



Critical Pathways Forward in the Treatment of Renal Cell Carcinoma

Based on an Expert Summit convened
in Washington, DC, July 30-31, 2012

Key Points

1. The approval of seven agents, all targeting angiogenesis, has produced a true paradigm shift over the past seven years in the treatment of advanced clear cell renal cell carcinoma (RCC), the predominant form of kidney cancer. To fully benefit from this flood of new drugs, the oncology field now needs corresponding data comparing the effectiveness of these agents and their use, whether as single agents, used sequentially or in combination with one another.
 - Oncologists, particularly those in the community setting, are struggling to determine which agent will be most efficacious while producing the fewest adverse side effects.
 - Patients are struggling to deal with the uncertainty about the most appropriate treatment options and the ultimate course of their disease.
2. More independent leadership that critically advocates for better data and better drugs would move the field beyond the status quo and yield optimal results for patients.
 - Support is insufficient for research on renal cell carcinoma that would lead to a cure and move beyond the status quo.
 - The concerns of patients, regulators and payers are not adequately reflected in most clinical trials.
3. There is a critical need for both basic and translational research to address unanswered questions that act as barriers to the optimal diagnosis and treatment of RCC with the advent of today's therapies.
 - The pathobiology of RCC is still inadequately understood, particularly the roles that the tumor microenvironment and the immune system play in the development and control of this disease.
 - There are no biomarkers for the early detection of RCC that would enable more patients to be cured via surgical removal of non-metastatic disease.
 - There are no biomarkers for therapeutic efficacy or for disease progression, making it difficult for oncologists to prescribe the optimal course of therapy for individual patients.
 - The scarcity of clinical data enabling head-to-head comparisons of efficacy and toxicity leave oncologists guessing or relying on clinical experience to guide their choice of therapy for individual patients.
4. Most participants agreed that the RCC field needs a clinical trials consortium, which would complement existing cooperative groups and be funded independently of the pharmaceutical industry, to establish a program of clinical trials that would enable the development of truly objective treatment guidelines.
 - The consortium would develop standardized clinical trial designs using consistent measures of efficacy and adverse events. These studies would generate the data needed for comparative effectiveness analyses.
 - The consortium would involve community oncologists and patient advocacy groups to ensure that trials generate data that are meaningful for different treatment settings and reflect the needs of patients.
 - The consortium should help promote the creation of regional patient registries linked to cancer biorepositories.
5. There is a significant gap between existing knowledge and clinical practice that is leading to poorer outcomes in patients treated in the community care setting compared to those treated at academic medical centers.
 - Centers of excellence at academic medical centers need to form regional networks that provide information and support for oncologists in the community care setting.
 - These networks would not only improve outcomes for patients, but could also increase the number of patients available for enrollment in clinical trials that would then reflect a broader range of treatment settings.

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Background

What is Renal Cell Carcinoma?

An estimated 65,150 new cases of kidney cancer will be diagnosed in the United States in 2013, and an estimated 13,680 deaths will result from this cancer.¹ The incidence of RCC has been growing steadily for the past 65 years, in part because an increasing number of kidney cancers are diagnosed inadvertently during abdominal imaging ordered for other reasons.² Clear cell renal cell carcinoma (RCC) is the most common form of kidney cancer in adults, accounting for approximately 75 percent of kidney cancers and three percent of all cancers.³ It is estimated that the United States spends approximately \$3.8 billion each year on kidney cancer treatment.⁴

The von Hippel-Lindau (VHL) tumor suppressor gene on chromosome 3 is silenced in the large majority of clear cell RCC cases.⁵ Silencing of the VHL gene, either through sporadic somatic cell mutations or hypermethylation, causes hypoxia-inducible factor- α (HIF- α) levels to rise. The increase in HIF- α level triggers an overproduction of a variety of signaling molecules, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF- β), epidermal growth factor receptor (EGFR), and erythropoietin.⁶

Clear cell RCC starts in the lining of the very small tubes, known as the proximal convoluted tubules, which filter the blood and remove waste products in the kidney.⁸ RCC is largely asymptomatic until it has reached an advanced stage, accompanied by invasion of the tumor into the fatty tissue and fascia surrounding the kidney, and metastasis to lymph nodes near the kidney as well as to the lungs, bone, or brain. Although early stage (localized) RCC can be cured with surgery, metastatic RCC is generally incurable with rare exception.⁹ However, the advent of therapies targeting the HIF axis, and particularly VEGF-associated angiogenesis, has more than doubled the median overall survival in patients with metastatic RCC.

Paradigm Change

The field of research focused on targeting angiogenesis (new blood vessel growth) in disease, which began in the 1960s, made dramatic advances in the late 1990s, culminating in the identification of specific treatment approaches to control undesirable blood vessel growth in a range of diseases, including blinding disorders, skin diseases, and cancers such as RCC, that involve abnormally growing blood vessels. More than \$4

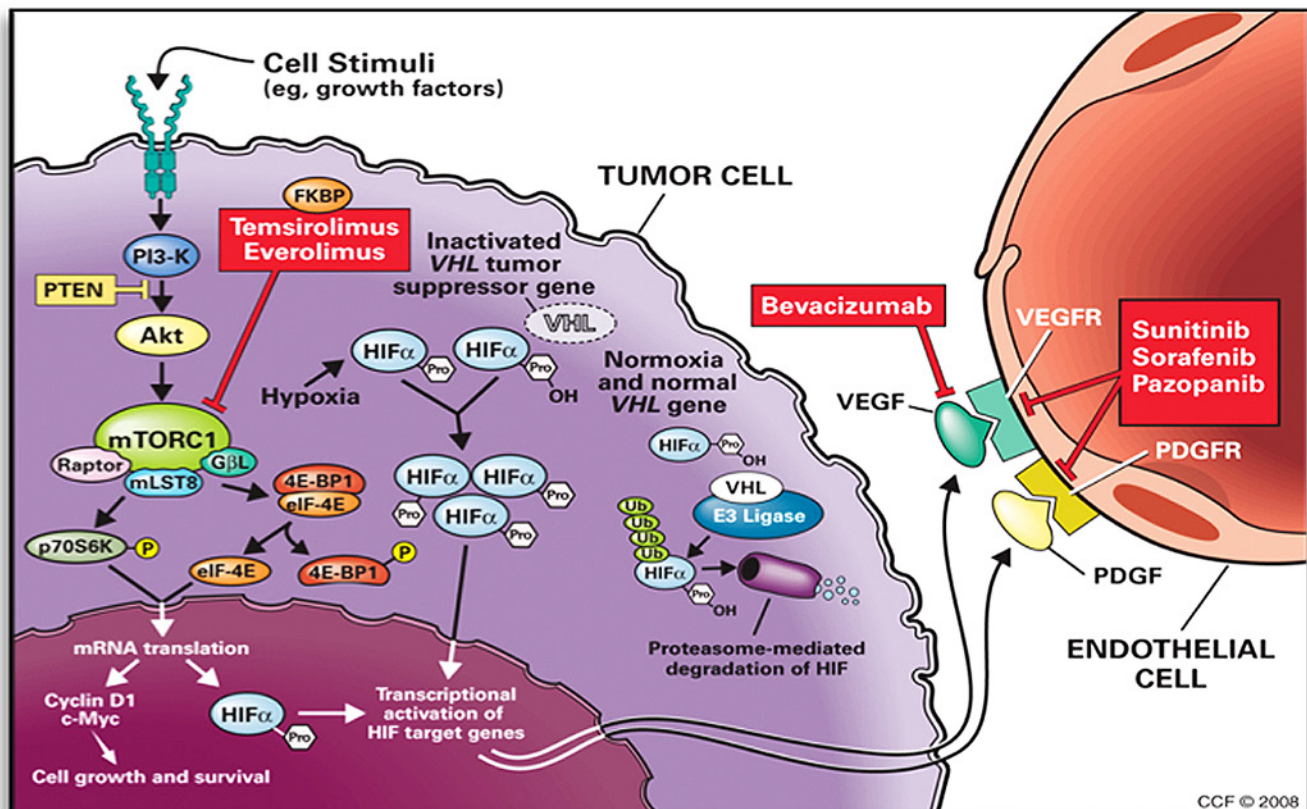


Figure 1. The molecular pathways and targeting therapies in renal cell carcinoma.

billion has been invested globally in treatment-oriented research and development around angiogenesis. Like all other cancers, the growth and metastatic spread of RCC is critically dependent upon the development of angiogenesis, where new blood vessels deliver oxygen and micronutrients to cancer cells.

