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Prioritization in Comparative Effectiveness Research: The CANCERGEN Experience in Cancer Genomics

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Abstract

Background—Systematic approaches to stakeholder-informed research prioritization are a central focus of comparative effectiveness research. Genomic testing in cancer is an ideal area to refine such approaches given rapid innovation and potentially significant impacts on patient outcomes.

Objective—To develop and pilot-test a stakeholder-informed approach to prioritizing genomic tests for future study in collaboration with the cancer clinical trials consortium SWOG.

Methods—We conducted a landscape-analysis to identify genomic tests in oncology using a systematic search of published and unpublished studies, and expert consultation. Clinically valid tests suitable for evaluation in a comparative study were presented to an external stakeholder

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group. Domains to guide the prioritization process were identified with stakeholder input, and stakeholders ranked tests using multiple voting rounds.

Results—A stakeholder group was created including representatives from patient-advocacy groups, payers, test developers, regulators, policy-makers, and community-based oncologists. We identified nine domains for research prioritization with stakeholder feedback: population impact; current standard of care, strength of association; potential clinical benefits, potential clinical harms, economic impacts, evidence of need, trial feasibility, and market factors. The landscape-analysis identified 635 studies; of 9 tests deemed to have sufficient clinical validity, 6 were presented to stakeholders. Two tests in lung cancer (*ERCC1* and EGFR) and one test in breast cancer (CEA/CA15-3/CA27.29) were identified as top research priorities.

Conclusions—Use of a diverse stakeholder group to inform research prioritization is feasible in a pragmatic and timely manner. Additional research is needed to optimize search strategies, stakeholder group composition and integration with existing prioritization mechanisms.

Keywords

landscape analysis; comparative effectiveness research; research prioritization; genomics; cancer

Introduction

With rapid technological innovation, competing interests, and a complex healthcare system, prioritizing research for evidence generation in healthcare is not easy. To improve the likelihood that stakeholders' needs are met in an environment of constrained research resources, a research prioritization process informed by stakeholder perspectives may offer significant value, and is a central theme of comparative effectiveness research (CER).[1-4]

Genomic testing in cancer is an ideal area to refine such approaches given the rapid pace of innovation and potentially significant impacts on patient outcomes. Genomic tests, defined herein as tests that detect genomic variation directly or in downstream molecular markers, are especially important in the realm of oncology due to the role of inherited and acquired genetic variation in tumor development, molecular classification of cancer subtypes and proliferation of a wide array of targeted therapies.

We describe the development and methods of a systematic and stakeholder-driven approach to prioritizing genomic tests in oncology for evaluation in a future comparative study. To our knowledge, this is one of the first undertakings to incorporate a systematic literature review, expert analysis, and external stakeholder input to inform research prioritization in collaboration with a clinical trials consortium.

Methods

CANCERGEN

The Center for Comparative Effectiveness Research in Cancer Genomics (CANCERGEN) is a consortium including the Fred Hutchinson Cancer Research Center (FHCRC), SWOG the largest cancer clinical trials consortium in the US, the University of Washington (UW), and the Center for Medical Technology and Policy (CMTP) - a non-profit organization involved in CER and stakeholder engagement activities. The CANCERGEN structure incorporates an external stakeholder group and the overall goal of CANCERGEN is to facilitate prioritization and the rapid design and implementation of prospective CER studies of genomic tests.

We developed a process to identify and select candidate genomic tests for presentation to stakeholders, and a process for prioritization based on stakeholder input (Figure 1).

Landscape-analysis

We refer to our process to identify genomic assays through evaluation of the literature, together with domain-specific expert consultation, as a ‘landscape analysis’, rather than as a ‘horizon scan’.[5-7] Horizon scanning efforts generally focus on interventions at the clinical horizon, and may not include expert review; our landscape analysis includes interventions still in the research phase, and therefore includes a larger range of technologies, coupled with expert consultation.

The unit of our search was studies of genomic and protein biomarkers in oncology that could be used for prediction (patient response to a particular therapy) and/or prognostication (patient disease prognosis). To ensure maximum population impact and manage the scope of the analysis, we limited our initial search to the five most prevalent cancers: lung, breast, colorectal, bladder and prostate. However, tests outside of these specific areas were included if identified by experts or collaborators.

The peer-reviewed literature search conducted in Medline was limited to the last five years (2004-2009); assays described in peer-reviewed published articles before this time with a high degree of importance should already be in development, or have further evidence published within our 5-year time window. We limited the search to “core” clinical journals (“jsubsetaim”, Abridged Index Medicus).

We searched the grey literature, [8] including oncology conference proceedings for 2 years prior to include studies that may not yet reached the peer-reviewed literature. We also reviewed evidence reports and topics of investigation from organizations such as the Early Detection Research Network (EDRN) and Evaluation of Genomic Applications in Practice and Prevention (EGAPP)[7].

