2017 SCIENTIFIC REPORT

Regulatory Advancements for Patients

FRIENDS of CANCER RESEARCH

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INTRODUCTION

Throughout the year, Friends of Cancer Research (*Friends*) develops and publishes white papers and publications that address leading-edge science and regulatory issues. Using our collaborative approach, *Friends* convenes multi-stakeholder working groups, hosts scientific conferences, and conducts original research to promote innovative and meaningful improvements in drug development and patient care.

Friends' white papers and publications stemming from expert working groups and discussions at conferences serve as resources for federal officials, regulators, drug sponsors, diagnostic companies, academics, and patient advocates. These publications help inform key stakeholders and catalyze the development of innovative strategies and regulatory policy for the expeditious development of novel treatments for cancer patients.

In 2017, *Friends*' white papers and publications focused on several key themes:

- Ensuring optimal development and oversight of diagnostic tests
- Promoting new strategies for expediting drug development
- Establishing recommendations for broadening eligibility criteria in oncology clinical trials
- Identifying approaches for updating drug labels
- Demonstrating the importance of the patient voice in value assessment frameworks

This booklet contains the full text of the *Friends* 2017 white papers and publications. We hope this collection will be a resource for those in the drug development and regulatory space and informative for those interested in science and regulatory issues in oncology.

FRIENDS of CANCER RESEARCH

A FRIENDS OF CANCER RESEARCH WHITE PAPER

TRENDS IN THE MOLECULAR DIAGNOSIS OF LUNG CANCER

RESULTS FROM AN ONLINE MARKET RESEARCH SURVEY

INTRODUCTION

Beginning in 2015, Friends of Cancer Research (*Friends*) and the Deerfield Institute began a research collaboration to study trends in the use of molecular diagnostics in oncology. The goal of the partnership was to fill knowledge gaps regarding the type of molecular diagnostics that oncology practices in the United States use to guide treatment with targeted therapy. These gaps exist because prevailing data sources, such as claims data, lack the granularity necessary to conduct research into the use of molecular diagnostics. To address these gaps, *Friends* and the Deerfield Institute designed and implemented a direct-to-physician questionnaire and patient chart audit to characterize trends in the use of specific diagnostic tools that are used to deliver personalized cancer care.

The first output of this research collaboration was in 2016, when *Friends* and the Deerfield Institute jointly published a study in the journal *Personalized Medicine in Oncology*.[1] This study addressed a major policy issue, and contributed to the debate over the use of laboratory-developed tests in non-small cell lung cancer (NSCLC). Following publication of the study, *Friends* and the Deerfield Institute participated in a briefing on Capitol Hill to discuss policy implications of the work and educate the public about the US Food and Drug Administration's proposal [2] to extend oversight to laboratory-developed tests.

In this white paper, *Friends* and the Deerfield Institute are releasing additional data captured through the course of their research partnership. The data presented below characterize trends in the collection of tumor tissue to support molecular testing, as well as the impact of the timing of molecular testing on treatment decisions.

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ABOUT FRIENDS OF CANCER RESEARCH

Friends of Cancer Research drives collaboration among partners from every healthcare sector to power advances in science, policy, and regulation that speed life-saving treatments to patients.

ABOUT THE DEERFIELD INSTITUTE

The Deerfield Institute is the internal research group at Deerfield Management Company, a healthcare investment firm dedicated to advancing healthcare through investment, information and philanthropy.

BACKGROUND ON MOLECULAR TESTING IN LUNG CANCER

In the last fifteen years, the treatment of lung cancer has been transformed by the identification of genomic alterations that play a role in tumor growth and maintenance. Termed "oncogenic drivers," these alterations produce downstream effects that can be negated by targeted agents. In lung cancer, several drugs have been approved by the US Food and Drug Administration (FDA) that successfully target oncogenic drivers, and which have been shown to significantly improve patient outcomes compared to traditional cytotoxic chemotherapy. In response to this development, clinical guidelines began to strongly recommend molecular testing, a process in which a laboratory test is ordered to identify the presence of oncogenic drivers in tumor cells and thus determine eligibility for targeted therapy.

A range of technologies are employed to perform molecular testing, from sophisticated genomic sequencing platforms to simpler single-marker assays. These tests, broadly referred to as molecular diagnostics, have quickly become an essential component of the treatment of advanced lung cancer. The simpler tests, which identify the presence of a single molecular marker, are often called "companion diagnostics" because they are developed and tested alongside targeted therapies in clinical trials. The more complex tests, which use genomic sequencing technologies to detect alterations in tens to hundreds of genes simultaneously, have been made possible by next-generation sequencing (NGS), a collection of technologies that allow rapid sequencing of large segments of an individual's DNA and even an individual's entire genome.[3] While the use of NGS panels for prescreening patients for biomarker-targeted clinical trials has been well documented,[4] the utility of this technology in direct patient care has not been fully characterized.

Some have argued that, given the expanding number of oncogenic drivers for which testing is recommended, NGS panels represent a more cost-effective and straightforward means of performing molecular testing.[5] However, the ability of the average physician to correctly interpret the results generated from these tests remains a concern.[6] Enhanced communication between oncologists and pathology departments has been encouraged to alleviate these concerns. Single-marker assays, on the other hand, have easily interpretable results, but may exhaust available tumor tissue before a satisfactory number of tests have been performed. Current guidelines accept the use of both methodologies.[7]

Three oncogenic drivers are targets for approved therapies in lung cancer: epidermal growth factor receptor (EGFR) mutations, and anaplastic lymphoma kinase (ALK) and *ROS1* gene rearrangements. *EGFR* mutations were discovered in 2004, followed by *ALK* in 2007 and *ROS1* in 2008. In adenocarcinoma, a major subtype of non-small cell lung cancer where oncogenic drivers have been most successfully targeted, *EGFR* mutations occur in about 10% to 15% of patients, while *ALK* and *ROS1* rearrangements occur in less than 5% of patients. Drugs targeting each of these drivers have been demonstrated to be superior to chemotherapy in head-to-head studies.[8]

In 2016, studies estimated that between 70% and 95% of US oncology practices perform molecular testing in lung cancer, up from an estimated 20% of practices in 2010.[1,9-11] Despite these gains, concerns have been raised that process inefficiencies in clinical practice may be preventing molecular diagnostics from having their greatest possible impact on patient management. One concern is that a slow, disorganized testing process may drive patients to receive chemotherapy before the likelihood of their benefiting from less toxic targeted therapies is known.[12] Another is that shortcomings in the communication between the various specialties involved in the molecular testing process have led to delays and uncoordinated care, especially in the tissue collection process, where lack of sufficient tissue has been cited as an impediment to testing.[13] Strategies for process improvement and physician education have been undertaken to address these concerns.[14]

SURVEY GOALS

To better understand the challenges that practices face in testing patients for oncogenic drivers, as well as the uptake of various testing technologies, a questionnaire was developed to obtain the opinions and experiences of practicing medical oncologists regarding the molecular testing process. Numerous specialties are involved in decisions about when and how to test patients and rarely does a single individual have full knowledge of all the steps in the process. However, as the primary point of contact with the patient, the medical oncologist was identified as the person most likely to provide insight into the entire process, from diagnosis, to testing, to treatment. The setting of non-small cell lung cancer (NSCLC) was identified as an area of focus due to the presence of multiple known oncogenic drivers and approved targeted agents, as well as the existence of several approved molecular diagnostics in that setting.

CHARACTERISTICS OF RESPONDENTS

The final sample included 157 respondents who both met the eligibility criteria and completed the survey (Appendix Table 2, page 18). The clear majority of respondents were medical oncologists (148, 94%), with an additional 6% either nurses or physician assistants. More than half of respondents reported spending most of their time in a private practice (88, 56%), while the remaining were split between community (36, 23%) and academic settings (29, 18%). The region with the largest number of respondents was the southern United States (63, 40%), with an additional 24% (37) from the Northeast and 18% from the Midwest and West, respectively.

CHARACTERISTICS OF TREATED PATIENT POPULATIONS

Respondents reported diagnosing on average 63 patients with NSCLC in the past 12 months, with an average of 53% presenting with stage IV disease (Appendix Table 1, page 17). Among their patients with stage IV disease, respondents reported an average histology breakdown of 62% adenocarcinoma and 29% squamous cell carcinoma.

SURVEY RESULTS

A selection of survey questions is reproduced below.

What proportion of your stage IV NSCLC patients of the following subtypes received a genetic test?

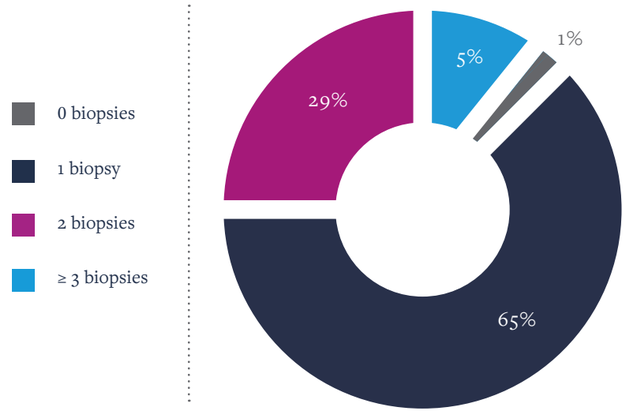
Proportion of Stage IV Patients Who Received Genetic Alteration Tests

		Type of setting				Region			
	Total n=157	Private Clinic n=88	Academic Center n=29	Community Based Center n=36	Other n=4	NE n=37	MW n=29	S n=63	W n=28
Squamous cell carcinoma	24%	20%	25%	29%	3%	28%	15%	25%	23%
Adenocarcinoma	87%	81%	96%	84%	94%	94%	88%	91%	62%
Large cell	68%	77%	71%	50%	70%	74%	44%	71%	78%
NSCLC not otherwise specified (NOS)	75%	75%	87%	43%	94%	85%	85%	67%	59%

The most common types of NSCLC are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma. Genetic alteration testing is recommended in adenocarcinoma, where *EGFR, ALK*, and *ROS1* alterations are most prevalent. At the time that this survey was implemented, clinical guidelines recommended against testing for squamous cell histologies. Since then, these restrictions have been loosened due to the presence of some positive cases and the possibility of incorrect histological classification.[5] In practice, 87% of stage IV adenocarcinoma patients in our sample received a genetic alteration test, although the testing rate was predictably higher at academic centers.

When testing for genetic alterations in NSCLC, how many separate tissue biopsies are typically performed per patient over the course of his/her disease progression?

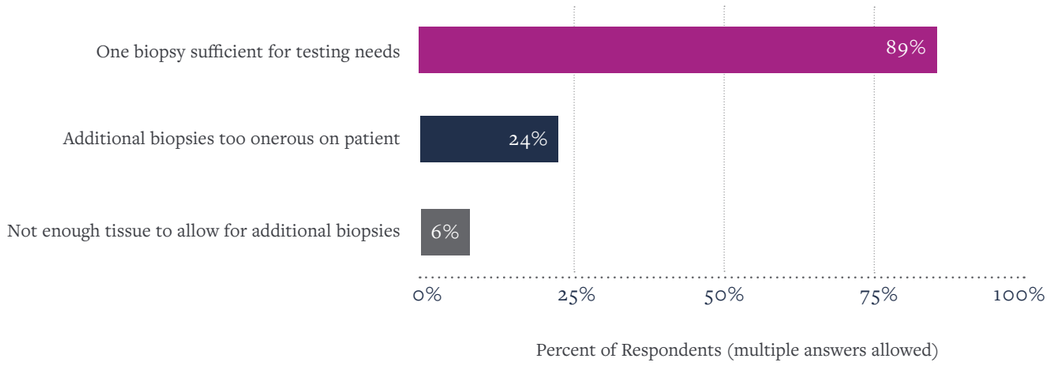
Number of Separate Tissue Biopsies Performed n=157



As routine molecular testing began to pick up speed following the FDA approval of crizotinib (Xalkori) in 2011 for ALK-positive lung cancer and the narrowing of the approval of erlotinib (Tarceva) in 2013 for EGFR-positive lung cancer from a broader lung cancer indication, many observers pointed to acquisition of adequate tissue samples as a primary barrier to molecular testing. Many patients with lung cancer have small tissue specimens acquired through biopsies. Since some tissue is required initially to determine histology, there is sometimes limited tissue left over for use in molecular testing. There is often the possibility of performing additional biopsies, but these are invasive procedures and can be burdensome on patients. Thus, many observers have called for biopsy techniques that gather enough tissue for multiple purposes.

You mentioned one tissue biopsy is typically performed to support genetic alteration testing in NSCLC. Why is only one tissue biopsy typically needed?

Reasons Cited for Performing One Biopsy n=102



The finding that most respondents in this survey perform only one biopsy coupled with their explanation that one biopsy was sufficient for testing needs can have two possible explanations. First, practices may be relying more heavily on techniques that collect more tissue, such as CT-guided lung biopsies using core biopsy needles, rather than fine-needle aspiration (FNA).[15] Another plausible explanation is that the widespread use of genomic sequencing, shown in the table below, has led to practices requiring less tissue to conduct molecular testing. Genomic sequencing using NGS has been shown to require substantially less tissue than first-generation genomic testing, allowing physicians to test for a range of markers using a small amount of tissue.[5]

What type of test is used when looking for genetic alterations?

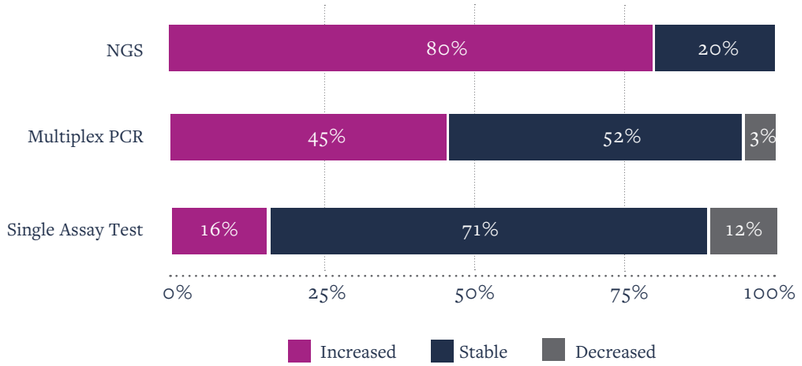
Type of Test Used Across Practice Setting and Region

		Type of setting				Region			
	Total n=157	Private Clinic n=88	Academic Center n=29	Community Based Center n=36	Other n=4	NE n=37	MW n=29	S n=63	W n=28
Single assay test	58%	52%	52%	78%	50%	57%	52%	59%	64%
Multiplex PCR	18%	17%	24%	17%	25%	11%	10%	17%	39%
Multi-gene panel sequencing	36%	33%	59%	28%	0%	32%	34%	32%	50%
Unsure / Info not available	21%	26%	10%	14%	50%	27%	17%	24%	11%

Single assay tests were used by 58% of respondents, with the remainder split between multi-gene panels using Next-Generation Sequencing (NGS) (36%) and multiplex PCR (18%). The use of NGS differed across practice settings, indicating a meaningful relationship between multi-gene panels using NGS use and practice setting (59% academic, 33% private, 28% community; p=.02). No similar relationship was observed between use of NGS across geographic region or hospital ownership category (p=.37, p=.53, respectively).

How has the utilization of the following test formats changed in the past year, if at all?

Changes in the utilization of the various test formats in the past year



Among the 56 respondents who reported using NGS-based panels to test patients for lung cancer mutations, 80% reported that the rate of test utilization increased in their practice during the past year. Among the 91 respondents who reported using single assay tests, 71% reported that usage of this testing technique was stable in the past year, suggesting that most practices are still heavily relying on single assay tests. Another popular category of tests called multiplex polymerase chain reaction (PCR) uses a methodology that can simultaneously determine the mutational status of a handful of genes using small tumor samples. Rather than identifying new or additional drug targets, multiplex PCR allows physicians to efficiently test for a series of known, or actionable targets.[3] Nearly half of the 29 respondents who reported using this type of test reported that usage has increased in the past year.

Of the patients you diagnosed with NSCLC in the past year, please indicate what proportion were screened for the following mutations.

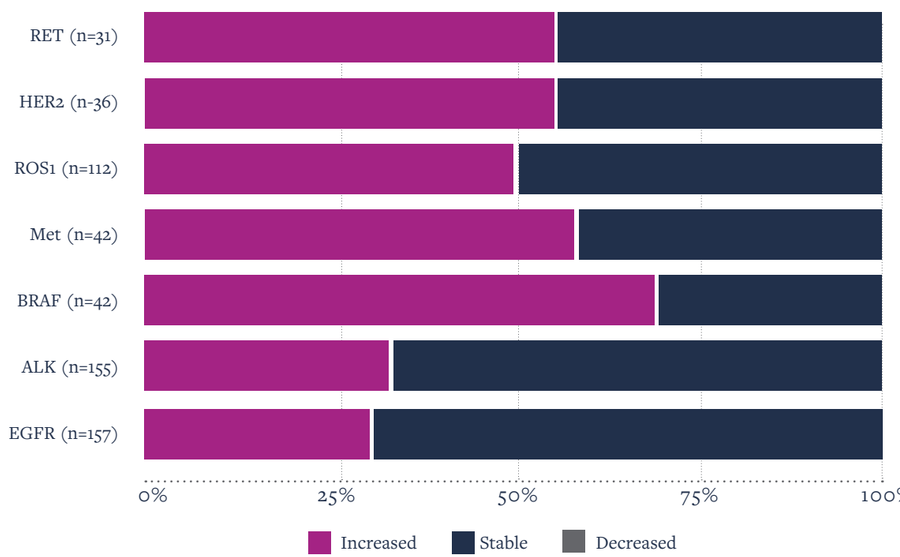
Proportion of Newly-Diagnosed Patients who were Screened for the Following Genetic Alterations

		Type of setting				Region			
	Total n=157	Private Clinic n=88	Academic Center n=29	Community Based Center n=36	Other n=4	NE n=37	MW n=29	S n=63	W n=28
EGFR mutations	72%	76%	72%	68%	31%	79%	66%	67%	79%
ALK rearrangement	69%	71%	70%	67%	31%	75%	66%	63%	78%
BRAF V600E mutation	18%	8%	36%	12%	1%	11%	18%	25%	13%
MET amplification	17%	13%	31%	6%	1%	11%	19%	24%	11%
ROS1 rearrangements	38%	36%	45%	32%	4%	29%	39%	36%	57%
HER2 mutations	16%	7%	33%	9%	1%	14%	15%	20%	11%
RET rearrangements	14%	7%	28%	8%	0%	12%	15%	17%	11%
Other	2%	0%	5%	0%	0%	0%	10%	0%	0%

Testing for *EGFR, ALK*, and *ROS1* alterations, which are the only oncogenic drivers that are currently associated with approved drugs in lung cancer were tested at the highest rates. Testing for *EGFR* was the highest (72% overall) most likely due to the presence of three FDA-approved therapies targeting *EGFR* mutations, the high prevalence of *EGFR*-positive status in patients with adenocarcinoma (10%-15%), and the fact that many sequential testing algorithms recommended in the literature suggest testing for *EGFR* prior to other drivers if single assay tests are used.

How would you describe the trend in genetic alteration testing for each of the following tests?

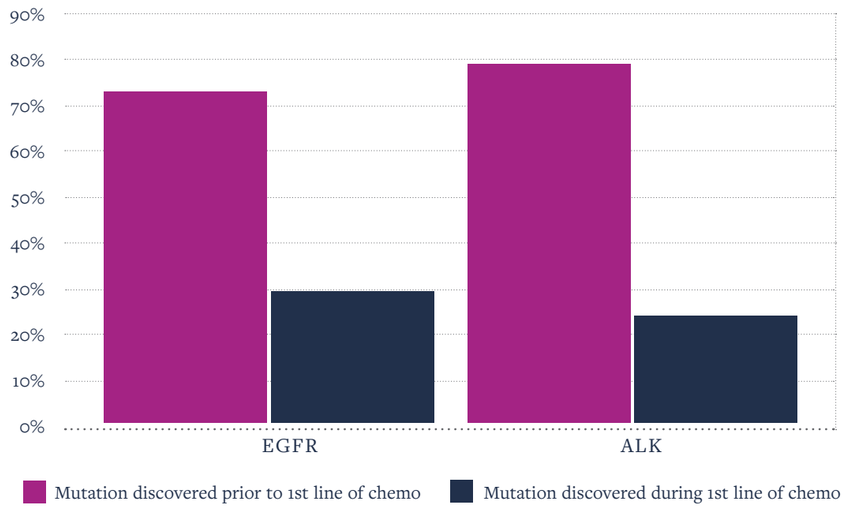
Trends in mutation testing 2014-2015



Mutation testing for *EGFR* and *ALK* was reported as stable between 2014 and 2015, while detection of other mutations increased. This is probably linked to an increase in use of multiplex *PCR* and *NGS*, which allows for more oncogenic drivers to be detected. Particularly sharp increases were reported for mutations associated with the *BRAF* and *MET* genes, which both occur in less than 5% of patients with adenocarcinoma, but which can be targeted with existing drugs. Dabrafenib (Tafinlar) was approved in 2013 for patients with metastatic melanoma with *BRAF* mutation, and early-stage trials testing the drug's effectiveness in lung cancer have been promising.[5] Crizotinib (Xalkori), which is already approved for several lung cancer indications, has been demonstrated to have activity in patients with *MET* amplification.

Thinking of your EGFR and ALK positive patients, what proportion had their mutation discovered prior to 1st line chemotherapy, and what proportion during 1st line chemotherapy?

Proportion of Patients who had Mutation Discovered Prior to 1st-Line Therapy



Respondents reported that among patients who tested positive for EGFR mutations and ALK rearrangements, 73% and 78%, respectively, had their mutation discovered prior to undergoing chemotherapy. Of the EGFR positive patients who were tested prior to undergoing chemotherapy, 81% received erlotinib and 17% afatinib. Of the ALK positive patients who were tested prior to undergoing chemotherapy, 95% received crizotinib and 4% ceritinib. For the patients who had their EGFR mutations discovered after treatment with chemotherapy had already begun, respondents reported that 71% completed chemotherapy prior to starting erlotinib or afatinib, 23% interrupted chemotherapy to start erlotinib or afatinib, and 6% added erlotinib or afatinib to current treatment. For the remaining ALK positive patients who had their mutation discovered during 1st line chemotherapy, 56% completed planned chemotherapy before starting crizotinib or ceritinib, 39% interrupted chemotherapy to start crizotinib or ceritinib, and 4% added crizotinib or ceritinib to current treatment.

DISCUSSION

In this survey, we asked oncologists to share their experiences and perspectives on how molecular diagnostics are used in the treatment of lung cancer. The role of molecular diagnostics in medical practice has changed rapidly in recent years, as have advances in the field of genomics. New targeted therapies and more sophisticated testing platforms have expanded the landscape of personalized medicine, particularly in lung cancer.

In developing this physician questionnaire, we sought to answer three questions about the use of molecular diagnostics:

1. **Is availability of adequate tissue samples a rate-limiting step in tumor molecular analysis?**
2. **What is the uptake of next-generation sequencing platforms across practice settings and regions?**
3. **How often is molecular testing performed too late to enable patients to be treated with a targeted therapy in the first-line setting?**

Broadly, these questions address whether practices are adapting to a changing environment to allow molecular diagnostics to have their greatest impact on patient management.

We found that most oncologists did not report that access to adequate tissue samples was a major impediment to molecular testing. Sixty-five percent of all respondents reported performing only one biopsy to support tumor molecular analysis, while also noting that it was sufficient for testing needs. Surprisingly, only 6% of respondents cited an inadequate amount of tissue in providing reasons for the number of tissue biopsies they typically perform. Despite these positive findings from physicians' self-reports, concern about adequate tissue remains high: 79% of respondents reported extreme to moderate concern about obtaining adequate tissue for molecular testing.

A second component of the questionnaire related to the methodology of the test that was used to perform molecular testing. Using three general categories of tests identified in NCCN guidelines—single gene assays, multiplex polymerase chain reaction (PCR) systems, and broad molecular profiling systems, such as next-generation sequencing (NGS)—we asked respondents to choose which test types they use. Respondents could choose multiple test types. Over a third (36%) of all respondents reported using NGS, with the largest number of users coming from academic settings. The finding that there existed a 31% difference in the proportion of respondents from academic centers who reported using NGS compared to respondents from community centers was unsurprising given that many academic centers have developed in-house NGS platforms for both routine patient care and research use.

Adequate tissue acquisition and uptake of new technologies are positive findings, although for these developments to have the greatest impact on patient care, testing needs to be timed so that patients can receive targeted therapy in place of less effective alternatives. Respondents reported that 27% and 22% of their EGFR and ALK patients had mutations discovered when patients had already begun treatment with a non-targeted agent. Furthermore, among these patients, 71% and 56%, respectively, completed chemotherapy before starting additional treatment with targeted therapy. It follows from this finding that nearly 20% of their EGFR positive patients and 12% of their ALK positive patients had targeted therapy delayed due to the timing of molecular testing. Testing at earlier stages of disease progression may prevent patients undergoing chemotherapy when they are eligible for targeted therapy.

This study has several limitations. First, a true response rate cannot be calculated for this survey. Physicians were invited by email or postal mail, and they voluntarily self-screened based on knowledge, interest, and experience level in treating this condition. They had the opportunity to respond to the survey invitation by logging on to the online survey. As it is unknown how many physicians successfully received, reviewed, and self-screened for this survey invitation, the true response rate cannot be calculated. Additionally, response to the survey was voluntary, which may introduce bias in the responses that were provided.

CONCLUSION

Despite widespread concerns regarding the adequacy of tissue samples to support molecular testing, we found that for most respondents, acquisition of adequate tumor tissue was not a rate-limiting step in molecular testing. However, timing of testing does appear to be preventing a sizable portion of patients from receiving targeted treatment prior to chemotherapy, highlighting the need for more early-stage testing. Finally, use of NGS is still primarily concentrated in academic research institutions, indicating that its use outside a research setting is not yet widespread.

FUNDING SUPPORT

Financial support for this research was provided by the Deerfield Institute, the internal research group at Deerfield Management Company, a healthcare investment firm dedicated to advancing healthcare through investment, information and philanthropy.

METHODS

Study sample design

A universe sample frame of NSCLC-treating oncologists was created by sourcing Symphony Health Analytics' 2014 insurance-claims activity for all oncologists in the United States for both the 162 series of lung cancer ICD9 codes as well as the claims-activity related to prescribing lung-cancer targeted therapies (Erlotinib, Afatinib, Crizotinib, and Ceritinib). By combining

both sources, we identified 10,184 oncologists with activity related to the care of lung cancer patients. In order to ensure that the physicians targeted for this research would have the required minimum number of patients to participate, we further limited this sample to those with at least three unique lung cancer patients in all of 2014. This reduced the list of oncologists to 8,129, all of which were invited to participate in the survey by e-mail or postal mail. Oncologists were eligible to participate if they personally managed at least 5 NSCLC patients per month, and diagnosed at least one NSCLC patient in the past 12 months. A total of 221 oncologists responded to the survey and 157 met eligibility criteria and completed the survey. Participants were offered an industry-standard honorarium as compensation for their time in completing the survey. The survey was administered online and was fielded from April 8, 2015 to September 14, 2015.

Data collection

A questionnaire was developed to assess current NSCLC treatment practices and level of use of molecular testing in the United States. We developed and pre-tested this instrument through interviews and consultations with 13 NSCLC-treating oncologists. The online questionnaire included both quantitative and qualitative questions, and covered the following topics: patients' characteristics such as disease clinical stages and stage IV histological subtypes, number of biopsies performed, proportion of patients who received a test, which genetic alterations was tested, what was the outcome of the test, what are the trends in genetic alterations testing, what type of test is used (single assay vs multiplex PCR vs next generation sequencing), sequencing of tests, detection of T790M mutation, management of EGFR positive and ALK positive patients.

Data analysis

All survey data were analyzed in aggregate and the individual identities of the survey respondents were blinded to the study authors. The planned analyses for quantitative data were descriptive and included means and percentages. Data were analyzed in total and split per type of practice and geographical location. Qualitative data were analyzed thematically and coded according to the main themes of the survey questions. Any response that addressed multiple themes was counted as multiple comments.

Statistical analyses

An analysis was conducted to determine if a relationship existed between test type and either practice setting, geographic region, or hospital ownership. For the purpose of the analysis, the test type variable was calculated to reflect the binary outcome of "Next-generation Sequencing" or "No Next-generation Sequencing". Chi-squared test of independence was conducted with the Python statistical library Scipy. Descriptive statistics were used to characterize aggregate responses to survey questions.

Ethics, consent, and permissions

By electing to complete the survey, respondents provided consent to use their anonymous responses to the survey questions. The study did not involve patients and data on patient characteristics within colonoscopy practices were provided only in the aggregate. As such, there was no institutional review board and/or licensing committee involved in approving the research and no need for informed consent from the participants per US regulations (§46.116 General requirements for informed consent. Available at: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.102).

APPENDIX

Table 1. Respondents' Report of Treated Patient Populations

CHARACTERISTICS		TOTAL SAMPLE N=157
MEAN NUMBER OF PATIENTS DIAGNOSED IN PAST 12 MONTHS		62.9
DISEASE STAGE	STAGE I	8%
	STAGE II	13%
	STAGE III	27%
	STAGE IV	53%
HISTOLOGIC SUBTYPE	SQUAMOUS CELL CARCINOMA	29%
	ADENOCARCINOMA	62%
	LARGE CELL	4%
	NSCLC NOT OTHERWISE SPECIFIED (NOS)	4%
	OTHER	0%

APPENDIX

Table 2. Characteristics of Survey Respondents

CHARACTERISTICS		TOTAL SAMPLE N=157 NO.	%
ROLE	ONCOLOGIST	148	94%
	NURSE	4	3%
	PHYSICIAN	5	3%
GEOGRAPHIC REGION	MIDWEST	29	18%
	NORTHEAST	37	24%
	SOUTH	63	40%
	WEST	28	18%
TYPE OF PRACTICE	ACADEMIC CENTER	29	18%
	COMMUNITY BASED CENTER	36	23%
	PRIVATE CLINIC	88	56%
	OTHER	4	3%
PRACTICE OWNERSHIP	PHYSICIAN-OWNED	91	58%
	HOSPITAL-OWNED	63	40%
	OTHER	3	2%
CENTER DESTINATIONS	CANCER CENTER	39	25%
	COMPRENSIVE CANCER CENTER	26	17%
	NCI COMMUNITY ONCOLOGY RESEARCH PROGRAM	13	8%
	NONE OF THE ABOVE	73	46%
	UNSURE	6	4%

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ADOPTING CONSENSUS ANALYTICAL STANDARDS AND STREAMLINING APPROVAL PATHWAYS FOR POST-MARKET MODIFICATIONS FOR NGS TESTS IN ONCOLOGY

GOAL

This whitepaper aims to provide recommendations to establish minimum analytical performance characteristics for somatic mutation testing in oncology, particularly for Next Generation Sequencing (NGS)-based panels, using a standardized, transparent, and optimized approach. In addition, this whitepaper will propose a regulatory process that could reduce the need for premarket review to support modifications of US Food and Drug Administration (FDA)-approved NGS diagnostics to ensure tests reflect the most up-to-date information for clinical decision-making.