In the 1990s, the mainstays of treatment for advanced RCC were high-dose interleukin-2 (IL-2) or interferon-alpha (IFN- α), a form of immunotherapy that produced durable, complete responses—albeit with significant toxicities—in fewer than 10 percent of eligible patients with advanced RCC.¹⁰ Indeed, the vast majority of patients with metastatic RCC do not benefit from immunotherapy and their disease progresses quickly.

On December 20, 2005, the world changed for patients with RCC and the oncologists who treat them when the U.S. Food and Drug Administration (FDA) approved sorafenib, a kinase inhibitor that blocks the activities of many angiogenesis signaling pathways, including those involving the molecules VEGF and PDGF, as a therapy for advanced RCC. A month later, the FDA approved sunitinib for the treatment of advanced RCC. Sunitinib is also a kinase inhibitor that targets multiple receptor tyrosine kinases, particularly those involved in angiogenesis. Then, in May 2007, the FDA approved temsirolimus, an inhibitor of an enzyme known as mTOR, which is activated as part of the HIF response and also promotes angiogenesis, as well as cell growth, metabolism and proliferation.

By 2007, anti-angiogenic therapy had supplanted immunotherapy as the standard of care for advanced RCC. Currently, there are four tyrosine kinase inhibitors (TKIs), two mTOR inhibitors, and one monoclonal antibody inhibitor of VEGF approved for the treatment of advanced RCC.

Each of these agents produces significant gains in progression free survival (PFS), though the data are less clear on improvements in overall survival; for the most part, expert opinion holds that the lack of increase in overall survival is the result of the inclusion of crossover treatment options in a majority of the studies published. However, regardless of which agent or agents a patient first receives, the disease ultimately recurs. Fortunately, if a patient fails to respond or no longer responds to one therapy, other agents are often efficacious in delaying disease progression, so the use of second- and third-line therapies is common.

Today, oncologists and their patients are faced with multiple treatment choices for advanced RCC. Though sunitinib is currently the most commonly used first-line therapy, there are as yet no clear evidence-based guidelines to help oncologists choose which drug is best

for which patients. It is not yet clear which agent is best to give first or second, or for which patients. Importantly, the data are very limited on how to administer these drugs for RCC according to a dosing schedule that maximizes effectiveness and minimizes toxicity, which can be severe and lead to discontinuation of therapy or non-compliance by the patient.

Despite the new paradigm for treating advanced RCC, this field has reached a point where the growing number of agents, both FDA-approved and in the pipeline, and the lack of comparative data are overwhelming oncologists' confidence in their ability to choose the right drug and the right regimen for a given patient. Each new drug approval makes therapeutic decisions more difficult because of a lack of standardization across clinical trials. There is little incentive for drug developers to conduct comparative trials to help clarify decision-making since the developers would risk their drug being shown as inferior. Indeed, some in the oncology community have begun to question whether there is a need for additional new angiogenesis inhibitors for treating advanced RCC because, without comparative data, the approval of additional agents would further muddy the waters of clinical decision-making. As two leaders of the field put it in a journal commentary, "Drug development in metastatic renal cell carcinoma has outpaced our knowledge of how and in whom the drugs work. This knowledge gap would not be a problem if the drugs were equally effective in all patients, but a huge spectrum of clinical activity exists."¹¹

The Expert Summit

Given the opportunities and challenges that have come with the advent of multiple effective therapies, and the fact that these therapies have revolutionized a field in such a short period of time, it is an opportune time for the RCC stakeholder community to take a step back and review the progress it has made, the challenges it faces, and the questions that need answers in order to meet the needs of those with advanced RCC. The Angiogenesis Foundation, a scientific nonprofit organization whose mission is to conquer disease through the control of neovascularization, is well positioned to play the role of a neutral facilitator of such a review.

As the first major step toward helping physicians and their patients choose a particular therapeutic course that will optimally benefit each individual patient, the Angiogenesis Foundation convened the Expert Summit on Renal Cell Carcinoma on July 30, 2012, to develop pathways forward in the treatment of renal cell carcinoma that would reflect patient-centered values.

At this meeting, held in Washington, D.C., the chosen experts identified, discussed and agreed on a research agenda designed to move the field from its current state to one in which patients will have far greater certainty that they are receiving optimized, individualized therapy. The goals of the summit were to:

- Review the current management of emerging treatments for RCC.
- Identify opportunities, in the context of multiple targeted therapies, for improving clinical strategies and outcomes by identifying the kind of data needed and the best approach to obtaining such data.
- Assess opportunities for analyzing the comparative effectiveness of multiple therapies in the context of patient-centered values.
- Provide input for setting clinical and health services research agenda for RCC that includes not only efficacy but also side effects and other patient-centered issues that affect quality of life.
- Identify collective actions that will improve outcomes for patients with RCC.

This white paper provides an overview of the discussion and recommendation for concrete steps to advance the treatment of RCC using anti-angiogenesis therapies. After a thorough review and vetting process, the Angiogenesis Foundation will deliver the white paper to the National Institutes of Health, the Centers for Medicare and Medicaid Services (CMS), Food and Drug

Administration, and other organizations with a stake in improving the treatment of advanced RCC in ways that best benefit patients while reflecting the needs of oncologists, industry, regulators and payers.

The Expert Summit was not a traditional scientific meeting, but rather an interactive, professionally moderated set of short presentations and roundtable discussions aimed at establishing a dialogue and agreement among the participants. The summit began with two short presentations reviewing the current therapies approved for treating advanced RCC and those that are in the pipeline. Under the direction of the professional moderator, the assembled experts engaged in a series of discussions that defined the desired future state for developing patient-centered, personalized therapeutic regimens for advanced RCC, and then identified the barriers that lie in the path of achieving such a state. A graphical facilitator captured key points of the discussion, enabling the participants to visually review the content of their conversations as they worked through the tasks at hand. The group prioritized those barriers according to two criteria. Which barriers, if eliminated or reduced, would:

- Have the biggest impact on the desired future state of the field.
- Result in joint action by the RCC community.



Figure 2. A diverse group of experts was convened in Washington, D.C. by the Angiogenesis Foundation to discuss critical pathways forward for RCC. Experts included physicians, academics and patient advocates.

Over the course of the summit's second day, the experts focused on issues specific to developing new clinical strategies and identifying leadership to move the field to take action. They also discussed how to define and incorporate patient-centered values in future research and clinical decision-making. Working off of the

foundation that has been built by these discussions, the experts then developed a research agenda and a set of action items that could move the field toward the desired future state in which patients with advanced RCC would be treated in the most effective manner possible, with the smallest negative impact on quality of life.

