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When oncologic treatment options outpace the existing evidence: Contributing factors and a path forward[☆]

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ABSTRACT

Oncology is one of the most multidisciplinary areas of medicine, with most patients encountering multiple treatment modalities during the course of their disease. Rapidly occurring innovations in cancer care are continuously expanding the number of treatment options available. However, substantial variation in the amount and quality of evidence supporting new drugs, devices, and surgical approaches exists, compromising evidence-based treatment decisions. To address this important issue, the professional societies representing cancer care providers appointed a multidisciplinary working group: American College of Surgeons Commission on Cancer, American Society for Radiation Oncology (ASTRO), American Society of Clinical Oncology (ASCO), Society of Interventional Radiology (SIR), and the Society of Surgical Oncology. In addition, the working group included a patient and National Cancer Institute (NCI) representative. This manuscript identifies five factors contributing to differences in evidence development for cancer treatment modalities: (1) research funding, (2) methodological challenges to conducting randomized controlled trials in many therapeutic options, (3) regulatory agency oversight, (4) payment policies, and (5) hierarchy and sociological factors in medicine. It makes a series of consensus recommendations that address the need for more cross-disciplinary research and wider adoption of observational research, pragmatic trials, and reimbursement strategies.

1. Introduction

Due to rapidly occurring innovations in cancer care, the number of treatment options such as new drugs, devices, and radiation approaches is continuously expanding. For patients and clinicians to choose the most appropriate treatment when there are multiple treatment modalities available, it is vital they have information on the expected outcomes of each option. Ideally, such information includes average outcomes for the intended use population (e.g., overall response rate and survival benefit) as well as the range of outcomes observed across heterogeneous groups of patients. In reality, however, patients and clinicians' abilities to make well-informed, evidence-based, and tailored

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Table 1
Local Treatment Options for Stage IV Colorectal Cancer and Supporting Evidence.

	RCTs	Remarks	Other studies	Remarks
Hepatic resection	Several: - Surgery +/- systemic chemotherapy [71,72,73,74] - Surgery vs MWA [75] - Surgery vs cryo-ablation [76]	Underpowered for OS Risk of bias Risk of bias	Many	When feasible (i.e. in a minority of patients), hepatic resection is currently the treatment of choice [77]
^{90}Y RE	Several: - ^{90}Y RE + HAI vs HAI [78] - ^{90}Y RE + systemic chemotherapy vs chemotherapy [79,80,81,82,83]	Modest degree of benefit; trials with modern chemotherapy ongoing	Many	Heterogeneity between studies compromises pooling and interpretation of outcomes [84,85]
HAI	Several: - HAI vs TACE vs no treatment [86] - HAI vs systemic chemotherapy [87,88,89] - HAI vs RE [78]	TACE nor HAI improved survival None used modern chemotherapy	Several	Evidence is patchy and inconclusive [90,91,92,93,94,95,96]
RFA	Few: - RFA + systemic chemotherapy vs systemic chemotherapy [97] - RFA vs SBRT [98]	Insufficient accrual Results not yet published	Many	Limited follow-up, mixed populations, wide range of endpoints and outcomes [99]
TACE	Few: - TACE vs HAI vs no treatment [86] - TACE vs chemotherapy [100] - TACE + chemotherapy vs chemotherapy [101]	TACE nor HAI improved survival TACE improved PFS & OS TACE improved objective response and PFS	Several	Not recommended by the NCCN [102]
MWA	One: - MWA vs surgery [75]	Risk of bias	Several	Hard to interpret due to heterogeneous study populations and design [99,103,104,105]
Cryo-ablation	One: - Cryo-ablation vs surgery [76]	Risk of bias	Many	Wide range of outcomes [99]
SBRT	One: - SBRT vs RFA [98]	Insufficient accrual	Few	No large, prospective studies [106,107,108]
ILT	None		Few	Largest observational series provided no details on additional anti-cancer treatment [109]
Brachy-therapy	None		Few	Evidence is patchy, with inconsistent findings [110,111,112,113]

Few: one to five studies. Several: six to twenty studies. Many: more than twenty studies. RCT: randomized controlled trial. ^{90}Y RE: Yttrium 90 microsphere radioembolization. HAI: hepatic artery infusion of chemotherapy. RFA: radiofrequency ablation. TACE: transarterial chemoembolization. MWA: microwave ablation. SBRT: stereotactic body radiation therapy. ILT: interstitial laser thermotherapy. OS: overall survival. PFS: progression free survival. NCCN: National Comprehensive Cancer Network.

treatment decisions is often hampered by absent or incomplete evidence on the benefits and harms of the available treatments.