INTRODUCTION

Transformative medicines are quickly changing the landscape of oncology treatment and care. Genomic information from NGS panels has led to a deeper understanding of tumor biology. As a result, treatment modalities are shifting from using primarily systemic cytotoxic chemotherapies to employing molecularly targeted therapies or a combination of both. The success of targeted therapies is dependent on diagnostic tools that can accurately identify patients with the appropriate molecular target(s) to confer a higher chance of benefit from these therapies. Currently, there are over 30 in vitro diagnostics (IVDs) approved as companion diagnostics by the FDA's Center for Devices and Radiological Health (CDRH). Many of these IVD tests are for a single biomarker and are linked to a single corresponding therapeutic product. In disease settings where there are multiple targeted therapeutic options, patients may require multiple tests that in turn neces-

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sitates the need for obtaining sufficient biopsy material to find all actionable mutations and thus an appropriate therapy. By maximizing the information obtained from diagnostics tests, patients can be assessed for all potential genomic variants of clinical relevance using the least number of tests necessary to achieve reliable answers.

Progress towards the goal of developing high content assays that can detect multiple biomarkers of clinical significance is rapidly increasing, and one key enabler is NGS technology. By sequencing multiple sections of a person's genome concurrently, NGS-based tests have the capability to detect hundreds of mutations simultaneously that could potentially be matched to a variety of approved targeted agents. Consequently, as the number of biomarkers and corresponding targeted agents continue to increase, test developers are focusing on NGS technology to query multiple markers in a single test. Three NGS-based oncology tests have been approved by the FDA and many laboratory developed tests (LDTs) have been reviewed under the College of American Pathologists (CAP) accreditation program and/or by New York State's Clinical Laboratory Evaluation Program. Despite these strong signs that NGS platforms are increasingly available and used by physicians, NGS tests have some issues that need to be addressed so that each patient receives results that appropriately inform the use of the many available therapeutic options.

One of the key issues to be addressed is the accuracy of results amongst diagnostic platforms. Due in part to the fragmented regulatory landscape for diagnostic tests in the United States, physicians and patients relying on these tests often do not know whether the test went through the FDA approval process or is being offered as an LDT. This bifurcated regulatory system may result in divergent analytical performance characteristics of similar tests used by physicians and patients. Many physicians and patients may expect that all tests offered in a clinical setting are equally accurate and interchangeable. In reality, tests may demonstrate variability in both accuracy and precision. This can be a barrier to selecting the most appropriate test and consequently the therapy for a given patient. Ideally, principles should be established that allow for identification of an agreed upon and modifiable set of clinically actionable genomic alterations, analytical performance characteristics for test comparisons, and the ability to rapidly add new information to test claims as science and medicine generate new associations between markers and therapies regardless of the regulatory path to the clinic. Addressing these issues in a concerted effort will help reduce the number of uncertainties that affect development, clinical use, and regulatory oversight of NGS-based tests. This will help ensure the regulatory pathway is sufficiently flexible to support future precision medicines while still ensuring that diagnostic tests remain safe and effective for patients.

This paper will discuss two major issues in the validation and approval of NGS-based oncology tests, as well as propose incentives for assuring test comparability:

❶ The lack of consensus on what analytical performance characteristics are important to assess
❷ The need for a more streamlined regulatory approval pathway for changes to NGS-based tests

ESTABLISHING ANALYTICAL PERFORMANCE CHARACTERISTICS

There is no shortage of measurement parameters available to help establish a test as a valid tool for physicians to make treatment related decisions. For physicians and patients to benefit from this rapidly evolving technology, it is important that minimum baseline analytical performance characteristics are established to ensure consistency of test results. Reducing variability and establishing baseline analytical performance characteristics for diagnostic tests are critical to ensure high-quality patient care and aid in clinical decision-making processes. High analytical concordance can provide reassurance that the clinical outcomes of the drug/diagnostic pairing are likely to be similar in the absence of a clinical trial. Guidelines developed by several entities, including the New York State Department of Health, Association for Molecular Pathology (AMP) and CAP, and the FDA outline basic principles for establishing the analytical validity of NGS-based tests and/or mechanisms for testing proficiencies of laboratories that offer them (see appendix A for comparison of guidelines).

The relative importance of specific analytical performance criteria is an area of continual discussion but identifying and agreeing on the minimal measures critical for analytical standardization can help establish concordance between tests. These include accuracy, analytical sensitivity, limit of detection/quantitation, analytical specificity, precision, reproducibility, and coverage. To move the field forward, consensus should be established on the minimal analytical performance characteristics that every NGS diagnostic used in clinical care should meet, and these performance characteristics should be utilized uniformly. The evidence necessary to meet each core standard may vary depending on the type of diagnostic and its intended use.

Evaluation of analytical performance requires access to appropriate clinical samples and/or reference materials that can be used to demonstrate test performance and assess comparability between tests and laboratories. As samples with clinical outcomes from therapeutic trials (the "gold standard" of samples) are necessarily limited and not widely available, other sources and types of adequate samples or material standards need to be identified and developed as acceptable for analytical performance characterization. Solutions to address access to samples that will appropriately assess analytical performance of a test to infer clinical performance of follow-on tests need to be explored. An established set of criteria for samples that contain a range of analytes and analyte types (e.g., single nucleotide and copy number variants, indels, fusions, etc.) and a roadmap for how these materials should be utilized would likely incentivize their use and increase their availability by encouraging increased development and curation.

It is suggested that a multi-stakeholder group be convened to establish harmonized analytical performance characteristics for NGS-based oncology tests. Likewise, further multi-stakeholder efforts are needed to oversee the development of reference materials that can be used to evaluate assay performance across different test platforms and laboratories. Subsequently, there is a need to ensure that laboratories meet these established analytical performance standards and demonstrate appropriate accuracy when challenged by reference materials. There are several approaches that could be performed alone or in some combination. First, laboratories could provide test performance characteristics in a standardized format available in a public database, on company websites, or on third party sites (e.g., NIH, ASCO, AMP, CAP, etc.). This transparency would allow physicians and patients the opportunity to assess potential limitations of individual tests because understanding test performance and how it was assessed is relevant to understanding how to use and interpret the test results. A second approach would be to provide a publicly available list of individual tests that meet the harmonized analytical performance characteristics and demonstrate appropriate performance using the reference materials. This would provide patients and their physicians with assurance that the test being used to guide their care is accurate and reliable, without placing the potential burden of test evaluation on the patient or treating physician. A third approach would be for laboratory accrediting agencies to mandate that labs performing NGS tests meet certain analytical performance characteristics. Ultimately, the incentive for performing these studies is to ensure maximum benefit for patients.

Questions on Analytical Standards:

- **What are the core performance characteristics and how can we get the necessary groups to reach consensus on the necessary performance characteristics to be assessed and how good performance should be?**
- **Should a Standards Development Organization, such as CLSI, be charged with developing an internationally recognized format for collecting data and a rigorous but reasonable method for establishing minimal analytical performance characteristics and assuring cut-offs (decision points) have been adequately set?**
- **Where should these standards be published to encourage adoption and should there be an enforcement strategy?**
- **How should the claims and limitations of a test be reported to patients and physicians?**

ENCOURAGING RAPID INNOVATION OF NGS-BASED TESTS

Under the current FDA regulatory framework, proposed modifications for an approved IVD test must be submitted to the FDA via the supplemental Premarket Approval (PMA) process, which can take up to 180 days. However, this timeframe for review of modifications to an existing IVD may delay the incorporation of emerging, validated data and prevent physician and patient access to information critical to the clinical decision-making process. To deliver the best patient care, tests should evolve with technology and clinical science in a near simultaneous manner, which may require regulatory review timeframes faster than the currently available 180-day supplemental PMA pathway for such proposed device changes. Because high-throughput technologies, such as NGS-based tests, can rapidly generate large amounts of clinically relevant data leading to identification of new genomic alterations that can impact patient care, reevaluating the regulatory pathway to modify tests and update labels without compromising patient safety is necessary. FDA recognizes the need for an improved regulatory framework and has published two draft guidances,[1,2] proposing methods to streamline oversight of NGS-based tests incorporating adaptability and flexibility into the regulatory framework. The recommendations presented in this paper are intended to describe additional options that may be considered by FDA to help encourage innovation without compromising patient safety.

The Establishment of a Process for a Pre-Specification Plan for Anticipated Expanded Claims or Test Modifications

We propose a pre-specified modification plan developed by sponsors in consultation with FDA prior to or at the time of PMA submission to streamline the incorporation of new analytical and clinical claims to FDA-approved NGS-based oncology tests. While the framing of the proposal is around the FDA approval process, a parallel process could be considered by other review bodies (e.g., New York State Department of Health, CLIA/CAP, etc.) as well. The pre-specification process could be used for modifications to variants, analytes, or clinical claims on tests. For instance, if clinical trial data is being collected for a variant of interest, an agreed upon pre-specification plan could streamline the incorporation of this information onto the label without the need to submit a supplemental PMA. Updates to NGS-based oncology tests can often be predicted in advance of specific analytes having established analytical and/or clinical validity, and will require routine validation to assure the performance meets preset goals. Ideally, with multiple tests making similar clinical claims available for clinical use, all (or most) tests should incorporate the same changes at nearly the same time, in order to provide optimal information for physician/patient clinical decision-making. The necessary data to support a modification change would be context dependent and would require the sponsor and FDA to agree on the necessary steps for a sponsor to follow. As part of the discussion, the sponsor and FDA could outline a pre-specification plan that may include the following steps:

1. **Develop a protocol and acceptance criteria for each analytical and clinical performance metric;**

2. **Outline a documentation plan to demonstrate that the modification meets the pre-determined performance parameters;**

3. **The sponsor and FDA should reach agreement on how and when modification validation will be communicated to the FDA; and**

4. **If the modification(s) will lead to a label change, the sponsor and FDA should reach agreement on the labeling update as part of the pre-specified plan.**

Once the plan has been agreed upon, subsequent modifications that follow the pre-specified plan would not need to be submitted to the FDA using a supplemental PMA, and the requirement for FDA approval, if acceptance criteria are met and labels are as anticipated, would be replaced by a "post-market" addition to the original PMA file. As such, the 180 day review time associated with the submission of a supplemental PMA would be avoided and modifications to tests would be more streamlined. Permitted modifications in this proposed system would be gated by approval of a new drug or label with altered Indications and Usage, Dosage and Administration, Contraindications, Warnings and Precautions, Use in Specific Populations, and approval of an IVD test that supports such changes. Data supporting the modification would be required to meet the agreed upon performance metrics in the pre-specification plan. The development of a portal to report modifications and whether the modifications are self-reported or independently verified may also be considered. The label would be updated as agreed upon in the pre-specification plan, and FDA would have the ability to audit the data within a pre-determined amount of time. This process could be implemented similarly to the FDA administrative and scientific process currently used to address replacement reagents[3] or FDA's new Software Pre-Certification pilot program, which is developer-focused rather than product-focused allowing for reduced or streamlined submissions. While such a system must be scientifically robust, it would generate up-front agreement on analytical validation of system modifications, which would result in consistency of biomarker data collected and thus lower variability in clinical study outcomes (e.g., ensuring homogeneity with respect to biomarker status in intent-to-treat (ITT) population), a reduced number of iterative submissions, and an expedited pathway to marketing new claims.

Additional Considerations for Implementing a Pre-Specification Plan

To monitor the robustness of modifications, an evaluation of the data generated through the use of the pre-specification plan may be needed. Modifications should follow the defined criteria in the pre-specification plan and a summary of the results should be provided as part of the PMA annual report or other report as specified. A template prescribing how modification validation results will be reported should be part of the modification plan and may include the following: list of the new variants detected/reported, agreement between the previous and current sensitivity, description of changes, and labeling changes. An important process of the PMA and PMA supplement pathway is reviewing the information to be included on labels; and therefore, label changes should be specified and agreed upon in the modification work plan and followed closely.

Questions on Streamlining Modifications to NGS-based Tests:

- **What should the labeling process look like and what are the potential implications for drug labels?**

- **Is FDA review of the modification data needed? Should another entity review the data (e.g., CMS, CAP inspectors, peer medical reviewers)?**

POLICY CHALLENGES AND OPPORTUNITIES FOR PRECISION MEDICINE

To fully consider and implement the processes and strategies outlined in this whitepaper, regulatory and legislative changes may be required. In addition, key stakeholders may need to be called upon to fully implement necessary steps to ensure these can be appropriately carried out. Several areas identified as requiring significant stakeholder input are listed below.

- **A survey should be performed of existing guidelines for establishing agreed upon analytical performance characteristics to avoid redundant standards and to build upon existing consensus standards.**

- **FDA should describe which materials are acceptable for validation of modifications given that clinical samples from clinical trials will not be widely available.**

- **Adopting analytical performance standards requires standardized reference material. Standard setting bodies such as National Institute of Standards and Technology (NIST) and others should be encouraged to develop reference materials such that they are made available to sponsors and labs for use to assure standardization of test results across test platforms.**

- **Multi-stakeholder groups should identify high quality reference materials that are available for establishing analytical performance characteristics, identify gaps in needed reference materials, and work toward development of these materials.**

- **Incentives should be identified and fostered for demonstrating analytical validation across laboratories.**

- **Where possible, real-world evidence should be gathered about test performance and patient outcomes through expanded use of registries and databases (clinical claims). This is keeping with FDA's draft guidance on the "Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics" use of databases.**

- **Organizations administering proficiency testing should make overall performance results widely available so that there is a better understanding of the comparability of analytical performance across platforms and laboratories.**

- **FDA expertise should be leveraged to develop innovative regulatory strategies for regulatory review and approval of modifications to NGS-based tests. FDA is familiar with reducing review burden in using a variety of methods, including use of special 510(k)s, use of migration studies for introducing new versions of old tests, and use of the replacement reagent protocol to reduce redundant review. While these strategies do not directly fit the regulatory paradigm currently being proposed, they may serve as the basis for creating a reliable but efficient mechanism for addressing the data opportunities and burdens of NGS technologies.**

- **Standardizing the information reported to patients and physicians, and ensuring the interpretability of lab report information.**

- **In addition to diagnostic modifications, stakeholders should be encouraged to propose novel approaches to the process of modifications to use of approved drugs. For example, if additional variants are shown to be clinically relevant to the use of an approved drug, patients and physicians would benefit from an expansion of not only the diagnostic label but also the drug label to reflect the expanded ITT population.**

- **Reimbursement and coverage challenges. The extensive efforts of sponsors that have demonstrated analytic and clinical validity of their IVDs via FDA review should be recognized in some way such that it provides an incentive for sponsors undergoing FDA review (e.g., differential reimbursement).**

Appendix A. Comparison of Analytical Validation Guidelines from New York State; Association for Molecular Pathology (AMP) and College of American Pathologists (CAP); and U.S. FDA*

	New York State[i]	AMP and CAP Joint Guidelines[ii]	FDA[iii]
Identification of samples and performance characteristics	• "Performance characteristics must be established and validated separately for each type of variant the assay is intended to detect." • "Performance characteristics for each sample type must be established and validated, along with the demonstration of quality sequences for all target areas without sample type bias."	• "Massively parallel sequencing of multiple genes cannot be validated as if it were a single-analyte test. There is far too much variation in the types of samples, types of variants, allele burden, and targeted exons or regions." • "Performance is certainly expected to vary considerably for different sample types, variant types, and allele burden, and therefore it is essential to establish performance characteristics by these factors. . . laboratories should strive to include samples with hotspot mutations relevant to the test's intended use." • "The validation protocol should start with an explicit statement of the intended use, which will determine the types of samples and the performance characteristics that need to be addressed."	• "FDA believes that one approach for supporting the analytical validation of NGS-based tests may be through conformity with one or more FDA recognized standards (if available) or special controls." • "FDA believes that for a standard to be recognized by FDA it should include, among other things, a description of the design activities that should be carried out and the performance characteristics that should be validated, as well as specific methodology, materials, and performance thresholds, where appropriate and justifiable." • "Establish and document minimum acceptable thresholds for coverage, base quality, and other test run quality metrics relevant to the specific design and test processes."
Accuracy	• "Sequence a minimum of 3-well characterized reference materials to determine a robust laboratory specific error rate across all target areas. This error rate is expected to be <2%."	• "Accuracy should be stated in terms of PPA and PPV." • "Because the performance will likely vary by mutation type, the PPA should be determined for each."	• "FDA recommends that PPA, NPA, and TPPV be set at no less than a point estimate of 99.9% with a lower bound of the 95% confidence interval of 99.0% for all variant types reported by the test." • "The minimum acceptable overall and target accuracy of an NGS-based test may vary depending on the type of variations and on whether variants are confirmed using an orthogonal assay." • "Evaluate and document accuracy by comparison to a method identified as appropriate by FDA, such as bidirectional sequencing or another well-validated method." • "Calculate PPA, NPA, and TPPV separately for each type of variant claimed."
Initial Validation	• "Must include a minimum of 50 patient samples comprising specimens of all intended sample and tumor types."	• "We recommend that the validation samples include. . . a minimum of 59 samples to assess quality metrics and performance characteristics... We recommend that PPA and PPV should be documented for each variant type." • "By testing a minimum of 59 samples during validation, conclusions can be drawn as to the tolerance intervals of essentially any performance characteristic whether parametric or nonparametric in nature."	• "After design and development of the test, validation studies will indicate if the predefined performance is met. If the test does not meet any one of the predefined performance specifications, the test should be modified and revalidated. The cycle of design, development, and validation should continue until the test meets the predefined performance specifications."
Full Validation	• "10 positive samples for each type of intended variant in each target area must be sequenced and confirmed." • "SNVs: Confirmation can be ceased once a minimum of 20 target areas have been fully	• "The quantitative analytical performance of a laboratory test does not necessarily predict performance at a clinical level." • "We recommend that clinical validity and clinical utility of the NGS assays needs to be	• "The complete NGS-based test should be analytically validated in its entirety. . . prior to initiating clinical use of the test."

* This table contains the exact text found in the New York State guidelines, joint guidelines from the Association for Molecular Pathology and College of American Pathologist, and FDA guidance

Appendix A. Comparison of Analytical Validation Guidelines from New York State; Association for Molecular Pathology (AMP) and College of American Pathologists (CAP); and U.S. FDA* (con't)

	validated/confirmed with accuracy greater than or equal to your established specificity." • "Indels: Confirmation can be ceased once a minimum of 29 target areas have been fully validated/confirmed with accuracy greater than or equal to your established specificity." • "CNVs must always be fully validated."	defined during design of the test and need to be evaluated during the validation process." • "Full scale of clinical validation is required for multianalyte NGS tests with prediction algorithms and should be performed using the guidelines and calculations as defined for an analytical validation." • "It is expected that laboratories would be able to acquire quality metric data for 59 samples that contain SNCs. Ideally these 59 samples would also have other variants such as indels [but] it is acknowledged that ascertainment of samples containing indels is more challenging."	
Precision (within run)	• "For each type of variant a minimum of 3 positive patient samples containing variants near the stated sensitivity of the assay must be analyzed in triplicate in the same run using different barcodes."	• "Replicate (within run) and repeat (between run) testing should be performed." • "Acceptance criteria need to be set before the acquisition of validation data."	• "FDA recommends thresholds for reproducibility and repeatability that meet or exceed 95.0% for the lower bound of the 95% CI, calculated by conditions tested and genomic context, separately for each variant type." • "When presenting the results of reproducibility and repeatability studies, indicate the failed quality control rate, and list all "no calls" or "invalid calls." Data from runs that do not meet coverage depth, coverage uniformity, and other technical metrics are typically considered quality control failures."
Reproducibility (between run)	• "For each type of variant, a minimum of three positive patient samples containing variants near the stated sensitivity of the assay must be analyzed in three separate runs using different barcodes on different days by 2 different technologists."	• "Replicate (within run) and repeat (between run) testing should be performed." • "Acceptance criteria need to be set before the acquisition of validation data." • "It is recommended to asses a minimum of three samples across all steps and over an extended period to include all instruments, testing personnel, and multiple lots of reagent."	• "For reproducibility studies, document results for each variant or variant type. Indicate the number of replicates tested for each variant and the conditions that were tested (e.g., number 934 of runs, days, instruments, reagent lots, operators)."

Appendix A. Comparison of Analytical Validation Guidelines from New York State; Association for Molecular Pathology (AMP) and College of American Pathologists (CAP); and U.S. FDA* (con't)

[i] NYSDOH "Next Generation" Sequencing (NGS) guidelines for somatic genetic variant detection (https://www.wadsworth.org/sites/default/files/WebDoc/Updated%20NextGen%20Seq%20ONCO_Guidelines_032016.pdf)
[ii] Jennings et al. Guidelines for Validation of Next-Generation Sequencing–Based Oncology Panels: A Joint Consensus Recommendation of the Association for Molecular Pathology and College of American Pathologists. 2017. J Mol Diagn. 19(3); 341-365.
[iii] Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Used for Diagnosing Germline Diseases (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM509838.pdf)

Appendix B. Considerations for Streamlining Diagnostic Development Requirements and Proposed Implementation of a Pre-specified Plan for OncomineDx

The Oncomine™ Dx Target Test is intended for use on the Ion PGM™ Dx Instrument System and is intended for in vitro diagnostic (IVD) use by trained personnel in a professional laboratory environment.

The device is indicated as a companion diagnostic to identify:

- **ROS1 fusion positive NSCLC patients for treatment with XALKORI® (crizotinib)**
- **BRAF V600E positive NSCLC patients for treatment with Tafinlar+Mekinist® (dabrafenib in combination with trametinib)**
- **EGFR L858R and Exon 19 deletions positive NSCLC patients for treatment with IRESSA® (gefitinib)**

The product's intended use:

The Oncomine™ Dx Target Test is a qualitative in vitro diagnostic test that uses targeted high throughput, parallel-sequencing technology to detect sequence variations in 23 genes in DNA and RNA isolated from formalin-fixed, paraffin-embedded tumor (FFPE) tissue samples from patients with non-small cell lung cancer (NSCLC) using the Ion PGM™ Dx System.

The test is indicated to aid in selecting NSCLC patients for treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling.

Results other than those listed in Table 1 are indicated for use only in patients who have already been considered for all appropriate therapies (including those listed in Table 1). Safe and effective use has not been established for selecting therapies using this device for the variants in Table 1 in tissue types other than NSCLC.

Analytical performance using NSCLC specimens has been established for the variants listed in Table 2.

The test is not indicated to be used for standalone diagnostic purposes, screening, monitoring, risk assessment, or prognosis.

Table 1 - List of variants for therapeutic use

Gene	Variant	Targeted therapy
BRAF	BRAF V600E	TAFINLAR®(dabrafenib) in combination with MEKINIST® (trametinib)
ROS1	ROS1 fusion	XALKORI® (crizotinib)
EGFR	L858R, Exon 19 deletions	IRESSA® (gefitinib)

Table 2 - List of variants with established analytical performance only

Gene	Variant	Targeted therapy
BRAF	BRAF V600E	TAFINLAR®(dabrafenib) in combination with MEKINIST® (trametinib)
ROS1	ROS1 fusion	XALKORI® (crizotinib)
EGFR	L858R, Exon 19 deletions	IRESSA® (gefitinib)

In the original Oncomine Dx Target Test assay pre-market approval (PMA), pre-clinical laboratory studies were assessed by comparing the effectiveness and concordance of the diagnostic test to that of externally validated comparator methods. No pre-clinical animal studies were conducted as part of the PMA. The clinical studies performed were used to determine the clinical utility of the product including selection of the correct patients for the designated therapy. The studies performed are listed in Table 3.

Sequence variations in DNA for the following 23 genes are reported: AKT1, ALK, BRAF, CDK4, DDR2, EGFR, ERBB2, ERBB3, FGFR2, FGFR3, HRAS, KIT, KRAS, MAP2K1, MAP2K2, MET, MTOR, NRAS, PDGFRA, PIK3CA, RAF1, RET, and ROS1. Sequence variation in RNA for ROS1 gene is also reported.

Table 3 - Original PMA Submission Studies for the Oncomine Dx Target Test assay

Pre-clinical laboratory studies	Clinical Studies
Parameters	Parameters
Analytical Accuracy	Study Design
Analytical Sensitivity	Inclusion and exclusion criteria
Limit of detection (LoD)	Follow-up schedule
Nucleic acid input	Clinical endpoints
Tissue input	Accountability of PMA cohort
Tumor content	Study population demographics and baseline parameters
Analytical Specificity	Safety and effectiveness results
Inclusivity/cross-reactivity	Concordance study
Interference	Bridging study
Endogenous interference	Sensitivity analysis
Exogenous interference	
Antimicrobial testing	
Precision and Reproducibility	
Assay reproducibility across testing sites	
Sample processing reproducibility	
Assay precision	
Tissue Heterogeneity	
Extraction Method Equivalency Studies for DNA/RNA	
Contrived Sample Functional Characterization Study	
Guard Band Studies	
Workflow tolerances	
Tissue fixation	
Contamination studies	
Stability Studies	
Shelf-life stability	
In-use stability	
Designated hold times	
Kit lot interchangeability	
Extracted DNA and RNA sample stability	
Pre-clinical laboratory studies	Clinical Studies
Parameters	Parameters
Stored slide stability	
Stored block stability	
Transport stability	

Having a regulatory process such as the PMA application that establishes the minimum analytical performance characteristics for somatic mutation testing in oncology, particularly for Next Generation Sequencing (NGS)-based panels, using a standardized, transparent, and optimized approach is necessary. However, in order to reduce burden and decrease the time required for modifications to approved products, it is recommended to reduce the need for premarket review to support modifications of US Food and Drug Administration (FDA)-approved NGS diagnostics to ensure tests reflect the most up-to-date information for clinical decision-making.

In order to deliver the best patient care, tests should evolve with technology and clinical science in a near simultaneous manner, which may require regulatory review timeframes faster than the currently available 180-day supplemental PMA (sPMA) pathway for such proposed device changes. This case study identifies suggestions to reduce the regulatory burden and decrease the regulatory review time. These suggestions need to be vetted between NGS assay developers and the FDA to understand how these proposals can be put into action and utilized in the PMA and sPMA approval process.

In developing a streamlined modification process, the minimum analytical performance testing for initial development that is standardized and transparent needs to be defined. This will set the stage for a pre-specified modification plan process which is developed by sponsors in consultation with FDA prior to or at the time of PMA submission to streamline the incorporation of new analytical and clinical claims to FDA-approved NGS-based oncology tests. The pre-specification process could be used for modifications to variants, analytes, or clinical claims on tests. For instance, if clinical trial data is being collected for a variant of interest, an agreed upon pre-specification plan could streamline the incorporation of this information onto the label without the need to submit a supplemental PMA.

The following areas describe the potential changes to testing and development requirements for the PMA and sPMA process to enable FDA-approved NGS diagnostics to incorporate emerging, validated data and enable physician and patient access to information critical to the clinical decision-making process in real-time. The areas indicated in this case study require thoughtful review and consideration by the FDA and industry as they dramatically reduce time and cost. The areas for review include software, product controls, DNA origin from tissue type and representative validation, clinical sample availability, and validation.

SOFTWARE

Software development is a prime area where the burden could be lessened for product modifications. The software validation submitted in the original PMA would contain all required validation needed to ensure safety and effectiveness following appropriate guidelines and standards.

Allowing the software to include multiple tissue types in the sample program menu regardless of the tissue type defined in the original approved indication would greatly benefit both industry and patients without compromising safety. This change would provide the user the ability to select the tissue type tested and would decrease the software development and validation burden on future programs as the information would already exist in the program menu.

Selecting from a multiple tissue menu would benefit users of clinical studies and allow the companies to progress on existing software development without requiring a new software version. In addition, this would allow clinical cases for which there are no other approved tests to use validated software and assay combinations.

PRODUCT CONTROLS

Product controls increase the reliability of the results often through comparison of the control to other measures. Requiring a clinical biomarker to be present in each control, however, is burdensome and can cause delays in development.

Instead, a control would be considered a 'representative control' and each clinical marker would not need to be present as assay performance would be determined using the biomarkers for each class (SNV, SNP, insertions, deletions, etc.). A biomarker class-based approach would eliminate the need to update the control for each new clinical/therapeutic biomarker added and the requirement to manufacture a new control for each modification.

The classes that would be included in the "represented control" would represent:

- **SNV/ SNP**
- **Insertions**
- **Deletions**
- **CNV**
- **Fusion**

DNA ORIGIN FROM TISSUE TYPE

The laboratory community and numerous researchers utilize the hypothesis that DNA extracted from each tissue type perform similarly when tested with a validated assay regardless of the tissue type and, therefore, DNA is DNA. In order to provide evidence for the FDA to accept this concept, which is well accepted within the industry, it is suggested that a well-controlled study of significant size and scope be performed across multiple tissue types showing that the variants across numerous tissue types perform similarly. This study could be leveraged for future NGS assay development.

The agreement that DNA performs the same regardless of tissue type would lessen the requirement to validate performance for each tissue type (i.e. sample stability [slide, block, nucleic acid] and sample reproducibility). With the acceptance of this hypothesis, testing would still be needed for tissue specific interfering substances specifically when there is a specific tissue with a specific interfering substance (i.e., melanoma); as well as marker specific testing, limit of detection, panel reproducibility, and accuracy.

In addition, regardless of tissue type, a representative analytical validation approach could be used where all biomarkers within the panel would be reported. As a result of the representative analytical validation, the need for additional updating of the software would be eliminated as all biomarkers would be unmasked. Software updates would only be needed to add clinical biomarker information/ therapeutic information. In this scenario, submissions would be for clinical information and require limited software information due to the addition of new clinical biomarkers. This approach would be less burdensome for the manufacturer and review timeframes would be faster than the currently available 180-day supplemental PMA pathway for such proposed device changes.

REPRESENTATIVE VALIDATION

Representative/class-based analytical validation would lessen the burden with established minimum analytical performance characteristics for somatic mutation testing for Next Generation Sequencing (NGS)-based panels. Using a standardized, transparent, and optimized approach would potentially eliminate additional analytical validation requirements.

CLINICAL SAMPLE AVAILABILITY

As described in the white paper, demonstrating analytical performance characteristics is required and it is necessary to have access to appropriate clinical samples and/or reference materials that can be used to demonstrate test performance and enable comparability between tests and laboratories. As samples with clinical outcomes from therapeutic trials (the "gold standard" of samples) are necessarily limited and not widely available, other sources and types of adequate samples or material standards need to be identified and developed as acceptable

for analytical performance characterization. Solutions to address access to samples that will appropriately assess analytical performance of a test to infer clinical performance of follow-on tests need to be explored. An established set of criteria for samples that contain a range of analytes and analyte types (e.g., SNVs, indels, CNAs, fusions, etc.) and a roadmap for how these materials should be utilized would likely incentivize their use and increase their availability by encouraging increased development and curation.

It is burdensome to the assay developer performing specific tissue/biomarker testing when a specific tissue type cannot be located due to rare variants or limited availability of tissue; in these instances, the use of a cell line or plasmids are needed, and in some instances, it may even be necessary to eliminate the test requirement. Requiring the manufacturer to develop a cell line or to pay to have a cell line developed is cost prohibitive and very lengthy. In most cases, the manufacturer will abandon the development process due to little or no return on investment.

PRE-SPECIFIED MODIFICATION PLAN TO INCORPORATE ADDITIONAL BIOMARKERS INTO ONCOMINE DX TARGET TEST ASSAY

In order for the pre-specified modification plan to be successful there would need to be clear direction from the agency on requirements via a guidance document including information about needed studies.