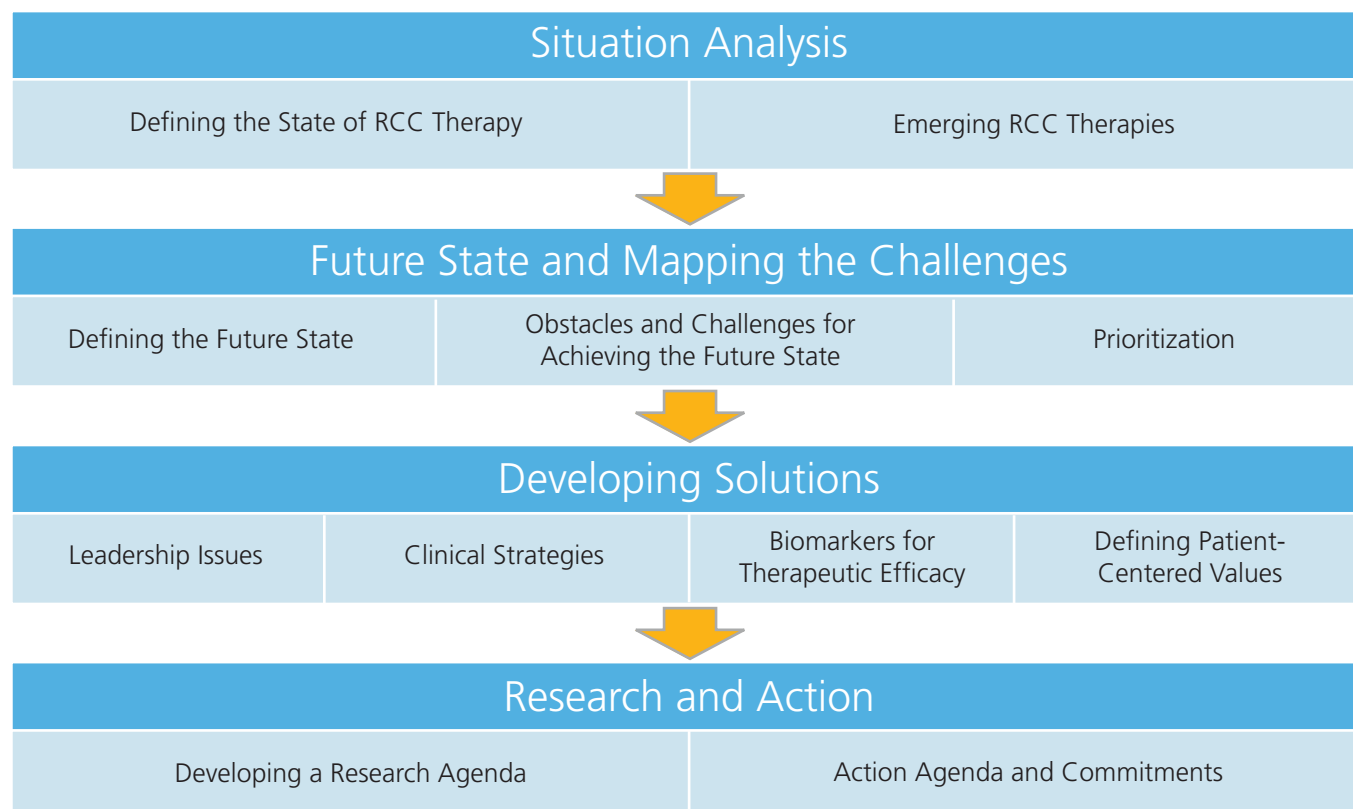


Figure 3. Schematic Flow of the Expert Summit

The Role of The Angiogenesis Foundation

Founded in 1994, the Angiogenesis Foundation is the world's first 501(c)(3) nonprofit organization dedicated to conquering disease using a new approach based on angiogenesis, the growth of new blood vessels in the body. Based in Cambridge, MA, USA, the Angiogenesis Foundation is committed to helping people around the world benefit from the full promise of angiogenesis-based medicine, and to make life-, limb-, and vision-saving treatments available to everyone in need.

As a scientific organization, the Angiogenesis Foundation is independent of any individual, institution, or commercial entity and, as such, it takes a unique, objective and expert approach to achieving its mission to help people lead longer, better and healthier lives. The

Foundation has extensive experience with, and insights into, key success factors with angiogenesis stimulating and inhibiting therapies across multiple disease states, and the challenges of optimizing care and outcomes with paradigm-shifting technologies. With the expertise, time and resources needed to deeply understand the complex needs of multiple stakeholders, including patients, caregivers, physicians, researchers, scientists, industry leaders, regulators, policymakers, payers and financiers, the Angiogenesis Foundation facilitates processes that achieve increasingly better outcomes for patients. Its guiding philosophy is that patients collectively benefit when the needs of the different stakeholder groups involved, in both developing and delivering treatment, are well aligned and met. It is in this spirit that the Foundation executes programs such as the Expert Summit to make a positive impact in improving outcomes for patients with renal cell carcinoma.

Current Status

To open the summit, two experts gave 15-minute presentations as background for the subsequent roundtable discussions. **Dr. Sandy Srinivas**, of Stanford University, summarized the current status of RCC therapy and the shortcomings of current therapies. **Dr. Michael Atkins**, of the Georgetown-Lombardi Comprehensive Cancer Center and the Georgetown University Medical Center, described some of the emerging treatment strategies for metastatic RCC.

Defining the Present State of RCC Therapy

As has been noted, there has been an explosion in the number of approved therapeutic agents for treating advanced RCC. The approved agents belong to three different classes: immunotherapies, VEGF inhibitors, and mTOR inhibitors. These drugs were developed based on a new understanding of the molecular pathways involved in RCC and the subsequent identification of targets for therapy. Despite the advent of these new agents and the resulting progress made in treating patients with advanced RCC, the field has reached a plateau in terms of the benefits for patients.

One of the issues facing the field is lack of a means of stratifying patients for therapy. For example, immunotherapy using high dose IL-2 is the only regimen shown to produce durable and complete responses, albeit in only five to seven percent of patients so treated and with considerable toxicity. Unfortunately, it is not currently possible to preselect the patients who would unquestionably benefit from high-dose IL-2 therapy. While research has identified a panel of prognostic risk factors that are used to classify patients according to the risk for disease progression, clearly predictive molecular markers for RCC have yet to be discovered. Patients who are good candidates for anti-VEGF therapy include those with good performance status, those who need rapid response, and those who have refractory diabetes and elevated, poorly controlled levels of cholesterol and other lipids. Candidates for mTOR inhibitor therapy include patients at poorer risk of progressive disease, those who have failed prior anti-VEGF therapy, those with poorly controlled hypertension or congestive heart failure, and those with no need for reducing tumor burden to alleviate disease-associated symptoms.

Published clinical data show that targeted drugs, when used as first-line agents, more than double the time to progression-free survival, as compared to immunotherapy or best standard of care.^{12,13,14,15} These studies also show that there is an average 10-12 month

survival benefit for any of the anti-VEGF therapies, but that almost all patients eventually develop progressive disease. Second-line therapy, using a different agent from the approved list, adds another five to seven months before progression occurs again.^{16,17,18}

Approved RCC Therapies in 2012
Immunotherapy IL-2 INF- α
VEGF Inhibitors Sorafenib Sunitinib Pazopanib Axitinib Bevacizumab + INF- α
mTOR Inhibitors Temsirolimus Everolimus

Figure 4. FDA approved drugs for the treatment of advanced renal cell carcinoma.

Currently, several groups are running randomized trials to investigate various sequencing schema of agents. These trials are testing two different approaches known as horizontal and vertical blockade. Horizontal blockade, using agents such as sorafenib or sunitinib plus bevacizumab, inhibits multiple downstream pathways in RCC. Vertical blockade, using combinations such as everolimus plus bevacizumab, inhibits multiple sequential targets along a single pathway. Neither approach has so far proven to be particularly successful, and vertical blockade has been shown to result in more severe toxicities. One limitation that these trials have from the start is their design: they use progression-free survival as their primary endpoint. An increasing body of evidence suggests that in renal cell carcinoma there may be an uncoupling of the traditional relationship between progression-free survival and overall survival.¹⁹

One of the hopes among researchers in the field is that genomic profiling will identify biomarkers that correlate with treatment success and that such biomarkers will be validated in clinical trials. So far, biomarker discovery and validation efforts have not been successful. The one biomarker that has shown promise as a prognostic indicator of efficacy for anti-VEGF therapy is the occurrence of hypertension during treatment.²⁰ VEGF is involved with the body's normal control of blood pressure, so blocking this pathway leads to increased blood pressure. In RCC, hypertension seen

with anti-VEGF therapy is associated with increased response, prolonged progression-free survival and, most importantly, increased overall survival.²¹ Controlling blood pressure with medication does not diminish the efficacy effect and can be achieved easily with common blood pressure treatments used in general medical practice.²² This correlation has been observed in trials with sunitinib, bevacizumab, and axitinib.

Targeted therapy is associated with a number of adverse events that are often distinct from those seen with traditional chemotherapy and immunotherapy. These include fatigue, rash, hand-foot skin reaction, hypertension, diarrhea, stomatitis (inflammation of the mucous tissue lining the mouth), cytopenia (reduced cell counts in the blood), metabolic syndrome, bleeding, proteinuria (an increased level of protein in the urine) and hyperlipidemia (an increase in cholesterol and other blood lipids).²³

Surgical removal of the affected kidney containing localized RCC tumors is curative for early stage disease. There have been few studies, though, of whether surgically removing the affected kidney is appropriate in later stage, metastatic RCC, and if so, which patients

would benefit and whether surgery should be done before or after administering first-line drug therapy. Two Phase 3 trials examining these issues are planned, but have not yet been initiated.

Another major problem in the current state of RCC therapy is that the therapeutic landscape is changing rapidly due to new agents being approved almost annually. As a result, designing meaningful clinical trials is difficult—the trial results become an answer to yesterday’s approach, but may not be relevant to today’s challenges.

In summary, although an abundance of agents are now approved to treat RCC, how best to use these agents in the clinic still needs to be clarified. Few patients with advanced disease are cured because, even with currently available treatments, the disease will ultimately progress. The management of toxicities is challenging, and the development of successful combination therapies has proven to be elusive as well. The lack of biomarkers for either therapeutic response or disease progression is a major obstacle to improving patient care despite the wealth of new drugs available to treat this disease.

