Green Park Collaborative

*A partnership for innovation and effectiveness*

# Recommendations for Comparing Therapeutic Sequences for Patients with Breast, Kidney, and Other Advanced or Metastatic Cancers

## EFFECTIVENESS GUIDANCE DOCUMENT

The Green Park Collaborative is a major initiative of the Center for Medical Technology Policy

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**BETTER HEALTH.**

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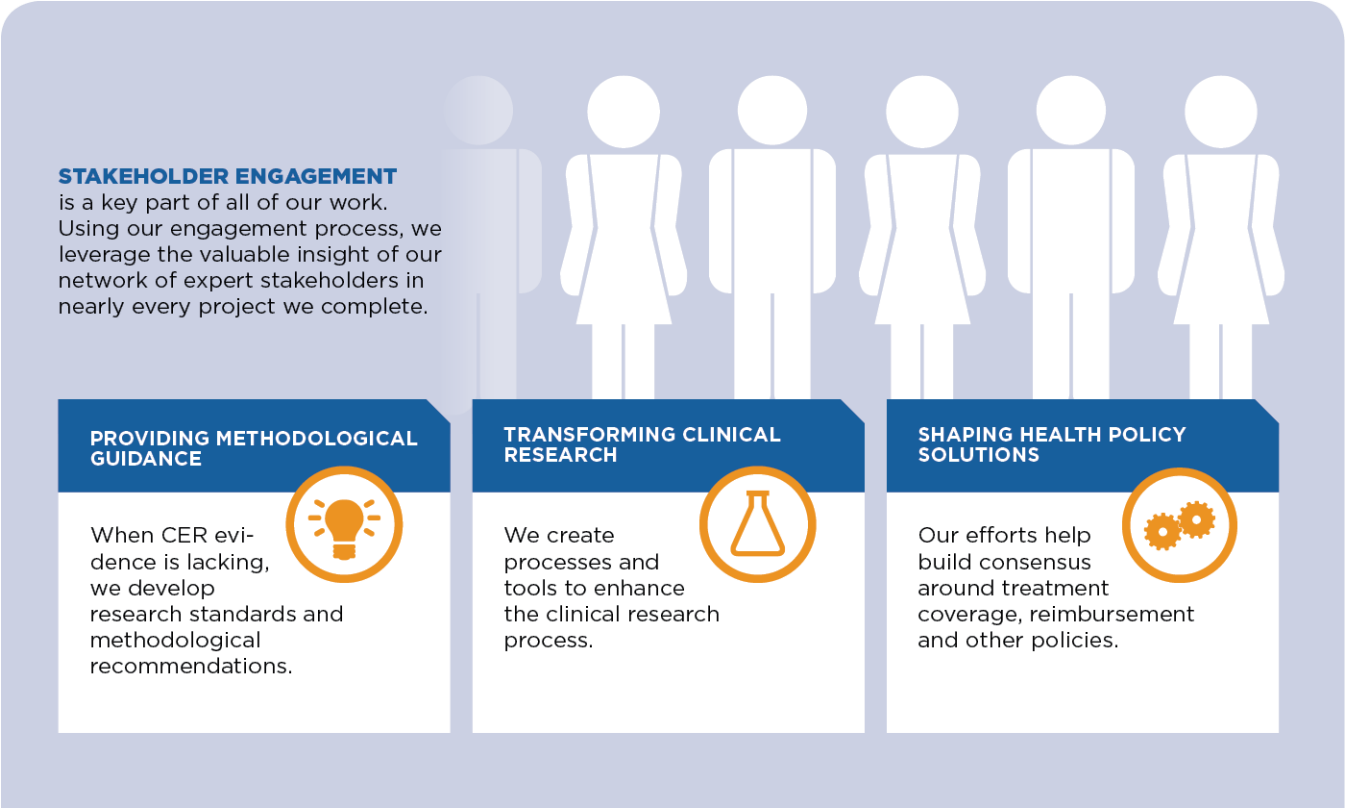
## ABOUT CMTP

The Center for Medical Technology Policy (CMTP) is an independent, non-profit dedicated to developing a health care system where patients, clinicians, health care policymakers, and payers have the evidence they need to make informed health decisions. We convene and collaborate with a national and international network of thought leaders, patients, patient advocates, clinicians, policymakers, and payers. Together, we support the next generation of clinical research. We do this by providing methodological guidance, shaping health policy solutions, and transforming clinical research.




## GREEN PARK COLLABORATIVE – USA

The Center for Medical Technology Policy hosts the Green Park Collaborative – USA (GPC-USA), a multi-stakeholder forum that develops condition and technology-specific study design recommendations to guide the generation of evidence needed to inform both clinical and payment decisions in the United States. GPC-USA includes a diverse mix of payers, life sciences companies, patients, clinicians, researchers, regulators, and other stakeholders.

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# PREFACE

The Green Park Collaborative (GPC) supports the development of effectiveness guidance documents (EGDs) to provide specific recommendations on the design of studies intended to inform decisions by patients, clinicians, and payers. EGDs do not provide general methodological advice, but rather offer specific study design recommendations that are relevant to a defined clinical condition or category of clinical interventions. The purpose of EGDs is to better align the design of clinical research with the information needs of patients, clinicians, and payers.

EGDs are developed through an extensive consultative process involving a broad range of experts and stakeholders, and with the support of a Technical Working Group (TWG) consisting of experts in clinical care and research methods specific to the clinical domain of interest. Recommendations are made available for public review and comment through targeted distribution to key stakeholders, posting on the CMTP website, and discussion in meetings to address the most complex or controversial issues. All feedback on the draft EGD is considered by CMTP staff in consultation with the TWG to develop a final version of the EGD.

The primary audience for EGDs is clinical researchers who are developing research protocols for studies that are intended to be helpful to patients, clinicians, and payers in making clinical or health policy decisions. EGDs are intended to be analogous to FDA guidance documents, which provide guidance on the design of clinical studies that are intended to support regulatory decision-making. While EGD recommendations do not establish standards for research to be considered adequate for coverage, payment or pricing decisions, they are developed with payer input and thus likely to be aligned with evidence preferences of public and private payers.

There are three primary features that distinguish EGDs from the majority of other methods guidance documents: 1) EGDs focus on a specific clinical area or category of interventions, while most other available methods guidance documents are more general; 2) many other documents provide guidance on reviewing the quality of existing studies, while EGDs provide recommendations for the design of future studies; and 3) we are not aware of any other documents that actively engage patients, clinicians, and payers in the process of developing recommendations.

The methods recommendations in EGDs aim to achieve an acceptable balance across sometimes competing priorities in research design (e.g., validity, relevance, feasibility, etc.). Overall, the objective of EGDs is to offer study design recommendations that, when followed, would give decision-makers a reasonable level of confidence that positive study results mean that the intervention would improve net health outcomes. EGDs may be updated as the state of knowledge underlying the recommendations changes.

There are a number of potential benefits of the creation and use of EGDs. First and foremost, they could help increase the consistency with which the body of clinical research reflects the information needs articulated by patients, clinicians, and payers. In addition, EGDs could contribute to greater consistency of trial design across studies of related treatments within specific clinical conditions, allowing for higher quality meta-analysis and systematic reviews due to reduced heterogeneity across multiple studies. By considering existing regulatory guidance in the EGD process, it is hoped that EGDs will help to achieve optimal alignment between study design elements intended for regulatory approval and study design elements targeted to clinical and health policy decision making.