To address this important issue, five of the primary professional societies representing cancer care providers in the United States appointed a multidisciplinary working group with expertise in multimodality cancer research: American College of Surgeons Commission on Cancer, American Society for Radiation Oncology (ASTRO), American Society of Clinical Oncology (ASCO), Society of Interventional Radiology (SIR), and the Society of Surgical Oncology. In addition, the working group included a patient and National Cancer Institute (NCI) representative. The working group met via a series of conference calls, held an in-person workshop where additional stakeholders were invited to provide input, and reviewed the literature. Based on this information, the working group developed consensus recommendations. This paper represents the professional societies' joint statement. It identifies the main factors contributing to differences in evidence development between cancer treatment modalities and presents a series of recommendations for improving the evidence base. Although some of the recommendations have been made previously in different contexts, they have not been endorsed in their totality across the major professional organizations representing cancer care providers in the United States. This endorsement by a broad range of stakeholders should be influential in developing evidence across cancer treatment modalities and in leading to timely implementation of the proposed recommendations.

2. Clinical implications

The working group used a clinical case study on liver metastases from colorectal cancer (CRC) to identify the challenges of making informed healthcare decisions when there are multiple potential treatment modalities with varying levels of evidence to support their effectiveness:

> A 62-year old male patient is diagnosed with a stage IIIC colon carcinoma. The patients' tumor is surgically resected and adjuvant chemotherapy is given. Three years later, the patient is diagnosed with multiple liver metastases. There are no signs of extra-hepatic disease. The patient is in good condition and fit for surgery, but complete resection of the metastases is expected to leave inadequate liver remnant and is therefore not feasible. Because the patient fears toxicity of systemic chemotherapy, he is particularly interested in local treatment options. He and his clinician identify many potential treatment options (summarized in Table 1). Choosing between these options, however, remains rather arbitrary because available evidence does not provide answers to many questions that this patient and his clinician may have. For example, which option has the best chance of leading to long term cancer control and survival? Which option has the best chance to preserve liver function? Which treatment is easiest to deliver with the lowest risk of complications? For a patient who is older, non-Caucasian, suffering from significant comorbidities, and /or belonging to any other subgroup that is generally underrepresented in clinical trials, what evidence is available to support the use of the intervention?

Every cancer care provider will recognize this scenario and the difficulty of choosing the most appropriate treatment option in the absence of comprehensive supportive data; this situation is not limited to local therapy and devices. Oncology guidelines suffer similarly from the lack of evidence supporting some treatment modalities and are often unable to make strong clinical recommendations [1,2]. As a result, patient care may be guided by factors other than evidence, such as physician preference or experience, institutional bias, socioeconomics, regional variation in care, reimbursement policies, etc. Whether prostate cancer is treated by prostatectomy or radiation therapy, for example, is often dependent on whether patients first see an urologist or radiation oncologist [3]. Other examples include the probability of receiving chemotherapy for indolent lymphoma, or sphincter-sparing surgery for distal rectal cancer: depending on institutional practices, probability varies from 51% to 100% and from 30% to 90%, respectively [4].

3. Factors contributing to unequal evidence development

Oncology is one of the most multidisciplinary areas of medicine, with most patients encountering multiple treatments and multiple modalities of treatment during the course of their disease. In many circumstances, various modalities of treatment are available but substantial variation exists in the amount and quality of evidence supporting their use. Five major factors contributing to these differences in evidence are: (1) research funding to support evidence development, (2) methodological challenges to conducting randomized controlled trials (RCTs) in many therapeutic options, (3) regulatory agency oversight, (4) payment policies, and (5) hierarchy and sociological factors in medicine.

3.1. Research funding

Specialties that prescribe pharmaceutical products (i.e., medical oncology) generally have access to larger research budgets than non-pharma specialties (i.e., interventional radiology, radiation oncology, and surgery). In 2016, for example, the leading biopharmaceutical researchers and biotechnology companies in the United States reported spending $52.4 billion on research and development across diseases [5], whereas the medical device technology industry spent $16 billion [6]. Part of the explanation could be the difference in expected “shelf-lives” of these treatments. Whereas some devices have short commercial lives of 18–24 months, drugs often remain on the market for the entire duration of their patents (e.g., 20 years) or longer [7]. In addition, the clinical successes of complex, large equipment is not readily predictable and the evolution and benefits of such equipment is typically incremental [8–10]. This makes drugs a more attractive investment for commercial sponsors. Federal funding is unlikely to equalize the discrepancy in funding given its modest role in research support: the National Institutes of Health provided only 27% of total cancer research funding in 2012, while almost 50% was provided by biopharmaceutical companies and just 10% by the medical device industry [11].

