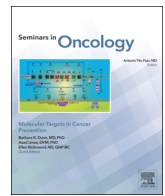




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# What constitutes an “unmet medical need” in oncology? An empirical evaluation of author usage in the biomedical literature

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## ABSTRACT

The phrase “unmet medical need” has important regulatory implications, but there is no empirical analysis of its real world usage. We sought to determine the annual US incidence, 5-year survival, and number of National Comprehensive Cancer Network (NCCN)-recommended regimens for indications described in the literature as an “unmet medical need.” We queried Google Scholar to identify publications where authors used the phrase “unmet medical need” to refer to a specific cancer indication. For each indication, we investigated the annual US incidence, 5-year survival, and number of NCCN recommended regimens. We identified 237 cancer indications considered by authors an “unmet medical need.” The term was found most frequently appended to breast cancer indications comprising 30 of the 237 citations (12.7%). This was followed by lung 24/237 (10.1%), hepatocellular 18/237 (7.6%), and prostate cancer 13/237 (5.4%). In 55 of 237 (23.2%) instances where an indication was described by the authors as an unmet medical need, the incidence was 1,000 cases per year, there were five regimens recommended by NCCN, and there was a 50% or greater 5-year survival. Forty-three of 237 (18.1%) indications had at least an incidence of 10,000 cases a year, 10 recommended regimens, and a 50% 5-year survival. In conclusion, “unmet medical need” has been used to describe cancer indications that are rare, and have few options and poor survival outcomes. However, the term has also been used to describe indications that occur commonly, have many treatment alternatives, and are clinically indolent with more encouraging expectations for survival. Some standardization is needed.

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## 1. Introduction

The phrase “unmet medical need” is important for cancer drug regulation. Evoking these words allows for expedited approval via the fast track and breakthrough pathway [1–3], as well as use of the accelerated approval program, which allows for drug approvals based on improvements in surrogate endpoints with unknown effects on survival or quality of life [4,5]. While the term has important implications, US Food and Drug Administration (FDA) guidance on the topic is understandably imprecise (Box 1). Consequently, some have suggested unmet medical need is quite broad, and can be used

to describe any cancer indication that lacks a curative option [6]. While others use the phrase, colloquially, to refer to cancer indications with few treatment options, infrequent annual incidence, poor survival outcomes, or some combination of these three [7,8].

We set out to evaluate the use of “unmet medical need” in the cancer biomedical literature. Specifically, we sought to estimate the annual incidence in the United States, the number of recommended National Comprehensive Cancer Network (NCCN) regimens, and the estimated 5-year survival for each indication called an “unmet medical need” in a systematic sample of contemporary articles.

## 2. Methods

### 2.1. Article selection

We searched Google Scholar on Oct 30, 2015 for the phrase “unmet medical need” AND cancer. We restricted the search to

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**Box 1**—FDA guidance (<http://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf>). The US FDA defines an unmet medical need as a condition not adequately addressed by available therapy. This occurs wherever there is no therapy, or where there is an existing therapy, a new treatment may nevertheless satisfy an unmet need if it:

- Addresses an aspect of the disease not addressed by prior therap(ies)
- Is superior to prior therapy(ies) regarding a serious outcome
- Has a measurable effect on a serious outcome for those who cannot tolerate the prior therapy(ies)
- Can be combined with other beneficial agents, while the prior therap(ies) cannot
- Avoid serious toxicity present in the prior therapy(ies), or avoids a toxicity which is a frequent cause of discontinuation, or avoids drug-drug interactions present with prior therapy(ies)
- Has similar safety or efficacy, but improved compliance to prior therap(ies)
- Addresses a drug shortage
- Has a novel mechanism of action, though similar safety or efficacy (which may in time prove useful) to prior therapy (ies)

2014, the last complete year at the time of our study, which resulted in 1,350 entries. Given that Google Scholar does not load beyond the first 100 pages of results, we retrieved the first 992 entries.

All articles were read by one of three reviewers (J.S., E.L, or F.S). Articles were included if “unmet medical need” was specifically used to describe a cancer indication (eg, first line, triple-negative breast cancer), or a treatment for a specific indication. All article types were eligible; including randomized controlled trials, meta-analyses, review articles, case reports, abstracts, etc.