	HFSR	HTN	Cytopenia	Proteinuria	GI Mucosal	Hyper-lipidemia
Sunitinib	Yes	Yes	Yes	Yes	Yes	No
Sorafenib	Yes	Yes	Yes	Yes	Yes	No
Pazopanib	No	Yes	No	Yes	Yes	No
Bevacizumab	No	Yes	No	Yes	Yes	No
Temsirolimus	No	No	Yes	No	Yes	Yes
Everolimus	No	No	Yes	No	Yes	Yes

Figure 5. Adverse events associated with specific drugs approved to treat renal cell carcinoma. HFSR = hand-foot skin reaction; HTN = hypertension; GI = gastrointestinal.

Emerging RCC Therapies

While major limitations exist to all current therapies for RCC, there are many unexplored avenues for improving therapy. The development of the so-called third generation TKIs, such as axitinib and tivozanib suggest that it is possible to boost efficacy while simultaneously reducing adverse side effects. Data from a clinical trial comparing tivozanib and sorafenib, for example, have shown that the incidence of side effects was lower in patients treated with tivozanib compared to those treated with sorafenib.^{24,25}

One active area of clinical research with these newer drugs involves testing dose titration as a means of maintaining efficacy while reducing adverse events. Results from these studies have suggested that the efficacy of VEGF inhibitors may relate to the levels of drug measurable in the blood.²⁶ It may turn out that dosing patients to hit specific blood levels, as is now done with antibiotics and anticonvulsants, could

ultimately make more sense than the current “one size fits all” approach.

Other signaling molecules that drug developers are targeting include HIF-2 α , TORC2 and PI3 kinase, all of which are associated with the mTOR-signaling pathway. Investigators are also targeting the angiopoietins as another approach to suppressing angiogenesis. Angiopoietins are involved in stabilizing and destabilizing blood vessels as they are being created. Early stage clinical trials, however, have not yet demonstrated an enhanced therapeutic effect when an anti-angiopoietin agent is used in combination with an anti-VEGF TKI. One investigational drug, known as cabozantinib, targets both VEGF and another pathway called MET, which is involved with angiogenesis and cell growth regulation. Early clinical trial data suggests that this dual-targeting approach (anti-VEGF/MET) has promise in reducing both primary and metastatic tumor burden in advanced RCC patients.



Figure 6. Moderated discussion at Expert Summit

Where Do We Want to Be?

As the first step toward developing an action plan for improving clinical strategies and patient-centered outcomes in the treatment of RCC, the moderator asked each summit participant to name the single intervention that would most improve outcomes for RCC patients. He then repeated this exercise later with a second solicitation of “where we want to be” that together created a picture of the desired future state of patient-centered RCC treatment.

Based on these two roundtable exercises, it was clear that the desired future state would be one in which clinical data from well-designed Phase 3 trials and Phase 4 studies would drive patient-centered clinical decision making for treating RCC in the community at large and not just at academic medical centers. These clinical trials would need to include head-to-head comparisons of the available drugs, as well as various sequences of drugs and combinations of drugs and surgery, with an emphasis on defining and comparing efficacy, toxicity and patient compliance across different therapies. Ideally, these clinical trials would also test biomarkers that have the potential to provide a more sophisticated method of selecting the right therapeutic approach for a given patient.

Clinical trial design in the desired future state would be driven by a consensus approach developed between manufacturers and researchers concerning consistent endpoint measures to enable better comparisons among trials. Clinical trials should be designed using

more uniformly defined criteria for disease progression and more objective measures of toxicity. In addition, prospective biomarker discovery would be an integral part of all trials.

A comprehensive clinical trials program, developed and managed by an RCC-focused clinical trials consortium, would need to be supported by a structured financial plan. Such a program would answer the type of patient-centered questions and payer concerns that are not always of paramount importance—and may even be disincentives—to drug developers, and that may fall outside of the scope of interest of the National Cancer Institute (NCI). Through such a program, it should be possible to develop treatment guidelines that would define best practices that could be followed by all oncologists regardless of treatment setting, i.e., community practice versus academic center. An RCC clinical trial consortium with a stable source of funding would also provide a platform for:

- comparative effectiveness research
- optimizing existing therapies
- developing biomarkers and companion diagnostics that stratify patients for treatment selection
- defining adjuvant and/or neoadjuvant treatments
- measuring the benefits of adjuvant and or neoadjuvant treatment in the context of surgery

The desired future state would include a host of validated predictive biomarkers that would guide therapy selection and function as early surrogate endpoints of

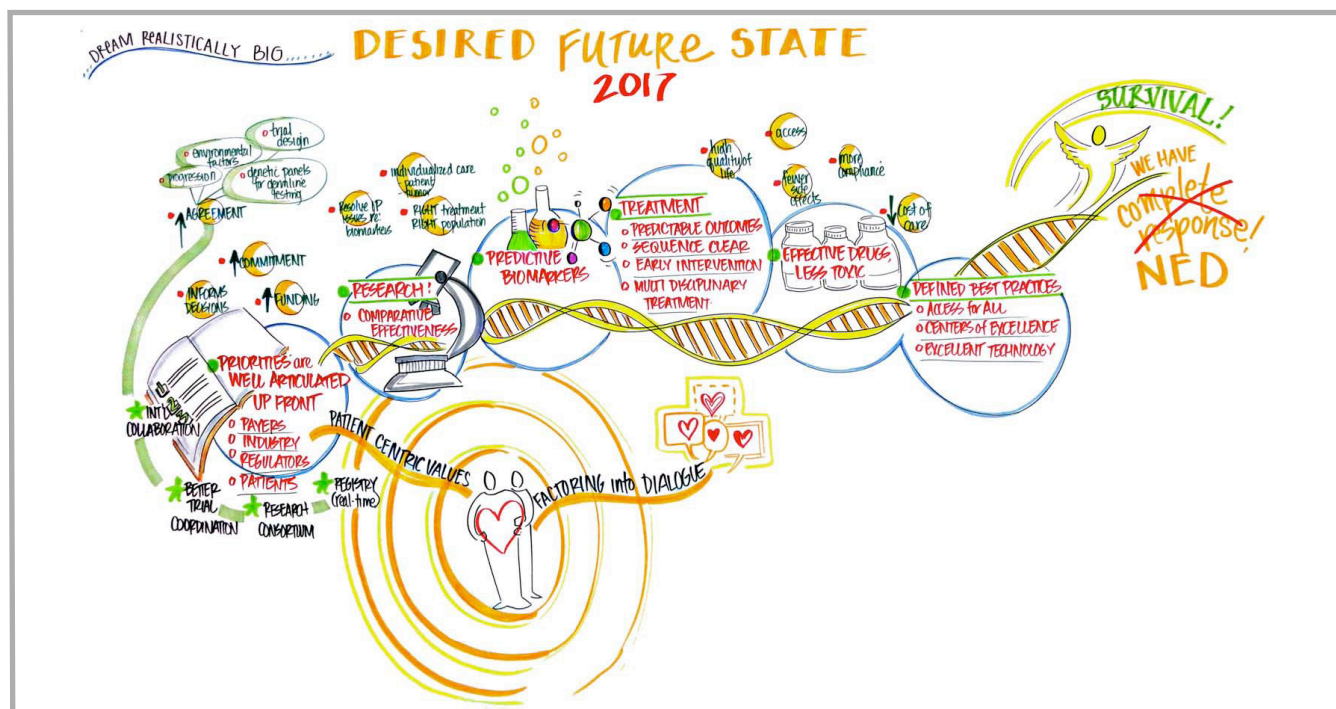


Figure 7. Graphical representation of the desired future state as identified by the discussion among the expert panelists.

therapeutic response. The experts noted that in addition to biomarkers that would guide therapy selection, the desired future state would include validated biomarkers or other measures of disease susceptibility that would enable early detection of RCC. Given that surgical removal of localized, early stage tumors is often curative, such biomarkers could have a tremendous impact both in terms of overall survival of patients and the need to subject patients to additional therapy with their attendant costs and toxicities.

To enable both biomarker discovery and the development of a database of outcomes from clinical trials, the desired future state would include extensive and thoroughly annotated patient registries. The participants also remarked that since it is likely that at least some of these biomarkers will be based on genetic screening, the desired future state would include inexpensive genetic testing of germ line and somatic cells. Inexpensive genetic testing methods would also enable population screening for RCC-associated mutations, though one panelist voiced the concern that screening the general population for somatic mutations would produce more false positives than true real positives and may not be cost effective. An idea was suggested for a feasible population-based screening initiative founded on a simple, relatively inexpensive urine test that, if positive, would be followed up by mutation analysis or imaging.