In developing the pre-specified modification plan to incorporate additional biomarkers into the Oncomine Dx Target Test assay, tests to measure the following would be proposed:

- **Interfering substances**
- **Accuracy**
- **Clinical validation using samples from the intended use patient populations' tissue type to be added**
- **Small reproducibility study with enough samples, including those that can challenge the assay (e.g., samples near LoD, samples with low tumor content, etc.)**
- **Software validation**
- **Sample stability**

As part of the modification process, the following considerations need to be reviewed and resolved:

- **Same tissue type; is it the same intent to treat population as what is on the market already (NSCLC)? Is the biomarker already on panel (example ERBB2)?**
- **Is the biomarker already on panel with existing analytical data? Is it a new tissue type (example KRAS)?**

Table 4 - The proposed pre-specification plan would include the required tests to be performed with an appropriate justification

Study Type	Description
Development	Integration Development Study and Test Pass/Fail Criteria Setting
Development	Detection of Variants Using In Vitro Transcripts
Analytical	Panel Reproducibility
Analytical	Analytical Accuracy
Analytical	Tumor Content
Analytical	Kit Lot Interchangeability
Clinical	ALK Clinical Study
Clinical	ROS1 Clinical Study

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FRIENDS of CANCER RESEARCH

A Friends of Cancer Research White Paper

CAPITALIZING ON THE TOTALITY OF EVIDENCE TO STREAMLINE APPROVALS FOR SUPPLEMENTAL INDICATIONS

INTRODUCTION

The FDA approves new drugs for sale and marketing in the U.S. after careful review of new drug applications (NDA). Every NDA contains a large amount of data about the new therapy; from discovery in a laboratory, to drug metabolism and toxicology in nonclinical studies, to safety and efficacy in the clinic, to chemistry and manufacturing processes. Only after a drug has demonstrated significant evidence of safety and efficacy in the form of clinical benefit through well-powered and appropriately-controlled studies, it is approved and made available to patients.

As our understanding of drug mechanisms and the natural history of disease increases, we are witnessing a greater number of drugs being used for multiple cancer types and patient populations, which are also known as treatment settings or indications. This is especially true for targeted therapies, which block specific proteins or receptors that participate in cancer growth and progression. As we become more aware of the mechanisms by which cancer forms, more precise therapies are created that modulate targets and pathways that are relevant in the formation of cancer arising in several different tissues and patient populations. Targeted therapies, therefore, are prime examples of drugs that can be used in different indications. The use of therapies in combination will also increase the number of indications for which each drug is used.

Every time a drug manufacturer, or sponsor seeks regulatory approval for a drug in a new indication, whether that refers to a different patient age group, cancer type, or molecular tumor subgroup, the FDA requires a supplemental NDA (sNDA), consisting of the same quality and content as the drug's first or original NDA. The review and assessment of sNDAs is very similar to that of the original NDA, which consume considerable time and

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Friends of Cancer Research drives collaboration among partners from every healthcare sector to power advances in science, policy, and regulation that speed life-saving treatments to patients.

resources and may not always add much value to the regulatory determination of safety and efficacy of a drug for which previous submissions have established a well-characterized profile. Indeed, approved drugs are backed up by a wealth of high-quality data collected from previous submissions, along with post-marketing experience and published literature, which should also be considered when seeking approval for a new indication. These robust data could provide an additional level of confidence on the drug's efficacy and safety, and expedite its regulatory approval process for a new indication.

In the past, approvals were hastened when enough evidence was presented to provide confidence that a drug's efficacy could be based on reliable and well-established intermediate endpoints. Under some circumstances, an intermediate endpoint—an early measure of treatment effect on patients in a clinical trial—may be used as a reliable surrogate marker of clinical benefit, which refers to a patient's ability to survive, feel, or function. Usually, clinical benefit is evaluated after a long period of time and when comparing drug response between patients in the treatment and control arms in the context of a randomized clinical trial (RCT). However, there are cases in which a RCT with conventional clinical endpoints such as progression-free survival (PFS) or overall survival (OS) is not feasible, possible, or ethical, and clinical benefit needs to be assessed in different ways, such as by single-arm studies determining objective response rate (ORR)—a direct measure of tumor shrinkage using standard criteria, or duration of response (DoR). In these rare cases, especially when new therapies are needed for patient populations with large unmet clinical needs and who face no other treatment options, an intermediate endpoint such as ORR, or DoR is considered the most appropriate way, or sufficient to assess clinical benefit. The FDA has recently addressed the need for expedited approvals in these cases. The Accelerated Approval pathway bases approval decisions on intermediate endpoints of clinical benefit, but full approval is contingent on sponsors demonstrating clinical benefit using more conventional clinical endpoints through additional confirmatory trials that commonly occur in a slightly different indication and which may take several years to culminate.

As fully approved drugs start to be evaluated in multiple indications, sNDAs may be submitted to meet an urgent clinical need for which clinical benefit is measured using an intermediate endpoint. In these cases, historical data for the drug's original NDA are available and may be taken into consideration in the decision to fully approve this drug, knowing that conventional clinical endpoints have already been evaluated for the first indication. Currently, the FDA grants full approval to sNDAs based on an intermediate endpoint on a case-by-case scenario, but there are no available or standardized guidelines that could help (1) weigh the urgency in a scenario of unmet clinical need, and (2) assess the type and quality of evidence necessary to provide sufficient confidence in the decision to grant full approval to drugs used for a supplemental indication.

The objective of this white paper is to provide a framework that will aid in examining the unmet clinical need of a patient population and leveraging the totality of evidence available for an approved drug to determine whether there is sufficient data to support full approval in a new indication based on an intermediate endpoint.

LEARNING FROM THE PAST: WHAT CHARACTERISTICS HAVE LED TO THE FULL APPROVAL OF DRUGS BASED ON AN INTERMEDIATE ENDPOINT IN A NEW INDICATION?

Unmet clinical need

Gauging the urgency for a new indication by taking into consideration the unmet clinical need of the population is crucial in determining whether a drug's supplemental indication should be approved based on an intermediate endpoint. Evidence generated during clinical trials, post-market studies and investigator-initiated studies contributes to the totality of evidence that may support the decision to grant full approval for a supplemental indication; however, it is the urgency for filling a medical gap that prompts the evaluation of whether the potential benefit could outweigh the known and unknown risks to expedite the approval of these indications.

How serious or life-threatening is the disease? How rare is the disease? What are the current treatment options available to these patients? These are all factors to assess when considering the benefits and risks that will inform the decision-making process. These factors should contribute to the discussion of whether it is reasonable and feasible to grant full approval to a drug for a novel indication based on an intermediate endpoint (Table 1). Previous scenarios where an earlier measure of efficacy has been used as basis for full approval of supplemental indications have all demonstrated a high degree of unmet clinical need. For example, the combination treatment of daratumumab with pomalidomide and dexamethasone was approved for patients with refractory multiple myeloma (MM) who had received at least two prior therapies including lenalidomide and a proteasome inhibitor such as bortezomib. Eighty-nine percent of patients in the study were refractory to lenalidomide and 71% to bortezomib, with 64% refractory to the combination of lenalidomide and bortezomib. Therefore, limited to no further treatment options were available for these patients. A response rate was observed in 59.2% of patients in the open-label single armed trial, with a median DoR of 13.6 months. These efficacy outcomes were considered substantial in this unique population and supported the full approval of this combination therapy in the absence of further therapies for patients with relapsed or refractory disease.[1]

Table 1. What need-based factors should be taken into consideration?

UNMET CLINICAL NEED
Rarity of disease
Availability of treatment options
RANDOMIZED CONTROLLED TRIAL IS NOT FEASIBLE
Length of time for patient accrual
Ethical considerations

Patients with metastatic non-small cell lung cancer (NSCLC) that have failed or progressed on standard therapies have very poor prognosis and limited treatment options. Targeted therapies are becoming more common for the treatment of NSCLC patients with tumors harboring unique molecular or genetic alterations. The large unmet need of these patients is driving research and clinical trials that test the efficacy of targeted therapies in subsets of patients selected based on a diagnostic test. Mutations in the proto-oncogene, BRAF, are very rare in NSCLC, accounting for about 1% of all NSCLC cases and have been associated with a particularly poor prognosis, with a low proportion of patients achieving a response to platinum-based chemotherapy. The combination of dabrafenib—an inhibitor of BRAF—and trametinib—an inhibitor of MEK, a protein downstream of BRAF—was granted full approval based on a durable ORR for patients with metastatic BRAF V600 positive NSCLC as an alternative to, or in patients that failed to respond to platinum chemotherapy.[2] Likewise, ROS Proto-Oncogene 1 (ROS1) rearrangements in NSCLC are also very rare, accounting for another 1% of NSCLC cases. Crizotinib, a kinase inhibitor that targets aberrant ROS1, was given full approval based on ORR, possibly because patients with metastatic ROS1+ NSCLC had no further therapeutic options. The original indication approvals for the combination of dabrafenib and trametinib, and crizotinib tested these drugs in more common tumors (BRAF V600 mutated melanoma, and ALK+ NSCLC, respectively), where the larger population sizes enabled the appropriate benefit: risk comparisons from well-conducted randomized Phase III studies.

Since the supplemental indications were seeking to help a rare subset of patients with large unmet medical needs, urgency may have played an important role in the decision to approve the use of these drugs in the new indication without demonstrating definitive survival benefit with a RCT, but still demonstrating substantial early efficacy outcomes in these rare lung cancer subpopulations.

Optimal understanding of natural history of disease:

Having a thorough understanding of the natural history of disease is imperative when seeking to expand the use of a well-characterized drug in a new cancer subtype. This includes a greater awareness of the mechanisms by which cancer arises, and its evolution in a patient over time.

The advent of powerful molecular technologies has enabled the study and characterization of a tumor's genome, epigenome, and transcriptome, which can be unique to a single tumor type or shared across several tumors with similar etiologic pathways. For example, leading research in lung cancer has identified multiple oncogenic driver mutations and rearrangements that are currently targeted through different therapies.[3] In NSCLC, some targeted agents, such as kinase inhibitors have demonstrated a greater clinical benefit than cytotoxic platinum-based chemotherapy. Crizotinib inhibits several receptor tyrosine kinases, that when altered, drive the development of NSCLC. This product was first approved for the treatment of patients with metastatic NSCLC whose tumors were positive for the anaplastic lymphoma kinase (ALK). A supplemental indication was sought for use in patients with NSCLC whose tumors were positive for ROS1, a receptor tyrosine kinase with a similar structure to ALK. Because these two tyrosine kinases are related and have been shown to drive the growth and progression of NSCLC, it could be expected that this well-characterized targeted agent would have similar

effects on these tumors harboring different genomic aberrations. Since Crizotinib had already demonstrated substantial evidence of safety and efficacy in the same tissue type and stage (metastatic NSCLC), and there were no treatment options available for this small and unique group of patients, the FDA fully approved this drug for the treatment of patients with metastatic ROS1+ NSCLC using ORR and DoR as the efficacy outcomes, which were measured in a single-arm trial with 50 patients.[4] Due to a clear understanding of the role of receptor tyrosine kinases in the growth and metastatic progression of NSCLC, there was increased confidence that crizotinib would have a similar therapeutic effect on both indications. Thus, when the safety profile and intermediate endpoint for the drug in the new indication were consistent with the original indication, it was reasonable to conclude that the drug would demonstrate substantial clinical benefit.

Well-understood drug's mechanism of action and performance in different disease settings:
Understanding a drug's mechanism of action, including its pharmacokinetics, pharmacodynamics, and drug interactions, as well as how well it performs in different cancer settings is critical when seeking to expand its use. For example, daratumumab is an anti-CD38 monoclonal antibody approved for the treatment of patients with MM. Daratumumab binds CD38, which is a receptor commonly found on the surface of hematopoietic cells. MM cells express CD38 on their cell surface, therefore the binding ability of this drug is unique to these cancerous cells. Daratumumab demonstrated clinical benefit as a monotherapy in patients with MM who had received at least three prior lines of therapy. Because daratumumab's mechanism of action was well-known, it was then tested in combination with the current standard of care for MM patients: lenalidomide and dexamethasone, or bortezomib and dexamethasone, in patients with MM who had received at least one prior therapy. The supplemental approval of daratumumab in combination with pomalidomide and dexamethasone for the treatment of patients with MM who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (such as bortezomib) was based on an open-label single arm trial where ORR was the efficacy outcome.[1] For the supplemental indication, daratumumab was studied in combination with a second thalidomide analogue (pomalidomide), which is in the same family as lenalidomide, a drug combination for which daratumumab had already received approval; therefore, efficacy had already been demonstrated in combination of daratumumab and a thalidomide analogue.

In addition to understanding how the drug works as a single agent and in the context of combination therapies, it is important to evaluate whether the efficacy benefit translates into other diseases. Dabrafenib and trametinib are kinase inhibitors that modulate two independent targets in the Mitogen Activated Protein kinase (MAP kinase) pathway. Together, they have been successfully used in the treatment of patients with BRAF V600-mutant metastatic melanoma, and metastatic NSCLC. However, when the combination therapy was used in BRAF-mutant metastatic colorectal cancer, which is typically refractory to standard treatments and confers a poor prognosis, the response rate observed was modest and the impact of this treatment on disease was much lower than the robust clinical response observed in BRAF mutated metastatic melanoma.[5] Even though the mechanism of action for these kinase inhibitors were well-understood and efficacy had been previously demonstrated in controlled trials, a more detailed pre-clinical investigation on critical factors such as the drug's pharmacodynamics and potential heterogeneity of tissue-unique mechanisms of resistance, was necessary to validate and understand the performance of these drugs in a new indication.

Robust and well-established safety database
Relying on a well-established and robust safety database for a product, that includes drug interactions, adverse reactions, warnings and precautions, and dosage, is essential when seeking approval for new indications. Supplemental NDAs require sponsors to submit the safety profile of a drug in a new patient population and provide relative indirect summary comparisons to previously approved indications. Further support for the effectiveness of a drug in the new indication is obtained when the safety profile in the new indication resembles that of the original indication, demonstrating that the drug behaves similarly in both settings. Dabrafenib and trametinib were granted full approval as monotherapies and in combination for the treatment of patients with metastatic melanoma carrying BRAF V600 mutations. These two drugs demonstrated substantial evidence both as monotherapies and combination therapy, to support their safety in a large number of patients with metastatic melanoma. When a new indication of the combination of these two small molecule inhibitors was sought for a smaller cohort of patients with metastatic NSCLC carrying BRAF V600 mutations, a similar safety profile was observed that was considered manageable and did not substantially differ despite different tumor type. The consistent safety profile observed in the new indication may have contributed to increased confidence to approve the combination therapy in patients with metastatic BRAF V600 mutation-positive NSCLC based on ORR in a three-cohort, non-randomized trial.[2] Similarly, daratumumab's safety profile had been characterized when used as a monotherapy and combination therapy for the treatment of a large number of patients with melanoma during different lines of treatment before it was approved for the new indication of treatment with pomalidomide and dexamethasone in a smaller cohort of patients who had received at least two prior therapies.[1] Lastly, the safety profile of crizotinib for its new indication in patients with ROS1+ NSCLC was consistent with the profile in ALK+ NSCLC, which provided confidence to approve the drug's new indication based on an earlier measure of efficacy.[4]

Reliable study endpoint that has consistently demonstrated clinical benefit
The reliability of an intermediate endpoint as a surrogate marker of clinical benefit is very important in determining whether a drug should receive full approval. In all the examples described so far, ORR per the Response Evaluation Criteria In Solid Tumors (RECIST) as assessed by independent review committee and DoR were the study endpoints measured to predict clinical benefit, and because previous trials had demonstrated these to be reliable surrogates, they were considered sufficient to grant full approval. In all original indications for daratumumab, crizotinib, and the combination of dabrafenib and trametinib, ORR was an intermediate endpoint that was later confirmed to demonstrate clinical benefit through randomized, appropriately-controlled clinical trials. Considering the totality of evidence, including the fact that ORR translated into robust and durable clinical responses and increased survival in the original indications, approvals were granted for additional indications in which response rate, a well-characterized and objectively determined intermediate endpoint, was high.

Accurate and well-instituted companion diagnostics
Targeted therapies rely on diagnostics that consistently and accurately identify a group of patients whose tumors carry the alterations being targeted. When sponsors seek supplemental indications for targeted therapies, sensitive, specific, and reproducible companion diagnostics provide greater confidence that the therapies will have a substantial effect on disease because the patient group is well-characterized. For

example, the combination of dabrafenib and trametinib used for treatment of patients with BRAF V600 mutation positive NSCLC and melanoma, and crizotinib for treatment in patients with ROS1+ NSCLC rely on tests that reliably and consistently identifies single nucleotide variants and rearrangements in tumor tissue, such as the FDA-approved companion diagnostic (Oncomine™ Dx Target Test) that identifies alterations in several genes including BRAF and ROS1.[6] Having a reliable diagnostic test, that performs consistently regardless of the laboratory in which it is performed, is necessary to properly identify patients who would benefit from targeted therapies and provide greater confidence that a substantial effect will be observed in the selected population.

DEVELOPMENT OF FRAMEWORK OUTLINING FACTORS TO CONSIDER WHEN SEEKING APPROVAL FOR A NEW INDICATION

The above examples illustrate different factors that contributed to the decision-making process that ultimately led to the full approval of supplemental indications. Although each case is unique, two general themes have emerged from these examples: consideration of the clinical need of the new indication and the available data. Table 2 outlines a list of these factors and questions that will help facilitate the clinical trial development, curation of available data, and decision-making process to inform approvals of a supplemental indication.

Table 2. Framework to help inform the decision-making process for the approval of a drug seeking a supplemental indication based on an intermediate endpoint

Category	Factors	Questions
Need	Unmet clinical need	Is there an unmet medical need for the patient population? What are the limitations or availability of existing therapies?
	Rare disease	What is the epidemiology of the patient population and how feasible is it to accrue enough patients in a reasonable amount of time to run a randomized control trial?
	Equipoise	Is there early data or strong scientific justification suggesting that a randomized control trial for the supplemental indication may lack equipoise?
Data	Natural history of disease	Are the disease etiology, epidemiology, molecular profile, evolution, and mechanisms of resistance known?
	Relatedness	How closely related is the disease in the supplemental indication to that of the original indication?
	Drug mechanism & pharmacology	Is the drug's mechanism of action, pharmacokinetics, and pharmacodynamics, well understood, and does it perform similarly in different cancer types?
	Dose & regimen	Is the dose and regimen of the drug well supported for the new disease setting?
	Drug's safety profile	Is there an adequate understanding of the drug's adverse event profile and safety management guidelines from randomized trials?
	Efficacy	Are efficacy outcomes significantly greater than those observed with the current standard of care?
	Benefit: risk ratio	Is the magnitude of the benefit significantly high and does it outweigh any known, or unknown, potential risks?
	Contribution of components	For combination therapies, is the contribution of each component to efficacy, or safety, outcomes known?
	Study endpoint	Is the intermediate endpoint a reliable proxy or is it sufficient proof of clinical benefit?
	Diagnostics	For targeted therapies, are well-established and reliable diagnostics available to identify defined population?

LOOKING AHEAD: UTILITY OF FRAMEWORK IN APPROVAL OF SUPPLEMENTAL INDICATIONS

A streamlined approach that guides the evaluation of the confidence and consistency of the totality of evidence available for a drug's new indication is necessary to expedite the approval process while maintaining strict standards of safety. This working group proposes the use of the framework outlined above, to identify whether a supplemental indication has sufficient grounds based on need and previously generated data, to seek full approval based on intermediate endpoints measuring efficacy.

How could this framework be used to guide future cases?
Entrectinib (RXDX-101)[7] and Larotrectinib (LOXO-101)[8] are tyrosine kinase inhibitors that are currently being tested in tissue-agnostic open-label, multicenter, global Phase 2 basket studies for the treatment of patients with solid tumors that harbor a fusion affecting tropomyosin receptor kinase fusions (NTRK1/2/3), ROS1, or ALK. These drugs may potentially work across multiple indications, therefore using the proposed framework outlined in Table 2 would be helpful in guiding the decision-making process that may grant full approval to the supplemental indications based on intermediate endpoints. The factors suggested could be taken into consideration to provide confidence on the expected clinical benefit in the new indication. Master protocols, which refer to one overarching protocol designed to answer multiple questions by investigating efficacy on a single disease after treatment with multiple therapies (umbrella trial), or multiple diseases after one therapy (basket trials)[9] are changing the face of clinical trials. These comprehensive studies will require innovative ways to capitalize on the totality of evidence established for drugs seeking several indications. Likewise, with the increasing number of drug combinations, new indications will arise for the use of approved drugs in new therapeutic permutations. For example, indoleamine (2,3)-dioxygenase (IDO) inhibitors are immunomodulatory drugs that could be used in combination with immune checkpoint inhibitors. There are currently many clinical studies that are investigating the efficacy of these drug combinations in several tumor subtypes,[10, 11] and as these, and other combination therapies become more common, especially in the nascent field of immuno-oncology (see Appendix Table 1), a streamlined approach that relies on the use of historical data and takes into consideration the medical need to expedite the approval of drug combinations will be necessary.

DISCUSSION

In the scenarios described in this white paper, full approval was given to drugs seeking a supplemental indication based on the degree of medical urgency in the affected population and the type and level of evidence available. In these scenarios, after assessing the lack of available options for patients and the drug's historical data, the agency determined that the magnitude of benefit observed when measuring an intermediate endpoint was a substantial improvement over what could be expected with the standard of care, and considering the context of the new indication, sufficient confidence existed to believe that the drug would be efficacious and safe in the new indication.

However, as we better understand the limitations and capabilities of data collected outside of traditional clinical trials to assess the long-term efficacy and safety of approved drugs on the market, it may be interesting to determine whether approvals for supplemental indications based on an intermediate endpoint actually derive clinical benefit in the long term. Programs that use electronic health records and claims data to track safety of regulated medical products, such as the Sentinel system, are already being set into place and may be the key to answer questions about not only a drug's long-term safety, but also efficacy. These surveillance programs could be utilized to examine how well intermediate endpoints are able to predict clinical benefit in order to further improve our confidence on the reliability and accuracy of these surrogates.

Moreover, as the future of cancer research moves from treating to preventing disease, the field will have to more heavily rely on earlier markers of response that predict a prolonged benefit to patients. For example, studies in disease interception, which focus on the development of medicines that stop or delay disease progression for patients with premalignant disease, will require a refined understanding of surrogate endpoints early within the disease continuum that demonstrate elevated predictive power.

Demonstrating clinical benefit outside of the traditional overall survival estimates will require innovative thinking from multiple stakeholder groups working together to assure a fine balance between the most optimal level of efficacy and safety that matches the urgency patients have for life-saving therapies.

QUESTIONS

- **How do we define efficacy and how can different intermediate endpoints predict efficacy in patients?**
- **Would simplified mechanisms of approval for supplemental indications incentivize sponsors to submit sNDAs? What role would these mechanisms play in helping to keep product labels updated?**
- **Is there a need to confirm clinical benefit for drugs approved based on an intermediate endpoint?**

APPENDIX

Additional Examples:

Pembrolizumab

The advent of precision medicine has been a catalyst in the development of molecular targeted drugs and immunotherapies, which work in very specific populations. As we learn more about how these drugs work and what other populations it may help, we will see an increase in the number of their indications. Pembrolizumab is a good example of this phenomenon. In 2014, Pembrolizumab was first approved under accelerated approval for the treatment of patients with unresectable or metastatic melanoma[12] (Appendix Table 1). In under three years, the sponsor of this PD-1 inhibitor has submitted applications for 10 other indications, some of which were approved under accelerated approval and some of which were fully approved after the confirmation of clinical benefit based on overall survival. None of these supplemental applications have been granted full approval based on an intermediate endpoint; however, this may be due to how new the field of immuno-oncology is and the lack of long-term efficacy and safety data available for immunotherapies. As our understanding of this nascent field increases, more indications will be identified and a streamlined approach to expedite the submission of supplemental applications will be a largely beneficial tool.

Ibrutinib

This kinase inhibitor was initially granted accelerated approval for the treatment of patients with mantle cell lymphoma (MCL) who had received at least one prior therapy in an open-label, multi-center, single-arm trial based on ORR as the efficacy outcome. Additional indications for treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with or without 17p deletion were fully approved after various randomized multicentered, open-label trials based on progression free and overall survival as their efficacy outcomes.

Additional indications for treatment of adult patients with Waldenström's macroglobulinemia (WM), marginal zone lymphoma (MZL), and chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy, were given approval after open-label, multicentered, single arm trials based on a surrogate endpoint (ORR) as the efficacy outcome.[13] Factors that may have supported the decision to grant full approval of supplemental indications based on ORR include: great efficacy as demonstrated by very high response rates (90.5%) observed in adult patients with WM who had received a median of 2 prior therapies, and unmet clinical need (for example, WM is very rare and although this is a slow-growing B-cell lymphoma, eventually patients progress and require therapy. Current therapies are limited for patients with WM).

Appendix Table 1: Summary of Indications for Pembrolizumab in Chronological Order By Date of Submission

Action Date	Submission	Supplement Category	Tumor Type	Indication	Type of approval
09/04/2014 12/18/2015	ORIG-1 SUPPL-4 SUPPL-6	Original Approval	Metastatic melanoma	patients with unresectable or metastatic melanoma	Accelerated approval (9/14), full approval (12/15)
10/02/2015 10/24/2016	SUPPL-5 SUPPL-8	Efficacy-New Indication	Metastatic NSCLC	treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 [Tumor Proportion Score (TPS) ≥ 1%] as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy	Accelerated approval (10/15), full approval (10/16)
08/05/2016	SUPPL-9	Efficacy-New Indication	Metastatic HNSC	treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (metastatic HNSC) with disease progression on or after platinum-containing chemotherapy	Approved under accelerated approval
10/24/2016	SUPPL-12	Efficacy-New Indication	Metastatic NSCLC	expansion of the metastatic NSCLC indication to include first-line treatment of patients whose tumors have high PD-L1 expression (TPS ≥ 50%) as determined by an FDA approved test, with no EGFR or ALK genomic tumor aberrations.	Full approval
03/14/2017	SUPPL-15	Efficacy-New Indication	Refractory classical Hodgkin Lymphoma	treatment of adult and pediatric patients with refractory classical Hodgkin Lymphoma, or who have relapsed after 3 or more prior lines of therapy	Approved under accelerated approval
05/10/2017	SUPPL-16	Efficacy-New Indication	Metastatic non-squamous NSCLC	in combination with pemetrexed and carboplatin, for the first-line treatment of patients with metastatic non-squamous, NSCLC.	Approved under accelerated approval
05/18/2017	SUPPL-17	Efficacy-New Indication	Metastatic urothelial carcinoma	for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy	Approved under accelerated approval
05/18/2017	SUPPL-18	Efficacy-New Indication	Metastatic urothelial carcinoma	for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy	Full approval
05/23/2017	SUPPL-14	Efficacy-New Indication	MSI-H, dMMR solid tumors	unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options	Approved under accelerated approval
05/23/2017	SUPPL-14	Efficacy-New Indication	MSI-H, dMMR CRC	metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.	Approved under accelerated approval
09/22/2017	SUPPL-24	Efficacy-New Indication	Metastatic gastric cancer	for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu targeted therapy	Approved under accelerated approval

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Broadening Eligibility Criteria to Make Clinical Trials More Representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement

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ABSTRACT

Purpose
The primary purposes of eligibility criteria are to protect the safety of trial participants and define the trial population. Excessive or overly restrictive eligibility criteria can slow trial accrual, jeopardize the generalizability of results, and limit understanding of the intervention's benefit-risk profile.

Methods
ASCO, Friends of Cancer Research, and the US Food and Drug Administration examined specific eligibility criteria (ie, brain metastases, minimum age, HIV infection, and organ dysfunction and prior and concurrent malignancies) to determine whether to modify definitions to extend trials to a broader population. Working groups developed consensus recommendations based on review of evidence, consideration of the patient population, and consultation with the research community.

Results
Patients with treated or clinically stable brain metastases should be routinely included in trials and only excluded if there is compelling rationale. In initial dose-finding trials, pediatric-specific cohorts should be included based on strong scientific rationale for benefit. Later phase trials in diseases that span adult and pediatric populations should include patients older than age 12 years. HIV-infected patients who are healthy and have low risk of AIDS-related outcomes should be included absent specific rationale for exclusion. Renal function criteria should enable liberal creatinine clearance, unless the investigational agent involves renal excretion. Patients with prior or concurrent malignancies should be included, especially when the risk of the malignancy interfering with either safety or efficacy endpoints is very low.

Conclusion
To maximize generalizability of results, trial enrollment criteria should strive for inclusiveness. Rationale for excluding patients should be clearly articulated and reflect expected toxicities associated with the therapy under investigation.

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INTRODUCTION

Eligibility criteria are a foundational component of clinical trials and serve to define the patient population under study. They can be inclusionary, by, for example, specifying a tumor type or molecular alteration needed for study entry, or exclusionary, by specifying certain characteristics, such as laboratory test values, history of prior and concurrent malignancies, minimum age, or comorbidities, that would render a patient ineligible for enrollment. The primary purposes of eligibility criteria are to protect the safety of patients who participate in clinical trials and to define the characteristics of the study population. Excessive or overly restrictive eligibility criteria can impair clinical trial accrual and completion and prevent patients from accessing investigational interventions that may provide clinical benefit. Narrowly defined trial populations may also jeopardize the generalizability of trial results and limit the ability to understand the therapy's benefit-risk profile across the broad patient population who ultimately may receive the intervention in the postmarket setting. The clinical

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generalizability of a study is directly connected to the degree to which trial participants reflect the range of characteristics of the patient population for whom the intervention has been devised.[1]

Common inclusion and exclusion criteria have developed over time, primarily through experience with cytotoxic chemotherapeutics. Eligibility criteria are often duplicated from previous trials as a start or template for the next study, but instead, they should be modified as appropriate to meet the objectives of each study in consideration of the anticipated safety of the investigational agent in the new study or the ability to recruit trial participants from the patient population. Given the increase in complexity of cancer treatments, the advent of novel therapeutic modalities with differing safety profiles, and the targeting of specific patient subpopulations, many have called for simplified, rational, modernized eligibility criteria that accurately reflect the population of patients with cancer who are the intended users of the investigational therapy once it reaches the market.[2-5] Newer precision medicine agents are often studied in populations with specific genomic alterations because preclinical data indicate that the agent targets a specific molecular abnormality or pathway and is uniquely or preferentially effective in tumors that harbor the alteration. The fact that many of the alterations occur in low frequencies heightens the need to be maximally inclusive of patients whose tumors harbor the given alteration, as long as safety of the participants is considered.

Restrictive eligibility criteria may preclude enrollment of trial participants who represent the range of characteristics of the overall patient population with a given disease. For example, Kaiser Permanente conducted an analysis of 326 consecutively diagnosed patients with non–small-cell lung cancer (NSCLC) to determine how many would qualify for two trials involving chemotherapy and antiangiogenic therapy. The majority of patients (approximately 80%) were ineligible for the trials as a result of failure to meet eligibility criteria requirements and comorbidities.[6] In addition, reviews of the National Cancer Institute clinical trials program concluded that exclusionary criteria arbitrarily eliminate patients and recommended that eligibility criteria be simplified and broadened.[7,8]

ELIGIBILITY CRITERIA INITIATIVE

Modernizing eligibility criteria was a key objective of the November 2011 ASCO Blueprint for Transforming Clinical and Translational Cancer Research.[9] ASCO believed that an increasing number and complexity of eligibility criteria were compromising recruitment to clinical trials. A working group of the ASCO Cancer Research Committee conducted an analysis of clinical trials and survey of investigators and developed a recommended strategy to formulate inclusion and exclusion criteria, as well as encourage continuous reassessment of criteria throughout the research process.[4] The resulting article provided a list of key questions to help focus trial designers on the relationship of criteria to the study objectives, generalizability of results, and risks to patients.