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# TABLE OF CONTENTS

**CMTP EFFECTIVENESS GUIDANCE DOCUMENT WRITING AND EDITORIAL TEAM ..... I**

**FUNDING ..... I**

**ACKNOWLEDGEMENTS ..... I**

**EFFECTIVENESS GUIDANCE DOCUMENT TECHNICAL WORKING GROUP (TWG) ..... II**

**ABOUT CMTP ..... III**

**GREEN PARK COLLABORATIVE – USA ..... III**

**PREFACE ..... IV**

**EXECUTIVE SUMMARY ..... 1**

**EFFECTIVENESS GUIDANCE DOCUMENT RECOMMENDATIONS ..... 2**

**Population ..... 2**

**Outcomes ..... 2**

**Methods ..... 2**

**Reporting ..... 2**

**ACRONYM GUIDE ..... 3**

**METHODS ..... 5**

**RATIONALE AND SCOPE OF EGD ..... 5**

**STATE OF THE EVIDENCE ..... 7**

**Metastatic Breast Cancer ..... 7**

**Metastatic Renal Cell Carcinoma ..... 9**

**RECOMMENDATIONS ..... 11**

**Population ..... 11**

Recommendation 1: Populations potentially suited for the recommended studies ..... 11

**Outcomes ..... 12**

Recommendation 2: Overall survival ..... 12

Recommendation 3: Time to first treatment after metastatic diagnosis ..... 17

Recommendation 4: Time to change in therapy ..... 17

Recommendation 5: Serious health-related adverse events ..... 18

Recommendation 6: Patient-reported outcomes ..... 18

Recommendation 7: Health care resource use ..... 19

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Recommendation 8: Out-of-pocket cost to patient ..... 19
**Methods (Statistical methods and estimation) ..... 20**
Recommendation 9: Marginal structural modeling ..... 20
**Reporting ..... 22**
Recommendation 10: Plain language summaries of results ..... 22
**DISCUSSION ..... 22**
**Importance of patient-reported outcomes (PROs) to inform optimal sequence of therapy ..... 22**
**Importance of decision tools for patients in advanced cancer ..... 24**
**REFERENCES ..... 25**
**APPENDIX A ..... 1**
**GLOSSARY OF TERMS ..... 1**

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# EXECUTIVE SUMMARY

This effectiveness guidance document (EGD) provides recommendations to conduct studies comparing sequences of therapies in areas of advanced and metastatic cancer where a range of therapeutic options exist but evidence is lacking on the optimal choices for sequential or combination therapy. The focus is on settings where the expected outcome of therapy is not a cure since patient decisions in these settings often involve negotiation of more complex tradeoffs than in curative settings—tradeoffs in which factors other than overall survival may have heightened importance. Metastatic breast cancer and renal cell carcinoma served as example disease areas for developing this EGD, but this approach may be relevant for other incurable cancers as well.

EGDs typically focus on prospective methods; yet the large clinical trials needed to evaluate multiple drug comparisons are not only costly and often lengthy, but the results are often outdated by the time they become available. Hence, while not discounting the continuing value of randomized trials, the working group felt strongly that alternative methods using existing data sources could be of great value in adjudicating the optimal treatment sequences in these complex settings. This document therefore makes recommendations for advanced methods of extracting and analyzing data from large, existing repositories (retrospective studies), and targets researchers having a high level of expertise in analytic and modeling techniques.

While calling for advanced modeling techniques, a chief innovation of this EGD is not in the recommendations for analysis, but in calling for novel outcomes having the potential to be more meaningful for decision making to patients and their clinicians than traditional cancer clinical trial outcomes. These include: time to first treatment after first diagnosis of metastatic disease, time to next change in therapy, and novel elements of patient burden (which we define not merely in terms of toxicity-related adverse events and cumulative toxicities across sequences, but also in terms of numbers of visits to the clinic, doctor's office, emergency room, etc., and total out-of-pocket costs to patient). While novel, most of these outcomes can be measured using existing data sources, which was a criterion for the working group in developing these recommendations.

Nevertheless, some of the recommended outcomes entail data collection procedures that are aspirational. In particular, data on the indirect costs of health care resource use (e.g., travel time and distance, costs for patients and caregivers for office visits, missed work days) are sparsely available in existing sources, if at all. The goal of including these types of data elements in the recommendations is to suggest that they should be collected in the future, not only to compare treatment sequences as described here, but also to improve patient care by building an awareness of how treatment decisions may differentially impact patients depending on their transportation and caregiver status, or other "life situation" variables often not taken into consideration when making treatment decisions in the metastatic setting. Moreover, any of the outcomes recommended for retrospective study here could readily be targeted for measurement in a prospective clinical trial.

In addition to the ten recommendations that follow, the discussion section recommends other improvements to current data collection practices. Specifically, it is recommended that patient-reported outcomes (PROs) be routinely collected as part of the regulatory approval and post-approval process, and that PROs be collected as part of routine care of cancer patients and incorporated in the medical record in structured fields. Finally, the development of tools for use in advanced cancer settings to translate study outcomes into a form that can be readily communicated to patients is strongly encouraged.

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| EFFECTIVENESS GUIDANCE DOCUMENT RECOMMENDATIONS |
|---|
| **Population** |
| **1. Select patients diagnosed with a specific type of advanced cancer for whom many treatment options exist but the optimal treatment sequence is not known (e.g., metastatic breast cancer or renal cell carcinoma). Subgroups of patients can be studied according to selected characteristics such as patient race, body mass index, or biomarker status.** |
| **Outcomes** |
| **2. Whenever possible, use overall survival as an outcome of the study** |
| **3. Measure time to first treatment after diagnosis of advanced disease** |
| **4. Measure the time to change in therapy for each change of treatment regimen identifiable in the sequence** |
| **5. Measure serious adverse events** |
| **6. Whenever possible, collect a complete range of patient reported outcomes** |
| **7. Assess health care resource use for each treatment sequence** |
| **8. Assess total out-of-pocket cost to patient for each treatment sequence** |
| **Methods** |
| **9. For each outcome, use marginal structural modeling to adjust for the dynamic relationship between duration of time on drug(s), confounders, and outcomes.** |
| **Reporting** |
| **10. Study sponsors or authors should provide plain language summaries of all published comparative studies of cancer therapy sequences and make them publicly available.** |

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## ACRONYM GUIDE

| TERM | DEFINITION |
|---|---|
| ACA | Affordable Care Act |
| AHRQ | Agency for Healthcare Research and Quality |
| AIs | Aromatase Inhibitors |
| BC | Breast Cancer |
| CER | Comparative Effectiveness Research |
| CMMI | Center for Medicare and Medicaid Innovation |
| EGD | Effectiveness Guidance Document |
| EMR | Electronic Medical Records |
| ER+ | Estrogen Receptor |
| ER | Emergency Room |
| FDA | Food and Drug Administration |
| GPC-USA | Green Park Collaborative – USA |
| HCRU | Healthcare Resource Use |
| HER2 | Human Epidural Growth Factor 2 |
| IPTW | Inverse Probability of Treatment |
| MBC | Metastatic Breast Cancer |
| mRCC | Metastatic Renal Cell Carcinoma |
| MRCT | Harvard Multiregional Clinical Trials Center |
| MSM | Marginal Structural Modeling |
| mTOR | Mammalian Target of Rapamycin |
| NCI | National Cancer Institute |
| OS | Overall Survival |

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| | |
|---|---|
| PFS | Progression-Free Survival |
| PR+ | Progesterone Receptor |
| PROs | Patient Reported Outcomes |
| QOL | Quality of Life |
| RCC | Renal Cell Carcinoma |
| RCTs | Randomized Clinical Trials |
| RR | Response Rate |
| SAE | Serious Adverse Events |
| TCT | Time to Change in Therapy |
| TFT | Time to First Treatment |
| TKI | Tyrosine-kinase Inhibitor |
| TOOP | Total Out of Pocket costs |
| TWG | Technical Working Group |
| VEGF(R) | Vascular Epithelial Growth Factor (Receptors) |

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## METHODS

The principles and recommendations in this EGD were formulated through the following process. A series of potential topics in oncology were previously identified by CMTP staff through literature review. Potential topics were then further evaluated for their importance to stakeholders through semi-structured interviews with GPC members conducted by CMTP staff in August and September of 2013. These topics were further deliberated in the first meeting of the GPC-USA Oncology Consortium on September 19, 2013. After final topic selection, a technical working group (listed above) was identified and convened for a series of meetings between December 2013 and December 2014. This included an in-person meeting in Baltimore on March 26, 2014, where the recommendations were developed. Periodic updates were sent to the GPC Oncology Consortium by email, and a progress report was presented at an in-person meeting on April 19, 2014. An initial draft of the document (v. 1.0) was completed in December 2014. The current document (v. 1.1) has been refined and updated based on additional working group input.