We excluded articles that (1) did not refer to cancer in the United States; (2) did not refer to a specific cancer indication, for example, cancer-related cachexia or pain; (3) referred to cancer or hematology-oncology in general; (4) used the phrase “unmet medical need” not to describe cancer treatment but another aspect of cancer management for example, a biomarker for cancer, risk assessment/stratification; and (5) could not be retrieved through multiple search engines (Google Scholar or Medline through our institutional access). Our intention was not to create a comprehensive set of articles, but a representative cross-section, as we were concerned with only relative usage frequencies (and not absolute usage).

## 2.2. Incidence and survival

For each cancer indication, incidence and 5-year overall survival rates were retrieved from the Surveillance, Epidemiology and End Results (SEER) Cancer Stat Fact Sheet where available (found on <http://seer.cancer.gov/statfacts>). For incidence and 5-year overall survival rates for specific subtypes, we queried the primary literature. The [supplemental appendix](#) lists all articles used to more precisely estimate incidence or survival.

## 2.3. Number of regimens

By reviewing NCCN guidelines for each subtype of cancer and counting the number of unique treatments, we obtained the number of regimens available for treatment. We included

neoadjuvant, adjuvant, locally advanced, maintenance, and recurrent/metastatic regimens if the author(s) did not specify setting. In these instances, however, if a regimen appeared in multiple settings, for example, Adriamycin plus Cytoxan in adjuvant and metastatic breast cancer, it was counted only once.

## 2.4. Statistical analysis

Simple descriptive statistics are reported. Histograms were made using STATA v 13.0 (College Station, TX) and Excel. When ranges were reported, the median was used for the histogram, and ranges reported in [Table 1](#).

## 3. Results

We were able to identify 227 articles that used the phrase “unmet medical need”. Among these articles, a specific cancer indication was stated to constitute “an unmet medical need” 237 times. [Table 1](#) lists the specific cancer indications, the annual US incidence, the 5-year overall survival, and the number of available regimens according to the NCCN for each “unmet medical need”. The gray rows represent summary statistics, grouped by histology.

Of note, breast cancer indications were the most frequently referred to as “unmet medical need” 30/237 (12.7%), followed by lung cancer 24/237 (10.1%), hepatocellular cancer 18/237 (7.6%), and prostate cancer 13/237 (5.4%). [Figure 1](#) panels A-C show histograms for the 5-year survival, available number of NCCN regimens, and annual US incidence.

“Unmet medical need” was used to describe indications that are relatively common, indolent, and for which several options exist. Specifically, in 55 of the 237 (23.2%) instances the term “unmet medical need” was used to describe indications with an incidence of at least 1,000 cases a year, with five recommended regimens, and with at 5-year survival of at least 50% ([Table 1](#)). Forty-three of 237 (18.1%) uses of “unmet medical need” described indications with an incidence of 10,000 cases a year, at least 10 recommended regimens, and a 5-year survival of at least 50% ([Table 1](#)).

## 4. Conclusion

Our analysis is the first to examine real world usage of the phrase “unmet medical need” to describe cancer indications. We found this phrase has been often used to refer to situations with poor 5-year survival rates, have a low incidence in the United States and for which few treatment options exist ([Fig. 1](#)). But the phrase has also been evoked in situations that lacked these characteristics. We conclude there is little professional consensus for what constitutes an “unmet medical need.” Given this phrase has important regulatory connotations we believe some guidance is needed as to what constitutes an unmet medical need. Current FDA guidance is vague, and does not provide direct clarification for a field such as oncology ([Box 1](#)).

Cancer indications with “unmet medical need” can take advantage of US FDA programs to expedite the review of drug applications [1–3], as well as allow approval based on surrogate endpoints [4]. The practical result is that “unmet medical need” denotes cancer indications where, in the interest of bringing drugs to market rapidly, the standard of efficacy is lower. While there may be compelling reasons to do this in dire and rare situations with few treatment alternatives; these reasons may be less compelling if the indication being considered is more common, indolent in its clinical course, and has many treatment alternatives available.

Our study has several limitations. First among these is the fact our review was not comprehensive. We searched for articles in a

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