CANCERGEN investigators identified one independent expert at the FHCRC and UW in each of the five cancer areas, to whom a list of studies was sent, after applying 2nd round exclusion criteria (described below). Experts were asked to rate the potential healthcare impact of the genomic technologies as well as provide feedback on any potential tests our landscape process failed to identify. We also elicited expert input from SWOG leadership, including disease-specific committee members on tests of potential interest, as well as external stakeholder input for identification of tests.

Inclusion/Exclusion criteria

Exclusion criteria were applied in four rounds. First, studies were excluded if they were non-quantitative reviews, did not include predictive or prognostic endpoints, and were not associated with any genomic tests. Second, studies that were not validated, study size too small ($n < 50$), prediction/prognostication effect uncertain, and study not validated (not replicated in independent, separate finding) were excluded. Third round exclusion criteria increased the stringency for acceptance in terms of trial size ($n > 90$), clinical impact on affected population, predictive rather than solely prognostic tests, and those interventions with large RCTs already in progress. Fourth round inclusion/exclusion criteria for final selection included strength of biomarker validity, the potential for healthcare system impact, availability of patients for trials, SWOG investigator expertise and interest in subject area, relevance to current clinical development programs, availability of trial funding, and evidentiary gaps. These criteria were developed iteratively based upon the studies identified, rather than being pre-specified.

Stakeholder Selection Criteria

An external stakeholder advisory group (ESAG) was formed to engage stakeholders in the evidence-generation and feedback process. Potential categories for stakeholder participation (patient/consumer, payer, clinician, policy-maker/regulator, industry) were established requiring nominees that were senior-level members within their affiliated organization, and possessed a working knowledge of genetics, personalized medicine, and/or oncology. Practical experience in evaluation of technology including genomic tests was also desirable.

Stakeholder education and prioritization framework

We developed a prioritization framework modeled on the approach used by EGAPP, an evidenced-based recommendation group for genomic tests, and refined these with the input of the external stakeholder group. [9-11] One-page Test-Target-Profiles (TTPs) were created summarizing these nine criteria alongside more detailed Topic-Briefs of 3-5 pages. The TTPs and Topic-Briefs were sent to stakeholders approximately two weeks ahead of an in-person meeting.

Prioritization process

Before the in-person meeting, stakeholders were asked to rank tests in order of importance. At the meeting, each of the tests was presented by the investigator who led the preparation of the respective TTP and Topic Brief. Stakeholders could bring up tests of particular interest to them, not previously identified through the landscape analysis and/or expert input. After all genomic applications were discussed, stakeholders were asked to again rank the tests in terms of research prioritization. A written meeting summary was shared with the entire ESAG and a follow-up teleconference was held two weeks post-meeting with those members that were unable to attend in-person. A third round of voting on prioritization was conducted on-line immediately following the teleconference. A modified-Delphi procedure [12] with an electronic audience polling system was used to obtain stakeholder responses throughout the prioritization process.

Results

Landscape analysis

The Medline search identified 199 studies; 436 studies were identified through the grey literature. These 635 studies were then narrowed to 188 studies based on the first set of exclusion criteria (1st round), and to 49 studies by applying 2nd round exclusion criteria. 3rd round exclusion criteria narrowed the number of unique tests to 9. After joint consultation with SWOG leadership and application of 4th round inclusion/exclusion criteria, 6 tests remained for presentation to stakeholders (Figure 2).

Stakeholder composition and prioritization process

Thirty-one total members were identified of which 13 were recruited; 2 of 4 from patients and consumers, 3 of 6 from health care providers, 2 of 6 from industry, 3 out of 6 from purchasers and producers, and 3 of 9 from policy makers and regulators. The domains of the prioritization framework (Figure 3) included population impact; current standard of care strength of association (analytical and clinical validity); potential clinical benefits, potential clinical harms, economic impacts, evidence of need clinical trial feasibility; and market factors (reimbursement status). The 6 tests selected for presentation to stakeholders (for which TTPs and topic briefs were prepared) are shown in table 1. Eight of 13 ESAG members attended the in-person meeting and voted; in the follow up teleconference all 13 members of the external stakeholder group submitted their votes.

Genomic tests

The three top ranked tests were: 1) EGFR mutation testing for erlotinib maintenance therapy after 1st line chemotherapy in NSCLC, 2) ERCC1 expression testing for platinum-based adjuvant therapy in resected NSCLC, and 3) CEA, CA15-3/CA27.29 tumor markers for detection of breast cancer recurrence after primary therapy (1,2,3 in Table 1). Prospective studies and designs in these areas are now in different stages of preparation/submission.