## RATIONALE AND SCOPE OF EGD

The purpose of this EGD is to recommend methods for comparing sequences of therapies in areas of advanced and metastatic cancer where a range of therapeutic options exist but evidence is lacking on the optimal choices for sequential or combination therapy. Breast cancer and renal cell carcinoma were chosen as example disease areas for the working group to consider while thinking through the recommendations. It was reasoned that the contrasts between these two diseases, both in terms of prevalence and in terms of the differences in drug treatment options and approaches, might provide insights into the data sources and methods needed for analyzing treatment sequences in many clinical areas. Ultimately, the recommendations have converged for both diseases, leading to the suggestion that these methods can apply to studies of many other (or most) incurable cancer settings. However, the “state of the evidence” section of this document will provide brief reviews for breast cancer and renal cell carcinoma to illustrate the need for the types of sequencing studies recommended here.

Although the terms “advanced” and “metastatic” refer to different clinical states, they are both generally used to imply situations in which a cure is not the expected outcome of therapy. There are exceptions for some locally advanced cancers that may not be life-threatening. However, the focus of the following discussion is on cancer that is expected ultimately to cause a patient’s death. Hence, for the purposes of this document, the terms “advanced” and “metastatic” will be used interchangeably or collectively referred to as “incurable cancers.”

As discussed in more detail below, there is no consensus on the optimal sequential use of therapies for metastatic renal cell carcinoma (mRCC), where multiple therapeutic options exist, many of them approved for use within the last decade. Likewise, in advanced breast cancer, many drug treatment options are available, the decision tree is complex, and the relative benefits of a particular choice are unclear.[1,2] In both diseases, local therapy options (surgery, radiation, radiofrequency ablation) may be used to control specific sites of metastasis. The availability of multiple options for treatment presents a significant challenge to patients and clinicians trying to make informed care decisions.

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In these incurable cancer settings, survival and quality-of-life are the highest concerns for patients and providers. However, survival is often eschewed in clinical trials in favor of surrogate endpoints which can facilitate more timely drug or device evaluation, but which offer little insight to patients on tolerability and clinical benefit. In addition, provider reports are the primary tool used to assess treatment-related adverse events, with a paucity of patient-reported outcomes.[3] Neither patients, nor their doctors, can anticipate the individual variability of toxicity effects, or the cumulative toxicities associated with different treatment sequences.

With the advent of the FDA's new breakthrough drug designation, potentially important future cancer drugs are even more likely to be developed and receive initial approval on the basis of limited evidence, primarily related to measures of disease progression that are not the most meaningful to patients. Yet in these complex decision-making contexts, prospective randomized trials often cannot produce information in a timely enough fashion to inform the rapidly changing clinical arena. Post-approval, post-market data collection can fill this void but has not yet yielded clinically rich, patient-accessible information.

For these reasons, the GPC Oncology Consortium identified as a priority topic, methods to evaluate the optimal treatment sequences for advanced cancer patients. Advanced, incurable cancer was selected as the focus of these recommendations because patients facing these conditions must weigh more limited treatment benefits against both treatment- and disease-related burdens, and good information for assessing these tradeoffs is typically lacking.

These recommendations focus on the use of existing data sources (e.g., claims, electronic health records, registries, results of completed clinical trials) to establish patient-meaningful outcomes for entire sequences of treatment from the first diagnosis of metastatic disease to the final endpoint of treatment (usually expected to be end of life). The expert working group created a definition of an "optimal treatment strategy" to provide a framework for data collection:

> The optimum strategy for cancer treatment is the strategy that gives the best results with the least burden (including financial burden) to patients. When competing strategies have similar results and burden, the optimum strategy is the one that utilizes fewer health care resources.

The committee emphasized that health care resource utilization (HCRU) was specifically relevant in context where results and burden were similar, and did not endorse this as superseding treatment strategies with better results and burden.

This definition is not intended to serve as a guide for patient decision-making, but rather is conceived as a framework for data selection and method design in the analysis and comparison of treatment sequence outcomes. According to this framework, data need to be collected and outcomes determined in relationship to three key axes of decision-making for patients: treatment results, patient burden, and patient cost. We defined each of these axes in the following terms:

- **Treatment Results: This concept describes how effective the treatment is.** However, treatment effectiveness may be evaluated differently depending on the setting in which it is delivered. In a potentially curative setting (non-metastatic), a planned treatment or series of treatments has a

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reasonable likelihood to result in complete eradication of cancer and effectiveness is measured by the proportion of patients who remain alive and free of disease. However, this project focuses on the advanced and metastatic setting, in which complete eradication of cancer is considered highly unlikely, or extremely rare (as in the case of most Stage IV solid tumors), and death from cancer is the expected outcome. In this setting, effectiveness of the treatment strategy is measured by the length of overall survival (OS), and by reduction in cancer symptoms.

- **Patient Burden: This concept describes the hardships faced by patients receiving treatment.** This may include the inconvenience or intrusiveness of the treatment, out-of-pocket costs to the patient, loss of income, and the specific side effects or toxicities of the therapy (as distinguished from inconvenience or discomfort from the cancer symptoms themselves, which can sometimes be indistinguishable from adverse effects of the therapy). Increased patient burden may be reflected as worsened quality of life (QOL), despite improvement in overall survival and cancer symptoms.

- **Health Care Resource Utilization:** This includes HCRU of all aspects of cancer treatment, including procedural costs (surgery, radiation, devices, and procedures to implant devices), drug costs, drug administration costs, costs related to necessary supportive care drugs and/or procedures. This manner of looking at healthcare resource utilization, as opposed to drug costs alone, is increasingly relevant to the evolving format of health care delivery, from fee-for-service to population management.

This document places an emphasis on elucidating aspects of patient burden because, in the non-curative setting, aggregate burdens associated with different treatment pathways may provide an important basis for patient preferences between treatments. Entire sequences of therapy are evaluated, rather than head-to-head comparisons of individual treatments or combinations, to allow for assessment of the cumulative or chronic toxicities, costs, and other impacts that can mount or intensify as the patient progresses on different pathways. The working group has attempted to balance availability of existing data against unmet needs for patient-important information and reasonable possibilities for future collection of new information.

There is a strong need to address the lack of consistently collected, reliable data on patient burden, including out-of-pocket cost. Where survival advantage of differing sequences is negligible, patients are keenly interested in knowing whether, for their specific situation, one treatment pathway leads to more office visits, more emergency room visits, more days of feeling ill, less days of work – in short, more time, more expense, or less quality of life. Metastatic patients, for example, worry whether they will be able to attend landmark family events like weddings and graduations, or whether they will leave spouses and other descendants saddled with depleted resources or medical debts. These factors figure into patients' treatment selections and accurate information pertaining to different treatments would help them feel more secure in their decisions. The discussion section provides suggestions for improving current data collection to make the types of studies contemplated in these recommendations more practicable and informative.

## STATE OF THE EVIDENCE

### METASTATIC BREAST CANCER

Breast cancer is the most frequently diagnosed cancer in women worldwide.[4] Approximately 5% to 10% of newly diagnosed patients present with locally advanced or metastatic disease.[5,6] Of those women diagnosed at earlier

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stages, another 30% are estimated to subsequently develop metastatic disease, despite the use of endocrine or chemotherapy adjuvant therapies.[6–8] There have been meaningful improvements in survival in recent years, but median survival is only 2-3 years[9,10] and metastatic breast cancer (MBC) is considered incurable, although treatable.[8] Treatment is palliative in nature, attempting to alleviate cancer symptoms and prolong survival.[8,9,11–13]

Treatment of MBC should be individualized, taking into account several different disease- and patient-related factors.[6,11] While surgery or radiotherapy may be considered for certain limited metastatic presentations,[6] most patients with MBC receive some sort of systemic treatment, such as chemotherapy, endocrine therapy, or targeted biologic agents.[6,11,12] Although no prospective randomized clinical trials (RCTs) have demonstrated that systemic therapy prolongs survival in MBC patients compared to best supportive care alone,[13] median survival has increased over time, in concert with the availability of newer, more effective therapies.[14–16] Furthermore, newer systemic therapies have resulted in longer overall survival compared to older ones.[17–21]