3.2. Methodological challenges

Phase 3 RCTs are the current mainstay of evidence-based medicine but they have well-recognized limitations in external validity and generalizability. Most RCTs focus on systemic treatment and compare placebo or standard treatment to one isolated intervention; whereas in clinical practice, patients get combination and/or serial treatment and outcomes are a culmination of treatment events. Moreover, conducting RCTs in surgical disciplines, radiation therapy, and interventional radiology is often challenged by slow accrual and the need to control for provider skills and biases [12,13]. Surgery, for example, cannot be fully placebo controlled; blinding of the operator is not possible and randomizing surgical experience as well as standardizing surgical procedures is challenging [14–16]. Treatment standardization via certification or auditing programs can only overcome some of these barriers [17–19]. As a result, it is difficult to obtain RCT-level evidence for many new therapeutic options.

3.3. Regulatory agency oversight

Regulatory agency oversight, such as by the U.S. Food and Drug Administration (FDA), explains another part of the evidence inequality available to medical specialties that employ pharmaceutical and non-pharmaceutical products because legal requirements for bringing new drugs to the market differ from those for new devices. FDA approval of new drugs requires extensive clinical testing and proof of safety and effectiveness before registration [20]. Moderate- and high- risk devices, meanwhile, can achieve FDA approval via either (1) the more stringent premarket approval or (2) the less stringent 510(k) notification/clearance process. The former requires evidence from clinical studies, a premarket manufacturing inspection, and postmarket studies, but is only used for 1% of devices [21,22]. The latter is used for the vast majority of devices and does not require any of these items; demonstration that the device is “substantially equivalent” to a device already on the market is sufficient [23].

Multiple organizations have raised concerns about the adequacy of FDA’s review of devices [22–24]. The FDA recently reorganized its oversight of drugs, biologics, and devices for cancer care under one office, the Oncology Center of Excellence [25,26]; whether and how this will impact FDA’s review of cancer drugs and devices is unclear. However, increasing premarket standards for devices in the United States may have the opposite effect to that intended: given devices’ short life-spans, the great variability in types of devices used in clinical care, and the fact that some countries might have lower standards for marketing new products [27], increasing oversight of devices could reduce (rather than increase) research and development investments.

3.4. Payment policy

Another disincentive to invest in thorough pre-market evaluation of devices and procedures (and thus contributing to the paucity of supporting evidence) is their less certain payment environment. In the United States, for example, the evidentiary burden for FDA device-approval is low, but extensive evidence is needed for insurance coverage and reimbursement. The Centers for Medicare and Medicaid Services (CMS) only covers devices and procedures if they have been proven to be “reasonable and necessary” (i.e. safe, effective, and leading to improved health outcomes) [28]. In addition, CMS has interpreted the “reasonable and necessary” standard for its National Coverage Decisions (NCD) more stringently in recent years [29]. CMS’s explanations for denying coverage in NCDs often cite specific methodologic flaws in existing evidence, such as the lack of representative populations or the lack of meaningful outcome data [28,30].

Conversely, CMS has interpreted existing regulations as requiring it to cover most cancer drugs [31]. Medicare Part B covers any intravenous drug used in an “anticancer chemotherapeutic regimen” as long as the use is “for a medically accepted indication.” [31,32] Acceptable indications are those approved by the FDA, those listed in a drug compendia (such as the National Comprehensive Cancer Network’s guidelines), or those supported by the peer-review literature. Under Part D, Medicare private contractors are required to cover virtually all oral chemotherapy drugs because they meet the standard of treating a “major or life-threatening disease.” It is likely that similar differences in private insurers’ coverage of drugs and devices exist.

3.5. Hierarchy and sociological factors in medicine

Evidence development for some treatment modalities may be further challenged by the historically hierarchical culture of medicine, competition between specialties, and other sociological factors [33]. Suboptimal multidisciplinary teamwork, for example, has been well described in studies on tumor board behavior where some specialties are routinely under-represented and certain group members may dominate decision-making behavior [34–37]. Surgeons and medical oncologists often contribute most to decision-making, whereas radiologists' and radiation oncologists' opinions are routinely incorporated downstream [38]. Similarly, hierarchy within journal editorial boards, scientific review committees, or committees formed to inform policy decisions could contribute to unequal evidence development across treatment modalities, as members of these committees may have biases towards their own specialties, making it more challenging for others to obtain publication, to receive funding, or to achieve supportive public policies.