An important component of the desired future state would be a comprehensive educational program for all oncologists, regardless of whether they practice in a community setting or an academic medical center. Such a program would reflect best practices based on an extensive clinical database, provide universal access to state-of-the-art care, and stress a multi-disciplinary approach to patient care. An additional focus of this education activity would be to foster the development of relationships among physicians that would create a network of community-based oncologists supported by regional academic and non-academic centers of excellence. Educational efforts should also include patients and their families, both in terms of conveying patient concerns to oncologists and to better inform patients about the various therapy choices and potential adverse side effects, particularly in the face of terminal disease.

Aside from these clinical features, the desired future state would include a larger basic research effort. Basic research and development activities in the desired future state would focus on developing drugs for novel targets that would produce complete and durable responses – cures – after a finite course of therapy that would likely involve a paradigm shift away from current conventional monotherapy. These more effective drugs would also be less toxic and have a minimal impact on a patient's quality of life. Research would also aim to find therapies for other types of kidney cancer beyond clear cell RCC and to better understand the environmental factors involved in RCC.

In summary, the desired future state would feature more predictable outcomes, improved early detection methods and therapies that yield complete and durable responses. The desired future state would have new classes of drugs with lower toxicities that do not negatively impact quality of life, and it would involve multi-disciplinary therapeutic approaches that produce disease cures. Based on clear and substantial evidence, the field would have defined best practices and systems for educating patients and physicians. Connecting patients and doctors with centers of excellence would foster greater access to treatment. The total cost of care would be lower in the desired future state and compliance with therapy would be improved. Finally, there would be a clear definition of disease-specific, patient-centered values that would feed into treatment development strategies and aid in policymaking for reimbursement.

The expert panel voiced the opinion that this desired future state could be reached in five years with concerted action from the RCC community. Accomplishing that goal will require independent leadership comprising a critical mass of opinion leaders and patient advocates. This leadership would promote the type of research and development activities that could move the field away from the current status quo and its seeming contentedness with today's drugs, which offer only incremental improvements in efficacy while carrying substantial toxicities.

Barriers and Prioritization

With the desired future state defined, the moderator then asked each participant to list one barrier that is standing in the way of reaching this desired state. The identified barriers included:

- Nobody is leading the charge to change.
- Inadequate funding for basic research, clinical trials and advocacy.
- A limited number of researchers interested in kidney cancer and in answering all the questions that remain, compounded by a lack of funding to conduct such research.
- Dogma-driven research, a consequence of the small researcher base.
- Fragmentation among medical oncologists and urological surgeons.
- Undefined mechanisms in tumor biology.
- A disincentive to develop better agents because of market saturation – the market is small and there are already eight drugs approved.
- Access to patients for clinical trials, given the number of approved drugs.
- Mis-aligned incentives among multiple parties.
- Intellectual property issues blocks research on combination therapy.
- Difficulty engaging all the parties needed for biomarker validation studies.
- Ego, trust and competition getting in the way of focus on patient-centered issues.
- Mindset of incremental change versus further paradigm shift.
- Fragmentation of delivery of care and quality of care between community setting and academic medical centers.
- Low priority for clinical research in health care delivery.
- Lack of thoroughly annotated patient registries.
- Patient desire for certainty.
- Ignorance among community physicians about state-of-the-art therapy.
- Ignorance within the patient community about the value of participating in clinical trials.
- Academic researchers allowing industry to drive the clinical agenda.
- Lack of coordinated tissue acquisition for research.
- Inadequate guidelines for therapy, which are intentionally broad (accommodating many or all agents).
- Guidelines that do exist are not followed.



Figure 8. After articulating the desired future, the group brainstormed barriers and under-utilized resources that stand in the way of achieving the desired state.

The participants were asked to prioritize these barriers according to two different criteria: Which barriers, if surmounted, would produce the biggest impact on the field, and which barriers are most addressable through joint action by the assembled participants and their colleagues. Each participant was allowed to cast several votes according to each of the two criteria. The results are shown graphically in Figure 9.

In terms of impact, the most important barriers were ranked as follows:

1. No leadership to drive the field to the desired future state.
2. Treatment disparities due to practitioner ignorance of current state-of-the-art treatments and practices, and of patient concerns.
3. Poor understanding of tumor biology.
4. Inadequate funding for clinical trials and basic research, resulting in part from the missing voice of advocates.
5. Therapeutic guidelines are too broad to be useful for informing decisions about state-of-the-art care for specific patients.
6. Difficulty accessing patients for studies, in part because of the low number of patients with RCC and the low priority for clinical research in health care.
7. The interests of the various stakeholders, i.e., drug developers, oncologists, patients, regulators and payers, are not aligned.
8. Patient ignorance about the value of participating in clinical trials.
9. Fragmented delivery of care resulting from the fact that every community oncologist is running his or her own business.
10. No tissue bank for RCC samples.
11. A mindset of incremental change instead of further paradigm shift.

In terms of joint barriers addressable through joint action by the participants, the most important barriers were ranked as follows:

1. Treatment disparities due to practitioner ignorance of current state-of-the-art treatments and practices and of patient concerns.
2. Patient ignorance about the value of participating in clinical trials.
3. No leadership to drive the field to the desired future state.
4. Difficulty accessing patients for studies, in part because of the low number of patients with RCC and the low priority for clinical research in health care.
5. Inadequate funding for clinical trials and basic research, resulting in part from the missing voice of advocates.
6. Therapeutic guidelines are too broad to be useful for informing decisions about state-of-the-art care for specific patients.
7. No tissue bank for RCC samples.
8. Best drugs are not being developed because of market size and market saturation with the current generation of drugs.
9. A mindset of incremental change instead of further paradigm shift.
10. The patient voice is not being heard.
11. Unclear expectations on the part of industry and of patients.

While there was widespread agreement that incomplete understanding of tumor biology and misaligned incentives among the many stakeholders in the RCC field are major obstacles to moving the field forward, none of the participants believed there was much that this group could do to address those barriers in the short-term. However, five items did rank highest in terms of importance and the ability to take meaningful action:

- Practitioner ignorance about the therapeutic state-of-the-art treatments and practices.
- No leadership to move the field away from the status quo.
- Poor access to patients for clinical studies.
- Limited funding for independent clinical trials and basic research.
- Existing guidelines are not guiding.

In the ensuing discussion, panelists voiced the opinion that there are two themes underlying many of these barriers. The first theme was that the RCC market is small and saturated with the current crop of therapeutics. The second theme was that RCC has not reached the consciousness of the government and its leaders. This latter theme has created a void that industry has filled based on its own agenda because the community, at large, lacks the kind of leadership and advocacy that has driven significant gains for patients in other areas of cancer research, such as breast cancer.

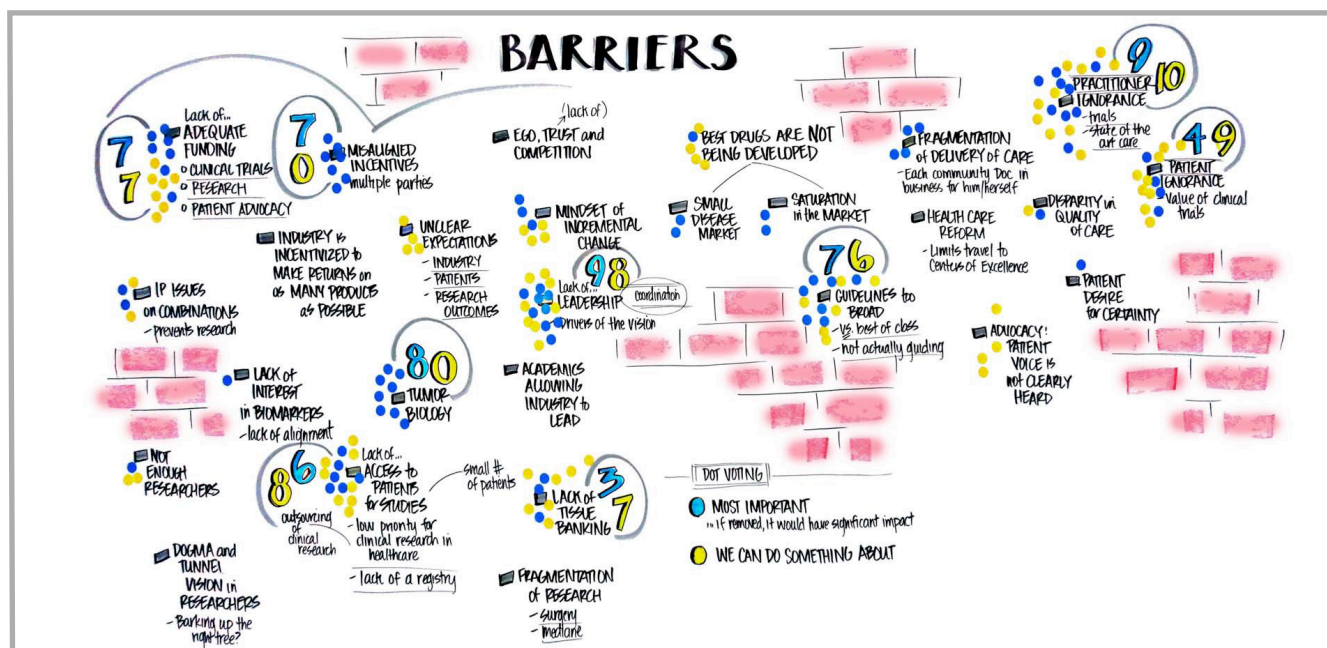


Figure 9. Graphical representation of the barriers identified by the Expert Summit and the results of the prioritization process

Developing Solutions

With the barriers defined and prioritized, the summit participants engaged in an intensive moderated discussion about their findings. These discussions were wide ranging, but most of the comments concerned the lack of leadership, the need to account for patient needs in planning an agenda for the future, and the gap between knowledge and clinical practice.