In terms of measurement of therapeutic efficacy, overall survival (OS) is considered the gold standard. Although OS is highly relevant over a multi-step treatment course, it requires prolonged follow-up and may be difficult to interpret in the context of a single therapeutic step because of the effects of subsequent treatment.[22] Other potential endpoints, such as progression-free survival (PFS), time to tumor progression, and objective response rate (RR), have not been shown to be good surrogates for OS in the advanced cancer setting.[23]

Present drug treatment options are largely determined by the biologic markers of the tumor, currently: (1) whether the tumor is hormone receptor-positive (estrogen receptor (ER+) and/or progesterone receptor (PR+)), and; (2) whether the tumor overexpresses human epidermal growth factor 2 (HER2-positive). It is expected that the number of individual subtypes of breast cancer will increase further over time, as knowledge of cancer biology and options for targeted treatment increase. Because metastatic disease may not have the same biologic marker profile as the primary disease, experts recommend a biopsy of a metastatic lesion and reassessment of biologic markers.[9,22]

In general, endocrine therapy is appropriate only for patients with hormone receptor-positive breast cancer, and HER2-directed therapy is appropriate only for patients with tumors that overexpress HER2. Chemotherapy may be indicated for patients with hormone receptor-negative cancer or patients who have become resistant to endocrine therapy, as well as for patients with rapidly progressing disease. Non-drug therapies, such as radiation, surgery, and radiofrequency ablation, are typically reserved for management of specific symptoms and have not been well studied as means to improve survival.

Compared to the hundreds of RCTs examining first-line treatments for MBC, the data from such trials on second-line therapies are much more limited and, until recently, the literature failed to provide insight for third-line treatment.[24] Although many patients will receive multiple lines of therapy, there is little high quality data to inform treatment choices on later lines. Furthermore there is little information on the burdens and costs of various treatments from the patient perspective. There is, however, accumulating evidence that the frequency and severity of many symptoms that affect patients' quality of life (QOL) are under-reported, under-recognized, and under-treated.[9,25] These gaps significantly affect patients' ability to balance competing interests and make informed decisions.

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## METASTATIC RENAL CELL CARCINOMA

Historically, metastatic renal cell carcinoma (mRCC) has had a poor prognosis. Until the introduction of novel targeted therapies, the median survival time was less than one year.[26] Standard treatment with cytokines interleucin-2 (IL2) and interferon-alpha (IFN-α) was associated with low rates of response and high toxicity.[27] As knowledge of the pathogenesis of mRCC grew, molecular-targeted therapies directed at the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) signaling pathways were developed.[28] The first few targeted therapies were initially approved by FDA in late 2005/early 2006. At the present time, tyrosine kinase inhibitors (TKIs) such as sunitinib and pazopanib are widely considered the standard front line agents for most patients,[29–31] although temsirolimus is also used for patients with poor prognosis.[32] As a result of these new therapies, median survival for mRCC has improved to approximately two years.[33,34] Nevertheless, drug resistance eventually develops in the majority of patients, who typically go on to receive sequential single agents.[30] (Multiple studies have demonstrated that combination therapies cause substantial toxicity.[29,30,35]) Current interest has focused on determining optimal sequencing of therapies as well as on drugs with new mechanisms of action.

RCTs of treatment sequences followed the development of targeted therapies and RCTs of third-line therapies have begun to appear although optimal sequences have not yet been clearly defined.[29] Table 1 summarizes available targeted therapies and their labeled indications for mRCC.

Table 1. Summary of Drugs for mRCC

| DRUG | DELIVERY | MECHANISM | INDICATION | YEAR APPROVED BY FDA |
|---|---|---|---|---|
| sorafenib | oral | TKI | advanced RCC | 2005 |
| sunitinib | oral | TKI | advanced RCC | 2006 |
| temsirolimus | IV | mTOR inhibitor | advanced RCC | 2007 |
| everolimus | oral | mTOR inhibitor | advanced RCC after failure of a TKI | 2009 |
| bevacizumab with interferon-alfa | IV | anti-VEGF | advanced RCC | 2009 |
| pazopanib | oral | TKI | advanced RCC | 2009 |
| axitinib | oral | anti-VEGF | advanced RCC after failure of one prior systemic therapy | 2012 |

As an initial matter, most studies of targeted therapies for mRCC are evaluated in terms of patient overall survival (OS) or surrogate endpoints such as progression-free survival (PFS) or response rate (RR). However, trials such as the INTORSECT study[36] (which compared an mTOR inhibitor with a VEGFR inhibitor as second-line treatment following progression on sunitinib) have raised questions about the value of these surrogate

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endpoints. In that trial, although there was no significant difference between treatment arms in terms of PFS or objective RR, there was a statistically significant difference observed in OS (a difference of greater than 4 months).[36] Some limited information is available on the effect of certain therapies on patient quality of life[31,37] and two recent studies have investigated sunitinib versus pazopanib in terms of both quality of life and patient preference.[38,39] More common side effects observed in the latter two studies included diarrhea, fatigue, and nausea,[38,39] all of which can adversely affect quality of life.

Because first-line use of cytokines in the U.S. is now rare, this summary will address results for second-line therapy following only first-line targeted treatment. A recent systematic review of sequencing and combination of systemic therapy in mRCC noted that most of the available RCT evidence on second-line therapy is based on first-line sunitinib; sequences after mTOR inhibition, for example, are not well defined.[29] There are data from RCTs that support the use of both VEGFR inhibitors and mTOR inhibitors as second-line therapies,[29] but only everolimus and axitinib presently have labels that specify sequence, both reflecting the clinical trials that led to their approvals.[40,41] There is a theoretical basis for following first-line anti-VEGF treatment with a second-line mTOR inhibitor – they target different signaling pathways. However, there is increasing evidence (including the INTORSECT trial[36] as well as retrospective studies) demonstrating clinical benefit with a different VEGF/VEGFR inhibitor as second-line treatment.[30,42] This may be because the different therapies have varying target activity and pharmacokinetic profiles.[30]

Despite ongoing attempts, studies have not yet determined specific factors to identify which patients would be expected to benefit from a given second-line treatment.[29] One area of discussion, for example, is whether the duration of first-line therapy has any correlation to the outcome of the second-line therapy. One retrospective study of 464 patients who received second-line VEGFR inhibition after first-line VEGF/VEGFR inhibition found that clinical response to first-line therapy did not predict response to second-line therapy.[43] On the other hand, in a prospective RCT, OS with second-line sorafenib was significantly longer in patients who received longer prior therapy compared to shorter prior therapy (true for prior therapy with sunitinib, or prior therapy with cytokines).[44] Most recently, potential molecular biomarkers in RCC have been identified and are being investigated for prognostic and predictive value.

Most data on third-line treatments have come from retrospective cohort studies; only recently have data become available from RCTs.[29] For example, subgroup analysis within the RECORD-1 RCT showed everolimus had a significant effect on PFS versus placebo as a third-line treatment for patients previously treated with two VEGFR inhibitors.[45] Additionally, retrospective studies, small case series, and a recent prospective and retrospective study of sunitinib rechallenge (the RESUME study)[46] have suggested that rechallenge with a specific drug can be of therapeutic benefit, perhaps due to changes in the tumor microenvironment associated with a treatment break.[30] ESMO clinical practice guidelines “generally recommend” rechallenge with the same TKI as a third-line treatment option[47] and purely prospective studies of third-line sunitinib rechallenge are ongoing.[48] Studies of other treatments are underway but the sparseness of quality data prevents drawing any conclusions at this time.