ASCO, in collaboration with Friends of Cancer Research (Friends), launched a collaborative initiative to reassess the approach for determining clinical trial eligibility. ASCO, Friends, and the US Food and Drug Administration (FDA) used the recommendations from ASCO's original work to identify specific eligibility criteria that were most likely to restrict patients' participation in trials and were least likely to impact the safety of trial participants. The project leadership initially selected the following four topics that commonly lead to exclusion of patients from clinical trials: brain metastases, minimum age for enrollment, HIV infection, and organ dysfunction and prior and concurrent malignancies. Each of these topics was explored by working groups composed of multiple stakeholders, including investigators, patient advocates, biostatisticians, pharmacologists, manufacturers, and regulators. The working groups reviewed the state of the science and existing studies in the literature and attempted to balance the needs of protecting patient safety, facilitating access to investigational therapies, and protecting trial integrity (including safety, efficacy, statistical, and operational considerations). The working groups engaged in multiple meetings to discuss their concerns and reached consensus on approaches that could be implemented to broaden eligibility criteria and enable recruitment of a trial population that is more representative of the population of patients with the given cancer who are the intended users of the intervention being studied. The draft recommendations were presented and vetted among all the working groups at a May 2016 workshop and were discussed at a public meeting in November 2016—the Friends Annual Meeting on Clinical Cancer Research.[10] Representatives from the National Clinical Trials Network (NCTN) provided examples at the November meeting of ongoing efforts within the NCTN groups to appropriately expand eligibility criteria.

WORKING GROUP RECOMMENDATIONS

Detailed discussion of each of the working group recommendations is included in separate manuscripts that have been submitted for publication. This statement provides a high-level summary of each of the working group recommendations and discusses overarching principles to guide implementation. Recommended language for use in clinical trial protocols is included in Table 1.

Brain Metastases

Broad or conditional exclusion of patients with brain metastases is common despite the high incidence of brain metastases in some tumor types.[11] An FDA analysis of 250 Investigational New Drug applications for 2015 found that less than half permitted enrollment of patients with previously treated, inactive, and/or stable brain metastases (Jin et al, manuscript submitted for publication). Although life expectancy may be reduced for some patients with brain metastases and there have been concerns regarding a potentially greater risk of neurologic toxicity, existing literature does not indicate that these patients experience higher rates of serious adverse events.[12] This working group developed recommendations specific to patients with treated or stable brain metastases; patients with new, active, or progressive brain metastases; and patients with leptomeningeal disease.[13]

- Patients with treated and/or stable brain metastases (eg, no progression for at least 4 weeks after local prior therapy)

Table 1. Recommended Protocol Text

Patient Subgroup	Text Template
Patients with treated/stable brain metastases	Template for inclusion: Patients with treated brain metastases are eligible if there is no evidence of progression for at least 4 weeks after CNS-directed treatment, as ascertained by clinical examination and brain imaging (MRI or CT) during the screening period.
Patients with new, active, or progressive brain metastases	Guidance for inclusion in early-phase trials: Patients with active brain metastases should be included early in clinical development when there is strong scientific rationale for likelihood of benefit, based on molecular pathways or histology and preclinical data. For drugs/modalities with less robust preclinical information on potential CNS activity, inclusion of patients with active brain metastases should still be considered, particularly if brain metastases are common in the intended use population. The inclusion of a CNS-specific cohort can provide valuable dosing and preliminary efficacy data to either support or refute inclusion in later phase trials. Guidance for inclusion in later phase trials: Ideally, data from earlier phase trials, in concert with the strength of the scientific rationale and preclinical data, can inform decisions on inclusion of patients with active brain metastases in later phase trials. When such data are not available, several potential trial designs could allow patients with active brain metastases to enroll, either as a parallel cohort or as a defined subset within the larger clinical trial.
Patients with LMD	Guidance for inclusion: See above considerations. • If patients with LMD are to be excluded, the following wording is suggested to avoid unnecessary exclusion of patients with imaging-only equivocal findings. Guidance for exclusion: For the purposes of exclusion, LMD is a clinical diagnosis, defined as positive CSF cytology and/or unequivocal radiologic or clinical evidence of leptomeningeal involvement. Patients with leptomeningeal symptoms in the setting of leptomeningeal enhancement by imaging (MRI) would be considered to have LMD even in the absence of positive CSF cytology, unless a parenchymal lesion can adequately explain the neurologic symptoms and/or signs. In contrast, an asymptomatic or minimally symptomatic patient with mild or nonspecific leptomeningeal enhancement (MRI) would not be considered to have LMD. In that patient, CSF sampling is not required to formally exclude LMD, but can be performed at the investigator's discretion based on level of clinical suspicion. Template for exclusion: No known LMD
Patients younger than age 18 years	Guidance for inclusion in early-phase trials: Pediatric-specific cohorts should be included when there is strong scientific rationale for likelihood of benefit, based on molecular pathways or histology as well as preclinical data. Templates for inclusion • Adolescent/pediatric patients age [*protocol author to insert age minimum and maximum specific to the study under consideration*] will be included after enrollment of adult patients after safety and toxicity in the adult population have been established. Participating sites will be notified when adolescent/pediatric patient enrollment may begin. • Adolescent/pediatric patients age [*protocol author to insert age minimum and maximum specific to the study under consideration*] will be included starting one dose cohort behind the current adult cohort in which there are no dose-limiting toxicities identified. Participating sites will be notified when enrollment onto the adolescent/pediatric stratum may begin. • Adolescent/pediatric patients age [*protocol author to insert age minimum and maximum specific to the study under consideration*] will be included in age-specific cohorts that will be staggered starting one dose cohort behind the current adult cohort in which there are no dose-limiting toxicities identified. Participating sites will be notified when each adolescent/pediatric cohort enrollment may begin. • Adolescent/pediatric patients age [*protocol author to insert age minimum and maximum specific to the study under consideration*] are included in this trial in a separate cohort that will accrue simultaneous to the adult cohort [*specify age 18 and older or protocol-specific upper age limit*]. Guidance for inclusion in later phase trials: Patients age 12 years and older should be included in trials for diseases that span pediatric and adult populations. Patients younger than age 12 years may also be included if clinically appropriate.
Patients with HIV infection	Template for inclusion: HIV-infected patients who are healthy and have a low risk of AIDS-related outcomes are included in this trial. • Guidance for inclusion: HIV-related eligibility criteria should be straightforward and focus on appropriate CD4+ T-cell thresholds for a given study based on current and past counts, history (if any) of AIDS-defining opportunistic infections, and status of HIV treatment, including requirements (if any) for standard-of-care antiretroviral agents. • Patients should generally be treated with antiretroviral therapy for HIV. If there is ADME data to predict drug-drug interactions between specific HIV medication(s) and the investigational agent(s), specific anti-HIV medication(s) should be listed as contraindicated in the protocol. Patients on contraindicated medications should be evaluated for alternate HIV therapy that would allow eligibility in the study.
Kidney function	Guidance for renal function criteria: Measure based on creatinine clearance, rather than serum creatinine levels. Template for inclusion for investigational agent(s) that are not nephrotoxic or have renal excretion as a significant component of pharmacokinetics: Patients with creatinine clearance > 30 mL/min, (measured using Cockcroft-Gault equation or the estimated glomerular filtration rate from the Modification of Diet in Renal Disease Study) are included in the study. Established dose-modification strategies can allow safe and effective administration. Guidance for drugs that are nephrotoxic or have renal excretion as a significant component of pharmacokinetics: Conservative criteria for creatinine clearance are appropriate.
Liver function	Guidance for liver function criteria: Liver function tests used to determine eligibility should be assessed relative to institutional normal ranges, not a universal cutoff point.

(continued on following page)

Table 1. Recommended Protocol Text (continued)

Patient Subgroup	Text Template
Cardiac function	Guidance for cardiac function criteria: Measurement should include investigator assessment of a potential participant's risk for heart failure with a validated clinical classification system (eg, the New York Heart Association Functional Classification).
Prior and concurrent malignancies	Guidance for inclusion: Inclusion of patients with prior or concurrent malignancies is recommended, especially when the risk of the malignancy interfering with either safety or efficacy endpoints is very low. Template for inclusion: Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen should be included.

Abbreviations: ADME, absorption, distribution, metabolism, and excretion; CT, computed tomography; LMD, leptomeningeal disease; MRI, magnetic resonance imaging.

should be routinely included in prospective clinical trials of all phases and only excluded if there is compelling rationale for exclusion. If there are specific safety concerns, then tailoring specific criteria to the concern is preferable to general exclusion of all patients with brain metastases.

- For patients with active (eg, untreated or progressive) brain metastases, the working group recommends that such patients not be automatically excluded. However, a one-size-fits-all approach is not appropriate, and factors such as natural history of the disease, trial phase and design, and the drug's mechanism of action, pharmaceutical properties, and potential for CNS penetration should determine whether such patients are included in a trial. If patients with active brain metastases are included, additional prospective planning may be required to better define safety and treatment response. Early stopping rules may be appropriate should excessive toxicity and/or lack of efficacy be observed.
- In most trials, it remains appropriate to exclude patients with leptomeningeal disease as a result of their poor prognosis, although there may be situations that warrant a cohort of such patients in early-phase trials (eg, when CNS activity is anticipated), and these data could then support inclusion of such patients in later phase trials. If patients with leptomeningeal disease are excluded, justification for such exclusion should be provided alongside the exclusion criteria.

Minimum Age for Enrollment

Children and adolescents under the age of 18 years have traditionally been excluded from participating in clinical trials with novel agents until extensive data are available from studies of adults, often years after the introduction and approval of an agent. Because pediatric patients have historically been considered a vulnerable population, there is concern that a high-profile adverse event in a child could endanger the entire drug development program. However, a review of successful and failed development of oncology drugs over the past three decades yields no evidence to support this concern (G.H. Reaman, personal communication, March 2017). Drug exposure in adolescents (age 12 to 18 years) and adults is similar, supporting the enrollment of adolescents in adult trials that involve the same disease and/or therapeutic target.[14,15] The Minimum Age Working Group developed recommendations for inclusion of pediatric patients in early- and late-phase trials.[16]

- In initial dose-finding trials, pediatric-specific cohorts should be included when there is strong scientific rationale for likelihood of benefit, based on molecular pathways or histology or preclinical data. These cohorts would assess dose and pharmacokinetics separately in the pediatric population. Staggered enrollment starting with older children followed by younger children could be considered to address potential concerns specific to younger pediatric patients, including not only metabolic differences but also challenges related to the availability of appropriate formulations for young children.
- Later phase trials in diseases and/or therapeutic targets that span adult and pediatric populations should include pediatric patients. Given the similarity in metabolism and excretion between adults and adolescents, patients age 12 years and older should be enrolled onto such trials. In some instances, it may also be appropriate to enroll patients younger than age 12 years with the proper clinical support and expertise.

HIV Infection

Many people infected with HIV now have a normal life expectancy as a result of substantial improvements in HIV treatment over the past 20 years.[17,18] Cancer is now a leading cause of mortality in people with HIV; however, most oncology studies exclude this population, as confirmed by the FDA analysis of 2015 Investigational New Drug applications. Only five (1.7%) of 250 protocols allowed enrollment of HIV-positive patients with stable disease and/or adequate CD4+ T-cell counts (Jin et al, manuscript submitted for publication). A review of HIV eligibility criteria in recent industry-supported studies leading to successful new drug applications conducted by the working group found that zero of 46 studies contained inclusion criteria for patients with HIV, 30 studies contained exclusion criteria, and nine studies discussed general exclusion of patients with active infection but did not specify HIV infection. The HIV Working Group recommended the following eligibility considerations in cancer studies.[19]

- Patients with cancer with HIV infection who are healthy and have a low risk of AIDS-related outcomes should be included in cancer clinical trials unless there is a specific rationale to exclude such patients.
- Eligibility criteria should be straightforward and focus on current and past CD4 and T-cell counts, history (if any) of AIDS-defining conditions (eg, opportunistic infections), and status of HIV treatment. Healthy HIV-positive participants who are included in cancer clinical trials should be treated using the same standards as trial participants with other comorbidities. Antiretroviral therapy should be considered a concomitant medication.
- Eligibility criteria for cancer clinical trials should allow for the patient to be treated concurrently with standard antiretroviral therapy (ART) following Department of Health and Human Services treatment guidelines.[20] In cases where ART therapy may interact with cancer therapy, specific ART agents may be excluded.

Organ Dysfunction and Prior and Concurrent Malignancies

This working group first evaluated the types of organ dysfunction that were likely to drive most clinical trial exclusion criteria. The areas of focus included kidney, heart, and liver dysfunction, as well as exclusion based on a history of a previous malignancy. The group conducted analysis of these criteria from a large, representative data set that included a cohort of nearly 13,000 newly diagnosed patients with breast, colon, lung, and bladder cancers from 2013 to 2014. The analysis, as well as review of the literature, helped determine which of the organ dysfunction criteria to prioritize for development of recommendations.[21]

- Renal function criteria should be based on creatinine clearance rather than serum creatinine levels. In situations where renal excretion is not a significant component of a drug's clearance, liberal creatinine clearance criteria (eg, > 30 mL/min) should be used. Both the Cockcroft-Gault equation and the estimated glomerular filtration rate from the Modification of Diet in Renal Disease Study are reliable methods to estimate creatinine clearance.[22] Trial sponsors should choose one of these methods and use it consistently across the research process. Established dose-modification strategies can allow safe and effective administration. Conservative criteria remain appropriate for nephrotoxic drugs.
- Current clinically available tests of hepatic function (eg, tests of serum aminotransferases [ALT and AST] and bilirubin) inadequately describe liver function, particularly drug metabolism capability. In the absence of alternate testing methods, trials should continue to use standard clinical assessments of liver function relative to institutional normal ranges and avoid imposing a universal cutoff point that may be unnecessarily restrictive.
- If an investigational therapy is not known to pose cardiac risks, arbitrary ejection fraction values should not be used to exclude patients from clinical trials. Trials should recommend investigator assessment of a potential participant's risk for heart failure with a validated clinical classification system, such as the New York Heart Association Functional Classification.[23] Concern about cardiac effects often leads to frequent ECG monitoring in early-phase trials to determine eligibility and ongoing risk for QT/QTc prolongation.[24] Continued ECG monitoring should be eliminated in later phases if cardiac risk is not determined to be a concern.
- Exclusions based on a history of prior malignancy or presence of concurrent malignancy should be liberalized, both in terms of when the malignancy occurred and was treated and types of prior malignancies. Inclusion of patients with prior or concurrent malignancies is recommended, especially when the risk of the malignancy interfering with either safety or efficacy endpoints is very low. Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen should be included.

DISCUSSION

Through the course of the working group discussions, potential benefits and risks of expanding eligibility criteria were identified (Table 2). As previously stated, the primary purpose of eligibility criteria is to protect the safety of clinical trial participants who may have characteristics that place them at increased risk for an adverse event from the intervention being studied. Thus, arguments against the use of broader eligibility criteria center on the concern that the development of an effective drug could be jeopardized if a serious adverse event occurs in a patient population that is inherently sicker or vulnerable. Inclusion of some patients may require additional screening or monitoring or the engagement of additional expertise to manage safety issues specific to that patient population. This would help to mitigate risk in these patients but could also increase trial cost and complexity.

In some cases, the working groups concluded that eligibility criteria should be broadened for all trial participants, particularly when a drug's known or expected safety profile does not pose inordinate risks to participants. In other cases, sponsors could consider enrolling an expanded, more heterogeneous population and exclude these patients from the primary efficacy analysis, so as not to compromise assessment of the drug's efficacy, but include them in the safety analysis. Strategies could include enrolling restricted and expanded populations in the same clinical trial (Jin et al, manuscript submitted for publication), conducting simultaneous clinical trials and analyzing separately, or using an extended trial design to expand knowledge in particular populations, such as the elderly, by enriching the primary study population with such individuals.[25] Additional potential study design options that can be considered to address these concerns and potentially mitigate risk are listed in Table 3.

Although incorporation of an expanded trial population could present additional operational considerations, this practice could be accompanied by incentives such as the potential for expanded label indications resulting in competitive marketing claims. In addition, there is the potential for inclusion of additional information in the label's prescribing information to help guide clinicians in adjusting administration and dosing in different populations. Adequate data generated in the clinical trial on underrepresented populations, such as those with organ impairment, may obviate requirements for postmarketing studies. Discussion with regulators is encouraged to determine the best approach for each situation.

Cooperative groups have adapted eligibility criteria over the years. A review of Eastern Cooperative Oncology Group lung cancer trials determined that patients with prior malignancies were excluded from 94% of trials that used survival as a primary end point and 73% of trials that used other primary end points.[26] Prior

Table 2. Benefits and Risks of Expanded Eligibility Criteria

Benefit and Risk	Patients and Physicians	Sponsors and Investigators
Benefits	Earlier access to investigational agents and expanded trial and treatment options More complete safety data, which can inform clinical use and enable safe delivery if investigational agent becomes commercially available Availability of efficacy and safety data can inform weighing of commercially available treatment options across a broader array of patients and increase confidence in therapy selection Earlier identification of drugs that may not be efficacious in a particular patient population or that may cause more harm than good	Ability to generalize to real-world patients and potentially reduce postmarketing requirements Faster accrual; more patients may be eligible at each site, which may reduce the overall number of sites needed to successfully complete accrual Identification of potential safety issues during clinical trials may facilitate early development of mitigation strategies, enabling broader uptake after approval Efficacy in traditionally understudied population could potentially result in expanded marketing claims and provide a differentiating factor between drugs of same class
Risks	Limited data from small cohorts may not be adequate for clinical decision making Patients who are inherently sicker may have higher risk of experiencing an adverse event as a result of the drug or disease Additional procedures for increased safety monitoring in some situations may incur additional costs to patients and/or the study Additional resources may be required to ensure clinical and research staff are capable of managing the additional patients on study	More variability in outcomes: may require larger sample sizes and inferences may not be as precise Potential safety concerns: may require separate cohorts or analysis plans and early stopping rules for excess toxicity May complicate attribution of adverse events: consider randomization and data from other drugs in class Increased costs associated with additional cohorts, statistical requirements, additional testing, or special expertise to manage specific patient needs

malignancies did not impact survival outcomes in patients with stage IV lung cancer or locally advanced lung cancer, suggesting that clinical trial outcomes would not be adversely impacted by inclusion of patients with a history of prior cancer.[27,28] This analysis led the Alliance in Clinical Trials in Oncology Group to develop more inclusive criteria for patients with advanced lung cancer. The National Cancer Institute NCTN is also broadening eligibility criteria and changing clinical trial designs to address slow patient accrual. The Southwest Oncology Group revised the eligibility criteria of phase III trials of advanced NSCLC in a stepwise manner. From 1995 to 2014, the Southwest Oncology Group launched three NSCLC trials (S9509,[29] S1400, and S1403) and progressively expanded its approach to inclusion of patients with brain metastases and prior malignancies.

ASCO's Targeted Agent and Profiling Utilization Registry (TAPUR) Study has broad inclusion criteria of patients with prior and concurrent malignancies not requiring treatment, brain metastases, and HIV infection, and is in the process of lowering eligibility age from 18 to 12 years for drugs that have an established pediatric dose or drugs in which the pediatric dose can be derived from data from adult clinical trials.[15] The TAPUR protocol enables patients with any prior or concurrent cancer to participate. Patients with brain metastases can participate, as long as the treatment of the brain metastases has been completed, the metastases are not progressive, and the patient has been off corticosteroids for at least 1 month. Patients also cannot have experienced a seizure or had a clinically significant change in neurologic status within 3 months of enrollment. Patients with HIV infection are allowed to enroll at the clinical investigator's discretion, except for two study drugs with exclusions based on active HIV infection.

Fundamentally changing the approach to eligibility criteria requires a culture change across the entire clinical trials enterprise. At the design phase, investigators and trial sponsors should approach study development with an inclusive mindset, taking into consideration the safety profile of the investigational therapy, standard-of-care treatment, and the characteristics of the indicated population. A standard of inclusion, unless otherwise specified, would give investigators the responsibility to provide rationale and use their own clinical judgment and discretion as to why patients should be excluded from trial participation. Known or suspected risks of the investigational therapy should be the primary factors that warrant exclusion of patients. These risks should be outlined in a concise, easy-to-read format and provided to investigators, pharmacists, and the clinical research team for review. As

Table 3. Potential Trial Designs and Considerations

Trial Designs and Considerations
Early-phase trials
Expansion cohort restricted to a specific patient population (eg, pediatric and elderly populations, patients with poor performance status, or patients with active brain metastases).
Maximum-tolerated dose, dose-limiting toxicities, and pharmacokinetics may be assessed separately in that population.
Serious safety issues could prompt the cohort to be closed without compromising the entire drug development program.
Results in early phase can inform the decision as to whether and how to include (or not) the patient population in later phase trials.
Later phase trials
Simply expand eligibility criteria to include a specific patient population (may be appropriate for patients with prior and concurrent malignancies, brain metastases, or HIV).
Allow broad enrollment while restricting primary analysis to defined patient population.
Protects integrity of trial while enabling data collection in broader populations.
Data may be helpful to inform safe clinical use in real-world patients.
Expand trial eligibility to include a specific patient group, but stratify enrollment such that the traditional subset and the special subset are randomly assigned separately.
May be appropriate when early-phase data show that special subset can tolerate drug but only at a lower dose or when life expectancy is shorter in special subset.
Consider adaptive designs where trial is expanded or restricted based on initial data and recommendations from a data safety monitoring board.
Initiate a companion protocol restricted to a specific patient population.
Similar to expanded access protocols, may only include safety monitoring.

information is gathered over the duration of a trial, eligibility criteria should be reconsidered at predefined time points or events and adjusted, if needed, during the clinical development plan to enable greater inclusion with an aim of having the study population in late-stage or registration trials reflect as closely as possible the indicated population. Discussions with regulatory officials can also stress the importance of gathering safety data and including data on a broader array of patients in prescribing information. Eligibility criteria that affirmatively state inclusion of patients will help to overcome potential investigator or research staff bias against inclusion of patients such as those with prior and concurrent malignancies and comorbidities.[30] Outreach to institutional review boards and scientific review committees to educate them on the importance of being inclusive will also help to overcome concerns that may arise from these oversight bodies.

In conclusion, to maximize the generalizability of clinical trial results, eligibility criteria should strive for inclusiveness to enroll participants who are representative of the intended users of the intervention under study in a timely manner. Rationale for excluding patients with characteristics should be clearly articulated and reflect expected toxicities associated with the therapy under investigation based on existing data. In cases where the toxicity profile of the drug is unknown, eligibility criteria should be adjusted over the course of the research process as greater understanding of the agent's pharmacokinetics and tolerability are developed. We anticipate that current efforts to expand eligibility in several ongoing and planned clinical trials will help to demonstrate the feasibility of expanding eligibility and that future FDA guidance will assist sponsors in designing more representative trials. ASCO and Friends plan to work with the clinical trial community to encourage incorporation of these recommendations in new and existing trials and identify opportunities to track progress.

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Broadening Eligibility Criteria to Make Clinical Trials More Representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement

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Modernizing Clinical Trial Eligibility Criteria: Recommendations of the American Society of Clinical Oncology–Friends of Cancer Research HIV Working Group

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ABSTRACT

Purpose
People with HIV are living longer as a result of effective antiretroviral therapy. Cancer has become a leading cause of morbidity and mortality in this patient population. However, studies of novel cancer therapeutics have historically excluded patients with HIV. Critical review of eligibility criteria related to HIV is required to accelerate development of and access to effective therapeutics for HIV-infected patients with cancer and make studies more generalizable to this patient population.

Methods
From January through April 2016, the HIV Working Group conducted a series of teleconferences; a review of 46 New Drug Applications from registration studies of unique agents studied in adults with cancer that led to the initial US Food and Drug Administration approval of that agent from 2011 to 2015; and a review of HIV-related eligibility criteria from National Cancer Institute–sponsored studies. Results were discussed and refined at a multistakeholder workshop held May 12, 2016. The HIV Working Group developed recommendations for eligibility criteria that focus on pharmacologic and immunologic considerations in this patient population and that balance patient safety, access to appropriate investigational agents, and study integrity.

Results
Exclusion of patients with HIV remains common in most studies of novel cancer agents. Models for HIV-related eligibility criteria in National Cancer Institute–sponsored studies are instructive. HIV infection itself should no longer be an exclusion criterion for most studies. Eligibility criteria related to HIV infection that address concurrent antiretroviral therapy and immune status should be designed in a manner that is appropriate for a given cancer.

Conclusion
Expanding clinical trial eligibility to be more inclusive of patients with HIV is justified in most cases and may accelerate the development of effective therapies in this area of unmet clinical need.

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INTRODUCTION

In the modern era of HIV therapeutics, many people infected with HIV are expected to have a normal life expectancy.[1,2] Despite this dramatic outcome as a result of improvements in the treatment of HIV over the past 20 years, and despite the increasing public health need to treat cancer in people with HIV, most oncology studies exclude all people with HIV. The goal of this working group was to assess the scope of problem and develop recommendations for modernized clinical cancer trial eligibility criteria related to HIV infection to enable appropriate inclusion of people with HIV in cancer clinical trials.

An estimated 1.2 million people in the United States[3] and 37 million people globally[4] are infected with HIV. Since 1996, treatment of HIV has consisted of combination antiretroviral therapy (ART). As of April 2016, ongoing advances in ART drug development have led to 29 agents approved by the US Food and Drug Administration (FDA), which has revolutionized HIV care. Most patients with HIV take once-a-day antiviral medications that have minimal adverse effects.[5] Treatment of HIV allows for substantial preservation or reconstitution of immune

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function, and in the era of ART, infectious complications have become increasingly rare. The US Department of Health and Human Services (DHHS) guidelines[6] and WHO[7] recommend ART for all people with HIV. Intensive efforts in the United States and globally to increase the proportion of patients with HIV on ART are ongoing.[8] The life expectancy of people with HIV on ART now approaches that of the general population, especially for those who start therapy with a normal $CD4^+$ T-cell count (ie > 350 cells/uL).[1]

Cancer in People With HIV

With increased longevity of people with HIV, cancer has become a leading cause of morbidity and mortality.[9,10] This is largely because HIV increases the risk of some cancers, the prevalence of HIV increases with improved life expectancy, and the population of people living with HIV is aging. The cancers most closely linked to HIV[11,12] comprise approximately two thirds of cancers in this population. These cancers include AIDS-defining cancers, such as aggressive B-cell lymphomas (ie, diffuse large B-cell lymphoma, Burkitt's lymphoma, plasmablastic lymphoma, primary effusion lymphoma, primary CNS lymphoma), Kaposi sarcoma, and cervical cancer, and non–AIDS-defining cancers, such as classic Hodgkin lymphoma, lung cancer, anal cancer, liver cancer, and head and neck cancers. Most other cancers occur at the same frequency or slightly increased frequency compared with the general population, and cumulatively, the burden of cancer in people with HIV is expected to increase in the United States and globally for the foreseeable future.

Management of cancer for people with HIV should focus on approaches that are appropriate for the malignancy. This generally consists of standard regimens integrated with treatment of HIV and appropriate supportive care when indicated.[13] In appropriately selected patients treated with this approach, outcomes are comparable to those of the general HIV-uninfected population. This has been demonstrated for diffuse large B-cell lymphoma,[14] Burkitt's lymphoma,[15] classic Hodgkin lymphoma,[16] and lung cancer.[17] Likewise, autologous[18] stem-cell transplantation is feasible in people with HIV, with outcomes comparable to those of the background population. The feasibility and safety of allogeneic transplantation in people with HIV have been evaluated in an 18-person study conducted since September 2011 (Blood and Marrow Transplant Clinical Trials Network 0903/AIDS Malignancy Consortium 080). The trial has recently closed, and results will be reported in the near future. As is true for the general population, there is an ongoing public health need for less toxic and more effective targeted oncology drugs for many cancers in people with HIV. In many instances where standard therapy has failed to control a given cancer, experimental therapy should be the preferred approach.

HIV-specific studies for many types of common cancers that are not associated with HIV are impractical given the diversity of cancers that may occur in this patient population, and therefore, inclusion of appropriately selected patients with HIV in studies of a given disease type or molecular characterization is needed. Lack of prospective data on therapies in people with HIV limits evidence-based treatment decisions and contributes to suboptimal oncology care for people with HIV. Prospective data on novel approaches in this patient population are critical to address unnecessary treatment disparities both within clinical studies and with subsequent use of FDA-approved agents. Routine exclusion to clinical trial participation is not justified, and eligibility criteria related to HIV should be assessed on the basis of current medical knowledge and scientific rationale.[19] Individuals who are healthy from the perspective of their HIV should be eligible for participation in clinical trials provided they meet the other eligibility criteria of a given study. Exclusion based on HIV infection alone is generally not appropriate, and exceptions should be based on sound medical rationale that is clearly articulated in a specific protocol. Recommendations from the HIV Working Group address some of the most common considerations related to modernizing eligibility for this patient population.

PROCESS

HIV Working Group

To address the public health need to update the eligibility criteria related to HIV in oncology studies, the HIV Working Group of the ASCO–Friends of Cancer Research Modernizing Eligibility Criteria Project for Modernizing Eligibility Criteria in Cancer Studies held a series of teleconferences from January through April 2016 to develop an initial draft of recommendations on this topic. The committee consisted of government, academic, and industry investigators with clinical trial and pharmacology expertise, representatives from the FDA, policy experts, and patient and cancer research advocates. The committee reviewed recent clinical oncology studies to evaluate HIV-related eligibility criteria in both industry-sponsored studies and studies sponsored by the National Cancer Institute (NCI). Results were discussed and refined at a multistakeholder workshop held May 12, 2016.

Current HIV-Related Eligibility Criteria

Eligibility criteria for both industry-sponsored and NCI-sponsored cancer studies were reviewed to evaluate current approaches to eligibility and quantify the need for specific recommendations related to HIV. The group reviewed eligibility criteria from studies supporting 46 New Drug Applications (NDAs) of unique agents in patients with cancer that led to initial FDA approval from 2011 to 2015. Eligibility criteria in the relevant clinical studies were evaluated on ClinicalTrials.gov (where available), in the FDA application, and/or in the Methods sections of published results. We evaluated studies for specific HIV-associated inclusion criteria and HIV-associated exclusion criteria. When these were not available as a result of inadequate details about entry criteria, we noted more general exclusion criteria that would likely include HIV (ie, exclusion for active infection or HIV exclusion criteria in studies of the same agent). This review revealed no studies with HIV-specific inclusion criteria, 30 studies with specific HIV exclusion criteria, and an additional nine studies with likely HIV exclusion (Fig 1).

Of the 46 NDA agents examined, as of May 1, 2016, 15 subsequently became available for HIV-infected patients with cancer who met additional eligibility criteria through a variety of

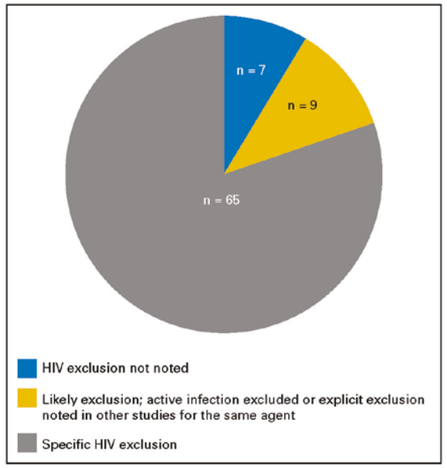

Fig 1. HIV-related eligibility in New Drug Applications from 2011 to 2015.

studies developed in partnership with NCI (Table 1). This included eight drugs that were subsequently used in one or more studies for HIV-specific populations and/or tumor-specific studies that allowed patients with HIV, as well as seven of the first 12 agents currently used in the NCI Molecular Analysis for Therapy Choice (MATCH) trial. Nonetheless, deferring the undertaking of studies that allowed treatment of patients with HIV until after FDA approval resulted in a delay in availability and specific FDA labeling for these novel agents in patients with HIV. For example, the median delays to availability of novel agents for people with HIV and cancer through either market availability or through HIV-specific studies in the 46 NDAs leading to FDA approval reviewed were 6.8 years (range, 2.3 to 19.7 years) for phase I to approval, 3.9 years (range, 1 to 7.6 years) for NDA study to approval, and 6.3 years (range, 3.5 to 11.7 years) for phase I to HIV-specific study.