A prominent example of this is a committee formed by the American Association for Cancer Research, FDA, and the National Cancer Institute (NCI) to review biomarker-use in cancer drug development [39]: although image-guided biopsies for biomarker-purposes are most commonly obtained by interventional radiologists, only one radiology-representative was included in the 122 member panel [40]. Similarly, the NCI Cancer Moonshot Blue Ribbon Panel failed to include radiation oncologists and interventional radiologists, despite their key role in cancer treatment [41].

4. The path forward

The wealth of anti-cancer treatment modalities comes with the challenge of generating broad evidence supporting each treatment option in a given clinical circumstance. The professional societies representing cancer care providers developed a series of recommendations to limit situations when oncologic treatment options outpace existing evidence. The recommendations include promoting cross-disciplinary evidence-development, increasing the use of observational research and pragmatic trials, and implementing reimbursement strategies.

4.1. Promote cross-disciplinary teamwork in cancer research

Due to the complexity and multidisciplinary nature of cancer care, high-quality cancer research cannot exist without cross-disciplinary teamwork. Improving clinicians' awareness about the benefits of multidisciplinary teamwork [42] and the pernicious effects of hierarchical biases may help to achieve this, as may interdisciplinary educational programs [43]. In addition, inclusion of representatives from all relevant specialties in multidisciplinary review panels of funders, journals, guidelines panels, and policy committees may prevent funding and publication-bias towards otherwise underrepresented specialties. Considering the potential overall value of study results (including clinical effectiveness, societal impact and costs, as well as more patient-centered endpoints) when scoring research proposals could further enhance cross-disciplinary evidence development. When doing so, the fact that defining "value" may require different frameworks for systemic vs. loco-regional cancer treatments should be borne in mind [9].

Action Items:

- Multidisciplinary review panels of funders, journals, guidelines panels, and clinical guideline developers should include representatives from all relevant specialties involved in cancer care and should be aware of the impact of underrepresentation.
- Academic institutions and professional societies should develop interdisciplinary education programs.
- Academic institutions, NCI, and other funders should increase the academic value, visibility, support, and stature of cross-disciplinary research, through funding prioritization, promotion of presentations at scientific meetings, and publication in top journals.

4.2. Conduct (more) pragmatic trials

Pragmatic trials are an approach to collecting evidence from real world practice on cancer treatment modalities. They prospectively evaluate outcomes in real-world conditions and may thus produce results that are generalizable to routine clinical practice [44–46]. In addition, because they can be embedded into practice, pragmatic trials leverage existing resources and are relatively inexpensive to conduct [47]. Even when all of the criteria for pragmatism cannot be met, adoption of pragmatic trial-features whenever feasible and sensible could help to improve the relevance of evidence to everyday decision making [44].

ASCO's ongoing TAPUR Study (Targeted Agent and Profiling Utilization Registry) [48] and the Dutch DRUP Study (Drug Rediscovery Protocol) [49] are two examples of pragmatic trials that attempt to learn from the application of precision medicine in oncology practice; examples in surgical and radiation oncology include the NIHR ROMIO trial (Randomised Controlled Trial of Minimally Invasive or Open Oesophagectomy) [50,51], the ROLARR trial (Robotic versus Laparoscopic Resection for Rectal Cancer) [52], the ROCS trial (Radiotherapy after Esophageal Cancer Stenting) [53], and the TARGIT-E trial (Intraoperative Radiotherapy in Elderly Patients With Small Breast Cancer) [54]. For future pragmatic trials to address key questions about the effectiveness of various cancer treatment modalities, it will be important to involve providers and patients in prioritizing and formulating research questions [55,56]. Although PCORI is following this best practice and gives patients a prominent role in its research program [57], broad stakeholder involvement in setting research priorities remains limited [55,56].

Action Items:

- Researchers and funders should increase support for pragmatic studies that can be conducted in routine clinical care settings.
- Researchers and funders should prioritize pragmatic trials that are informed by broad stakeholder input, including providers, patients, and their families.