One new class of agents, anti-PD-1 drugs that target an inhibitory T-cell co-receptor or its ligand expressed by tumor cells, has shown promise in treating mRCC.[29,49] FDA has approved two anti-PD-1 drugs for treating cancers other than mRCC: pembrolizumab for treatment of unresectable or advanced melanoma that is no longer

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responding to other drugs (September 2014)[50] and nivolumab both for unresectable or advanced melanoma that is no longer responding to other drugs (December 2014)[51] and for squamous non-small cell lung cancer that has progressed on or after platinum-based chemotherapy (March 2015).[52] Because of their mechanism of action, however, anti-PD-1 drugs have the potential for severe immune-mediated side effects such as pneumonitis, colitis, and hypophysitis. Studies are underway of combination therapies that may provide greater clinical benefit but also be associated with a greater risk of toxicity. For example, in a recent study investigating nivolumab in combination with ipilimumab (a cytotoxic T-lymphocyte-associated antigen 4 checkpoint inhibitor) for treatment of metastatic melanoma, the combination resulted in substantially longer median PFS compared to monotherapy, but 55% of patients receiving the combination experienced treatment-related adverse events of grade 3 or 4 and >36% discontinued the drugs because of treatment-related adverse events.[53] Issues that will need to be explored for these agents in treating mRCC include which patients will benefit most from treatment, where in the sequence of therapies this class of agents can best be used, and whether they can be safely and effectively combined with existing therapies.

There are substantial gaps in the available evidence that create significant uncertainty for decision-makers. As a threshold matter, the meaning of surrogate outcomes used in many trials is not clear and data on patient-centered outcomes are lacking. The optimal sequence of drug therapies has not been determined and it is not currently possible to identify which groups of patients are most likely to benefit from any given first-, second-, or third-line treatment. Evaluations of combinations of therapies have not shown treatment benefit and have been impeded by toxicity. The emergence of a new class of agents will further complicate decision making and create new evidentiary demands.

# RECOMMENDATIONS

**POPULATION**

## Recommendation 1: Populations potentially suited for the recommended studies

**Select patients diagnosed with a specific type of metastatic or advanced cancer for whom many treatment options exist but the optimal treatment sequence is not known (e.g., metastatic breast cancer or renal cell carcinoma). Subgroups of patients can be studied according to selected characteristics such as patient race, body mass index, or biomarker status.**

**Rationale**: As described above, these recommendations are designed for patients in the non-curative setting for whom consideration of cancer care sequences includes not only survival, but many other factors. These patient populations have the ability to live long lives, even with their metastatic cancers, making it valuable for all concerned to identify their optimum treatment pathways.

**Implementation:** Patient data should be extracted from patient health records (electronic or paper) and other sources to identify the diagnosis of metastatic disease. Baseline data should be collected, including: patient age, initial diagnosis, date of initial diagnosis, previously received treatment, date of metastatic diagnosis, and comorbidities. Collection of the baseline elements provides information on patient characteristics that can be stratified for potentially relevant use to the outcomes studied. In addition to the data elements listed above,

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companion diagnostic or genetic testing data, the race or ethnicity of the patient, body mass index, and life status (whether the patient is married or has support of a family or a caregiver), also provide additional information for meaningful subgroup analysis.

**Limitations:** Availability of some of the suggested baseline data (e.g., caregiver status) is limited in existing data sources. Currently information from genetic or genomic analysis, when available, exists in unstructured data fields in the electronic health record, making automated retrieval for subgroup analysis impossible.

**OUTCOMES**

## Recommendation 2: Overall survival

**Whenever possible, use overall survival (OS) as an outcome of the study.**

**Rationale:** OS is a key decision criterion for patients in the advanced and metastatic setting. To the extent that measurable differences in overall survival exist between treatment sequences, these differences are likely to outweigh other decisional priorities for many patients. On the other hand, considerations of burden, including out-of-pocket cost, will likely increase in importance for patients if little difference is found in OS between sequences.

**Implementation:** Overall survival is defined as a period of time people in a group under study remain alive. This period of time may begin from the point of diagnosis, the point of initiating or concluding treatment, or another appropriate time point. OS is typically described in terms of standard time units, such as weeks, months or years. When described as a rate, the start of the time period and the duration of follow-up should be clearly stated. There are two variables that are important in defining and measuring OS: 1) Start of follow-up or date/diagnosis of cancer; and 2) Death date.

**Limitations:** OS can be difficult to study in retrospective data because of the lack of accurate or long-delayed capture of death status among many of the most available current data sources (see Table 1 for a summary of data sources, with supplemental descriptions provided in Box 1).

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Table 1. Data Sources for Recommended Outcomes

| | | DATA SOURCES | | | | |
|---|---|---|---|---|---|---|
| **OUTCOME** | **VARIABLE** | **CANCER REGISTRY** | **ADMINISTRATIVE CLAIMS DATA** | **ELECTRONIC MEDICAL RECORDS** | **CHART REVIEWS** | **OTHER** |
| Overall survival rate | Start of follow-up date | X | X | X | | |
| | Date of death | X | X | X | X | Social Security Death Index |
| Time to first treatment after diagnosis of metastatic disease | Date of diagnosis of metastatic disease | X | X | X | | |
| | Date of initiation of first treatment for metastatic disease | X | X | X | X | |
| Time to change in therapy | Date of initiation of "X" line of treatment for metastatic disease | X | X | X | X | |
| | Date of initiation of "X+1" line of treatment | X | X | X | X | |
| | Date of discontinuation of each line of treatment | X | | X | | |
| Serious adverse events | | X | X | X | X | |
| Patient-reported outcomes | | | | X | | |
| Health care resource use | | | X | X | X | |
| Total out-of-pocket costs | | | X | | | |

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Box 1: Descriptions of Data Sources

1. **Cancer Registry**: Cancer registry information that is collected through reliable methods can be an excellent source of diagnosis and treatment information. This information is best when collected from patient clinical records by trained oncology registry personnel. The strength of this source is the completeness of the data. The limitation of this data may be the timeliness of its availability, costs, and resources needed to collect this information from the patient clinical records.

2. **Administrative Claims Data**: Administrative claims data or health insurance claims data can provide accurate information on variables such as start dates for treatment and testing, patient co-pays, and out of pocket costs for prescription medications. It may also be useful for dates associated with the end of treatment when the treatment under study is directly associated with a claim (i.e., a final dose of IV chemotherapy, final dose of radiation, surgical procedure, etc.). Consideration should be given when using this data to assure continued eligibility of the patient for insurance coverage, as lapses may prevent follow-up and documentation of final results. Additionally, if multiple doses of treatment are paid for with a single insurance claim (e.g., a 30 day supply of an oral agent), the duration of therapy should be considered in the completion of therapy date. The strength of this data is that it can be available in a timely manner. The limitation of this data is that it only represents services that require an insurance claim and thus may not be complete.

3. **Electronic Medical Records Data**: Information from health record data can accurately determine treatment dates. Care should be taken to verify the completeness of the patient's data across multiple providers and healthcare encounters. Another potential variable that can be collected from electronic medical records (EMRs) is date of death. However, if a patient's death occurs while under the care of a different health care provider who does not contribute to the EMR or uses a different EMR system, it may not be recorded. The strength of this information is that it potentially represents complete information of the care delivered by that healthcare provider. The limitation is that it may have limited and/or complex accessibility through electronic methods and costs associated with obtaining access for researchers.

4. **Social Security Death Index**: The social security death index is the most accurate source of patient death records with in the United States. Efforts to link patients to these records will provide the most accurate and complete representation of death date. The limitations of this index are that its availability for linkage to health records is limited and it can take some time for a death to be recorded in the index.

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## Recommendation 3: Time to first treatment after metastatic diagnosis

**Measure time to first treatment (TFT) after diagnosis of metastatic disease**

**Rationale:** Treatment is not necessarily initiated immediately following initial diagnosis of metastatic disease, especially if the metastatic disease is found based on elevation of a tumor marker or an incidental imaging finding, rather than on symptoms. Depending on the natural history of the disease under study and the circumstances of the diagnosis, the clinician may wait to assess the indolence or aggressiveness of metastatic disease, especially if the drug treatment options are likely to cause significant toxicity. Therefore, the delay time between diagnosis of metastatic disease and initiation of first treatment can be indicative of the relative aggressiveness of disease. With this information, differential survival outcomes between sequences can be assessed taking into consideration differing levels of disease aggressiveness.

**Implementation:** Time to first treatment after diagnosis of metastatic disease is defined as the period of time from diagnosis of metastatic disease to initiation of first treatment and can be measured in days or weeks. To determine TFT, two variables are required: 1) Date of diagnosis of metastatic disease; and 2) Date of initiation of first treatment for metastatic disease. The difference in these two variables is TFT. See Table 1 for a summary of potential data sources.