We reviewed select NCI-sponsored studies specific to patients with HIV or open to the general population with explicit entry criteria allowing for patients with HIV. These studies were reviewed for criteria related to $CD4^+$ T-cell count, HIV viral load, concomitant HIV medications, and other factors relevant to HIV status. Entry criteria for 13 relevant NCI-sponsored studies, including the NCI-MATCH study, are listed in Table 1 and provide examples that inform future studies. Together, our review emphasized the need for recommendations on HIV entry criteria in oncology studies going forward and provided examples of successful development of studies through partnership between the NCI, academic institutions, and industry.

RISKS AND BENEFITS TO INCLUSION

Inclusion of patients with HIV in clinical studies may provide benefit to patients, physicians, and sponsors and investigators. Importantly, inclusion in studies may accelerate access of appropriate cancer therapeutics to HIV-infected patients, provide increased experience to guide treating physicians, and increase the use of appropriate anticancer agents in patients with HIV. For sponsors, inclusion of patients with HIV may reduce the need for some postmarketing studies, especially in common tumors not strongly associated with HIV, such as breast, colon, and lung cancer. The major risks to be mitigated in developing eligibility criteria in cancer studies in this patient population include avoidance of anticipated drug-drug interactions between cancer therapies and HIV therapies using approaches that are used for patients with other chronic medical conditions, and appropriate consideration of eligibility criteria related to the degree of HIV-associated immunosuppression that may be acceptable for a given study so as to avoid adverse events related to competing infectious morbidity.

RECOMMENDATIONS

The HIV Working Group emphasized that evaluation of the suitability of a patient with HIV for a given study can be accomplished in a straightforward and uniform manner across all studies. Eligibility can be determined through evaluation of present and historic $CD4^+$ T-cell counts, review of any history of any potential AIDS complications, and evaluation of use of effective ART. Specific eligibility criteria may vary based on the objectives of the study. It was emphasized that modernized eligibility will improve generalizability of early-phase studies of cancer therapies and improve access to experimental cancer agents to appropriate populations of HIV-infected patients. The committee defined important principles related to entry criteria for patients with HIV, as follows:

1. Criteria to define a population with HIV that is sufficiently healthy from this comorbid perspective to participate in almost any oncology study are recommended.
2. Criteria should select patients with probable long-term survival in the absence of cancer.
3. The later the phase of the trial, the more information is known about a particular therapeutic agent for the treatment of a particular condition. The level of experience with a given agent may inform eligibility criteria.
4. Criteria should not be more stringent than for HIV-uninfected patients with the same disease or treatment history.

The fourth principle above is particularly important in relation to $CD4^+$ T-cell criteria. $CD4^+$ counts are an essential component of assessing health status in HIV disease. However, it is important to avoid inadvertent exclusion of HIV-infected persons from clinical trials based on $CD4^+$ cell depletion mainly as a result of prior cancer therapy, because $CD4^+$ cell depletion occurs with certain cancer therapies in the general population. Well-known examples of fludarabine[20] or alemtuzumab[21] serve to illustrate this fact. If only HIV-positive patients are required to have $CD4^+$ levels greater than the institutional normal value for a given study, HIV-uninfected patients exposed to either fludarabine or alemtuzumab likely would be more vulnerable than the HIV-infected patients. $CD4^+$ counts before

Table 1. HIV Eligibility Criteria in Select NCI-Supported Studies From 2011 to 2015

Disease, Lead Organization, and ClinicalTrials.gov Identifier	Study Drug(s)	Study Phase	CD4⁺ Count (cells/μL)	ART	HIV Viral Load	Other
Open to HIV						
Advanced Kaposi sarcoma, CCR, NCT02659930	Pomalidomide + liposomal doxorubicin	I	None	Effective ART required	None	Allows for treatment-naive or uncontrolled HIV in patients with progressive or life-threatening disease
Myeloid malignancies, Princess Margaret Cancer Center, NCT02381548	Belinostat + AZD1775	I	Preleukemia ≥ 250	Willing to adhere to ART with minimal overlapping toxicity and PK interactions; AZT, ritonavir, and cobicistat contraindicated		No history of AIDS-defining condition other than CD4⁺ count < 200 cells/μL
Burkitt lymphoma, Intergroup CTSU 9177/AMC-086, NCT01092162	EPOCH-R	II	None	Suspend ART (with exceptions)	None	Exclude patients with advanced immune suppression and evidence of HIV resistant to all ART considered at high risk of non–lymphoma-related death within 12 months as a result of AIDS
Relapsed anal cancer, The University of Texas MD Anderson Cancer Center-P2C, NCT02314169	Nivolumab	II	≥ 300	Required	Undetectable	HIV care by infectious disease specialist required; HIV-related laboratory studies sent to study team
Relapsed refractory cancer, ECOG-ACRIN, NCT02465060	Genetic testing-directed therapy (12 agents*, some FDA approved)	II	≥ 250	Not required; if used, minimal interactions or overlapping toxicities	None	Exclude history of AIDS-defining conditions other than low CD4⁺ counts; probably long-term survival if cancer not present
Operable hormone receptor–positive HER2-positive breast cancer, NSABP-B-52, NCT02003209	Docetaxel, carboplatin, trastuzumab, and pertuzumab with or without estrogen deprivation	III	≥ 250	ART with potential overlapping toxicities excluded	None	No prior AIDS-defining conditions
Previously untreated CLL in patients ≥ 65 years old, Alliance 041202, NCT01886872	Rituximab and bendamustine *v* rituximab and ibrutinib *v* ibrutinib	III	≥ 350	ART with cytochrome P-interacting medications prohibited	None	NA
Ibrutinib *v* placebo before and after stem-cell transplantation in DLBCL, Alliance 051301, NCT02443077	Ibrutinib, autologous stem-cell transplantation	III	None	AZT, protease inhibitors, and cobicistat prohibited	Patients with multidrug-resistant HIV excluded	No history of AIDS-defining conditions other than low CD4 count; HIV expert opinion of long-term survival from HIV perspective
HIV-specific studies						
Relapsed refractory cancer, CITN12-CCR, NCT02595866	Pembrolizumab	I	Stratified: 100-199, 200-350, and > 350	ART ≥ 4 weeks	< 400 copies/mL	If CD4⁺ < 200 cells/μL; CD4/CD8 ratio > 0.4
Relapsed refractory solid tumors, AMC-095, NCT02408861	Ipilimumab + nivolumab	I	Stratified: 100-200 and > 200	ART > 4 weeks	Undetectable (< 75 copies/mL)	Opportunistic infection in past 3 months
Relapsed refractory solid tumors, AMC-087, NCT01822522	Cabozantinib	I	> 50	ART if clinically indicated	None	ART strata for PK studies; under care of physician with experience in HIV management; exclude patients with active infections requiring systemic therapy in past 28 days
				Required ART according to guidelines; prohibited AZT, ddI, ritonavir, cobicistat	None	Uncontrolled opportunistic infection
HIV-associated advanced Hodgkin lymphoma, AMC-085, NCT01771107	AVD + brentuximab	I/II	≥ 50	Concurrent ART; if not on ART, start after first cycle; AZT excluded	None	Excluded if serious ongoing infection
HIV-associated aggressive B-cell lymphomas, AMC-078, NCT01193842	Vorinostat + EPOCH-R	II	≥ 50			

Abbreviations: AMC, AIDS Malignancy Consortium; ART, antiretroviral therapy; AVD, doxorubicin, vinblastine, and dacarbazine; AZT, zidovudine; CCR, Center for Cancer Research, National Cancer Institute; CITN, Cancer Immunotherapy Trials Network; CLL, chronic lymphocytic leukemia; CTSU, Clinical Trials Support Unit; ddI, didanosine; DLBCL, diffuse large B-cell lymphoma; ECOG-ACRIN, Eastern Cooperative Oncology Group–American College of Radiology Imaging Network; EPOCH-R, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2; NA, not applicable; NCI, National Cancer Institute; NSABP, National Surgical Adjuvant Breast and Bowel Project; P2C, Phase II Consortium; PK, pharmacokinetics.
*Number of agents listed on ClinicalTrials.gov as of May 1, 2016.

cancer therapy can inform the HIV disease status better than the concurrent $CD4^+$ level if prior lymphocytotoxic therapy, including radiation therapy, was administered within the past 12 months or perhaps longer in some cases. For these reasons, accurate assessment of HIV disease requires more than one point of assessment. Developing eligibility criteria should take this last principle into consideration, especially in the setting of second-line and later cancer therapy.

The HIV Working Group defined criteria that can be used to define a patient with HIV who is sufficiently healthy from the HIV perspective to participate in almost any oncology study. These criteria are focused on the following two main areas: evaluation of immune function and criteria related to HIV therapy. A discussion, the working group's recommendation, and template protocol language are listed for each main area.

Recommendations for Eligibility Criteria

Immune criteria recommendations.

1. Patients with $CD4^+$ T-cell counts ≥ 350 cells/μL should generally be eligible for any study if otherwise eligible.
2. Lower $CD4^+$ count eligibility is often appropriate (Table 1).
3. Patients with no history of AIDS-defining opportunistic infections (or only remote AIDS-defining opportunistic infections; ie, none in the past year) should generally be eligible for any study if otherwise eligible.
4. Recommend time frame for exclusion of AIDS-defining opportunistic infections. For cancers common in people with HIV, a shorter time frame is appropriate (Table 1).
   - For many studies, recommend no opportunistic infections within past 12 months.
   - For studies of AIDS-defining cancers with curative potential, exclusion limited to uncontrolled opportunistic infections may be appropriate (ie, for studies evaluating therapy for lymphoma or Kaposi sarcoma that may commonly include patients with newly diagnosed HIV).
   - Patients on prophylactic antimicrobials need not be excluded, although specific agents may be excluded for drug-drug interactions or overlapping toxicities.

HIV therapy criteria recommendations.

1. Generally, recommend concurrent treatment with effective ART according to DHHS treatment guidelines (Table 2).
2. Recommend criteria specifying timing of ART initiation that are appropriate for study goals and take into consideration patients recently diagnosed with HIV or patients not on effective ART. Examples include the following:
   - Patients agree to ART if not currently on ART (timing at investigator discretion, often appropriate, and is important for first-line studies of curable malignancies such as aggressive lymphomas, where cancer therapy requires prioritization).
   - ART > 4 weeks (to ensure ART is tolerated and that toxicities are not confused with study drug toxicities)
   - ART > 4 weeks plus HIV viral load < 400 copies/mL (to ensure ART is tolerated and HIV controlled)
3. Recommend exclusion of specific ART agents, when indicated, based on predicted drug-drug interactions from absorption, distribution, metabolism, and excretion data or potential overlapping toxicities.
   - Although many drug-drug interactions occur with CYP3A4, other metabolic routes and drug transporters may be involved. Recommend assessment of the absorption, distribution, metabolism, and excretion data known to date for the anticancer agent. Contraindicated agents are then rationally selected based on drug-drug interaction potential using known sources (Table 2). Recommend providing tables of contraindicated agents that include ART and other drugs. For sensitive CYP3A4 substrates, concurrent strong CYP3A4 inhibitors (ritonavir and cobicistat) or inducers (efavirenz) should be contraindicated.
   - Consider exclusion of ART agents based on toxicity (eg, zidovudine [neutropenia], stavudine [neuropathy], didanosine [neuropathy], atazanavir [QT prolongation], ritonavir boosted lopinavir [QT prolongation], and saquinavir [QT prolongation]).
4. Although effective ART is generally recommended, exceptions to concurrent ART should be considered in both development of eligibility criteria and conduct of studies.[13]
   - Treatment interruption or deferred initiation is appropriate in curable malignancies when ART may compromise intended full-dose oncology therapy with investigational agent(s).
   - Treatment interruptions for toxicity management
   - Treatment interruptions to meet scientific objective of study

Table 2. Sources for Management of Concurrent HIV and Prevention of Drug-Drug Interactions

Management of concurrent HIV
DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents[6]: Includes up-to-date recommendations for preferred ART regimens. Physicians should be familiar with broad guidelines of HIV care, which include DHHS recommendations for laboratory monitoring, including $CD4^+$ monitoring at baseline and every 3 months and HIV viral load monitoring at baseline and every 3 months, or 2 months of follow-up after initiation or change of ART
Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents[22]: Physicians who treat HIV-infected patients on clinical studies should also be aware of guidelines for administration of concomitant antimicrobial prophylaxis in this patient population, including prophylaxis against HSV/VZV for patients with recurrent HSV infections or in studies of agents with immunosuppressive effects; prophylaxis against atypical mycobacterial infection with azithromycin 1,200 mg weekly if $CD4^+$ count < 50 cells/μL; and prophylaxis against *Pneumocystis* pneumonia with trimethoprim/sulfamethoxazole or alternative agent if $CD4^+$ count < 200 cells/μL, or at any $CD4^+$ count if study drug(s) has potential immunosuppressive effects
Available antiretroviral agents and relevant pharmacology to avoid drug-drug interactions
Rudek et al[23]: Review of antineoplastic agents in patients with cancer who have HIV/AIDS: Includes tables on drug interaction potential of antiretroviral agents
UpToDate Systemic Therapy for Malignancies in Patients on Antiretroviral Therapy: Includes table of relevant drug-drug interactions
University of Liverpool HIV Drug Interaction Web site (http://www.hiv-druginteractions.org): Searchable database
POZ List of HIV Medications (https://www.poz.com/drug_charts/hiv-medications): Comprehensive list of ART with dosing information and photos of medications

Abbreviations: ART, antiretroviral therapy; DHHS, Department of Health and Human Services; HSV, herpes simplex virus; VZV, varicella-zoster virus.

Studies of Cancers Common in People With HIV, Including Studies Specific to People With HIV

Although this template provides recommendations for development of eligibility criteria to allow for selection of appropriate HIV-infected patients with preserved immune function across a broad range of studies, particular emphasis should be placed on design of studies that disproportionately affect people with HIV. For all phases of studies, the HIV Working Group encourages commitment to eligibility criteria that allow for inclusion of a broader population of HIV patients for the most common malignancies associated with HIV (ie, lung cancer, lymphoma, anal cancer, head and neck cancer, cervical cancer, hepatocellular carcinoma, Kaposi sarcoma).

In addition, HIV-specific studies for malignancies remain critical, especially for cancers most strongly associated with HIV (Kaposi sarcoma, aggressive B-cell lymphomas, classic Hodgkin lymphoma). Long-term survival is feasible in most patients with these malignancies, and therefore, substantially different entry criteria are appropriate (Table 1). Furthermore, HIV-specific studies allow for analysis of the safety and efficacy of a given agent across a broader range of patients with HIV and allow for specific evaluation of the effects of an agent on immune parameters in this patient population. Partnership with the NCI or academic centers with expertise in HIV and cancer is encouraged for HIV-specific studies.

Additional Trial Design Practical Considerations

Once eligibility is established, HIV infection should be managed as part of standard of care and should not be dictated by the protocol, unless the protocol has specific objectives regarding HIV outcomes. ART should be considered concomitant medications, with avoidance of contraindicated ART agents and other concomitant medications during the duration of treatment with the study agent. This is consistent with the management of other chronic diseases such as hypertension and diabetes, which are generally not dictated in an oncology protocol. Management of HIV can be performed in collaboration with a study participant's primary care provider or HIV specialist. The physicians managing HIV for patients on cancer studies should be aware of DHHS guidelines (Table 2) regarding management of HIV and prevention of opportunistic infections.

For studies that include people with HIV, HIV-specific treatment–related considerations are not required in the informed consent. However, delineating who is responsible for treating and monitoring HIV is appropriate. For studies with eligibility criteria that require exclusion of specific ART agents, consider providing patient educational material with a list of acceptable and unacceptable ART agents.

CONCLUSION

Cancer is a leading cause of morbidity and mortality in the estimated 37 million people living with HIV globally. Modernization of eligibility criteria to include appropriate HIV-infected patients in cancer clinical studies is important for decreasing the burden of cancer in this patient population. A variety of NCI-sponsored studies have demonstrated that inclusion of patients with HIV on cancer clinical trials is feasible. HIV infection alone should no longer be an exclusion criterion in any study. Straightforward eligibility criteria related to HIV should take into consideration an approach to concurrent ART and criteria related to immune status appropriate for a given study.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Modernizing Clinical Trial Eligibility Criteria: Recommendations of the American Society of Clinical Oncology–Friends of Cancer Research Brain Metastases Working Group

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ABSTRACT

Purpose
Broadening trial eligibility to improve accrual and access and to better reflect intended-to-treat populations has been recognized as a priority. Historically, patients with brain metastases have been understudied, because of restrictive eligibility across all phases of clinical trials.

Methods
In 2016, after a literature search and series of teleconferences, a multistakeholder workshop was convened. Our working group focused on developing consensus recommendations regarding the inclusion of patients with brain metastases in clinical trials, as part of a broader effort that encompassed minimum age, HIV status, and organ dysfunction. The working group attempted to balance the needs of protecting patient safety, facilitating access to investigational therapies, and ensuring trial integrity. On the basis of input at the workshop, guidelines were further refined and finalized.

Results
The working group identified three key populations: those with treated/stable brain metastases, defined as patients who have received prior therapy for their brain metastases and whose CNS disease is radiographically stable at study entry; those with active brain metastases, defined as new and/or progressive brain metastases at the time of study entry; and those with leptomeningeal disease. In most circumstances, the working group encourages the inclusion of patients with treated/stable brain metastases in clinical trials. A framework of key considerations for patients with active brain metastases was developed. For patients with leptomeningeal disease, inclusion of a separate cohort in both early-phase and later-phase trials is recommended, if CNS activity is anticipated and when relevant to the specific disease type.

Conclusion
Expanding eligibility to be more inclusive of patients with brain metastasis is justified in many cases and may speed the development of effective therapies in this area of high clinical need.

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BACKGROUND

Broadening clinical trial eligibility to improve accrual and access and to better reflect intended-to-treat populations has been recognized as a priority.[1] To maximize generalizability, enrollment criteria should strive for inclusiveness, unless compelling safety or efficacy concerns mandate exclusion of specific populations. Inclusion of patients refers not only to lack of automatic exclusion but also to active inclusion to inform drug development and the standard of clinical care.

Patients with brain metastases have frequently been excluded from trials, using blanket exclusion (eg, any history of brain metastases excluded) or conditional exclusion (eg, active brain metastases excluded but treated brain metastases included). A 2014 systematic search of interventional drug trials listed on www.ClinicalTrials.gov for adult patients with advanced non–small-cell lung cancer (NSCLC) found patients with any history of CNS metastases were strictly excluded in 14% of 413 open trials.

Although 41% of trials allowed patients to enroll after local treatment of brain metastases, only 26% of trials allowed patients with untreated brain metastases. Patients with leptomeningeal disease (LMD) were explicitly excluded in 19% of trials.[2]

In the United States alone, approximately 70,000 patients with cancer will eventually relapse in the brain annually.[3-6] Data from 1973 to 2001 indicated that 28%, 37%, and 14% of patients presenting with de novo advanced lung cancer, de novo metastatic melanoma, and de novo advanced breast cancer, respectively, eventually developed brain metastases.[6] Moreover, the incidence is increasing, particularly in specific cancer subtypes. In crizotinib studies of anaplastic lymphoma kinase (ALK)–rearranged NSCLC, 31% of patients had asymptomatic brain metastases at study entry, 12% of patients had previously treated brain metastases, and an additional 20% developed brain metastases during the study.[7] In a study of alectinib for crizotinib-refractory NSCLC, 61% had CNS metastases at baseline.[8] In a pooled analysis of two single-arm studies of crizotinib-refractory NSCLC, 60% had CNS metastases at baseline, and the CNS overall response rate was 64%.[9] In patients with metastatic human epidermal growth factor receptor 2 (HER2)–positive breast cancer, or metastatic triple-negative breast cancer, up to half will eventually present with brain metastases.[10-13] In some populations, exclusion of patients with brain metastases from trials may mean that one half to two thirds of intended-use disease populations are not included in either safety or efficacy analyses, despite these populations frequently receiving such therapies postapproval.

PROCESS

In May 2016, ASCO convened a multistakeholder workshop to identify scientifically appropriate opportunities for expanding clinical trial eligibility. Preceding the workshop, panels composed of patient advocates, drug/biotech manufacturers, investigators, and regulators were charged with analyzing the state of the science and developing recommendations for the following topics: brain metastases, HIV/AIDS, organ dysfunction, and minimum age for enrollment. Our panel, focused on brain metastases, convened and deliberated on a regular basis to determine when and how patients with brain metastases could and should be enrolled in trials. We concluded that many of the historical concerns regarding inclusion of patients with brain metastasis into trials do not necessarily apply to patients treated in the modern era. Thus, the decision to include or exclude patients with brain metastases should be handled more thoughtfully.

The panel acknowledges that there may be unique safety and/or efficacy signals in patients with brain metastases. Nevertheless, a drug may still be used in the postmarketing setting among patients with brain metastases despite little to no data collection in the context of a prospective clinical trial, which is of particular concern in diseases with a high incidence of CNS metastases. It would be preferable to evaluate new agents' safety and efficacy in the premarketing setting rather than relying on postmarketing surveillance.

Finally, our panel discussed patients with primary brain tumors (eg, high-grade glioma), because these patients are also frequently excluded from trials.[14,15] Despite the overlap in rationale for exclusion, and the unmet medical need, the topic was deemed outside of the scope of the panel's expertise. The panel believes, however, this question should be addressed, because exclusions of such patients has slowed progress in this arena compared with other primary solid tumors.

RISKS AND BENEFITS TO INCLUSION

The inclusion of patients with brain metastases in trials may provide potential benefits to patients, physicians, and sponsors/investigators, but it is also associated with potential risks (Table 1). For patients, potential benefits include earlier access to investigational agents and the development of safety and efficacy data that may influence standard of care if the agent is ultimately approved. For sponsors, obtaining safety data early in development may reduce or eliminate the need for postmarketing studies in this patient subset. The demonstration of CNS activity may provide a key differentiating factor among multiple agents and could form the basis of a go or no-go decision in a crowded development space. Furthermore, early evidence of CNS activity in a setting of unmet medical need could serve as the basis for Fast Track designation. If there is substantial improvement in a clinically significant end point over available therapy, this could result in breakthrough therapy designation and allow for greater development guidance from regulatory authorities.[16] Finally, demonstration of safety and efficacy in the CNS may provide the basis for a broader labeling claim or novel indication.[17]

Inclusion of patients with brain metastases early in drug development has precedence, with some notable successes. The accelerated approval for alectinib specifically noted both its extracranial and intracranial activity among patients with ALK-rearranged NSCLC. A randomized phase III study comparing alectinib versus crizotinib subsequently demonstrated superiority for the primary endpoint of PFS, with a more favorable toxicity profile.[17a] Of note, 40% of the study population had brain metastases at baseline. Time to CNS progression was significantly longer in the alectinib arm (HR 0.16, $P < .001$), and the CNS ORR was 81% among patients with measurable CNS disease, with a median duration of intracranial response of 17.3 months. If the alectinib trials had excluded patients with brain metastases, the eligible population would have been decreased by nearly half, and the opportunity to identify clinically meaningful CNS efficacy would have been lost.

Still, patients with brain metastases continue to be routinely excluded from many trials because of numerous concerns. A detailed discussion of these, including concerns regarding drug penetration, lack of preclinical models, safety and efficacy concerns, costs, survival and others, are presented in Table 2.

RECOMMENDATIONS

Expanding eligibility to include patients with brain metastases early in drug development would be most valuable in settings where brain metastases are common in the intended-use population, such as melanoma, breast cancer, and lung cancer. Particularly in such disease settings, the inclusion of patients with brain metastasis should be the default position.

Table 1. Summary of Risks and Benefits for Stakeholders

Risk or Benefit	Patients/Prescribing Physicians	Sponsors/Investigators
Benefits	Earlier access to investigational agents. Expanded trial and treatment options.	Ability to generalize to real-world patients.
	More complete safety data in brain metastasis population, which can inform clinical use and enable safe delivery if/once investigational agent becomes commercially available	May reduce postmarketing requirements. Inclusion early in drug development may be essential in defining safety profile, particularly in disease with a high incidence of brain metastases. Identification of potential safety issues during clinical trials may facilitate early development of mitigation strategies, enabling broader uptake after approval. Inclusion early in drug development may potentially support broader enrollment in phase III, for a better reflection of the intended-use population and more rapid overall accrual.
	Availability of efficacy and safety data in the brain metastasis population can inform choice between multiple drugs in this patient population and provide greater confidence in therapy selection.	Efficacy in traditionally understudied population could potentially result in expanded marketing claims and provide a differentiating factor between drugs of the same class. Efficacy data may provide potential path for: Breakthrough Designation if early signs of CNS activity observed Accelerated Approval for unmet medical need Regular Approval
	Earlier identification of drugs that may not be efficacious in the CNS or that may cause more harm than good.	Improve risk/benefit ratio for later-phase drug development and postmarketing setting Generate more informative drug labeling
Risks	Limited data from small cohorts may not be adequate for clinical decision making. Patients who are inherently sicker may have a higher rate of adverse events due to the drug or disease. Additional procedures for increased safety monitoring in some situations may incur additional costs to patients and/or the study. Additional resources may be required to ensure clinical and research staff are capable of managing the additional patients in the study.	More variability in outcomes—may require separate cohorts or analysis plans and early stopping rules for excess toxicity May complicate attribution of adverse events Increased costs associated with additional cohorts, statistical requirements, additional testing, or special expertise to manage specific patient needs

While shifting to a position of inclusion, there may still be instances with concerns specific to the study drug, patient population, or trial end points that justify exclusion of such patients. In this case, the rationale for exclusion needs to be explicitly addressed in the trial design. The panel urges inclusion of patients with brain metastases, when appropriate, in such a way that contributes to the safety and efficacy profile of the treatment(s) under study.

The desirability of including patients with brain metastases may vary per clinical situation, study design and end points, and characteristics of the investigational agent. These recommendations generally apply to the inclusion/exclusion of patients in trials not focused exclusively on brain metastasis treatment. The development and conduct of brain metastasis–focused trials, when appropriate, should continue in parallel.

Recommendations for specific subgroups are described below and summarized in Table 3: (1) patients with treated/stable brain metastases, (2) patients with active brain metastases, and (3) patients with leptomeningeal metastases. In addition, a few practical issues, including baseline screening CNS scans, routine CNS surveillance in trials, and handing isolated CNS progression in systemic therapy studies, are discussed.

PATIENTS WITH TREATED/STABLE BRAIN METASTASES

The panel discussed inclusion of patients with treated/stable brain metastases, defined as patients who have received prior therapy for their brain metastases and whose CNS disease is radiographically stable at study entry:

- The panel strongly recommends that such patients should generally be included in systemic therapy trials.
- In diseases in which brain metastases are frequent, there is a strong rationale for including patients early in drug development and for considering either separate cohorts or a prespecified plan for subset analysis, from either an efficacy or a toxicity perspective.
- The mechanism of action of the drug or predicted blood-brain barrier (BBB) penetration should not necessarily influence a decision to include such patients. In addition, preclinical studies of intact BBB penetration are not necessarily reflective of blood-tumor barrier penetration.
- In defining stable brain metastases, the panel considered standardizing the interval over which a patient needs to have stable disease before trial entry. Typically, local therapies, such as stereotactic radiosurgery or whole-brain radiation therapy, are effective up front, but subsequent CNS progression events occur over time.[54-57] Thus, although a standard criterion in trials is to require minimum 3 months of disease stability in CNS, the panel believed a 4-week time frame was equally reasonable and, in fact, may reduce the chance of CNS progression during the time frame of the trial. There is a chance that, at 4 weeks after local treatment, patients may exhibit pseudo-progression and be deemed falsely ineligible for the trial (because CNS progression cannot be completely ruled out), although the panel concluded

Table 2. Concerns That May Lead to Exclusion of Patients With Brain Metastases

Concern	Rationale	Comment
Drug levels in the CNS	The BBB effectively excludes many chemotherapeutic and targeted agents from the intact brain. Although information about the ability of investigational agents to penetrate the intact BBB in animal models is often available, there is typically little to no understanding of whether an agent crosses the human BBB, even late in drug development. Although the BTB is leakier than the intact BBB, drug levels within and between metastatic lesions in the brain can be heterogenous.[20] Clinical data regarding a given compound's ability to cross a disrupted BTB are usually limited. Inadequate drug concentrations may affect the likelihood of objective response and may also directly affect PFS if CNS events represent the main site of tumor progression.	Although uncertainty regarding drug penetration into the CNS is a valid concern, there are several lessons on the basis of existing data. First, lack of penetration across an intact BBB does not preclude CNS response. Second, waiting until (or requiring) a demonstration in human patients with cancer that drugs can get into brain metastases will substantially slow clinical development. Of note, results of the lapatinib brief exposure study were published in 2014, 5-6 years after the initial phase II publications reporting on the efficacy of lapatinib in the CNS.[18,19,20] At the same time, CNS penetration is undoubtedly important for efficacy of most agents in the brain. For example, in ALK-rearranged lung cancer, the CNS-penetrant agent alectinib is associated with a CNS response rate of 57%, well in excess of the 18% CNS response rate reported with crizotinib.[7,8] The superiority of alectinib over critoztinib with respect to time to CNS progression and CNS response rate was confirmed in the subsequent phase III trial.[7e] Lack of good CNS penetration data also can be thought of as an opportunity, rather than an obstacle. Inclusion early in drug development of window studies (for example, exposure to drug before planned craniotomy resection with or without maintenance drug to follow), and studies in patients with leptomeningeal disease (in whom serial CSF sampling may be more feasible), can provide extremely valuable information, particularly if CNS penetration is a potential differentiating factor between agents in the same class.
Inadequate preclinical models	Frequently, investigational agents will not have been tested in intracranial tumor models at the time of introduction into clinical trials. Even when they have, intracranial models are only models and may not accurately predict CNS activity in humans.	Concerns about the limitations of preclinical models are certainly legitimate, though progress has been made, including the use of intracarotid/intraventricular injections to avoid artificial disruption of the BBB and to test prevention strategies, as well as use of PDX models to more accurately capture phenotype of metastatic tumors.[21-23] Understanding how well these models ultimately predict activity in the clinic will depend on broader inclusion of patients with brain metastases in trials. Information could then be used to improve the predictive capabilities of the models and create a feedback loop to inform future clinical trials.
Safety	Examples include the potential for bleeding with antiangiogenic agents, tumor flare with immunotherapies, or seizures with agents that lower the seizure threshold. There has historically also been a more generalized concern that patients with brain metastases may be frail and more generally susceptible to AEs than those without CNS involvement by tumor.	Existing literature, although limited, does not support a significantly higher rate of adverse events among patients with brain metastases who otherwise meet trial eligibility criteria.[24] A review of 1,181 consecutive patients' records with and without brain metastases treated in the phase I program at M.D. Anderson Cancer Center found among 93 patients with brain metastases, rates of neurologic toxicity were low (approximately 10%) and did not differ significantly between groups. Grade 3 and 4 non-neurological toxicity rates also did not differ compared with patients without brain metastases.[25] Although potentially biased in selecting patients who were well enough to enroll in a phase I trial, these data do support the contention that when patients with brain metastases are appropriate for trial participation on the basis of usual entry criteria (ie, performance status, organ function, and so forth), they seem to fare similarly from a toxicity standpoint to other patients in the trial. An increasing number of trials are reporting safety data in subsets of patients with brain metastases. As an example, in the EMILIA trial, a phase III study comparing trastuzumab-emtansine *v* the combination of lapatinib and capecitabine in advanced HER2-positive breast cancer, patients with treated stable brain metastases were allowed in the study.[26] No new safety signals were observed in patients with baseline CNS metastases, and results were generally consistent with those of the overall study population.

