explanation. In any case, the findings highlight the need for identification of predictive tissue biomarkers as part of a wider focus on more clearly characterizing these tumors of non-clear histology.

With the reexamination of the 2004 WHO classification scheme and more focused initiatives on identifying histologic variables as an important prognostic factor of survival, cytogenetic and molecular research has explored new pathological subtypes not previously recognized and that are part of what has been called cancer-specific or "localized non-conventional RCC (NCRCC)." These subtypes include Xp11.2t; renal medullary carcinoma, and RCC with neuroblastoma and MTSC RCC. A Korean retrospective study[14] compared clinical outcomes to determine independent prognostic factors according to histology in these non-conventional subtypes.

A total of 374 cases were examined, including 126 papillary (33.7%), 164 chromophobe (43.9%), eight collecting duct (2.1%), 40 unclassified (10.7%), 16 Xp11.2t (4.3%), seven mucinous tubular and spindle cell (1.8%) renal cell carcinomas and 13 oncocytomas(3.5%). During a mean follow up of 56.4 months, mean tumor size was 4.9 cm. The 4-year recurrence-free survival, overall survival and cancer-specific survival were inversely related to the increase of pathological T stages ($P < 0.001$). For histological type other than 13 oncocytomas and seven mucinous tubular and spindle cell renal cell carcinomas, the chromophobe showed the best prognosis of survival, followed by papillary, Xp11.2t, unclassified and collecting duct renal cell carcinomas, in this order. All survival rates were significantly different, as according to the histology ($P = 0.009$). The significant prognostic factors were preoperative body mass index (hazard ratio 0.76), serum albumin (hazard ratio 0.64), T stage (hazard ratio 2.28), the

sarcomatoid differentiation (hazard ratio 33.45) and lymphovascular invasion (hazard ratio 12.40) in pathology ($P < 0.05$).

The Korean study is significant as it helps clinicians to understand the comparative clinical course of different postoperative prognoses for each subtype of NCRCC, and to prepare for a better adjuvant management according to respective histology and prognostic factors. Not many studies have focused on subtypes of NCRCC with comparable numbers of patients with NCRCC over a long period of time like those of this study. Additionally, as molecular and cytogenetic biology have recently been spotlighted to identify the characteristics of RCC at gene and molecular levels, studies such as this one could have an important role. They may facilitate development of further management plans such as neo- or adjuvant targeted therapy for NCRCC patients; and this study could help to plan further analyses of molecular or cytogenetic biology on NCRCC as one of the differential references of different histologies from NCRCC, reflecting their clinically different prognosis .[15]

Conclusion

A dramatic change in the classification schemes for kidney cancer in the last two decades has important implications for determining prognosis and identifying therapeutic opportunities. As these new pathologic variants have been recognized, the traditional schemes used to characterize the disease are being replaced. With modifications and recommendations from groups analyzing these subtypes, an improved understanding of tumor heterogeneity will help guide clinical decision making.

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