**Limitations:** Use of an observation period is not uniform among clinicians, and varies depending on the subtype of cancer studied and the toxicity of the available treatment options. Our proposal to collect this information is novel, and could lead to practice-altering insights, especially if the routine use of an observation period does not adversely affect survival.

## Recommendation 4: Time to change in therapy

**Measure the time to change in therapy (TCT) for each change of treatment regimen identifiable in the sequence**

**Rationale:** Once assigned to a therapeutic regimen, patients will typically not switch to a different regimen unless: 1) the patient has progressed on the therapy; or 2) the patient experiences intolerable toxicity or other burden from the therapy but has need to continue treatment due to expected disease progression in the future. Hence, measurement of the time associated with administration of a given therapy provides information on how effective and acceptable a particular therapy is. While a short time of administration is less informative, since it can be a surrogate for either effectiveness or toxicity, both effectiveness and sustained tolerability could be inferred from longer periods of administration.

**Implementation:** Time to change in therapy (TCT) is defined as the period of time from the initial line of therapy to a subsequent line of therapy. TCT can be computed as the duration (days or weeks or months) of the initial line of therapy or until discontinuation of current therapy. In some patients, initial therapy might not be followed by re-initiation of a subsequent line of therapy. In this scenario, TCT is defined as the period of time (days or weeks) on initial therapy.

To determine TCT, two variables are required: 1) Date of initiation of first line treatment for metastatic disease; and 2) Date of initiation of second line treatment or date of discontinuation of first line treatment. See Table 1 and Box 1 for a summary of potential data sources.

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**Limitations:** TCT would be a more reliable endpoint if reasons for treatment discontinuation/change were also collected. For example, if a therapy was extremely effective in a short period of time, it may be discontinued with no subsequent therapy started. In this case, the TCT would appear short but the survival long. In contrast, if a therapy was both toxic and ineffective, a patient may choose to discontinue therapy and not accept another one; however, their survival may still be good if the disease is relatively indolent. TCT may not distinguish between these scenarios. Some EMRs do include field entries for reason for treatment discontinuation; however, these are not routinely used.

## Recommendation 5: Serious health-related adverse events

**Measure serious health-related adverse events (SAEs)**

**Rationale:** Serious adverse events (SAEs) can pose life-threatening circumstances, and they represent essential patient burden that can divert patients from what might otherwise be beneficial courses of therapy. For the purpose of comparing drug treatment sequences, measurement of SAEs may be useful to assess whether the risk of certain SAEs is higher for some sequences than others.

**Implementation:** A serious adverse event (SAE) is any undesirable experience associated with the use of a medical product or treatment in a patient when the patient outcome is: death, hospitalization, disability or permanent damage, required intervention to prevent permanent impairment or damage, congenital anomaly/ birth defect, or other serious medical event.[54] Please refer to the FDA website for specific details. The identification of SAEs may be best accomplished by any of the available data sources, however, direct reporting of SAE (via a SAE specific treatment event with associated ICD9 code) or documentation within a patient's record is preferred as opposed to indirect measures of these events through non-specific treatments or function measurements. An advantage to comparing sequences rather than merely individual treatments is that it may be possible to establish whether some sequences are associated with a higher level of cumulative or chronic toxicities.

**Limitations:** Direct reporting of SAEs in patients who are not on a clinical trial is not routinely performed.

## Recommendation 6: Patient-reported outcomes

**Whenever possible, collect a complete range of patient-reported outcomes (PROs)**

**Rationale:** The treatment for cancer is often accompanied by a significant amount of physical, emotional, psychological and financial burden for the patient. Burden can be due to the cancer itself, or it can be associated with the treatment. In addition to disease-specific clinical information, these outcomes can also be an important factor in informing a physician's decision to stop or switch to an alternative treatment. PROs of concern can include fatigue, depression, anxiety, among others. (Financial impact to a patient is assessed in a separate recommendation below.)

**Implementation:** A PRO is defined as any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else. The outcome can be measured in absolute terms (e.g., severity of a symptom, sign, or state of a disease) or as a change from a previous measure.[55]

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This EGD does not recommend a single PRO instrument or method as the preferred option given the complexity and variability in defining and measuring these outcomes. This technical working group recommends that the instruments and methods be selected according to the tumor type and associated treatment. Disease and symptom-specific validated instruments are preferred to general quality-of-life instruments.

**Limitations:** At the current time, most healthcare delivery systems do not routinely collect PRO information, though technology enabling this data collection is increasingly available.

## Recommendation 7: Health care resource use

**Assess healthcare resource use (HCRU) for each treatment sequence**

**Rationale:** While healthcare resource use is typically seen in terms of healthcare system burden, it can also be taken as an indicator of the time burden for patients associated with treatment sequences.

**Implementation:** Healthcare Resource Use (HCRU) is defined as the unit of resources required to address a health event or episode. HCRU is measured in terms of direct resources (e.g., physician office visits, emergency room (ER) visits, number of hospitalizations or length of stay for a hospitalization) or indirect costs (e.g., travel time to physician office or outpatient facility, caregiver time) used for each care episode. When measured as a rate (resources used per period of time), it is necessary to specify the period of time over which HCRU is assessed. For the purposes of these recommendations, HCRU should ideally be aggregated across entire treatment sequences for comparison. HCRU can be measured using different data sources, as described more fully in the "limitations" below.

**Limitations:** Measures of direct resources used (e.g., counting office visits, emergency room visits, hospitalizations, etc.) can be obtained from existing administrative claims data and electronic health records. However, gathering indirect cost data often involves primary data collection. Travel time and expenses for patients and caregivers associated with care episodes, as well as aspects of burden such as days of missed work or missing other events of personal importance, represent information rarely captured in medical records with the level of completeness required. To the extent that such records are available, they would be located in open text portions of the electronic records, not in structured data fields. As such, they would be inaccessible without manual inspection of individual patient records – a search currently not warranted due to the infrequency with which such notes are made.

## Recommendation 8: Out-of-pocket cost to patient

**Assess total out-of-pocket (TOOP) cost to patient for each treatment sequence**

**Rationale:** Along with clinical effectiveness, the financial cost associated with treatment is one of the most important factors that a patient considers in making a decision about his or her treatment. Recent research has shown that the cost of treatment for cancer can be so high (especially for newer therapies) that it is often a part of patient-physician treatment selection dialogue, and can sometimes influence the choice of treatment for a particular disease.

**Implementation:** Total out-of-pocket (TOOP) costs are defined as the costs paid by the patient from their own income or wealth for cancer treatment.[56] While TOOP may include both direct and indirect medical costs, results

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for these costs should be reported separately. Direct medical costs may include (but are not limited to) directly paid, co-payment or co-insurance charges for inpatient and outpatient care, non-covered care-related costs (e.g., non-formulary medications, non-covered treatments, out of network physician services) and devices. Indirect costs may include time or missed income opportunity costs incurred while travelling to a physician clinic or infusion center, lost wages for time taken off for treatment, caregiver burden, costs following completion of cancer treatment, etc.

**Limitations:** Administrative claims data can be a source for estimating TOOP, however, claims data often do not include supportive care medicines or over-the-counter medicines that might be prescribed for certain treatment-related events. Therefore, it is important to carefully describe any limitations of the available data and how it will impact the completeness of the TOOP. Because many of the most commonly used retrospective data resources do not include indirect TOOP costs, this data often requires prospective data collection from patients.