Leadership : Creating a Voice for Patient-Centered Treatment of RCC

The Expert Summit panelists first tackled the leadership barrier, with the initial phase of the discussion focusing on identifying the gaps in leadership and coordination. The panelists agreed that while the field does have opinion leaders, these respected experts are largely risk-averse academic researchers who are not challenging the current dogma and are following the lead of the pharmaceutical industry. What is missing, the panelists also agreed, is the type of strong advocacy voice that has driven progress – and increased funding – for breast cancer and prostate cancer, as well as for pancreatic cancer and multiple myeloma, the latter two of which are even less common than kidney cancer. The advocacy community has not only argued for increased funding for both basic and clinical research on these cancers, but also called upon the common good in a way that has led researchers to put aside parochial interests and instead

engage in the type of collaborations that would address many of the barriers raised by this Expert Summit.

Building an active advocacy community in kidney cancer is complicated by the fact that there are not many long-term survivors of this disease to act as advocates. Moreover, the major organizations focused on kidney cancer that do exist receive primary funding from the pharmaceutical industry and thus are reluctant to challenge the status quo and promote a larger vision for the field (though participants noted that existing organizations do a good job of getting information to patients). It was suggested that patient and family support groups, which already exist at most centers of excellence, could serve as the seeds from which larger advocacy activities could grow.

The participants added that a neutral third party, such as the Angiogenesis Foundation, could organize a gathering of the small, regional support groups and existing advocacy groups that do exist, such as the Genetic Alliance, the National Organization for Rare Disorders (NORD), Action for Cure, and Kure It, as a way of catalyzing the formation of a national organization that could take on a more ambitious, scientifically-based leadership role for RCC advocacy.

The participants agreed that the academic community should seize the opportunity to set a research agenda in order to support the mission and provide the type of scientific base that has served other leading disease

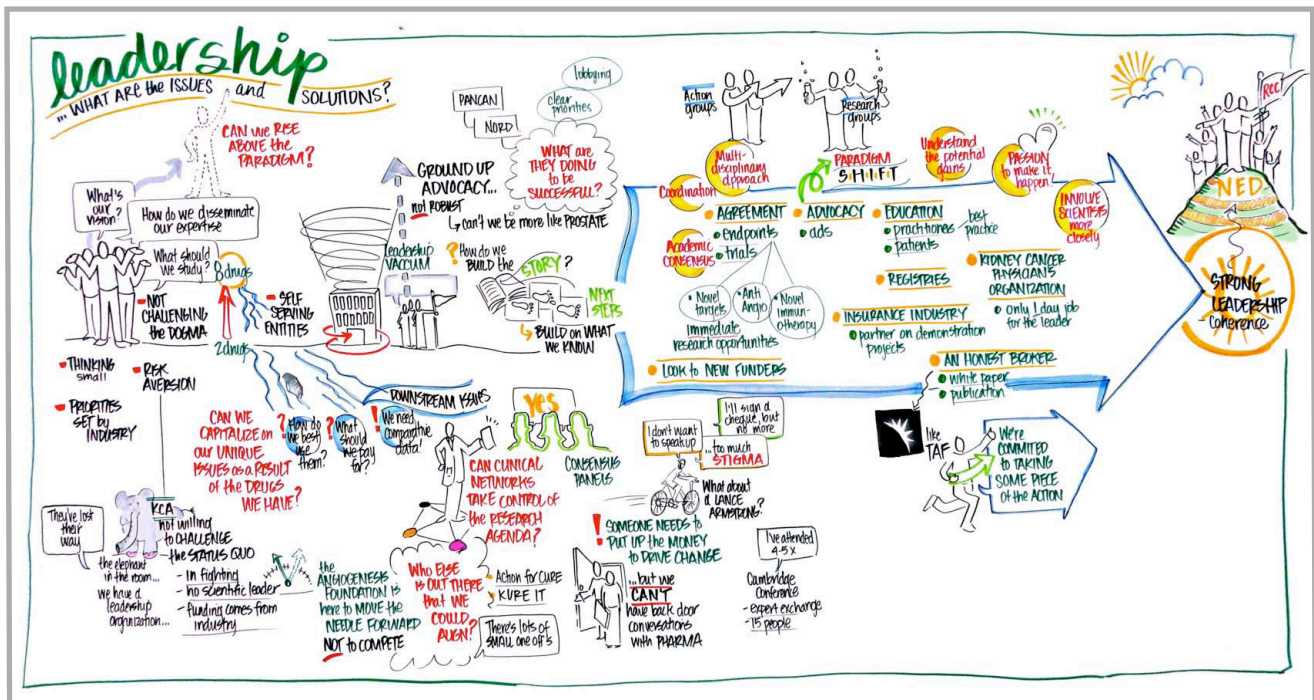


Figure 10. Graphical representation of the panelists' discussion on solutions to the leadership issue.

advocacy organizations. Such an agenda would both raise the profile of the field – and perhaps attract the kind of charismatic individuals that have become leaders in the breast and prostate cancer areas – and serve as a central theme for the new proposed national advocacy organization. In fact, with the growing balkanization of cancer research funding, the time is ripe for the research community to define some unique opportunities in the kidney cancer field that would have broad appeal beyond mere drug development. For example, one of the central messages of this Expert Summit is that while there are plenty of drugs approved to treat cancer, there is no clear idea of who should get which drug and which drugs should receive reimbursement in what specific settings. This situation is not unique to kidney cancer, so a reinvigorated RCC leadership could seize upon this situation, define the kinds of comparative studies or combination studies that would then impact what gets done with other cancers, and then serve as a test bed for the broader cancer community.

Possible mechanisms for creating a research agenda would be through a clinical trials consortium or consensus panels, both of which feature prominently in other areas of cancer. Another approach suggested was for the Angiogenesis Foundation to convene a meeting similar to the Cambridge Conference, though larger, that would bring together experts specifically to develop a detailed research agenda. The expert panelists agreed that it would be crucial to involve community-based oncologists as stakeholders in these activities.

Developing strong independent leadership reflecting the needs of the entire RCC community is critical because it will move the field to the paradigm that therapy should be curative. It will also help the field develop a consensus about clinical endpoints, appropriate trial design, measures of adverse events and clinical trial prioritization. Strong leadership would also help drive the development of patient registries linked to cancer biorepositories that would inform clinical trials and answer questions about cost effectiveness and patient stratification. Another benefit that will come from building leadership in this field will be improved education of both physicians and patients about the state-of-the-art, its limitations and its future potential.

Defining Patient-Centered Values Across Therapies

The expert panelists next focused their discussion on the issues that are most important to patients with RCC and the concern that disease-specific, patient-centered outcomes need to be better reflected in therapeutic decisions and the future design of clinical studies. The attendees agreed that maintaining a good quality of life was the most important concern for patients with RCC, particularly given that most will be on drug therapy for the rest of their lives. Patients, the participants noted, want to work, care for their families, minimize the burdens their disease places on their caregivers, be free of pain and have some certainty about their future. Cost of therapy is an important issue for many patients, particularly given that most drugs used to treat RCC are oral agents that come with substantial co-payments.

It was noted that patients with Stage 4 RCC in particular are hungry for accurate information about what the future holds for them. The participants observed, that there is a fine balance between true improved survival and the hope for better survival that depends on the perception each individual patient forms based on what their physician (medical oncologist or urological surgeon) tells them. However, given the state-of-the-art today, it is difficult for physicians to speak accurately to an individual in anything other than general terms.