Discussion

Implications

The processes developed here leveraged wide-ranging expertise coupled with stakeholder involvement in directing a research prioritization effort in CER. Our experience indicates the following aspects are valuable in stakeholder-informed CER prioritization: 1) systematic searches with explicit inclusion/exclusion criteria and expert input, 2) diverse stakeholder group with unique backgrounds, opinions and perspectives, 3) a formal prioritization framework including explicit domains, 4) concise stakeholder educational materials, 5) a ranking methodology involving multiple rounds of feedback and re-evaluation, and 6) early involvement of external stakeholders and leaders within the research organization.

Our findings also suggest that use of expert consultation to identify technologies in the landscape analysis may be more efficient, as interaction with SWOG experts would have independently identified 4 out of 6 of the candidate tests presented to stakeholders. However, a systematic approach may carry greater validity with stakeholders. Additional research is needed to identify an optimal combination of systematic and expert-informed landscape-analysis.

The implications of our study in regard to cancer genomics are as follows: only a small number of tests (9 in the 3rd round and 6 in the 4th round) passed our inclusion/exclusion criteria, suggesting that only a handful of genomic tests not yet already being evaluated are candidates for a large scale prospective clinical study. Notably, stakeholder involvement was influential in highlighting the priority of breast cancer tumor markers, which have been in use in practice for many years but lack high quality evidence supporting their benefit.

Following these efforts, the CANCERGEN team has designed and submitted a prospective cohort study for *EGFR* testing in lung cancer, and study design is underway for breast cancer tumor markers. Furthermore we are conducting a feasibility analysis on *ERCC1* testing in lung cancer, with preliminary studies on patient reported outcomes and preferences underway.

Limitations

There are several limitations of our study worth noting. Our landscape analysis was built upon studies that were published and accessible to us. However, since many studies are not published our results may incorporate a publication or reporting bias. CANCERGEN investigators, rather than stakeholders, were responsible for developing and application of inclusion/exclusion criteria. However, given the large range of studies analyzed and the iterative nature of inclusion/exclusion criteria developed, it would not be pragmatic and timely to engage stakeholders for a discussion of all studies.

We confined our literature search to core clinical journals and the five most prevalent cancers; a search of the entire literature might have revealed promising tests, but this was too resource and time-intensive to carry out. A search of Medline without restriction to core

clinical journals yielded over 4000 studies. We sought to mitigate the possibility of missing promising tests by the use of expert input.

We adopted an approach of bringing together diverse stakeholders consistent with CER principles; however, these stakeholders may bring in unique perspectives. By supporting an open discussion in a neutral forum we sought to bring out these opinions, allowing a constructive exchange of ideas and concerns, where specific interests and perspectives could be examined. Although the same stakeholder group was polled consistently throughout the process, the stakeholder group was too small to quantitatively assess patterns in the voting. Lastly, the process described above relied on qualitative evaluation of the potential value of research; we are currently working on formal value of information (or value of research) calculations to derive quantitative estimates for the top three candidates.[4, 13-15]

Conclusion

We developed a CER-based approach that provides diverse stakeholders a process for prioritizing research into genomic tests. SWOG, as one of the leading publically funded cancer cooperative groups, is actively exploring the use of comparative effectiveness principles and expertise in understanding how to better design and conduct relevant clinical trials that help better prevent, diagnose or treat people. Further research is needed to develop approaches for integration with existing prioritization mechanisms.

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Figure 1. Landscape Analysis and Test Selection Overview: CANCERGEN project milestones including landscape analysis, and stakeholder assessment.

Figure 2. Overall results, showing tests contributed by the landscape analysis through to stakeholder voting.

CANCERGEN Test Target Profile (TTP)	
Criteria	
Indication – Population Impact	
Current Standard of Care	
Strength of Association (Clinical Validity)	
Potential Clinical Benefits (Compared to current standard of care)	
Potential Clinical Harms (Compared to current standard of care)	
Economic Impacts (Cost of therapies, Cost of test)	
Evidence of Need (Likelihood evidence will change clinical practice)	
Clinical Trial Implementation and Feasibility (Patient recruitment and funding)	
Market Factors (Clearly defined and consistent coverage positions)	

Figure 3.
Sections of the TTP used to communicate with stakeholders

Table 1

Tests chosen for presentation to external stakeholders

1	EGFR mutation testing for erlotinib maintenance therapy after first-line chemotherapy in advanced NSCLC ¹³
2	ERCC1 expression testing for platinum-based (cisplatin/carboplatin) adjuvant therapy in resected early-stage NSCLC ¹⁴
3	CEA, and CA 15-3 and CA 27.29 markers for detection of recurrence after primary breast cancer therapy ^{15, 16}
4	EGFR gene copy number (FISH) testing and cetuximab therapy in advanced NSCLC ^{17,18}
5	GEP in multiple myeloma ¹⁹
6	BRAF mutation testing in colorectal cancer to guide use of cetuximab and panitumumab ^{20, 21}

CA indicates cancer antigen; CEA, carcinoembryonic antigen; FISH, fluorescence in situ hybridization; GEP, gene expression profile; NSCLC non-small-cell lung cancer.