## METHODS (STATISTICAL METHODS AND ESTIMATION)

### Recommendation 9: Marginal structural modeling

**For each outcome, use marginal structural modeling (MSM) to adjust for the dynamic relationship between duration of time on drug(s), confounders, and outcomes**

**Rationale:** Under ideal conditions, analyses would include patients with MBC or mRCC who have at least one treatment visit or other health care provider encounter within the period of interest. By the end of the follow-up or observation period, they would have been censored (due to disenrollment or end of observation period) or died. In between, we would have observed all of their treatments. The usual approach to the estimation of the effect of a time-varying exposure, such as treatment of advanced RCC, on survival is to model the hazard of failure at a given time as a function of past exposure history using a time-dependent Cox proportional hazards model. Robins[57] has shown this approach may be biased, whether or not one further adjusts for past covariate history, whenever (a) there exists a time-dependent covariate that is both a risk factor for the outcome of interest (e.g., mortality) and also predicts subsequent exposure; and (b) past exposure history predicts the risk factor. Covariates satisfying condition (a) are called time-dependent confounders. For example, symptomatic and/or radiographic progression is a time-dependent confounder for the effect of mRCC treatment on survival, because it is a risk factor for mortality and a predictor of subsequent initiation of a new therapy, and past treatment history is an independent predictor of subsequent progression. As noted by Hernán and colleagues[58] for the case of HIV, all standard methods (i.e., Cox or Poisson regression) that predict the mortality rate at each time using a summary of treatment (zidovudine) history up to that time may produce biased estimates of the causal effect of treatment whether or not one adjusts for past CD4 count in the analysis. The similarities to our cases of MBC and mRCC are striking as both treatment decisions and outcomes may be impacted by time-dependent confounders.

**Implementation:** Marginal Structural Models (MSMs) are tools developed by Robins and colleagues[57] that are used when the effect of a time-dependent treatment or exposure (in the case of advanced RCC, treatment with a TKI, mTOR inhibitor, and/or VEGFR inhibitor) is confounded by time-dependent covariates which may affect

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both the level of treatment and the outcome. In particular, the decision to remain on current treatment, switch to another, or discontinue all together, can be confounded by selection bias, as patients who are responding and tolerating the drug(s) are less likely to change to a new treatment, thus clouding the relationship between treatment sequence and outcomes. MSMs can adjust for this dynamic relationship between duration of time on a drug(s), confounders, and outcomes by using time-varying covariates to create a weighting scheme that may provide better estimates of the effect of treatment over time in an outcomes model.

MSMs are developed in two stages and can be adapted to most any outcome (e.g., survival, health care costs). The first stage is used to compute weights, based on treatment patterns and loss to follow-up, and these weights are applied to the second stage which models outcomes adjusting for treatment patterns that may vary over time as well as other covariates. It does require the ability to identify treatment and confounding factors in defined (and meaningful) time-periods (e.g., monthly). This data requirement is one reason for the limited use of the method in practice.

When studying the effect of a time-dependent treatment the assumptions of MSMs are noted by Robins and colleagues[57] but are less restrictive than those of standard methods. Most importantly, MSMs do not require the absence of time-dependent confounding by variables affected by previous exposure although data requirements to accurately capture such data are significant. As demonstrated by Hernán and colleagues,[58] failure to properly account for time-dependent confounding can lead to biased results and, in the extreme case such as their HIV study, erroneously suggested treatment can increase risk of death.

MSMs are in the class of "potential outcomes" (counterfactual) methods, and account for treatment patterns over time. While they originally examined survival, MSM can be used to deal with time-dependent confounding for any outcome (e.g., health care costs, number of hospitalizations) as they are basically generalizations of the inverse probability of treatment (IPTW) method of propensity scoring to time. In general, MSMs:

- Take all possible treatment patterns and weight them (based on observed confounders) to achieve balance
- Consider k time periods (there are 2k possible treatment patterns)
- Balance them similar to the way the IPTW approach to propensity scoring balances a single time period treatment

**Limitations:** While MSMs can un-confound patterns of treatment from confounders evolving over time and censoring is easy to address, there are certain limitations in practice that require adequate data.

Disadvantages include:

- Does not control for unobserved variables
- 2k can be a very big number resulting in small samples such that some treatments are not observed in some time periods and consequently, some patterns are not observed
- Low probability patterns get big weights with a resulting loss of precision (requiring large sample size)

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**REPORTING**

### Recommendation 10: Plain language summaries of results

**Study sponsors or authors should provide plain language summaries of all published comparative studies of cancer therapy sequences and make them publicly available.**

**Rationale:** Advanced cancer patients face complex decisions, especially those in therapeutic areas where many drug treatment options exist. This information is integral to patients being able to have meaningful conversations with their physicians and empower them to participate in shared decision-making.

**Implementation:** Summaries should follow a standard format and be provided on a public website or by request using a toll-free telephone number. Journals could also require a plain language summary to publish concurrently with the scientific article. We suggest that patient stakeholders be engaged in the development and refinement of these summaries. However, as discussed more below, this is only a first step in providing meaningful information to patients from these types of studies. More work is needed to develop effective decision tools for patients with advanced cancer. A 2015 resource for Return of Result study summaries is available through the Harvard Multiregional Clinical Trial (MRCT) Center.[59]

## DISCUSSION

For these recommendations to yield robust results, improvements should be made to current data collection practices, especially for elements of patient burden and out-of-pocket costs. Additionally, in theory, palliative or supportive care could be included as part of the sequences evaluated by these methods. However, patient data trails are often difficult to follow once active intervention has ceased. Moreover, more information is needed on the values and priorities of advanced cancer patients, and how to communicate findings of studies in a manner helpful for decision making. The following discussion highlights some inadequacies of current practices and recommends steps for enhanced data-gathering and reporting.

### IMPORTANCE OF PATIENT-REPORTED OUTCOMES (PROS) TO INFORM OPTIMAL SEQUENCE OF THERAPY

At present, therapeutic decision making when multiple treatment options are available rarely includes consideration of patient reported experience, which is most likely to inform aspects of patient burden. From a regulatory perspective, only efficacy and safety are mandated by the FDA approval process. In addition, when clinical information is presented to the FDA to support a drug indication, only one step of what is typically a multi-step drug treatment sequence is evaluated. While overall survival (OS) is uniformly accepted as the gold standard for efficacy, many FDA approvals in oncology are not based on a survival advantage; although as targeted therapies are increasingly developed, this situation may change. For now, surrogate endpoints like progression free survival (PFS) have come to be viewed as adequate measures of efficacy for a single treatment step. The presumption is that these surrogates are relevant for more clinically meaningful outcomes such as OS, when included within what is expected to be, in the incurable setting, a series of treatments. However, this is rarely validated post-approval. Similarly, the assumption that surrogate endpoints represent a clinical benefit to the patient, such as relief of symptoms or maintenance of quality of life, is rarely validated. This EGD proposes

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an evaluation of an entire sequence of therapies over the life span of the metastatic cancer patient, and in certain optimal sequences, the "most efficacious" therapy may not be used first.

In addition to efficacy, toxicity reporting is a widely accepted requirement for adoption of a new therapeutic in clinical practice. Although toxicity reporting is standardized, it is reported by the treating physician and the burden of the toxicity may or may not be significant to the patient. In fact, it is arguable that the significance of the particular toxicity needs to be considered in the context of perceived efficacy, therapeutic alternatives, malignancy associated symptom burden (and relief of these symptoms), and other patient-specific factors. In the circumstance where there are multiple palliative options available (including no treatment), quantification of the burden of this toxicity from patients should help inform decision making.

MBC patients commonly suffer from emotional distress, including depression and anxiety, and suffer fatigue, pain, and sleep problems that disrupt their lives.[60] Yet half of patients say that they are not routinely asked about these types of disturbances. Many validated instruments have been developed to quantitate symptoms related to cancer and its treatment. These instruments do not necessarily separate symptoms related to burden of illness from treatment toxicity; however, this may not be an important distinction. Ultimately, whether or not the patient experiences improvement or even delay in decline in quality-of-life, understanding particulars will help facilitate informed decision making. Though the technology for collecting these PROs has advanced rapidly, they exist outside traditional clinical research and certainly outside routine clinical care as documented in the medical record.

For these reasons, we also recommend the following measures for creating data resources to allow for systematic collection and study of PROs for comparing treatment sequences and other purposes.