The panelists noted that better-informed patients often want to know why surgery is not an option to accompany drug-based therapy. In other words, once a tumor becomes small enough, even in the metastatic setting, why isn't it removed? In large part, surgeons are rarely brought into these discussions, a situation that should change not just in the clinic but also in the design of clinical trials. While this approach may not produce a cure, it could lead to longer drug-free periods that would improve a patient's quality of life. For the appropriate patient – those with only a few metastatic lesions – this type of plan should be discussed at the beginning of therapy. Presently, such conversations occur only at centers of excellence where surgeons (not just urologists) and medical oncologists are integrated in disease management, and rarely in community practice settings. The expert panelists stated it should be possible to develop better care pathway models involving surgeons that would help patients and their physicians make these decisions.

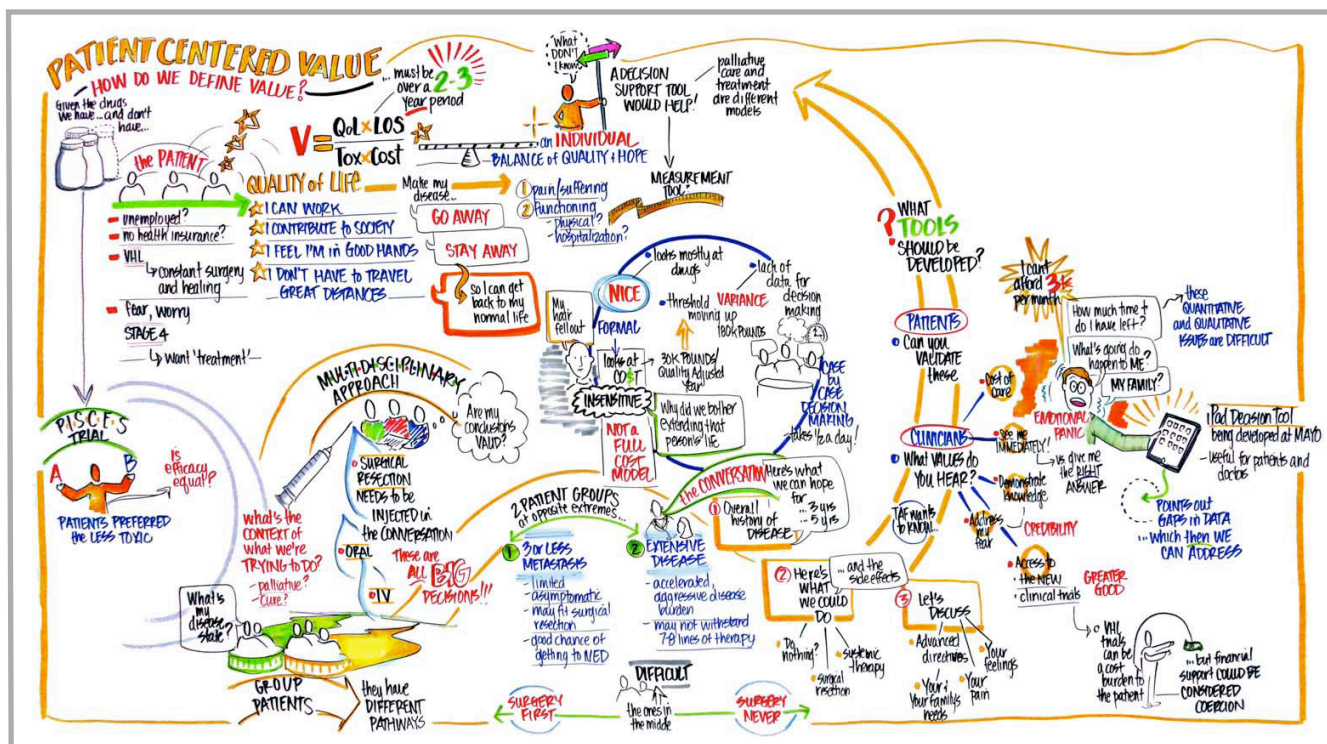


Figure 11. The Expert Summit discussed patient characteristics and values, emphasizing individual and categorical differences.

Characterizing the Gap Between Knowledge and Practice

The main thrust of this discussion was that there is too much information emerging on the concerning RCC management for the typical community oncologist to adequately assimilate, and that the clinical guidelines that are available are so general that they leave the physician believing they are justified in using whatever drug they want. In fact, the participants described the guidelines issued by the National Comprehensive Cancer Network (NCCN) and by the American Society of Clinical Oncologists (ASCO) as functioning more as compendia of treatment options that insurance companies use for reimbursement decisions. They noted that there are some specific recommendations in these guidelines but also stressed that choosing a drug is only the first step in creating a treatment strategy for a particular patient.

The nuances of using a particular drug depend on clinician expertise, something the community physician is not likely to have. Indeed, a study at Duke University has shown that RCC patients have better outcomes when treated at an academic medical center.²⁷ One option for addressing this gap between the knowledge embedded in academic medical centers and the decision making of community oncologists would be to develop expert systems or algorithms that suggest therapeutic options that are the state-of-the-art at academic medical centers. These could be delivered via a mobile app or

other technological solutions. Given that the knowledge gap is common across most areas in cancer, this type of activity could occur across multiple cancers while serving as a way of gaining more attention for the RCC field. The expert panelists noted that academic centers could not treat all of the patients now seen in the community, so it is important to develop mechanisms for improving communications with community oncologists about standards of practice and side effects management.

There was broad agreement with the notion that pharmaceutical companies are effective in educating and changing behavior among community oncologists, but that most companies are selective about the information they disseminate. It was also noted that new compliance restrictions placed on pharmaceutical companies concerning the type of information they can disseminate has created an even larger information gap. An important step toward filling this gap, the attendees agreed, would be to create registries for gathering detailed information on outcomes for patients in the community care setting. These registries could serve as an important link between oncologists working in the community care and academic medical center settings and provide an avenue for information exchange and discussion. They could also serve as a foundation for creating regional tumor boards that community care oncologists could call or log into to present data and receive advice.

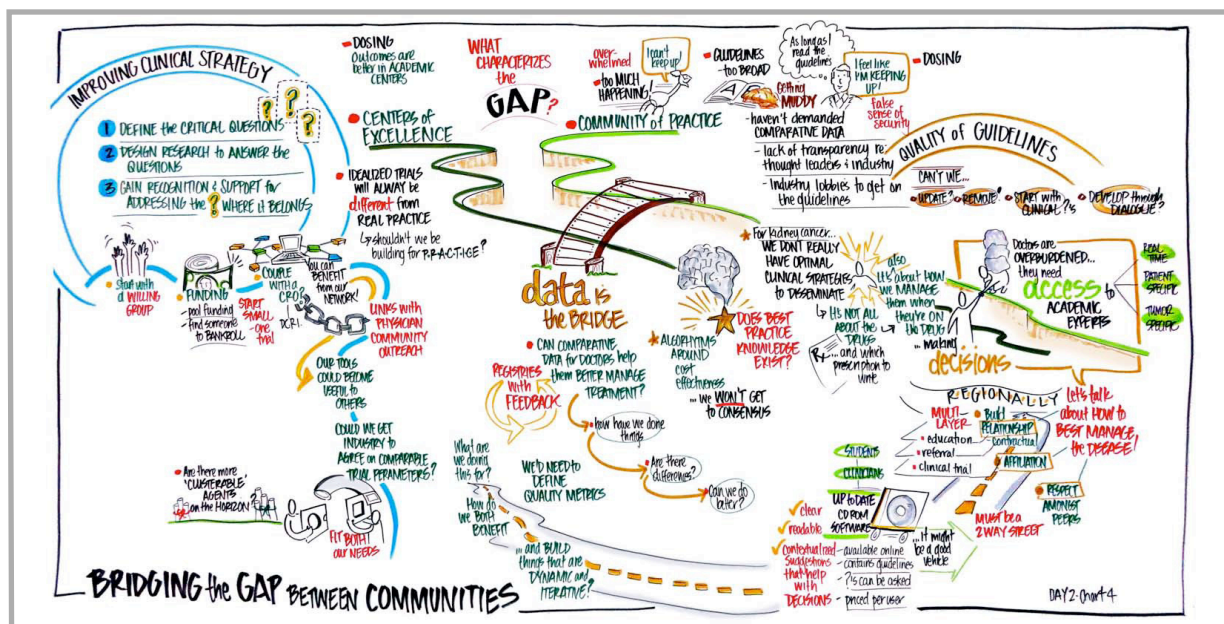


Figure 12. The Expert Summit revisited another priority barrier by characterizing the gap between centers of excellence and community oncology practice.