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Table 2. Concerns That May Lead to Exclusion of Patients With Brain Metastases (continued)

Concern	Rationale	Comment
		Analyses have also been done to evaluate safety of specific classes of drugs with toxicity concerns. For example, antiangiogenic agents predispose to bleeding, and thus there was concern for the potential of CNS hemorrhage. A retrospective analysis of 17 clinical trials of bevacizumab-based therapy for NSCLC found rates of CNS hemorrhage were low and seemed to be independent of bevacizumab therapy.[27] The multitargeted inhibitor sunitinib has also been evaluated for safety in 321 patients with brain metastases treated as part of an EAP.[28] The toxicity profile was consistent with that observed in the EAP program as a whole; no grade 3 or 4 CNS hemorrhage events were observed. There has been ongoing concern regarding immunotherapy in patients with brain metastases, given the potential for neurologic deterioration or brain herniation in the setting of initial tumor flare, and many trials of immune checkpoint inhibitors have excluded patients with CNS involvement for this reason.[29] In fact, studies of anti-CTLA4 and anti PD-1/PD-L1 therapies in patients with melanoma brain metastases have generally shown that the agents are reasonably well tolerated and efficacious.[30-31b] The panel does acknowledge that concerns regarding the risk of immunotherapy in the CNS may be valid for some patients, particularly those with extensive CNS metastases, posterior fossa involvement, or increased intracranial pressure. Work is needed to understand predictors of exuberant tumor flares in the CNS and to develop working algorithms on how to interpret and manage scan findings in the setting of immunotherapy. Nonetheless, we would argue that patients would be better served by careful evaluation of the safety profile of investigational new agents in the carefully controlled clinical trial setting rather than relying on postmarketing surveillance to identify and manage risk. Finally, a welcome trend has been an increasing number of trials specifically evaluating the safety and efficacy of investigational approaches in prospectively defined cohorts of patients with brain metastases, as well as the active inclusion of patients with brain metastases in more general clinical trial populations. Agents that have been studied in this way include lapatinib, afatinib, erlotinib, dabrafenib, crizotinib, and alectinib, among others. Although these trials have not always included a formal comparison group of patients without brain metastases, the overall safety profile has been consistent with those from trials of similar agents for systemic extracranial disease.[7,18,30,32-36] When patients with brain metastases are studied in defined cohorts, the risk that safety signals specific to such patients might derail a drug development program is mitigated. Such a strategy would permit simple closure of a single cohort rather than amendment of a full protocol with the need to reconsent all patients. Furthermore, if there is indeed a true safety signal, it would be preferable to identify it early in drug development so that the risk to patients can be appropriately managed as part of eligibility criteria and monitoring guidelines for later-phase studies.
AE reporting and attribution	Some have criticized the CTCAE in describing neurotoxicities. Distinguishing treatment-related AEs from neurologic signs and symptoms due to the disease itself may also be challenging. In nonrandomized trials, there is no control arm to put AEs into the context of the natural history of the disease.	Regardless of a patient's disease sites, investigators have always had to make individualized judgments about toxicity attribution. Patients with lung metastases are not generally excluded from trials of agents with low rates of expected pulmonary toxicity. Similarly, excluding all patients with brain metastases because of concern over theoretical excess CNS toxicity seems overly conservative. The CTCAE has limitations, but continued exclusion of patients with brain metastasis only reduces the motivation to improve the CTCAE for reporting of neurologic toxicities (because it reduces the clinical need for such improvements). Other tools suitable for use in patients with brain metastases, as well as those with primary brain tumors, also exist to characterize neurologic signs and symptoms, including the NANO scale and existing brain tumor–specific quality-of-life and symptom burden scales.[37-40]

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Table 2. Concerns That May Lead to Exclusion of Patients With Brain Metastases (continued)

Concern	Rationale	Comment
		Finally, concerns about AEs underscore the value of including patients with brain metastasis in randomized trials, especially in tumor types where brain metastases are particularly common. Inclusion of patients in randomized studies can help distinguish tumor-related from drug-related AEs and provide premarketing safety data in this patient population.
Drug interactions	Cytochrome P450 EIAEDs, such as phenytoin and carbamazepine, may affect levels of the investigational agent under study. For patients receiving EIAEDs, this may require as much as two- or three-fold increases in the dose of investigational agent to achieve the same drug exposure.	Over the past few decades, the proportion of patients with brain metastases treated with EIAEDs has fallen precipitously, because of availability of non–enzyme-inducing AEDs, such as levetiracetam or lamotrigine, as well as data suggesting that seizure prophylaxis is not useful in most patients. Indeed, a meta-analysis of four randomized trials indicated no difference in seizure incidence (OR, 1.09; 95% CI, 0.63 to 1.89; $P = .8$), seizure-free survival (OR, 1.03; 95% CI, 0.74 to 1.44; $P = .9$), or overall survival (OR, 0.93; 95% CI, 0.65 to 1.32; $P = .7$) associated with the use of prophylactic anticonvulsants. The Quality Standards Subcommittee of the American Academy of Neurology now recommends against routine use of anticonvulsant medications with newly diagnosed brain tumors in patients who have not had a prior seizure.[41] If there is known risk of drug-drug interactions between EIAEDs and an investigational agent, it would be appropriate to exclude patients receiving concomitant medications of concern and/or who have poorly controlled seizures, rather than excluding all patients with brain metastases.
Response assessment	RECIST has been most widely used for assessment of extracranial sites of disease. It has been modified to account for the unique nature of the CNS site, although there has not been one agreed-on standard.[46] In patients with involvement of both CNS and extracranial sites, there has been reluctance to sum target lesions across both types of sites, because of concerns this may negatively affect the objective response rate. If patients with CNS metastases are included in trials, the brain metastases are usually required to be pretreated and stable on trial entry and are rarely included as target lesions, limiting the ability to draw conclusions about CNS activity of investigational agents.	The heterogeneity of response criteria across trials has largely arisen out of the recognition that existing tools such as RECIST,[42,43] WHO,[44] or Macdonald Criteria[45] have gaps in addressing issues specific to the assessment of patients with brain metastases. The RANO group has published criteria for evaluating CNS response assessment in clinical trials, including criteria specific for patients with brain metastases.[47] The criteria provide guidance to investigators, as formulated by an international multidisciplinary group, and with input from the RECIST working group and the US FDA.
Efficacy	Differences in the brain microenvironment might render the same agents ineffective even if effective against other sites of metastases in the same patient. There may also be inherent differences in CNS tumors *v* non-CNS tumors, which may affect ORR, PFS, or OS. Thus, reduced efficacy on CNS metastases as compared with extracranial disease could lead to a negative readout of ORR, PFS, or OS and a clinical trial failure.	Blanket exclusions of patients with brain metastasis may make efficacy end points more difficult to interpret or impossible to generalize, particularly for diseases in which brain metastases are frequent sites of progression, such as ALK-rearranged lung cancer. A wide range of therapies, ranging from small-molecule tyrosine kinase inhibitors, to large monoclonal antibodies and immunotherapeutic approaches, have demonstrated CNS activity against brain metastases in patients with NSCLC, breast cancer, melanoma, and renal cell carcinoma.[24,48,49] Several study design options and statistical approaches are available to mitigate risk related to lack of efficacy, including: small expansion cohorts restricted to brain metastasis patients in the early drug development setting, such that lack of efficacy in the CNS does not jeopardize the overall drug development strategy; capping, stratification and/or preplanned subset analyses in randomized studies to minimize confounding and maximize interpretability of data; the inclusion of a parallel-enrolling brain metastasis exploratory cohort within a phase III trial that could allow safety and efficacy information to be collected on patients without affecting the primary trial end point; and early stopping rules specific to a brain metastasis subset. Many of these are already commonly used for inclusion of patients who may affect the interpretation of efficacy end points (eg, patients with visceral metastases, nonmeasurable disease, poor performance status, and so forth).

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Table 2. Concerns That May Lead to Exclusion of Patients With Brain Metastases (continued)

Concern	Rationale	Comment
Survival	Historically, patients with brain metastases have experienced limited OS.[50,51] This would clearly have an impact on studies in which the primary end point is OS but can also affect studies in which the end point is PFS, ORR, or toxicity because of concerns for missing data from patients who do not survive to subsequent restaging or toxicity assessments.	Although survival of patients with brain metastases is variable, this is true of patients with metastatic disease without brain metastases. Recent data indicate some subsets of patients with brain metastases now experience median survivals that far exceed historical control data. For example, patients with HER2-positive breast cancer and good performance status have a 2-year median survival after a brain metastasis diagnosis; patients with ALK-rearranged lung cancer experience median survivals as long as 4 years.[52,53] In a phase I experience, adjusted for other clinical covariates, the presence of brain metastases did not exhibit prognostic significance.[29] Collectively, the data would argue that patients with brain metastases should not be excluded a priori on the basis of projected poor survival. Common eligibility criteria, such as performance status, and estimated life expectancy may be more useful and accurate than exclusion of all patients with brain metastases. This is particularly true of phase I or phase II studies, in which OS is rarely the primary end point.
Cost considerations	The conduct of clinical trials requires considerable financial resources. In early-phase studies, adding additional cohorts of patients adds incremental costs. The potential for a clinical trial failure due to poor performance of a brain metastasis subset could jeopardize the overall drug development plan.	The panel urges a collaborative spirit among all stakeholders, including sponsors, regulatory agencies, and patient advocacy groups, to address cost considerations. We urge sponsors to consider paths to include patients with brain metastases into clinical trials in sufficient numbers focusing on end points that generate meaningful results; flexibility and collaboration on the part of regulatory bodies, in recognition of the unique nature of this patient population, to mitigate risks to both patients and sponsors, while preserving scientific and ethical rigor; and patient advocacy groups to emphasize the benefit from early study participation in the light of potentially required additional testing (eg, CSF samples to better understand drug penetration). The most urgent settings to include patients with brain metastases are those in which the prevalence is high, such that the potential tradeoffs are significantly more favorable and the potential impact the highest.

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; BBB, blood-brain barrier; BTB, blood-tumor barrier; CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; EAP, expanded access program; EIAED, enzyme-inducing antiepileptic drugs; HER2, human epidermal growth factor receptor 2; NANO, Neurologic Assessment in Neuro-Oncology; NSCLC, non–small-cell lung cancer; OR, odds ratio; ORR, overall response rate; OS, overall survival; PD-1, programmed death 1; PD-L1, programmed death ligand 1; PDX, patient-derived xenografts; PFS, progression-free survival; RANO, Response Assessment in Neuro-Oncology; RECIST, Response Evaluation Criteria in Solid Tumors; US FDA, US Food and Drug Administration.

that the potential benefits of providing access to a larger number of patients outweigh this risk. Patients who seem to have pseudo-progression could be re-evaluated and enrolled later if it becomes clear their CNS disease is not progressive.

- The panel recommends that for patients with a known history of brain metastases, baseline CNS imaging should be required to provide baseline CNS tumor measurements and document stability before study entry.
- Rather than a blanket exclusion of all patients with treated/stable brain metastases, trials could focus on specific areas of concern.
  - For drugs associated with an increased risk of bleeding, exclude patients with clinically evident CNS hemorrhage on scans and/or on therapeutic doses of concurrent anticoagulation.
  - For drugs that may lower the seizure threshold, exclude patients with seizures over the past month. If deemed clinically relevant, neurology can be consulted to provide input on the risk/benefit specific to the investigational agent as to whether patients with any seizure history should be excluded.
  - For drugs with potential cytochrome interactions, exclude patients on enzyme-inducing antiepileptic drugs, with appropriate washout on the basis of drug half-life.
  - For concerns regarding interpretation of CNS adverse events, require stable to decreasing corticosteroid dose over 1 week before study entry to avoid patients with rapidly escalating symptoms.
  - For investigational agents whose efficacy may be compromised by concurrent corticosteroids, exclude patients requiring corticosteroid use that exceeds a prespecified threshold.
  - To address poor prognosis, exclude patients with poor performance status or short anticipated life expectancy.

Recommendation

Unless there is a compelling rationale for exclusion, patients with treated/stable brain metastases for at least 4 weeks before study entry (ie, baseline CNS imaging should show at least stable disease compared with scans obtained at least 4 weeks before study entry) should be included in prospective trials of all phases. If there are specific safety concerns, then tailoring specific criteria to the concern is preferable to blanket exclusion of all patients with brain metastasis.

Template for inclusion criteria. Patients with treated brain metastases are eligible if there is no evidence of progression for at

Table 3. Summary of Recommendations

Patient Subgroup	Definition	Recommendation	Text Template
Patients with treated/stable brain metastases	Patients who have received prior therapy for their brain metastases and whose CNS disease is radiographically stable at study entry	Unless there is a compelling rationale to exclude such patients, patients with stable/treated brain metastases for at least 4 weeks before study entry (ie, baseline CNS imaging should show at least stable disease compared with scans obtained at least 4 weeks before study entry) should be included routinely in prospective clinical trials of all phases.	Template for inclusion: Patients with treated brain metastases are eligible if there is no evidence of progression for at least 4 weeks after CNS-directed treatment, as ascertained by clinical examination and brain imaging (MRI or CT scan) during the screening period.
Patients with active brain metastases	New and/or progressive brain metastases at the time of study entry	Guidance for inclusion in early-phase trials: Patients with active brain metastases should be included early in clinical development when there is strong scientific rationale for likelihood of benefit on the basis of molecular pathways or histology as well as preclinical data. For drugs/modalities with less robust preclinical information on potential CNS activity, inclusion of patients with active brain metastases should still be considered, particularly if brain metastases are common in the intended-use population. The inclusion of a CNS-specific cohort can provide valuable dosing and preliminary efficacy data to either support or refute inclusion in later phase trials. Guidance for inclusion in later-phase trials: Ideally, data from earlier-phase trials, in concert with the strength of the scientific rationale and preclinical data, can inform decisions on inclusion of patients with active brain metastases in later-phase trials. When such data are not available, a number of potential trial designs could allow patients with active brain metastases to enroll, either as a parallel cohort or as a defined subset within the larger clinical trial.	
Patients with LMD	LMD is a clinical diagnosis, defined as positive CSF cytology and/or unequivocal radiologic or clinical evidence of leptomeningeal involvement.	Inclusion of an LMD cohort in early-phase trials is encouraged where CNS activity is anticipated and when relevant in the specific disease type under study. Consideration of CSF PK measurements is also encouraged. When possible, inclusion of an LMD cohort in later-phase trials may be useful to provide access to investigational agents and to generate additional safety and efficacy data.	If patients with LMD are to be excluded, the following wording is suggested, to avoid unnecessary exclusion of patients with imaging-only equivocal findings. Template for exclusion: No known leptomeningeal disease NOTE. For the purposes of exclusion, LMD is a clinical diagnosis, defined as positive CSF cytology and/or unequivocal radiologic or clinical evidence of leptomeningeal involvement. Patients with leptomeningeal symptoms in the setting of leptomeningeal enhancement would be considered to have LMD even in the absence of positive CSF cytology, unless a parenchymal lesion can adequately explain the neurologic deficit. In contrast, an asymptomatic or minimally symptomatic patient with mild or nonspecific leptomeningeal enhancement would not be considered to have LMD. In that patient, CSF sampling is not required to formally exclude LMD but can be performed at the investigator's discretion on the basis of level of clinical suspicion.
Practical considerations	The panel recommends baseline CNS imaging in populations where the risk of brain metastases is high, if there are specific safety concerns related to inclusion of patients with brain metastasis, or if one of the objectives of the study is to determine the impact of the investigational therapy on CNS-related outcomes, whether a patient is known to have brain metastases before study entry. Where baseline imaging is required, patients with screen-detected brain metastases can be incorporated in one of several ways: Allowance of local therapy (such as SRS) followed by immediate enrollment in the main study once acute treatment-related toxicities have resolved Enrollment into a separate preplanned brain metastasis cohort Use of statistical approaches including stratification or capping to allow such patients into the intent-to-treat study population The panel recommends surveillance CNS imaging on a protocol-defined schedule, in patients with brain metastases identified at baseline. Required surveillance CNS imaging could also be considered in patients without brain metastases at baseline, particularly if the likelihood of the development of CNS during the time period of the study is considered moderate to high, and/or if the time to first CNS metastasis is believed to be a relevant end point. In accordance with RANO guidelines, protocols should prospectively specify whether patients with isolated CNS progression but responsive/stable extracranial disease can continue receiving protocol therapy. Concurrent allowed or prohibited local CNS treatments (eg, surgery, radiosurgery, WBRT) should also be prespecified. If a patient is allowed to remain on protocol, he/she should continue to be followed for extracranial progression. Dates of intracranial and extracranial progression should be noted and recorded separately.		

Abbreviations: CT, computed tomography; LMD, leptomeningeal disease; MRI, magnetic resonance imaging; PK, pharmacokinetic; RANO, Response Assessment in Neuro-Oncology; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy

least 4 weeks after CNS-directed treatment, as ascertained by clinical examination and brain imaging (magnetic resonance imaging [MRI] or computed tomography scan) during the screening period.

PATIENTS WITH ACTIVE BRAIN METASTASES

The term active brain metastases is defined as new and/or progressive brain metastases at the time of study entry. In contrast to patients with treated/stable brain metastases, the panel agreed that this was an area less amenable to a one-size-fits-all approach and that a decision framework for whether and how to include such patients would be more appropriate. There may be valid reasons to exclude such patients from specific trials; however, the panel recommended that such patients not be automatically excluded, because this is a population of patients with great need for innovative interventions.

Recommendations

Disease characteristics. There can be differences in tumor types regarding the propensity for specific toxicities (eg, CNS bleeding with metastatic melanoma), expected efficacy of local therapies, disease pace, and survival that may affect the risk-benefit of including patients with brain metastases in trials and affect the amount of preliminary data required to consider inclusion. For example, for diseases in which the CNS progression has been slow, and/or radiotherapy options are not likely to be especially efficacious, it is reasonable to include patients with active brain metastases fairly early in systemic therapy trials. Conversely, in fast-paced disease with availability of highly efficacious radiotherapy options, more preliminary data would generally be required.

Trial design. The desirability and feasibility of including patients with active brain metastases in trials will vary with design and intent of a trial and the position of an investigational agent in clinical development. The following are examples that the panel discussed to illustrate the process and recommendations, recognizing that they do not cover the full spectrum of possibilities.

Phase 1 dose-finding study with small expansion cohort(s). For early-phase studies, there are concerns with including patients with active brain metastases in early cohorts, because initial cohort findings can affect decisions to dose escalate and/or proceed with clinical development. The panel strongly encourages investigators to consider including such patients in a separate expansion cohort early in clinical development, particularly if the intention is to develop the drug for brain metastases or in a target population where brain metastases are common. In addition, first-in-human studies of next-generation agents could consider enrolling patients with active brain metastases in the initial dose-escalation cohorts if there are prior safety and efficacy data with similar drugs in the class, particularly if there seems to be class activity in the CNS.

In considering dose-limiting toxicity (DLT) definitions and reporting in the context of patients with brain metastasis, as with any phase I trial, DLT definitions should be thoughtfully and prospectively designed as part of protocol planning and could be tailored in the brain metastasis population. For example, the significance of a seizure in a patient without brain metastases exposed to a novel agent may be viewed quite differently than in a patient with multiple CNS lesions and history of prior seizure. Tailored DLT criteria would allow for a case-by-case review.

Single-arm, initial efficacy studies. Such studies can include either phase I expansion cohorts or more traditional phase II designs and typically include 20 to 50 patients, with frequent use of objective response or progression-free survival as the primary end point. Including patients with active brain metastases as a separate cohort would be ideal, affording sufficient patient numbers to draw preliminary conclusions about potential for further development and the ability to protect against early discontinuation of drug development because of safety or efficacy concerns.

As an example, many trials currently require a baseline brain MRI to identify patients with active brain metastases, who are then excluded from the study. The rates of screen failure due to asymptomatic, occult brain metastases can be quite high. Rather than excluding such patients, including them in a prespecified active brain metastasis cohort may provide valuable information on drug performance in this population and even allow differentiation of the investigational agent from others in its class. It may be excessively costly or infeasible to enroll a separate brain metastasis cohort in some trials; in that case, including patients with brain metastasis in the overall study with a prespecified subset analysis for both safety and efficacy is another option.

Randomized studies with a time-to-event end point. Randomized phase II or phase III designs are typically larger in size, with progression-free survival or overall survival frequently chosen as the primary end point. To date, nearly all such randomized trials have excluded patients with active brain metastases, and many have excluded even patients with treated/stable brain metastases.

In terms of study design, many strategies are already in common use with respect to factors that may affect primary efficacy/safety end points (eg, visceral metastases, nonmeasurable disease, organ dysfunction, or poor performance status) and could easily be adapted to handle concerns related to enrollment of patients with brain metastases. Table 4 summarizes possible strategies, including capping enrollment within a trial, stratification, prespecified sensitivity and subset analyses, early stopping rules, or even a parallel exploratory cohort that contributes supporting safety and efficacy data but is not included in the formal assessment of the primary efficacy end point.

Investigational agent. Another consideration is the profile of the investigational agent in question, including mechanism of action, expected CNS penetration, preclinical data, clinical data, and CNS-specific toxicity. In some situations, there is a reasonable body of evidence that at least some agents in the class have CNS efficacy and minimal unexpected toxicities. Such agents include BRAF inhibitors, ALK inhibitors, and HER2 inhibitors.[7,8,24,32,58,59] In these situations, including brain metastasis patients early in drug development of next-in-class medications may be reasonable, and inclusion in later-phase studies recommended, so long as no major safety signals are observed in early studies. More frequently, there exists only a limited body of evidence, ranging from no data, to some demonstration of safety in early drug development, to a few case reports or a small expansion cohort with observed CNS activity. In these cases, a decision to include patients in later-phase trials is more complicated; however, the panel would stress that the greater the efforts to include patients with brain metastasis early in drug development, the more data will be available for making key inclusion/exclusion decisions in registration and other later-phase trials.

Table 4. Examples of Study Designs and Mitigation Strategies to Address Potential Concerns of Inclusion of Patients With Brain Metastases in Clinical Trials

Potential Concern	Dose Finding	Early Efficacy Evaluation	Randomized/Later-Phase Studies
Safety in brain metastasis population, relative to nonbrain metastasis population	Include dedicated expansion cohort including patients with brain metastases. Include detailed description of risks and benefits in ICF.	Include dedicated brain metastasis cohort (either as a stand-alone study or a prespecified cohort in a larger study). Include detailed description of risks and benefits in ICF.	Incorporate prespecified plan to assess safety in brain metastasis subset Incorporate early stopping rules for excess toxicity. Include detailed description of risks and benefits in ICF.
Attribution of adverse events	Include prospectively defined, tailored DLT criteria, which exclude CNS signs or symptoms that may be related to underlying tumor. Perform case review of neurologic toxicities *v* symptoms for DLT attribution. Design case report forms to capture attribution.	Perform case review of neurologic toxicities *v* symptoms. Design case report forms to capture attribution.	Design case report forms to capture attribution. Consider statistical approaches (eg, in patients with *v* without CNS metastases).
Differences in CNS *v* extracranial activity	Include indicated expansion cohort including patients with brain metastases. Include prospective plan to evaluate response in CNS and extracranial compartments separately (eg, per RANO 1.0)	Include dedicated brain metastasis cohort (either as a stand-alone study or a prespecified cohort in a larger study). Design studies to include an adequate number of patients with brain metastasis from whom to draw conclusions. Include prospective plan to evaluate response and progression in CNS and extracranial compartments separately (eg, per RANO 1.0).	Include prospective plan to evaluate response and progression in CNS and extracranial compartments separately (eg, per RANO 1.0). Designate brain metastasis as a stratification factor for randomization. Cap the number of total patients with brain metastases allowed in study. Include a prespecified subset analysis in the brain metastasis population. Include early stopping rules for futility in the brain metastasis subset. Enroll patients with brain metastasis in a parallel exploratory cohort simultaneously within the same protocol, which can contribute to the overall safety and efficacy profile but is not included in the primary efficacy analysis.
Efficacy assessment in the CNS	Use standard end points, such as RANO 1.0. Explore novel, investigational methods of assessing CNS activity (eg, cfDNA in plasma or CSF) as a secondary end point.	Use standard end points, such as RANO 1.0. Explore novel, investigational methods of assessing CNS activity (eg, cfDNA in plasma or CSF) as a secondary end point.	Use standard end points, such as RANO 1.0. Supplement radiographic end points with neurologic examination scales (eg, NANO), quality-of-life scales, and/or neurocognitive testing. Explore novel, investigational methods of assessing CNS activity (eg, cfDNA in CSF) as a secondary end point.
Differences in overall survival between patients with *v* without brain metastases	Carefully delineate performance status, organ function, estimated life expectancy, and other inclusion/exclusion criteria to minimize the likelihood of early death.	Carefully delineate performance status, organ function, estimated life expectancy, and other inclusion/exclusion criteria to minimize the likelihood of early death.	Carefully delineate performance status, organ function, estimated life expectancy, and other inclusion/exclusion criteria to minimize the likelihood of early death. Include brain metastasis as a stratification factor for randomization. Cap the number of total patients with brain metastases allowed in study. Include prespecified subset analysis in the brain metastasis population. Build in a protocol-prespecified early look to check assumptions on overall survival in the brain metastasis subset (may or may not be feasible depending on rate of accrual relative to expected survival time).

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Table 4. Examples of Study Designs and Mitigation Strategies to Address Potential Concerns of Inclusion of Patients With Brain Metastases in Clinical Trials (continued)

Potential Concern	Dose Finding	Early Efficacy Evaluation	Randomized/Later-Phase Studies
Costs and potential harms associated with broader CNS baseline and surveillance imaging	Consider coverage of CNS imaging as part of trial if not covered by standard of care. Broaden trial eligibility to include patients with screen-detected metastases into main protocol or separate cohort/study. Include prespecified rules in the protocol regarding treatment of CNS-limited progression in setting of controlled extracranial disease.	Collect data on outcomes of patients with screen-detected brain metastases. Consider coverage of CNS imaging as part of trial if not covered by standard of care. Broaden trial eligibility to include patients with screen-detected metastases into main protocol or separate cohort/study. Include prespecified rules in the protocol regarding treatment of CNS-limited progression in setting of controlled extracranial disease.	Collect data on outcomes of patients with screen-detected brain metastases. Consider coverage of CNS imaging as part of trial if not covered by standard of care. Broaden trial eligibility to include patients with screen-detected metastases into main protocol or separate cohort/study. Include prespecified rules in the protocol regarding treatment of CNS-limited progression in setting of controlled extracranial disease.
Costs associated with additional patient cohorts		Include early stopping rules for futility in the brain metastasis subset.	Include interim analyses to check assumptions in the brain metastasis subset. Include early stopping rules for futility in the brain metastasis subset.
Lack of understanding of BBB or BTB penetration	Consider CSF sampling or presurgical window of opportunity study	Consider CSF sampling or presurgical window of opportunity in a side cohort.	Consider CSF sampling or presurgical window of opportunity in a side cohort.
Potential impact on overall trial outcomes	Consider separate cohort(s).	Consider separate cohort(s).	Consider capping and/or stratification. Include plan or efficacy reporting in predefined cohorts. Incorporate early stopping rules. Have early discussions and collaborations with regulators.

Abbreviations: BBB, blood-brain barrier; BTB, blood-tumor barrier; cfDNA, cell free deoxyribonucleic acid; DLT, dose-limiting toxicity; ICF, informed consent form; RANO, Response Assessment in Neuro-Oncology.

Increasingly, sponsors are generating data in preclinical models as part of early drug discovery efforts. There are legitimate limitations to this work, including biologic BBB distinctions between species, blood-tumor barrier leakiness, and limited intracranial solid tumor models. Notably, both crizotinib and lapatinib have been associated with CNS responses in NCLSC and HER2-positive breast cancer, respectively, despite limited intact BBB penetration.[7,18,20,33] The panel discussed that including additional strategies early in drug development to understand the CNS profile of investigational agents, such as CSF sampling, precraniotomy brief exposure studies and advanced imaging, could be quite useful. However, requiring such data before allowing patients with brain metastases to enter studies could present a significant barrier to patient inclusion. Instead, provisions requiring CSF and/or tumor sampling in a subset of patients could be a reasonable compromise and avoid a substantial burden for an entire patient population.

Finally, there may be situations wherein CNS-specific toxicities may be a concern, such as a drug lowering the seizure threshold, which may not be an ideal agent even for patients with treated/stable brain metastases. Thus, exclusion may be justified, particularly early in drug development.

LEPTOMENINGEAL METASTASES

In contrast to patients with parenchymal brain metastases, where there has been clear improvement in survival across several tumor types over time, many patients with LMD still have a poor prognosis and are often symptomatic, although prognosis is improving in some patient subsets, including ALK-positive NSCLC.[9,60,61] Treatment may include the placement of shunts to relieve intracranial pressure and delivery of chemotherapy to the intrathecal space. Even when patients respond, the duration of response tends to be short.[62-65] LMD is frequently not measurable in the traditional sense. Of note, the RANO group has recently published a proposal to standardize the assessment of LMD in clinical trials.[65a]

Several systemic agents have demonstrated efficacy in patients with LMD, and more studies focused on such patients are needed.[66,67] Patients with LMD provide a unique opportunity for serial CSF sampling with respect to pharmacokinetic studies that may be of considerable interest in drug development. At the same time, leptomeningeal enhancement is common and does not necessarily equate to clinical LMD. Thus, patients with imaging-only subtle or equivocal findings and no clinical evidence of LMD should not necessarily be considered to have LMD for trial eligibility/exclusion.

Despite the significant unmet clinical need, the natural history and treatment options for patients with LMD are sufficiently different from the general trial population that their inclusion could affect key trial end points. The panel stressed, however, that these patients need new options, and dedicated studies (or dedicated cohorts within a larger study) are strongly encouraged. Examples of trials specifically addressing this population include intrathecal

trastuzumab (ClinicalTrials.gov identifier: NCT01325207), tesevatinib (ClinicalTrials.gov identifier: NCT02616393), ceritinib (ClinicalTrials.gov identifier: NCT02336451), and abemaciclib (ClinicalTrials.gov identifier: NCT02308020).

Recommendations

- The panel recommends inclusion of an LMD cohort in early-phase trials of drugs with anticipated CNS activity when relevant in the specific disease type under study. Consideration of CSF pharmacokinetic measurements is encouraged in this context.
- When possible, inclusion of an LMD cohort in later-phase trials may be useful to provide access to investigational agents and to generate additional safety and efficacy data.
- If patients with LMD are to be excluded, justification for the exclusion should be provided, and the following wording is suggested, to avoid unnecessary exclusion of patients with imaging-only equivocal findings.

Template for exclusion criteria (if justified). No known LMD.
Note. LMD is a clinical diagnosis, defined as positive CSF cytology and/or unequivocal radiologic or clinical evidence of leptomeningeal involvement. Patients with leptomeningeal symptoms in the setting of leptomeningeal enhancement would be considered to have LMD even in the absence of positive CSF cytology, unless a parenchymal lesion can adequately explain the neurologic deficit. In contrast, asymptomatic or minimally symptomatic patients with mild or nonspecific leptomeningeal enhancement would not be considered to have LMD. In such patients, CSF sampling is not required to formally exclude LMD but can be performed at the investigator's discretion on the basis of level of clinical suspicion.