**Recommendation: Patient-reported outcomes (PROs) should be routinely collected as part of the regulatory approval and post approval process.**

The optimal choice of first line treatment for mRCC provides an instructive case for the impact of both routine efficacy and toxicity measures and PROs to inform clinical decision making. As noted above, in the last several years there have been numerous new agents approved for the treatment of mRCC. Most have been studied in the first line or second line setting, and most often compared to placebo. Because these novel therapies have been introduced into clinical practice in a staggered fashion, and because the historical drug treatment options produced such poor results, practice patterns developed based on "best available evidence" as well as physician preference. Sunitinib became the agent of first choice. However, with the introduction of pazopanib, with a similar mechanism of action and clinical benefit, but different toxicity profile, an alternative first line treatment became available. In a recent phase III trial, Motzer et al. compared the two agents,[38] and efficacy was comparable, but toxicity was less with pazopanib. Most importantly, QOL was found to be superior with pazopanib. The results of this trial were subsequently validated in an ingenious trial performed by Escudier et al.[39] In this trial, patients were exposed to each agent in a blinded fashion for 10 weeks, then crossed over to the alternative agent. It was presumed that efficacy was equivalent. In this trial, patients preferred pazopanib 70% of the time, and the toxicities reported by Motzer were confirmed. This ability to allow the identification of a preferred first-line therapy not based on efficacy but rather based on patient preference, provides a road map for trial design to inform sequence of therapy in the palliative setting.

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**Recommendation: Patient-reported outcomes (PROs) should be collected as part of the routine care of all cancer patients. Incorporation in the medical record in structured fields should ultimately be harvested for Comparative Effectiveness Research (CER).**

As part of the Affordable Care Act (ACA), the Center for Medicare and Medicaid Innovation (CMMI) has been empowered to explore alternative payment models in subspecialty care. Oncology has been a primary interest and a model has been published for comment. Important components of this model include the requirement that PROs be collected as part of routine care and integrated into the delivery of care. In addition, the model requires completion of the second phase of meaningful use which mandates, among other tasks, implementation of a patient portal. The ability to systematically collect this information and marry it to other data elements, including real world efficacy as well as consumption of health care resources, would allow the development of true comparative effectiveness research. Because there are many FDA approved therapies that will not be subject to the prospective collection of data proposed above, this may be the only mechanism by which these data can be collected. This information could contribute in a meaningful way to shared decision making and the personalization of care. Further, it would alert clinicians to potentially futile or sub-optimal sequences of therapy. This information does not exist today, but could dramatically improve care for many patients.

## IMPORTANCE OF DECISION TOOLS FOR PATIENTS IN ADVANCED CANCER

While the above recommendations are designed to generate more information for patients and clinicians to make decisions in the advanced cancer setting, tools are needed to translate the outcomes of these studies into a form that can be readily communicated to patients. Decision tools have been developed for patients in some early stage disease settings, where first-line decision-making provides a critical opportunity to receive effective treatment. However, patients newly diagnosed in the metastatic setting lack these types of tools, even though the decision making in this context is more complex than for early stage patients. In the metastatic setting, patients may be assessing tradeoffs between established non-curative “maintenance” therapies or clinical trials of promising new agents. They may need to choose between chemotherapy or immunotherapy or other approaches, taking into consideration not only potential survival differences and clinically significant toxic effects, but also relative cost impacts and the ability to remain engaged with individually meaningful pursuits. Additionally, as the experience of disease progresses, the patient’s personal values and priorities may change over time.

Research studies are needed to understand the complexities of decision-making in the metastatic setting – to gain insight into patient values and trade-offs in decision-making, and how priorities may change over time. In addition, work is needed to understand how to communicate with economically disadvantaged subgroups and other groups having poor literacy.

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# APPENDIX A

**GLOSSARY OF TERMS**

| Term | Definition |
|---|---|
| Adverse Events | Anything that a person might feel is a negative or harmful result of a treatment or test. For example, sleepiness is a common occurrence when people take certain allergy medications. Sleepiness is an adverse effect. (ARHQ, Observational Study-Glossary of Terms) |
| Claim Database | An itemized statement of services and costs from a health care provider or facility submitted to the insured for payment. (Elsevier, Mosby's Medical Dictionary, 8th edition, 2009) |
| Co-morbidity | The presence of one or more diseases or conditions other than those of primary interest. In a study looking at treatment for one disease or condition, some of the individuals may have other diseases or conditions that could affect their outcomes. (A co-morbidity may be a confounder.) (The Cochran Collaboration, Glossary) |
| Comparative Effectiveness Research (CER) | A type of health care research that compares the results of one approach for managing a disease to the results of other approaches. Comparative effectiveness usually compares two or more types of treatment, such as different drugs, for the same disease. Comparative effectiveness also can compare types of surgery or other kinds of medical procedures and tests. The results often are summarized in a systematic review. (ARHQ, Observational Study-Glossary of Terms) |
| Confounder, Confounding Variable | A factor that distorts the true relationship of the study variables of central interest by virtue of being related to the outcome of interest but extraneous to the study question and unequally distributed among the groups being compared. For example, age might confound a study of the effect of a toxin on longevity if subjects exposed to the toxin were older than those not exposed. (Elsevier, Glossary of Methodologic Terms) |
| Cost-Benefit Analysis | A type of analysis that compares the financial costs with the benefits of two or more health care treatments or programs. Health care interventions that have the same or better benefit at a lower cost are better values than treatments or programs that are more expensive. For example, cost-benefit analyses have been conducted to compare vaccinating people against a certain disease versus treating those people who get sick from the disease when no one is vaccinated. (ARHQ, Observational Study-Glossary of Terms) |

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| Cost-Effectiveness Analysis | A type of analysis that is similar to a cost-benefit analysis but is used when the benefits cannot be measured in financial terms or dollars. It would be hard to put a price-tag on living an extra year of life. For example, a cost-effectiveness analysis might compare the costs of two health care interventions that both helped people to live an extra year. (ARHQ, Observational Study-Glossary of Terms) |
| Electronic Medical Record (EMR) | A collection of a patient's medical information in a digital (electronic) form that can be viewed on a computer and easily shared by people taking care of the patient. (NCI, Dictionary of Cancer Terms) |
| Overall Survival (OS) | The lengths of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive. In a clinical trial, measuring the overall survival is one way to see how well a new treatment works. Also called OS. (NCI, Dictionary of Cancer Terms) |
| Patient Reported Outcome (PRO) | A PRO is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else. The outcome can be measured in absolute terms (e.g., severity of a symptom, sign, or state of a disease) or as a change from a previous measure. (FDA, Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims) |
| Prognosis | The way a health situation is likely to turn out. Prognosis refers to the usual progression and outcome of a condition. For example, breast cancer mortality rates can be significantly reduced by identifying cancers at earlier stages. Early detection and treatment of breast cancer gives a better chance of a full recovery or cure. The prognosis of breast cancer that is detected and treated early is better than the prognosis of breast cancer that is detected late. (AHRQ, Observational Study-Glossary of Terms) |
| Progression | In medicine, the course of a disease, such as cancer, as it becomes worse or spreads in the body. (NCI, Dictionary of Cancer Terms) |
| Progression-free survival (PFS) | The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. In a clinical trial, measuring the progression-free survival is one way to see how well a new treatment works. (NCI, Dictionary of Cancer Terms) |

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| Recurrence | Cancer that has recurred (come back), usually after a period of time during which the cancer could not be detected. The cancer may come back to the same place as the original (primary) tumor or to another place in the body (metastatic). Also called recurrent cancer. (NCI, Dictionary of Cancer Terms) |
| Retrospective cohort study | A research study in which the medical records of groups of individuals who are alike in many ways but differ by a certain characteristic (for example, female nurses who smoke and those who do not smoke) are compared for a particular outcome (such as lung cancer). Also called historic cohort study. (NCI, Dictionary of Cancer Terms) |
| Risk/Benefit Ratio | A method for comparing a treatment's benefits and risks, such as curing a disease (benefit) versus having a serious side effect from the treatment (risk). The risk/benefit ratio of a treatment is different depending on the disease or condition being treated. For example, some types of pneumonia often are fatal if not treated but can be cured with antibiotic medications. Antibiotics have a low rate of adverse events. The risk/benefit ratio of antibiotic treatment for serious pneumonia is low. This means that the risk of an adverse event is low compared to the probability of improvement from the treatment. (ARHQ, Observational Study-Glossary of Terms) |

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