It is important to remember that oncologists working in the community care setting are no less interested in doing the best for their patient and no less curious about the state-of-the-art. They are, however, overwhelmed. A major activity for the RCC community going forward must be to form networks that provide community oncologists with access to their colleagues at academic medical centers whose primary interest is not in growing a practice by seeing as many patients as possible, but in teaching and giving advice.

One participant remarked that there is a model for addressing knowledge gaps of this type: the educational UpToDate CD-ROM text book, an evidence-based, physician-authored clinical knowledge system developed by the Society of General Internal Medicine. Numerous studies have shown that quality of care improves when institutions subscribe to UpToDate. The surgical community is now in the process of creating a similar system, and efforts are underway to include diagnostic information in the internal medicine CD-ROM.

The Expert Summit then turned to the subject of creating a clinical trials consortium to improve the knowledge base for the entire field, not just community care oncologists. An RCC clinical trials consortium would define the critical questions facing the field and then design clinical research to answer those questions. The key obstacle will be a stable source of funding for the consortium that is not completely dependent upon the pharmaceutical industry. It was noted that there was a previous attempt to work with the Kidney Cancer Association

(KCA) to create such a consortium, but the investigators involved did not have sufficient time to follow through, and KCA could not commit the financial resources required to fund the consortium.

There was broad consensus that the time is right to issue a proposal to establish an RCC clinical trials consortium. Turning this idea into reality will require commitment from a critical mass of investigators and starting with a bare bones organization that would not need a huge amount of financial support in the initial stages. In fact, the consortium could use a clinical research organization (CRO) to run the trial – consortium members would provide clinical sites, payers would provide reimbursement, and consortium members would have access to data. It was noted that Duke Medical Center has a CRO designed to work in just this kind of setting.

If properly created and executed, the consortium could become a resource that pharmaceutical companies would approach. While companies would be unlikely to participate directly in trials involving head-to-head comparisons among competing drugs, the consortium could structure its trials so that all trials for individual drugs, combinations of drugs, or drug and surgical protocols would use a common format and common endpoints. Sophisticated statistical techniques could then be used to conduct comparative effectiveness analyses, which would be of value to payers and for technology assessment. Such a consortium would become increasingly important as the need increases for developing clinical assays for stratifying patients into ever-smaller groups.

Setting a Research Agenda

A constant theme voiced throughout the summit was the need for more research, and as a final item of business the summit participants listed their top research priorities in the areas of basic understanding of disease and translational science.

On the basic research front, the development of an immune-competent, transgenic animal model for clear cell RCC would represent a tremendous advance for the field. With such a model, researchers could identify the main oncogenic switch that leads to the development of RCC, develop a better understanding of the interface between the tumor and its microenvironment, and define the role that the microenvironment plays in kidney cancer. Given the central role that angiogenesis plays in RCC, the field would also benefit significantly if basic research could identify endogenous angiogenesis inhibitors in the microenvironment that intrinsically work to rebuff the growth of RCC.²⁸ Mapping the molecular pathways that lead to resistance to anti-angiogenic agents was also identified as a critically important program to fund.

On the translational side of the equation, the participants agreed that research is needed to identify some measure of minimal disease that correlates with overall survival, and to determine the optimal practical radiographic modality for determining response to therapy. One participant suggested studies aimed at understanding how patients react to the diagnosis of RCC in different service settings, as well as studies defining patient goals and the factors that drive their choices in RCC management after diagnosis.

The attendees also came up with a “wish list” of specific clinical trials to be conducted in a non-

registrational setting, that is, in clinical trials whose primary purpose was to gain regulatory approval. Optimally, these trials would be run in conjunction with biomarker validation protocols. This list included:

- A trial that compares a PD-L1 inhibitor (a new type of immune therapy) with a VEGF inhibitor with crossover at the time of resistance and biopsy both pre-treatment and at the time of crossover. This trial would test whether immune therapy is better as a frontline or second-line therapy, and it could help identify mechanisms of resistance to therapy.
- A trial in an intermediate risk RCC patient population of systemic therapy versus systemic therapy, plus consolidative, localized therapy such as surgery, radiotherapy or cryotherapy.
- A trial of a MET inhibitor and a VEGF inhibitor in a treatment-naïve patient setting.
- A trial of IL2 and a PD-L1 blocker in combination
- Trials designed to answer the question of what to add to, or substitute, for primary therapy in primary progressive patients—that is, those who do not respond at all to anti-VEGF therapy.

Biomarker studies were identified as an important area of research, including family and population studies that would identify biomarkers for susceptibility. One participant suggested research exploring the use of “liquid biopsy” technology that captures and analyzes circulating tumor cells to look for markers of resistance and therapy response. Another noted that data from the Cancer Genome Atlas Project needs to be analyzed to identify differences among primary, early and late progressing patients, and to look for genetic biomarkers for drug resistance.

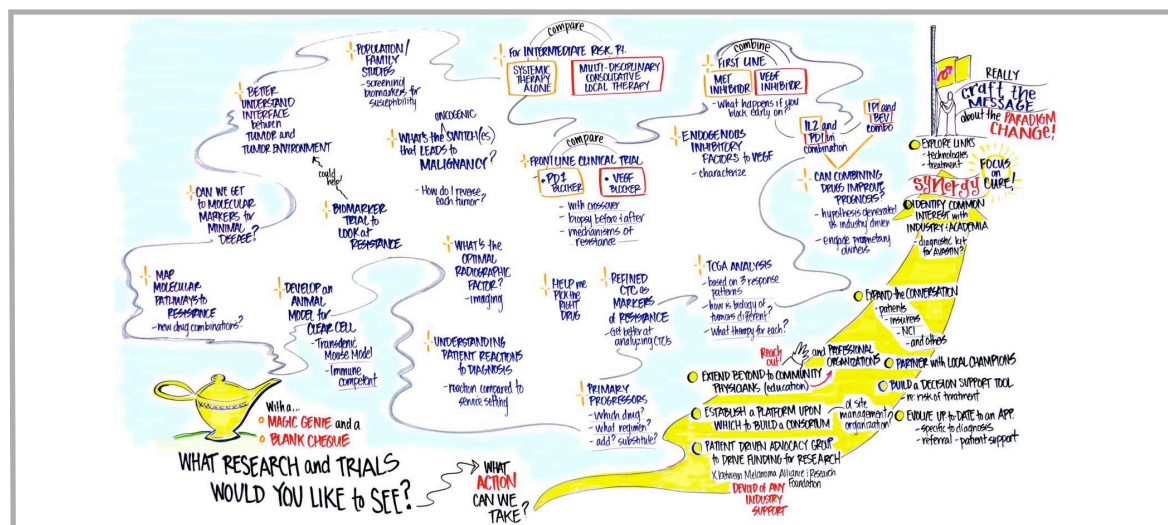


Figure 13. In the final discussion, the Expert Summit identified key components of a research and action agenda.

Recommended Actions

Based on the discussions by the assembled experts, the summit developed the following set of actions that the Angiogenesis Foundation could promote in collaboration with stakeholders in the field. It was noted that there were key stakeholders who were not present at this meeting, particularly representatives of NCI, CMS and other payer groups; non-physician leaders from existing advocacy and patient support groups; and community oncologists. Achieving success in the following endeavors requires buy-in from these groups. The recommendations are:

- ❖ Develop a platform for establishing a clinical trial consortium with a robust agenda beyond industry-sponsored, registration-type trials that complement the capabilities of existing cooperative groups.
- ❖ Establish a physician and patient-based advocacy organization that will amplify the voice for the RCC community and that would highlight the need for critical, novel research— both basic and translational.
 - Establish a funding mechanism that could resemble, as a benchmark, a cross between the Melanoma Research Foundation and Melanoma Research Alliance.
- ❖ Create mechanisms for establishing communication channels to promulgate information to the community practice setting, perhaps via existing professional research or advocacy organizations.
 - Partner with community champions to create a network of local physicians, both for educational efforts and for trial recruitment.
 - Lobby for the expansion of the amount of information on RCC in the UpToDate CD-ROM.
 - Leverage the UpToDate-style format to develop a digital media tool that practitioners or patients could use to obtain information and link to physician networks or patient advocacy groups.
- ❖ Establish regional patient registries associated with high-quality cancer biobanks.
- ❖ Build a decision support tool for physicians and patients that accounts for patient desires and willingness to take risk in therapy.
- ❖ Synergize the efforts of clinicians and pharmaceutical companies to develop biomarkers for patient stratification and therapeutic efficacy and/or toxicities.

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