4.3. Harness health information technology to facilitate observational research

Observational research, such as studies based on registry data, claims databases, and pooled electronic health records (EHRs), provides an important source of evidence and can be complementary to prospective clinical trials [58]. This is especially true for rare patient subgroups, for treatment modalities that are difficult to study in RCTs, for collecting data on uncommon events, and for post-market surveillance of new treatments [58–62]. A major benefit of observational research is that data are derived from routine clinical practice and include broadly representative patients. However, observational research has substantial limitations that need to be considered, including high risk of bias due to lack of randomization and blinding, absence of control groups, and incomplete or inconsistent data [58]. Nevertheless, technological advances in the healthcare system are enabling new types of observational research that address some of these limitations by using extremely large datasets. ASCO's CancerLinQ, for example, is a learning healthcare system that collects data on patient encounters stored in oncology practices' EHR systems. Similarly, PCORI is developing the Patient-Centered Clinical Research Network (PCORnet), which uses EHR data and patient-reported outcomes data to conduct new types of research. Health systems (e.g., Kaiser, Geisinger, U.S. Department of Veterans Affairs) and payers are also using existing databases to inform care and coverage decisions.

An obstacle to EHR-based observational research, is the fact that most EHRs use unstructured "free-text." Tools that can extract important clinical variables trapped in free-text narratives are currently being developed, but such technology is still nascent [63]. There are also ongoing efforts to develop interoperability standards and to advance common data models to improve the quality of EHR data. The HL7 Fast Healthcare Interoperability Resource is the emerging standard for transmission and exchange of healthcare information [64]. If broadly adopted, this standard would improve data retrieval and distribution through systematic integration of medical vocabularies into EHR systems. It would also overcome limitations of disease-specific/discipline-specific data dictionaries. Similarly, the Observational Medical Outcomes Partnership developed a standardized format for organizing, structuring, and studying observational clinical data, which could advance the use of EHR data for research [65].

Action Items:

- Professional societies, EHR vendors, and other stakeholders should work together to develop and implement standards for the transmission and exchange of healthcare information.
- Professional organizations should adopt a common data model to facilitate the exchange of analytic data, tools, and methodologies, and to promote consistent and reproducible analytic results.

4.4. *Use reimbursement strategies to incentivize evidence development*

CMS and private payers have several methods to incentivize data collection across cancer treatment modalities. Coverage with evidence development (CED), for example, is a tool used by payers when a promising new treatment has insufficient supporting evidence for a definitive coverage decision. Under CED programs, payers reimburse for a technology only if outcomes are documented in a registry or clinical study. Payers make a final coverage decision at the end of a study. Medicare used CED to cover PET for an expanded spectrum of cancer indications as part of the National Oncologic PET Registry, for instance, but could implement it more broadly to support the collection of evidence on cancer treatment modalities lacking strong supporting data [66]. Other CED examples include high-intensity focused ultrasound treatment for prostate cancer (France) [67] and stereotactic body radiotherapy for lung cancer (Belgium) [68].

In addition, the passage of the Medicare Access and CHIP Reauthorization Act (MACRA) of 2015 may create new opportunities for payment policy to influence evidence collection. Under MACRA, CMS will reimburse physicians under two new systems starting in 2019: (1) the Merit-based Incentive Payment System (MIPS), or (2), advanced alternative payment models (APM). Physicians participating in MIPS will report their performance across four major domains: (1) quality of care, (2) advancing care information, (3) improvement activities, and (4) cost or resource use [69]. The Oncology Care Model is an example of an advanced APM. Physicians participating in the Oncology Care Model will assume increased financial and performance accountability for episodes of care surrounding chemotherapy administration [70]. The data generated by physicians taking part in these payment models may be used for observational research and to inform the use of cancer treatment modalities. Moreover, the increased emphasis on performance and quality metrics in MACRA may lead healthcare providers to demand better data supporting potential treatment options.

Action Item:

- CMS and private payers should expand their use of CED and payment policies that may incentivize the collection of evidence across cancer treatment modalities.

5. Conclusions

This paper identifies five major factors that may contribute to differences in the quantity and quality of evidence supporting various cancer treatment modalities: (1) research funding, (2) methodological challenges to conducting RCTs in many therapeutic options, (2) regulatory agency oversight, (3) payment policies, and (5) hierarchy and sociological factors in medicine. The variability in evidence bases is problematic because it results in patients and clinicians confronting complex treatment decisions without sufficient supporting evidence. Promoting cross-disciplinary cancer research, conducting more pragmatic trials, facilitating efficient observational research via health information technology, and using reimbursement strategies to incentivize evidence development could all help to fill knowledge-gaps in scenarios where well-controlled phase 3 trials are absent, unachievable, or not necessary. The professional societies representing cancer care providers should collaborate to achieve this vision for multidisciplinary evidence development.

Declaration of interests

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