Recommendations

- The panel recommends baseline CNS imaging in populations where the risk of brain metastases is high, if there are specific safety concerns related to inclusion of patients with brain metastasis, or if one of the objectives of the study is to determine the impact of the investigational therapy on CNS-related outcomes. If baseline imaging is required, the panel recommends incorporating patients with screen-detected brain metastases in one of several ways:
  - Permit local therapy followed by immediate enrollment in the main study once acute treatment-related toxicities have resolved.
  - Enroll into a separate preplanned brain metastasis cohort.
  - Use statistical approaches, including stratification of randomization or capping, to allow enrollment of such patients into the intent-to-treat study population.
- The panel recommends both baseline and surveillance CNS imaging on a protocol-defined schedule in patients with brain metastases identified at baseline. Required surveillance imaging could be considered in patients without brain metastases at baseline if the patient population in question is at high risk of developing CNS involvement during the study, especially if the time to first CNS metastasis is a clinically relevant end point.
- Protocols should prospectively specify whether patients with isolated CNS progression, but responsive/stable extracranial disease, can remain on protocol therapy. Concurrently allowed local CNS treatments (eg, surgery, radiosurgery, whole-brain radiation therapy) should be prespecified explicitly in the protocol. If a patient can remain on protocol, they should continue to be followed, and intracranial and extracranial progression should be noted and recorded separately in the case report form.[46,47]

PRACTICAL CONSIDERATIONS

Use of surveillance brain MRI scans in routine care has been controversial and has varied by disease site. In patients with lung cancer, screening brain MRI scans are frequently ordered, whereas in patients with breast cancer, national and international guidelines currently discourage screening MRI, given absence of data supporting a benefit.[68,69] Clinicians have often been reluctant to order baseline CNS imaging, unless mandated, out of concern that the identification of asymptomatic lesions might jeopardize eligibility. Similarly, if identification of new or progressive CNS lesions jeopardizes continued trial participation (despite benefit in extracranial sites), there will be resistance to routine surveillance CNS imaging. The outcome of this situation is a loss of knowledge regarding the impact of investigational agents in the CNS.

The potential benefits to both patients and investigators are clear. Inclusion of patients with brain metastases in trials will decrease resistance to baseline CNS screening. If patients with isolated CNS progression can receive local CNS therapy, then resistance to protocol-mandated CNS surveillance will also decrease.

CONCLUSIONS

Treating brain metastases remains a challenge. Broader and more thoughtful inclusion of patients with brain metastases in clinical trials in all stages of drug development has the potential to provide tangible benefits to patients, both within clinical trials and in broader use, and to support new indications or enhanced labeling claims in oncology.

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Modernizing Clinical Trial Eligibility Criteria: Recommendations of the American Society of Clinical Oncology–Friends of Cancer Research Brain Metastases Working Group

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Modernizing Clinical Trial Eligibility Criteria: Recommendations of the American Society of Clinical Oncology–Friends of Cancer Research Organ Dysfunction, Prior or Concurrent Malignancy, and Comorbidities Working Group

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A B S T R A C T

Purpose
Patients with organ dysfunction, prior or concurrent malignancies, and comorbidities are often excluded from clinical trials. Excluding patients on the basis of these factors results in clinical trial participants who are healthier and younger than the overall population of patients with cancer.

Methods
ASCO and Friends of Cancer Research established a multidisciplinary working group that included experts in trial design and conduct to examine how eligibility criteria could be more inclusive. The group analyzed current eligibility criteria; conducted original data analysis; considered safety concerns, potential benefits, research, and potential hurdles of this approach through discussion; and reached consensus on recommendations regarding updated eligibility criteria that prioritize inclusiveness without compromising patient safety.

Results
If renal toxicity and clearance are not of direct treatment-related concern, then patients with lower creatinine clearance values of > 30 mL/min should be included in trials. Inclusion of patients with mild to moderate hepatic dysfunction may be possible when the totality of the available nonclinical and clinical data indicates that inclusion is safe. Ejection fraction values should be used with investigator assessment of a patient's risk for heart failure to determine eligibility. Patients with laboratory parameters out of normal range as a result of hematologic disease should be included in trials. Measures of patient functional status should be included in trials to better assess fit versus frail patients.

Conclusion
Expanding inclusion of these patients will increase the number and diversity of patients in clinical trials and result in a more appropriate population of patients.

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INTRODUCTION

Clinical trials are of fundamental importance to developing improved cancer therapies. Unfortunately, clinical trial participation in the United States is low, with only approximately 3% of adult patients with cancer participating in clinical trials.[1] Slow accrual retards the drug development process by delaying the collection and reporting of potentially useful data, and studies frequently close as a result of poor accrual. A number of explanations for poor clinical trial participation have been identified, including disease-related (eg, stage, diagnosis, scientific rationale), treatment-related (eg, experimental nature, risk of toxicity, complexity), trial design (eg, eligibility, placebo, follow-up, caregiver burden for testing), and other background factors (eg, trial competition, costs).[2]

Patients with organ dysfunction are often excluded from clinical trials, regardless of specific drug metabolism or relative function of the organ. For instance, the physiologic decline in renal function may make a patient ineligible even when the drug under study does not have significant

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renal excretion. The general population is aging and thus includes increasing numbers of patients with renal disease, hepatic dysfunction, cardiac disease, prior history of cancer, and other comorbidities.[3] Once a drug enters the marketplace, it may be prescribed to patients with these conditions for whom clinical trial safety and efficacy data have not been evaluated.

In the absence of understanding nonclinical pharmacokinetics (PK) and major routes of elimination in humans, it is reasonable to enroll patients with normal organ function, primarily renal and hepatic.[4] However, as data on toxicity, PK, and pharmacodynamics (PD) become available during drug development, protocols are rarely revised to include patients with compromised organ function where safe parameters have been determined.[5]

Standard criteria for normal organ function are included in most trial protocols. These criteria typically include the following: adequate renal function characterized as calculated creatinine clearance (CrCl; commonly set at > 60 mL/min); adequate hepatic function characterized as total bilirubin (commonly set at < 1.5 mg/dL) and/or ALT and AST (commonly set at < 2 to 3 × upper limit of normal [ULN]); and parameters for left ventricular ejection fraction (commonly set at > 50%). Although these criteria are often included in trial protocols, the degree to which deviation from normal organ function affects the overall trial objective and primary end point needs to be assessed. For instance, trials in which the PK of an investigational agent are being determined frequently exclude patients with any deviation from normal organ function. Sometimes, dosing for patients with organ dysfunction is determined through a dedicated phase I trial that evaluates PK exposure differences between patients with organ dysfunction versus normal organ function.

Herein, we address the safety and efficacy concerns of including patients with organ dysfunction, prior or concurrent malignancies, and comorbidities in clinical trials and provide recommendations where inclusion of such patients is appropriate.

PROCESS

ASCO and Friends of Cancer Research established a working group that included a multidisciplinary team of experts in oncology practice and clinical trial design and conduct to examine how eligibility criteria could be more inclusive for patients with organ dysfunction, prior or concurrent malignancies, and comorbidities. The group analyzed current eligibility criteria and considered safety concerns, potential benefits, research impact, and potential hurdles of enrolling greater numbers of trial participants. Recommendations regarding updated eligibility criteria that prioritize inclusiveness without compromising patient safety were reached through discussion until group consensus was met.

The organ dysfunction, prior or concurrent malignancy, and comorbidities group included clinical investigators, clinical pharmacologists, patient advocates, and industry and regulatory representatives. The recommendations stated here were drafted on the basis of analysis of clinical data and review of relevant literature and refined after discussion among similar groups assigned to consider other criteria and additional patient advocate, industry, and regulatory representatives.

The group reviewed clinical data from Kaiser Permanente Northern California (KPNC). The goal of this analysis was to explore whether changes in standard eligibility criteria would enable greater numbers of patients with commonly diagnosed cancers to participate in clinical trials.

KPNC is a fully integrated prepaid health care delivery system established in 1948. It has nearly four million members and serves approximately 20,000 new analytic patients annually. The median age of members is approximately the same as that of the SEER Program database.

Data for all KPNC patients who were diagnosed with breast, colon, lung, and bladder cancer between 2013 and 2014 (n = 12,881) were analyzed against organ function, comorbidity, and prior malignancy parameters commonly found in clinical trial eligibility criteria (Table 1). The specific parameters analyzed were as follows: diagnosis of prior malignancy in the past 5 years, history of congestive heart failure and/or cardiomyopathy, prior myocardial infarction, liver chemistries, glomerular filtration rate (GFR), and age. Total ineligibility score (TIS) is an empirically derived number that conveys the potential magnitude of ineligibility by summing the preceding columns (Table 1). In this model, TIS aided in determining what the potential effect of changing eligibility parameters would be on the number of eligible patients.

The KPNC analysis demonstrates the significant affect of renal function on patient eligibility. Results demonstrate a marked difference in renal function by diagnoses. Patients with breast cancer, many of them otherwise healthy and receiving adjuvant treatment, had a 15% incidence of GFR < 60 mL/min, whereas the incidence in patients with bladder cancer was 34%. This also correlated with patients with bladder cancer being much older (45% > 75 years old *v* 16% of patients with breast cancer) and having more comorbidities (Table 1). Additional analysis by degrees of renal dysfunction (Table 2) demonstrates how standardized inclusion and exclusion criteria affects patient eligibility across common cancer types and suggests that renal function criteria should be specific to the patient population under study (eg, adjusted for diagnosis, age, comorbidity, etc).

Exclusion of patients with CrCl < 60 mL/min would preclude between 20.3% and 45.9% of patients from participating in cancer clinical trials. This result is likely conservative because the patients were measured at diagnosis and not heavily pretreated or phase I trial candidates.

The KPNC analysis indicates that newly diagnosed patients across all four disease types rarely (< 1%) have significant hepatic dysfunction, defined as ALT > 2 × the ULN (Table 1). Congestive heart failure and myocardial infarction were present in greater percentages of patients with lung and bladder cancers (congestive heart failure: 11% in both lung and bladder cancer *v* 5% in breast cancer and 8% in colorectal cancer). Our analysis reveals how changing the standard criteria may increase the number of patients eligible for clinical trials.

Table 1. Kaiser Permanente Northern California 2013 to 2014 Data: Rates of Organ Dysfunction, Comorbidity, or Prior Malignancy Across Cancer Types

	% of Patients							
Cancer Site	Invasive Cancer in Past 5 Years	CHF/ Cardiomyopathy	MI	ALT > 2× ULN	Bilirubin > 1.5 mg/dL	GFR < 60 mL/min	Age > 75 Years Old	Total Ineligibility Score
Breast, n = 5,865	3	5	1	0.3	0.4	15	16	43.7
Colorectal, n = 2,927	5	8	3	0.9	1	18	30	69.9
Lung, n = 3,319	8	11	4	0.3	0.2	20	35	84.7
Bladder, n = 770	8	11	5	0.4	1	34	45	111.8

Abbreviations: CHF, congestive heart failure; GFR, glomerular filtration rate; MI, myocardial infarction; ULN, upper limit of normal.

RISKS AND BENEFITS TO INCLUSION

Standard organ function measurements and cutoff points may exclude patients without adequately assessing the function of the organ. In addition, the organ may not be clinically relevant to the therapy under investigation or raise any concerns about patient safety. Risks and benefits associated with including patients with organ dysfunction and prior or concurrent malignancies in trials are outlined in the following sections.

Renal Dysfunction

In a diagnosis that predominantly affects older patients, such as bladder cancer, the KPNC analysis demonstrated that rigid CrCl limits will exclude a significant number of patients (Table 1). The rationale to exclude patients with renal dysfunction from studies, particularly in early-phase trials, is to avoid adverse events as a result of renal insufficiency and potential renal toxicities associated with drugs that have renal clearance. Clinical trials have often mandated a calculated CrCl of > 60 mL/min for inclusion. Serum creatinine values have also been used, but serum creatinine does not accurately reflect renal function and CrCl should be the standard.[4] Studies of patients with normal serum creatinine values demonstrate varying degrees of renal insufficiency, emphasizing the need for calculating CrCl.[4] Although ideally a measured CrCl is preferable, it is not a practical solution. Twenty-four-hour urine collections for measured CrCl are often not accurately performed, particularly when collection takes place at home, and radionuclide assessment of CrCl is costly and unnecessary in the majority of patients.

There are various formulae available for CrCl calculation, but the two most common estimates are the Cockcroft-Gault equation and the Modification of Diet in Renal Disease (MDRD) equation. The National Kidney Foundation generally recommends the use of MDRD over Cockcroft-Gault as a result of improved agreement with directly measured GFR values, particularly in the elderly and obese populations.[6] However, when each equation is used and compared with GFR and PK is considered, the actual difference in drug dosing is clinically insignificant in the majority of patients.[7] Both the Cockcroft-Gault and MDRD equations are readily calculated from common clinical values and are incorporated in many electronic health record systems.

Because a large proportion of potential patients with cancer are older than age 65 years, the issue of aging physiology is significant.[8] Normal aging is associated with a decline in CrCl of approximately 0.8 mL/min per year after the age of 40.[9] Decline in renal function is often exacerbated by comorbidity, contrast dyes, or medication. Studies of patients with normal serum creatinine values demonstrate varying degrees of renal insufficiency, emphasizing the need for calculating CrCl.

The need for a specific CrCl eligibility criterion is dependent on the type of study contemplated and the agent(s) used. For a phase I trial in which PK data are required and the human renal toxicity and clearance may not be fully known, a normal CrCl of ≥ 60 mL/min is reasonable. When PK and PD data and renal safety have been explored, lower values are reasonable to prevent unnecessary patient exclusion.

A study by the Alliance for Clinical Trials in Oncology analyzed the effect of renal function on various outcomes in an adjuvant breast cancer trial in women older than age 65 years.[10] This prospective randomized study analyzed physician-selected multiagent regimens of capecitabine versus either cyclophosphamide plus doxorubicin or cyclophosphamide, methotrexate, and fluorouracil. Patients were required to have a CrCl > 30 mL/min, and doses of capecitabine and methotrexate were adjusted per on-study renal function. The authors concluded that there was no relationship between pretreatment renal function and the five end points (toxicity, dose modification, therapy completion, relapse-free survival, and overall survival) for any regimen. Patients with renal insufficiency who received a modified dose were not at increased risk for complications compared with those who did not have renal insufficiency and received a full dose. The investigators

Table 2. Kaiser Permanente Northern California 2013 to 2014: Lowest Glomerular Filtration Rate at Cancer Diagnosis

	% of Patients (N = 13,000)						
Cancer Site	< 30 mL/min	30-39 mL/min	40-49 mL/min	50-59 mL/min	30-59 mL/min	< 60 mL/min	≥ 60 mL/min
Breast	1.4	2.3	5.9	10.7	18.9	20.3	79.7
Colorectal	2.4	4.0	6.9	11.3	22.2	24.6	75.4
Lung	2.6	4.7	9.0	11.4	25.1	27.7	72.3
Bladder	9.1	9.5	10.9	16.3	36.7	45.9	54.1

NOTE. Calculated using Cockcroft-Gault equation.

concluded that the risk of excessive hematologic toxicity or poor outcomes in patients with renal insufficiency but good performance status may be mitigated with appropriate dosing modifications.

After a retrospective analysis, authors of the Gynecologic Oncology Group 182 trial concluded that their data do not support excluding patients with CrCl < 60 mL/min from clinical trials.[11,12] Patients were randomly assigned among five arms that incorporated gemcitabine, methoxypolyethylene glycosylated liposomal doxorubicin, or topotecan as a triplet compared with carboplatin and paclitaxel as doublet therapy. Eligibility criteria required a patient's creatinine to be ≤ 1.5 × the institutional ULN using the Jelliffe formula. The trial accrued 3,830 evaluable patients with a mean age of 58.7 years and a mean baseline CrCl of 81.9 mL/min (range, 23.4 to 239 mL/min). A cutoff value of CrCl < 60 mL/min would have deemed 15% of patients treated on the Gynecologic Oncology Group 182 trial ineligible.

Finally, the National Cancer Institute analyzed extramural phase I studies from 1979 to 2010.[13] Approximately 36% of patients enrolled onto phase I trials had mild renal dysfunction (CrCl, 50 to 80 mL/min). In a comparison with patients with normal function, mild renal dysfunction was associated with a statistically significant but small increase in grade 3 or 4 nonhematologic toxicity. The authors concluded that patients with mild renal dysfunction can be enrolled without clinically meaningful increase in the risk of toxicity and without altering the maximum-tolerated dose determination.

Hepatic Dysfunction

Eligibility criteria for hepatic function include liver function tests (LFTs), such as serum aminotranferases (ALT and AST), bilirubin, and, less frequently, alkaline phosphatase, γ-glutamyl transpeptidase, albumin, lactate dehydrogenase, and coagulation tests. Categorization of function is considered as synthetic (eg, albumin), cellular injury (eg, AST, ALT), and cholestatic and ductal function (eg, bilirubin). Concentrations of these enzymes are used to classify patients into groups for trial purposes (ie, normal function or mild, moderate, or severe dysfunction). The more conservative approach of excluding patients with values greater than the ULN is routinely done to ensure safety and is historically done on the assumption that elevated enzymes are surrogates for impaired drug metabolism. As an exception to this, patients with hepatic metastases are often allowed on trial with higher values, up to 5 × ULN, under the assumption that abnormal LFT values are a result of cancer and do not reflect intrinsic hepatic or metabolic function. This exception highlights the need to discern etiology of elevated LFT values in patients before initiating treatment, because some cancers (eg, colorectal) may be causative and, therefore, effective treatment may lead to a return to normal values.

Patients with hepatic impairment are often excluded from clinical trials where safety or efficacy is the primary objective. Dosing guidance for patients with hepatic impairment is on the basis of smaller trials specifically designed to evaluate exposure differences between patients with and without liver dysfunction. For drugs extensively metabolized by liver enzymes, it has been shown repeatedly that LFT values in patients with mild and moderate hepatic impairment do not reliably predict systemic exposure of anticancer agents.[14-17] Patients with mild and moderate impairment, as well as those with AST or ALT elevations defined as grade 3 by the National Cancer Institute Common Terminology Criteria for Adverse Events (> 5 to 20 × ULN), may be asymptomatic and able to take doses equivalent to patients with normal hepatic function. However, patients with severe hepatic impairment often do not tolerate approved doses. This intolerance, however, is often a result of poor performance status rather than an alteration in systemic PK measures.[18,19] Another complicating factor in patients with liver dysfunction is that an investigational agent may cause liver toxicity and therefore may exacerbate underlying liver dysfunction.

Current clinically available hepatic function testing does not fully describe liver function, particularly drug metabolism capability (ie, there is no reliable comparator to the relationship between creatinine and renal drug clearance). Hepatic metabolism may also be influenced by cancer and inflammation, even in the setting of normal test results.[20] Estimates of hepatic function that incorporate clinical variables as well as functional and laboratory values, such as the Child-Pugh and Model for End-Stage Liver Disease scoring systems, may more closely align with hepatic metabolism.[21] Despite limitations, LFT values are commonly used to provide guidance on anticancer agent dosing in clinical settings because of their routine availability and a lack of clearly superior alternatives. More reliable measures to predict both phase I and phase II hepatic metabolism function are needed.

Cardiac Dysfunction

Oncology clinical trials often exclude patients with a previous cardiovascular history, including coronary artery disease, symptomatic heart failure, and other cardiac events within specified time frames.[22] Exclusions on the basis of cardiac disease may decrease enrollment of older patients by approximately 5%.[23] Ejection fraction (EF) as a marker of current cardiac contractility is also commonly determined at study entry. Typically, patients must have an EF of 45% to 50% or higher by echocardiography or multigated acquisition scan. Accuracy of each method is reasonable; however, when continued EF measures are needed during the clinical trial, a consistent approach should be used for comparability to screening values.[24] The ability of a specific EF to predict anticancer agent cardiotoxicity tolerability is unclear, and entry criteria percentages have largely been chosen because of historical precedent.

ECG eligibility criteria focus on QTc interval, frequently with a baseline interval of 450 milliseconds. For some agents that have preclinical risk of QTc prolongation, frequent serial ECGs are required during early-phase trials to determine a concentration–QTc prolongation relationship.[25] However, an analysis of 8,518 ECGs in phase I anticancer studies found that none of the ECGs performed predicted a cardiac event and that prolonged QTc intervals did not lead to arrhythmic events. The study authors emphasize the importance of clinical evaluation and recommend more modest use of ECG monitoring in early-phase studies.[26] This should be in coordination with regulatory agencies, especially in early-phase studies.

Prior or Concurrent Malignancy

Diagnoses of more than one malignancy are not unusual, occurring in approximately 15% of patients.[27] By excluding individuals with previous cancers, as most trials traditionally do, trial recruitment favors younger patients.[23] Many patients with prior malignancies could be appropriate clinical trial participants for interventions related to subsequent malignancies. Diagnosis and treatment may have occurred many years prior and may be clinically insignificant, particularly in situations with few indicators of relapse. In the case of concurrent malignancies that do not require treatment and are clinically stable, there would be no interference with protocol therapy. Evidence is insufficient to determine the affect of previous, nonactive cancers on study-related outcomes.[23]

Explicitly including patients with prior malignancies rather than removing prior malignancy as an exclusion may have a positive effect on accrual. For example, trials that explicitly include older patients with impaired functional status were found to enroll higher numbers of older adults overall than trials that did not specify functional status exclusion.[23] To exclude a patient from intervention on current malignancy solely on the basis of a prior or clinically stable concurrent malignancy is inappropriate.

Hematologic Malignancies

Although group discussion and recommendations focused on solid tumors, issues for eligibility criteria are similar in hematologic malignancies. A 2016 analysis of randomized controlled trials in hematologic malignancies found that standard eligibility criteria include restrictions that may be overly conservative on the basis of the known toxicity profiles of the interventions being studied.[28] Exclusions on the basis of hematologic function abnormality may decrease enrollment of older patients by approximately 14%.[23]

Patients may be excluded from hematologic studies on the basis of non–drug-relevant organ dysfunction or performance status (PS) of ≥ 2. Some studies have allowed expanded PS if the worsened PS is from disease (eg, PS > 2 if secondary to neuropathy or acute bone event; S. Kumar, personal communication, January 2017). The Eastern Cooperative Oncology Group–American College of Radiology Imaging Network E1912 study is notable for the following more inclusive criteria: PS (0 to 2 allowed); liver function (eligible if value is higher as a result of hepatic involvement by chronic lymphocytic leukemia); GFR > 40 mL/min; and prior malignancy (the provision that "if there is a history of prior malignancy, [patients] must not be receiving other specific treatment [other than hormonal therapy for their cancer]" is relatively lenient).[29] This improved prior malignancy language may still need modification, as we see that chronic myeloid leukemia trial participants with a history of prior malignancies have the same outcomes as patients without prior malignancies.[30] Other laboratory parameters may be abnormal as a result of bone marrow infiltration (anemia, thrombocytopenia), and protocols should include accommodations to laboratory parameters to adjust for disease infiltration. Although this is most often seen in hematologic cancers, it is possible that solid tumors with bone marrow infiltration would also be treated off study and so not excluding patients in those circumstances may be warranted.

Comorbidities

Clinical trials do not usually include older patients, and when they do, geriatric-specific baseline data are almost never obtained.[8] The inclusion of baseline data on patients' comorbidities and function will make study results more applicable to a broader oncology population. When included in the final study analysis, these data will help guide clinicians to treat older patients with more precision.[8]

RECOMMENDATIONS

On the basis of a literature review, the KPNC analysis, and expert opinion, the working group makes the following recommendations for increased inclusiveness of patients with organ dysfunction, prior or concurrent malignancies, and comorbidities in clinical trials.

Renal Function

- Eligibility criteria should include assessment of CrCl rather than serum creatinine concentrations.
- The Cockcroft-Gault and MDRD equations are reasonable standards for calculating kidney function and are accepted in practice. A consistent measure should be applied throughout the drug development process. Inclusion of patients with renal dysfunction could be liberalized in the following specific settings: if renal toxicity and clearance are not of concern, then lower CrCl values of > 30 mL/min should be used for inclusion; when published dose modifications allow for safe and effective administration of the drug and are not likely to change outcomes (eg, carboplatin, methotrexate, capecitabine); and when the totality of the available nonclinical and clinical data, including PK and PD data, indicates that inclusion of patients with renal dysfunction is safe.

Hepatic Function

- Inclusion of patients with mild to moderate hepatic dysfunction may be acceptable when the totality of the available nonclinical and clinical data, including PK and PD data, indicates that inclusion of these patients is safe.
- New measures that adequately reflect hepatic function should be developed to improve the accuracy of identifying patients with true hepatic dysfunction.

Cardiac Function

- Treatment-emergent cardiac adverse events may be difficult to predict. Eligibility criteria should reflect a conservative approach to cardiac safety measures, so that patients with significant cardiac abnormalities or EF < 35% are excluded, especially in early-phase studies. Inclusion of patients with cardiovascular dysfunction may be possible when the totality of the available nonclinical and clinical data, including PK and PD data, indicates that inclusion of these patients is safe.
- EF values should not be used in isolation to exclude patients from trials. Trials should recommend investigator assessment of a potential participant's risk for heart failure with a validated clinical classification system (eg, the New York Heart Association functional classification).[31]

- If QTc prolongation is not identified as a concern in first-in-human studies, QTc interval eligibility criteria in phase IB and later trials should be re-evaluated, and ongoing ECG monitoring may not be required.
- Cardiovascular safety measures and close collaboration with cardiology should be considered, particularly when investigating compounds or regimens where trial-emergent cardiac contractility toxicity is a factor (eg, trastuzumab or sunitinib).[32,33]

Prior or Concurrent Malignancy

- Inclusion of patients with prior malignancies is recommended, especially when the risk of the prior malignancy interfering with either safety or efficacy end points is very low.
- Patients with a previously treated malignancy should be eligible to participate if all treatment of that malignancy was completed at least 2 years before registration and the patient has no evidence of disease.
- Patients who have a concurrent malignancy that is clinically stable and does not require tumor-directed treatment should be allowed to participate on a trial for another cancer that requires treatment.

Hematologic Malignancies

- Inclusion of patients with laboratory parameters that are out of normal range as a result of disease may be appropriate (eg, cytopenias from bone marrow infiltration, LFT abnormalities from disease involvement in lymphoma).
- Inclusion of patients with disease-specific comorbidities (eg, peripheral neuropathy or bone symptoms in multiple myeloma) that are thought to be unaffected by the study agents and would otherwise be treated in practice is recommended.

Comorbidities

- Inclusion of measures of function other than PS into trial design to better assess the safety and efficacy of an investigational agent in fit versus frail patients is recommended.

CONCLUSION

The working group has outlined a number of areas in which modifying current clinical trial eligibility can enhance trial participation. Implementation of these changes will take the cooperation of multiple stakeholders including individual clinicians, institutions and their investigational review boards, cooperative oncology groups, the pharmaceutical industry, and patients. Increasing the numbers of patients and including a broader array of patients in clinical trials will ultimately help all of these groups and enhance cancer treatment overall.

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Modernizing Clinical Trial Eligibility Criteria: Recommendations of the American Society of Clinical Oncology–Friends of Cancer Research Organ Dysfunction, Prior or Concurrent Malignancy, and Comorbidities Working Group

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Modernizing Clinical Trial Eligibility: Recommendations of the American Society of Clinical Oncology–Friends of Cancer Research Minimum Age Working Group

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ABSTRACT

Purpose
Children have historically been excluded from first-in-human studies of promising new cancer drugs and later phase adult clinical trials. Delays in evaluation may result in off-label use without dosing information as the only access to new drugs. A multistakeholder workshop was convened in May 2016 by ASCO and Friends of Cancer Research to identify opportunities for when it would be scientifically appropriate to expand trial eligibility to include children younger than age 18 years in first-in-human and other adult cancer clinical trials.

Methods
This group convened experts from academia, government, and industry to review barriers to enrolling children and adolescents in oncology clinical trials. We evaluated the historical context, published literature, regulatory considerations, and myriad risks and benefits associated with lowering the age of enrollment on oncology clinical trials.

Results
We conclude that many of the historical concerns about including children early in oncology clinical trials do not apply in the current scientific and clinical environment of pediatric oncology and drug development; we provide specific recommendations for how the inclusion of children in early-phase investigational cancer drug trials might be accomplished. Automatic inclusion of pediatric patients is appropriate in early-phase trials that assess dose, safety, and pharmacokinetics in a variety of tumor types and later phase trials that assess efficacy in a specific disease that spans adult and pediatric populations.

Conclusion
Including children in appropriately designed adult clinical oncology trials is feasible and can be done in a way that enhances their access to these agents without compromising safety or development strategies.

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INTRODUCTION

Although major progress has been made in the treatment and even cure of some pediatric cancers, other pediatric cancers, particularly if metastatic at diagnosis, are associated with unacceptably low survival rates based on inadequate existing treatment options and available drugs.[1] Cancer remains the leading cause of death from disease in children,[2] with approximately 2,000 children dying from cancer each year in the United States.[3] Many children who do survive experience a spectrum of short- and long-term toxicities, including cognitive deficits, growth and endocrine dysfunction, infertility, and a risk of developing secondary cancers.[4,5] There is substantial unmet need for more effective and less toxic agents in children with cancer.

Cancer drug development has been transformed in recent years by rapid advances in biomedical science and technology, and drug development in children has leveraged advances made in adult cancer. To date, children have benefitted less from these advances, because few new drugs are specifically developed for pediatric cancers and initiation of pediatric phase I trials is generally undertaken after extensive testing in adults, well after completion of one or more adult clinical trials, or sometimes not at all.[6] Meanwhile, many adult oncology clinical trials exclude

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pediatric patients by specifying 18 years as the minimum age of eligibility. Access to some agents for pediatric patients may come first in the form of off-label treatment only after these drugs have been approved for use in adults. Off-label use creates a situation where children may be receiving a drug for which there is no pediatric-specific information about dose, safety, and efficacy or for which long-term effects are not known. This situation further impedes the acquisition of such information because data are not systematically collected or evaluated as a part of off-label treatment. Accrual of patients to pediatric trials and successful completion of trials evaluating drugs whose superior efficacy has already been established in adults can be challenging once a drug is available on the market. This issue is particularly challenging in cancers such as melanoma, some sarcomas, and lymphomas because they occur in both pediatric and adult patients.

As the molecular mechanisms of action of new agents have become more precisely defined, the oncology community is increasingly prioritizing application of scientifically based, clinically relevant approaches to selection of eligibility criteria.[7] Taking this approach will result in criteria that are not unnecessarily restrictive and can help improve trial accrual and access and the applicability of trial results to real-world patients, which has been recognized as a priority.[8]

PROCESS

A multistakeholder workshop was convened in May 2016 by ASCO and Friends of Cancer Research to identify opportunities where it is scientifically appropriate to expand trial eligibility. Four working groups composed of patient advocates, drug and biotechnology manufacturers, investigators, and regulators were convened to address the following topics: brain metastases, HIV/AIDS, organ dysfunction, and minimum age for enrollment. Each working group participated in a series of teleconferences in advance of the meeting with the charge to develop specific recommendations based on the state of the science and regulatory guidelines in pediatric oncology and in drug development. This working group was convened to determine when and how the minimum age of eligibility may safely be lowered to younger than age 18 years for adult oncology clinical trials. Herein, we examine the barriers, both real and perceived, that traditionally have prevented patients younger than age 18 years from enrolling in adult oncology clinical trials and discuss how some of these barriers can be overcome. We conclude that many of the historical concerns about including children early in oncology clinical trials do not apply in the current scientific and clinical environment of pediatric oncology and drug development; we provide specific recommendations for how the inclusion of children in early-phase investigational cancer drug trials might be accomplished.

This working group acknowledges that there may be unique safety and/or efficacy signals in children and that children may have different toxicity or drug tolerance and administration profiles compared with adult patients, as has been seen with the use of fenretinide.[9,10] Nevertheless, we conclude that it is preferable to evaluate new agents in the preapproval setting rather than relying on postmarketing surveillance or off-label use of a new cancer therapy in children.

GENERAL RECOMMENDATIONS FOR INCLUSION OF PEDIATRIC AND ADOLESCENT PATIENTS

The Minimum Age Working Group recommends the following to mitigate risks and facilitate inclusion of pediatric and adolescent patients in general:

1. Adult protocols on which children may be enrolled should include pediatric oncologists as investigators to provide expertise and help address logistical issues. These issues may arise because clinical care of and research involving children occurs primarily at academic pediatric institutions, which most often do not admit adult patients or conduct adult clinical trials.
2. Trials involving children should use a central institutional review board and/or inclusion of pediatric expertise on the institutional review board or ethics committees of record to help educate and support the committee members and assist in review of such studies.
3. The inclusion of established pediatric centers with drug development expertise and infrastructure would help mitigate the operational and regulatory burden and lack of experience that might otherwise exist within a primarily adult clinical center.
4. Young children and any patient with oral or esophageal kinetic dysfunction may not be able to swallow tablets or capsules. Development of either bioavailable extemporaneous compounding of existing agents or pediatric- or adult-friendly oral drug formulations for these populations should be considered early; otherwise, unnecessary delay in pediatric evaluation will occur. If there is sufficient reason to believe a new agent will have potential application to a pediatric population or to adult patients who have similar needs for liquid formulations, the oral or liquid formulation should be tested earlier. Testing of liquid formulations to determine bioavailability when delivered through nasogastric or gastrostomy tubes would be a second consideration for these compounds, as tube composition may affect pharmacokinetics or dosing recommendations.

SPECIFIC SCENARIOS FOR INCLUSION OF PEDIATRIC AND ADOLESCENT PATIENTS AND RECOMMENDED TEMPLATE LANGUAGE

There are two specific trial scenarios in which the automatic exclusion of pediatric patients are appropriately challenged. These are early-phase trials that assess dose, safety, and pharmacokinetics in a variety of tumor types and later phase trials that assess efficacy in a specific disease that spans adult and pediatric populations, such as chronic myelogenous leukemia, Philadelphia chromosome–positive acute lymphoblastic leukemia, melanoma, Hodgkin lymphoma, and some sarcomas (Table 1). Recommendations for these scenarios are described in the following sections.

Early-Phase Adult Trials That Assess Dose, Safety, and Pharmacokinetics in a Variety of Tumor Types Should Include Children in Certain Circumstances

Summary. Shared oncogenic pathways or molecular alterations responsible for the etiology of different adult and some pediatric cancers may, depending on the mechanism of drug action, provide a rationale for testing that drug in pediatric patients as early as the phase I stage of testing in adults. Evidence of activity of an investigational drug in one or more pediatric tumor preclinical models could justify early pediatric evaluation, as may activity in adult patients with that same diagnosis or with a disease that shares the same molecular or biologic driver. The driving oncogenic mutation may be appropriately targeted by the same agent, although

Table 1. Possible Diseases That Could Be Studied (nearly) Simultaneously in Children and Adults

Disease	Molecular Target, Driver, or Mutation	Comparisons Between Children and Adults
CML and Ph-positive ALL	*BCR-ABL*	Disease biology is similar, although not identical, between children and adults with CML and Ph-positive ALL. Targeting *BCR-ABL* has been shown to induce remissions in both diseases regardless of patient age.
Ph-like leukemias	Various	Multiple abnormalities have been identified in Ph-like leukemias, many of which are or may be responsive to small-molecule inhibitors currently available, as well as newer targets in development. Examples include JAK, MEK, IL7 receptor, and CSF1.
Acute promyelocytic leukemia	*PML-RAR-α*	Differentiation therapies seem to have similar efficacy and toxicity in children and adults.
FLT3-positive acute myelogenous leukemia	*FLT3* mutation	*FLT3*-targeted agents are effective in inducing remission in children and adults with *FLT3*-positive acute myelogenous leukemia with similar toxicity profiles.
Ewing sarcoma	*EWS-FLI1*	Similar pathology and driving mutation seen across the age spectrum.
Hodgkin Lymphoma	CD30	Similar pathology and activity with anti-CD30 therapies regardless of patient age.
Anaplastic large-cell lymphoma	CD30	Similar pathology and activity with anti-CD30 therapies regardless of patient age.
Melanoma	*BRAF, CTLA-4*	Early evidence is that children with melanoma have a lower incidence of *BRAF* mutations, although they can respond to BRAF inhibitors. Similarly, children with melanoma treated with *CTLA-4*–targeted agents have similar responses and toxicities to adults treated with the same agents.
Neuroblastoma, sarcomas	*NTRK* fusions	Substantial response rates have been noted in early-phase clinical trials targeting *NTRK* fusion regardless of age of patient and histopathologic diagnosis reported.

Abbreviations: ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; Ph, Philadelphia chromosome.

in different tumor types in adults compared with children. Examples of this include an ALK inhibitor that may be used in adults for non–small-cell lung cancer but should be tested in children with ALK-positive anaplastic large-cell lymphoma or neuroblastoma.[11-13]

Recommendation. We recommend that study of a drug in a specific pediatric population could be conducted when there is scientific rationale to suggest that children with a specific diagnosis may benefit and when there is adequate nonclinical or clinical information to sufficiently mitigate patient risk. When such rationale exists, prospective inclusion of a pediatric-specific dose-escalation cohort within a larger adult trial should be considered, with the objectives of defining pediatric dose-limiting toxicities and recommended dose, as well as assessing safety and pharmacokinetics in younger patients. Generally, opening enrollment of a pediatric cohort in the phase I setting should occur when sufficient data in adults exist to guide dosing and toxicity monitoring, perhaps just before any cohort expansion at the recommended phase II dose. Pediatric patients may experience different dose-limiting toxicities and adverse event profiles than adults. Alternatively, a pediatric cohort could be treated as a separate stratum and escalated independently of adults until a dose appropriate for the specific age group is defined.

Younger age groups present additional considerations; therefore, it may be appropriate to use staged enrollment starting with older children once initial adult safety and toxicity data are known. For example, patients age 12 to 17 years could be enrolled first, because they are most likely to be physiologically like adult patients and are expected to tolerate dosing in a similar fashion, and then those age 6 to 11 years could be enrolled, followed by even younger children, as appropriate to the epidemiology of the disease(s) under study. Organ function, maturation of metabolic pathways, and body-surface area all change rapidly over time in young children; however, in many cases, children can receive the same weight-based or body-surface area–based doses as adults.[14]

Younger children may be at risk for developmental toxicities with certain drugs that would not have been identified in adults, but often, the classes of drugs with potential developmental toxicities are identifiable given the specific molecular targets or signaling pathways affected by the drug,[15] and protocols should include a longer period of follow-up to better assess toxicities when possible. Although this is not always easy, it is critical to be able to assess multiple parameters that may differ when newer agents are introduced to children and that may not be evident in adult patients.

Sample template for inclusion criteria.

1. Adolescent/pediatric patients age [*protocol author to insert age minimum and maximum specific to the study under consideration*] will be included after enrollment of adult patients once safety and toxicity have been established. Participating sites will be notified when adolescent/pediatric patient enrollment may begin.
2. Adolescent/pediatric patients age [*protocol author to insert age minimum and maximum specific to the study under consideration*] will be included starting one dose cohort behind the current adult cohort in which there are no dose-limiting toxicities identified. Participating sites will be notified when enrollment to the adolescent/pediatric stratum may begin.
3. Adolescent/pediatric patients age [*protocol author to insert age minimum and maximum specific to the study under consideration*] will be included in age-specific cohorts that will be staggered starting one dose cohort behind the current adult cohort in which there are no dose-limiting toxicities identified.

Participating sites will be notified when each adolescent/pediatric cohort enrollment may begin.

4. Adolescent/pediatric patients age [*protocol author to insert age minimum and maximum specific to the study under consideration*] are included in this trial in a separate cohort that will accrue simultaneously with the adult cohort [*specify age 18 and older or protocol-specific upper age limit*].

Later Stage Trials That Assess Efficacy in a Specific Disease That Spans Adult and Pediatric Populations, Such as Chronic Myelogenous Leukemia, Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia, Melanoma, Hodgkin Lymphoma, and Some Sarcomas, Could Enroll Simultaneously With Adult and Pediatric Cohorts

Summary. Currently, the front-line Children's Oncology Group trials for acute lymphoblastic leukemia include patients up to age 30 years, and some Ewing sarcoma and osteosarcoma trials allow patients up to age 40 or 50 years. These age considerations are made based on the biology of the disease and the age distribution of the patients affected by the diseases. For example, *EWS-FLI1* and related fusions are present in the vast majority of, if not all, Ewing sarcomas.[16-18] As such, an agent targeting *EWS-FLI1* should be tested in patients with that fusion regardless of age if the hypothesis is that disease activity is based on the fusion rather than the age of the patient in which it is tested. Similarly, for the anti-CD30–targeted agents, patients with Hodgkin lymphoma or anaplastic large-cell lymphoma can be tested regardless of age, because the disease spans age ranges but the driving tumor biology is similar.[19-23] Additional examples include the CD19-directed bispecific T-cell engager blinatumomab and the myriad chimeric antigen receptor T-cell therapy trials that have shown both efficacy and similar safety profiles in children and adults with CD19-positive disease, both acute lymphoblastic leukemia and non-Hodgkin lymphoma.[24-32]

Recommendation. We recommend that the age range of patients enrolled onto later phase, disease-specific trials should reflect the age range of patients with that disease. We recommend that late-stage trials for diseases that span the pediatric and adult patient populations routinely include patients 12 years of age and older on the basis of the similarity in drug metabolism and excretion between adults and postpubertal adolescents. Where growth and development could be adversely affected based on nonclinical or early clinical data, a more restrictive age cutoff may be appropriate or more stringent monitoring may be incorporated. In some cases, it may also be appropriate to include patients younger than age 12 years. In essence, the minimum age of eligibility specified in late-phase trials should be tailored to the biology of the disease under study, the scientific objectives of the trial, and the existing data regarding the mechanism of action and safety profile of the drug.

Template for inclusion criteria. Adolescent patients age 12 years and older are allowed with signed assent and parental consent according to institutional guidelines and requirements.

DISCUSSION

Children have historically been excluded from first-in-human studies of promising new cancer drugs and later phase adult clinical trials, even for cancers that occur in both adults and children. Development of new cancer drugs for children leverages discovery and development of drugs for adults with cancer. Thus, clinical trials of novel therapies for children are either delayed or never undertaken, and pediatric patients with cancer can only access these new drugs off-label for which no dosing information is provided. Off-label use eliminates the opportunity to collect data on safe and effective use of drug products in other children who might potentially benefit or be spared from the toxicity of an ineffective drug.

Despite progress in recent years, children with cancer need more timely discovery, access to, and evaluation of new investigational drugs. To spur pediatric drug development, two legislative programs have been implemented in the United States.[33] The Pediatric Research Equity Act (PREA) requires new drug applications and biologics license applications or supplements to applications for an adult indication to contain information from one or more studies for the same indication in pediatric patients, unless the applicant has obtained a waiver or deferral.[34,35] However, PREA does not apply to indications for which a drug has received orphan designation (for indications affecting < 200,000 people per year in the United States). Many cancer types, including those that span adult and pediatric populations, fall below this threshold. Moreover, the most common adult cancers, such as lung, breast, colorectal, and prostate cancer, would not be eligible for orphan designation because they do not occur with any frequency in children and pediatric evaluations; therefore, PREA requirements are waived. For these reasons, there has never been a PREA requirement for pediatric evaluation of a cancer drug. A significant recent advance is that Congress is considering legislation (the Research to Accelerate Cures and Equity for Children Act, H.R. 231/S. 456) that would modify PREA to address these problems. The legislation will apply the PREA requirements to drugs that receive an orphan drug designation and require pediatric testing if the molecular target of the drug is substantively relevant to pediatric cancers.

The United States also provides an incentive for pediatric drug development through the Best Pharmaceuticals for Children Act (BPCA), which allows for 6 months added market exclusivity if specific pediatric research agreed upon by the US Food and Drug Administration (FDA) and drug sponsor is completed.[36] However, even with the incentives of the PREA and BPCA, new strategies to promote and facilitate earlier investigation of oncology drugs in children are needed. Here, we recommend the inclusion of pediatric patients with cancer in adult clinical trials when appropriate. Even with this approach, pediatric-focused clinical trials will continue to be necessary, particularly for cancer types that occur exclusively in pediatric patients.

Although pediatric oncology drug development is complicated by many factors (Table 2), such as the rarity of pediatric cancers and additional ethical considerations and regulations for vulnerable populations, the prevailing pattern of excluding children from adult trials is derived largely from a concern for safety even when there may be reason to believe that an individual child could benefit from an agent being studied in an adult population. Historically, the tendency has been to protect children from research that may carry unknown risks rather than provide the potential for benefit to children through research, which, in some cases, has led to overprotection at the expense of access to a promising agent.

Table 2. Challenges in Pediatric Drug Development

Challenge	Considerations and Suggestions for Improvement
Too many new agents to study within reasonable time frames	• Could the scientific objectives be achieved in any other way that is either more efficient or less restrictive? Novel study design and limited numbers of dose cohorts and patients per cohort can reduce numbers of patients enrolled per study. • Are multiple trials needed if one could suffice? • Consider agents with similar mechanisms of action and ensure that duplicative studies are not being conducted without benefit or advancement of scientific understanding. • Are separate pediatric trials needed? • Consider circumstances or diseases where a new agent could be tested in the front line.
Regulatory restrictions	• Are current incentives for pediatric drug development plans sufficient to motivate sponsors? Could revisions and additional incentivization improve access for children and accelerate development? • Current requirement for individual regulatory approvals by national authorities slows overall approval without generally adding safety protections. Consider better harmonization and/or acceleration of development processes between regulatory agencies to make international clinical trials more efficient • Develop and adopt updated eligibility criteria recommendations such as those contained herein and from other workshop groups for brain metastases, HIV/AIDS, and organ dysfunction. • Cite examples from prior combination studies of children and adults to lessen concerns from sponsors.
Safety and toxicity	• Is patient safety being adequately protected? • Are potential toxicities and mechanisms of action accounted for and followed for the appropriate length of time? • Could postmarketing reporting be extended or altered to accommodate unique mechanisms of action or toxicities? • Does limiting or restricting protocol inclusion and exclusion criteria support or hinder the scientific goal(s) of the study?
Continuing protocol review and analysis on a regular schedule	• Should a protocol be closed as a result of poor accrual, or should inclusion and exclusion criteria be altered (relaxed) as a first step with subsequent reassessments? • On continuing review of protocol, do the scientific and clinical objectives remain relevant? • Can the objectives be met? • Can accrual be completed in a reasonable time frame? • Are corrective action plans needed for slow accrual?

Although the appearance of risk associated with a new drug may be amplified if a child experiences a serious adverse reaction to an investigational drug, we believe this is a perceived risk, rather than a real risk. There is concern among some that a high-profile adverse event in a pediatric patient could jeopardize the development of a new drug, ultimately limiting access to an effective therapy for a broader patient population. However, adverse events in pediatric patients have not impeded development of any oncology drug reviewed at the FDA, given all available evidence to date (G. Reaman, personal communication, May 2016). In fact, the FDA encourages the early design and conduct of pediatric trials with investigational agents or the inclusion of pediatric patients in certain adult clinical trials when appropriate to expedite the development of safe and effective therapies to treat cancer in children.[37]

In the approach we propose here, a serious adverse event in the pediatric population may appropriately interrupt or halt development in that population without impacting drug development in adults unless there is evidence that the safety signal may also apply to adults. Conversely, should pediatric patients tolerate a higher dose than adults, our recommendations will facilitate identification of that scenario and the most appropriate dosing in each patient population.

Not addressed here, but critical to the success of trials spanning a wider age range, are novel clinical trial designs that are more efficient and involve the fewest patients needed to achieve trial goals while simultaneously providing the best patient safety parameters. Indeed, the trial modifications proposed herein could require different analyses by cohort based on such designs.

Discussing reasons for why a pharmaceutical sponsor may choose to include or exclude children in early-phase trials using the recommendations we propose is beyond the scope of this article. The development prioritization for sponsors is typically focused on the most rapid path to approval of an agent that can reach the largest patient population once commercialized. Clearly, the market for pediatric cancers overall is a small one compared with adult oncology indications, and it would be the rare disease or indication that would prove to be commercially successful in children. Dinutuximab for neuroblastoma is a successful example of the use of pediatric disease priority review vouchers as a strategy to increase enrollment onto clinical trials by including the pediatric and adolescent patient populations.[38] Approval of pembrolizumab for solid tumors with a high-level microsatellite instability or mismatch repair deficient biomarker provides an example of trials that enrolled both adult and pediatric patients with a common biomarker.[39] Inclusion of pediatric patients in the trial provided simultaneous approval in adult and pediatric patients, in addition to being the first approval for all solid tumor types.

Children with cancer clearly stand to benefit from earlier investigation of novel agents. Drug sponsors stand to benefit as well. If sufficient numbers of pediatric patients are enrolled, they may provide meaningful information that can lead to early identification of drugs with a strong signal of antitumor activity against one or more cancers in children that should be studied further. An example of the success of early inclusion of pediatric patients was recently presented by Federman et al[40] and Hyman et al[41] and at the 2017 ASCO Annual Meeting. On the basis of early data demonstrating prolonged survival and a favorable adverse effect profile for the drug larotrectinib (a tropomyosin kinase receptor inhibitor) in adults with *NTRK* fusions, a phase I/II study was initiated in children harboring *NTRK* fusions.[40] The adult and pediatric trials were conducted simultaneously. Combined analysis of the trials reported an overall response rate of 78% in 12 unique tumor sites, with efficacy observed in both populations, as well as tolerability.[41] The safety and pharmacokinetic information derived from the study of cancer therapies in pediatric patients enrolled onto adult clinical trials can be used to help fulfill the terms of a Pediatric Written Request and can provide useful information for product labeling. Full adoption of these recommendations will require the engagement of all stakeholders,

including patients and families, investigators, the pharmaceutical industry, regulators, advocacy groups, and the institutional review boards tasked with protecting patient safety. This will be an organic process that requires regular review and revision within the context of the rapidly evolving drug development environment.

Finally, because clinical trials are increasingly being conducted globally, engagement of and coordination with international regulatory authorities will be necessary to assist sponsors in developing strategies that meet regulatory requirements within and outside the United States. Deeper and more frequent international collaborations, harmonization of regulatory processes where appropriate, and support and continued cooperation and advocacy from all stakeholders will be required.

CONCLUSION

Automatic inclusion of pediatric patients is appropriate in early-phase trials that assess dose, safety, and pharmacokinetics in a variety of tumor types and in later phase trials that assess efficacy in a specific disease that spans adult and pediatric populations. Sponsors, treating institutions, and funding agencies will be tasked with the duty of addressing the logistical processes and procedural hurdles to accommodate the inclusion of younger patients in clinically and scientifically appropriate clinical trials without jeopardizing the trial conduct. We must continue to work collaboratively to enhance the value of each trial conducted, because rapid technologic advances continue to outpace our current trial structure and capacities, and ultimately to improve the landscape for the patients who need new treatments the most. With continued communication, understanding, and collaboration among all stakeholders and the ability to study diseases and outcomes of treatment more carefully, pediatric patients with cancer can fully benefit from the great strides currently being made to conquer cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Modernizing Clinical Trial Eligibility: Recommendations of the American Society of Clinical Oncology–Friends of Cancer Research Minimum Age Working Group

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FRIENDS of CANCER RESEARCH

A Friends of Cancer Research White Paper

ENHANCING INFORMATION ABOUT OLDER PRESCRIPTION DRUGS

CAN DRUG LABELING BE MODERNIZED?

INTRODUCTION

This white paper presents a policy proposal designed to enhance the quality and utility of information about older prescription drugs. The proposal outlined below is a "straw man" intended to generate discussion and foster creative solutions rather than assert any definitive answer to the problem of outdated prescription drug information. To that end, this white paper describes a potential pathway to bring labeling in line with high quality, real-world practice. However, it is widely known that, today, labeling is not the only, or most frequently used, source of up-to-date information used by practitioners. Therefore, this paper also presents a series of additional considerations for policymakers to contemplate. The scope of this proposal extends to older drugs, both brand and generic, that are 15 years past initial approval that have outdated labeling, either due to the absence of critical information about drug safety or effectiveness or the presence of inaccurate prescribing instructions.

An effort to modernize information about older prescription drugs can have a number of benefits. First, it can correct inaccurate information that is currently contained on some product labels, thereby averting a public health hazard. Second, it can enhance the dissemination of high quality information about approved drugs and lead to greater confidence in the use of drugs for indications beyond those that were initially approved. Third, it can remove an impediment to reimbursement in certain disease settings where labeling is currently used to guide payment decisions. And finally, it can establish greater clarity around the use of real-world evidence (RWE) to inform regulatory decision-making.

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ABOUT FRIENDS OF CANCER RESEARCH

Friends of Cancer Research drives collaboration among partners from every healthcare sector to power advances in science, policy, and regulation that speed life-saving treatments to patients.

BACKGROUND ON PRESCRIPTION DRUG LABELING

A prescription drug product's labeling (also known as the "professional labeling" or "package insert") is a compilation of information about the drug product that is written for a health care practitioner audience.[1] Federal regulations state that labeling must contain "a summary of the essential scientific information needed for the safe and effective use of the drug," and that it must be "informative and accurate."[2] The content of labeling is written by drug manufacturers, but must be approved by the Food and Drug Administration (FDA) to ensure that it meets standards laid out in regulations.[3]

Under the 1984 Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act (FDCA), generic drug labeling necessarily relies on the brand name drug labeling as a matter of product approval. The Hatch-Waxman Amendments established the modern generic drug industry and required "sameness" for generics with the brand-name drug counterpart in all material respects. The statute mandates that generic drug products have the same active ingredients, strength, dosage, indications, and safety labeling as the reference drug. In fact, the Hatch-Waxman statute's whole premise is that generic drugs are materially indistinguishable from their brand-name counterparts, and so naturally must bear labeling that "is the same as the labeling approved for the [brand-name] drug" on which the generic product's approval is based.[4] In enacting the Hatch-Waxman Amendments, Congress provided that FDA cannot approve an abbreviated new drug application (ANDA) if, with certain exceptions not relevant to this paper (e.g., patent carve-outs), the labeling proposed for the generic drug is not the same as the labeling approved for the listed drug.[5] Those requirements subsequently were incorporated into FDA's regulations.[6]

When it is kept up to date, labeling represents the most authoritative drug-related information that is available to prescribers. However, for both brand name as well as generic drugs, labeling often falls out of date when new information emerges in the post-market setting. When sections of FDA-approved labeling become outdated they may lose value for prescribers and fail to communicate essential information about drugs to patients and physicians. In such cases, and even if labeling is kept up to date, prescribers routinely use other information such as peer-reviewed treatment guidelines in making decisions for patients.

Older drugs may be particularly susceptible to outdated product labeling, especially with regard to the "effectiveness" portions of labeling, including information relating to dosage and clinical studies. Both brand name and generic drug companies have an ongoing responsibility to report safety information to FDA, and the Agency has the authority to order changes relating to new safety information for both brand name and generic drugs.[7] Manufacturers of products that will soon lose or have already lost marketing exclusivity or patent protection often lack an incentive to maintain up-to-date labeling actively. In some cases, brand name manufacturers of older drugs will voluntarily withdraw their products from the market, leaving only generic manufacturers (if generic versions of the drug exist) to maintain labeling. However, some parts of

FDA-approved labeling routinely fall out of date even when products are still being actively marketed by the innovator company. The result is that most older drugs have aspects of FDA-approved labeling that need to be modernized to prevent the dissemination of incorrect information and to enable the communication of information pertinent to safe and effective prescribing.

BACKGROUND ON ADDITIONAL SOURCES OF INFORMATION USED BY PRACTITIONERS

It is important to acknowledge that there are many sources of information about medicines upon which prescribers routinely rely for patient care, especially for oncology drugs. Especially once drugs have been on the market for longer periods of time, prescribers turn to high quality sources of evidence beyond the FDA-approved labeling. These sources include:

- **Clinical practice guidelines and compendia.** Specialty societies and evidence-based practice organizations synthesize uses of drugs in areas such as oncology where therapies change rapidly. For example, the development of the National Comprehensive Cancer Network (NCCN) Guidelines "is an ongoing and iterative process, which is based on a critical review of the best available evidence and derivation of recommendations by a multidisciplinary panel of experts in the field of cancer."[8] According to NCCN, "Because new data are published continuously, it is essential that the NCCN Guidelines also be continuously updated and revised to reflect new data and clinical information that may add to or alter current clinical practice standards."[9]

- **Peer-reviewed medical journal articles.** In recognition of their potential public health value to prescribers, FDA has promulgated guidance on manufacturer dissemination of peer-reviewed medical journal articles.[10]

- **Real world evidence.** FDA has recently noted that "[t]he incorporation of 'real-world evidence'—that is, evidence derived from data gathered from actual patient experiences, in all their diversity— in many ways represents an important step toward a fundamentally better understanding of states of disease and health."[11]

Thus, aside from FDA-approved labeling, there are other sources of information that aid prescribers in making evidence-based treatment decisions.

SCOPE OF THIS WHITE PAPER

The proposal outlined in this white paper is intended to facilitate practitioner access to enhanced information about drugs initially approved at least 15 years ago (referred to as "older drugs" in this paper). The proposal is intended to apply to the following scenarios involving these older drugs:

1. The NDA for an older drug is still active but the drug's labeling is missing critical information about drug safety or effectiveness or contains incorrect prescribing instructions.

2. The NDA for an older drug has been withdrawn or discontinued for reasons other than safety or effectiveness.

WHY LABELING FALLS OUT-OF-DATE

Given the speed with which new, clinically-relevant information emerges in the post-market setting, it is impossible for approved labeling to be perfectly aligned with high quality real-world practice. However, there are many circumstances in which information that is essential to the safe and effective use of prescription drugs remains absent from labeling years after that information has been identified. Some of the reasons for why labeling may fall out of date are listed below.

- **Sponsor-initiated labeling updates.** With the exception of certain safety updates that the FDA can require manufacturers to make under the Food and Drug Administration Amendments Act of 2007 (FDAAA),[12] many types of labeling changes are made at a drug manufacturer's discretion. For example, new indications are generally added to labeling only if a drug manufacturer decides to pursue marketing authorization in a new treatment setting.[13] Factors such as the cost of preparing supplemental applications and the presence of generic competition may erode incentives for manufacturers to update labeling in a proactive manner.

- **Perceptions about the quality of post-market evidence.** The source of new evidence about a drug will often predict whether a drug manufacturer will submit a supplement to incorporate that evidence into labeling. Studies in the published literature to which a drug manufacturer does not have a right of reference, rather than manufacturer-sponsored studies, may serve as evidence supporting an application. However, there may be concerns that the quality of evidence from the literature is not high enough to support marketing approval. The regulatory standard for approval is the same for new drug applications and supplements.

- **Healthcare providers obtain information from other high-quality sources.** As discussed previously, there is a recognition by some practitioners that there may be other sources of information that synthesize clinical data, such as peer reviewed literature and practice guidelines, that are outside of FDA-approved labeling.

- **Withdrawal or discontinuation of a New Drug Application.** A brand name drug's manufacturer may withdraw a drug from the market if the cost of continued expenditures is not financially sound or consistent with corporate responsibility. When a drug has been withdrawn, its manufacturer is no longer involved in maintaining product labeling. Such withdrawals often take place if a drug has lost significant market share to generic competitors. The FDA will allow generic versions of a withdrawn drug to continue to be marketed if the agency finds that the drug was not withdrawn for reasons of safety or effectiveness.[14] Confusion then arises over how generic versions of a withdrawn drug can maintain updated labeling, given the statutory requirement that a generic product must have the "same" labeling as the generic's reference listed drug (RLD).[15]

- **Compendia-based reimbursement.** A Medicare policy dating back to 1993 permits reimbursement of an off-label use of a cancer drug if that use is deemed medically accepted by one or more federally-designated compendia.[16] Unlike many other conditions, where reimbursement is closely tied to approved labeling, special accommodation was made in oncology due to the severity of the disease, the time-sensitive nature of treatment decisions, and the fact that many anti-cancer agents have activity in multiple cancer types, but may only be approved for a portion.[17] The resulting compendia-based reimbursement paradigm in oncology has enabled Medicare coverage of drugs for indications separate from their initial FDA approval. This program circumvents regulatory delays and drug manufacturer inaction to optimize patient access to cancer care. However, some have raised concerns that the current reimbursement scheme in oncology has caused an increase in the amount of uncertainty about the evidence supporting drug use generally, due to a lack of transparency and consistency among compendia.[18, 19]

THE PUBLIC HEALTH IMPACT OF OUTDATED LABELING

Maintaining authoritative sources of information about prescription drugs, including FDA-approved labeling, is an important public health objective. When such labeling becomes outdated it loses its value for prescribers and inhibits the FDA's ability to validate accurate and reliable information about drugs to patients and physicians and may serve as the conduit of incorrect information.

- **Outdated labeling prevents important information from reaching prescribers.** Labeling is the FDA's primary means of validating information about drugs, and in some cases, it is updated with new urgent information about drug safety. Due to perceptions that labeling is outdated, prescribers may fail to consult labeling, missing important updates such as black box warnings. This was seen in the case of cisapride, a drug used to treat symptoms of nighttime heartburn, when a revised label warning of life-threatening adverse events did not change prescribing behavior.[20] If such information is not gleaned in FDA-approved labeling, it is important for other sources of information to capture it.

- **Outdated labeling contributes to the dissemination of incorrect information.** The information contained in approved labeling is ingrained into medical decision-making: it frequently informs clinical practice guidelines, payment decisions, decision support in electronic health records, and physician teaching materials. The failure to maintain accurate labeling may result in the spread of such information to other decision-making resources.

- **Outdated labeling may decrease reliance on high quality information.** As labeling falls out of date, its status as a useful resource may decline, causing prescribers to rely instead on other sources of information. Over-reliance on sources other than labeling, such as compendia, may result in misplaced confidence in some off-label uses. While compendia recommend many strongly-supported uses of drugs, they have also been shown to recommend uses that are supported by far less rigorous evidence.[21]

- **Outdated labeling hinders communication of combination and repurposed products.** Many older drug products whose labeling has fallen out of date are part of combination regimens with newer agents. The inclusion of a combination therapy on one product's label but not another's may lead to prescriber confusion. Similarly, there is a low likelihood that repurposed uses of older drugs will be incorporated onto product labeling.

- **The number of drugs with outdated labeling will increase in coming years.** The number of drugs with outdated labeling will likely increase as manufacturers choose to voluntarily withdraw their products from the market. In many cases, generic versions of those drugs remain available, leading to confusion over how to maintain up-to-date labeling in the absence of a reference listed drug. As of 2013, there were over 430 cases of approved drugs for which no brand-name product remains on the market.[22]

CURRENT REGULATORY PATHWAYS TO UPDATE LABELING

The following section outlines current regulatory pathways for drug manufacturers to update product labeling after a product has been approved.

Prior Approval Supplements[23]
Innovator drug manufacturers seeking to make a change to product labeling for their own approved drug must submit a supplemental new drug application (sNDA) to the FDA. A sNDA can come in the form of a Prior Approval Supplement (PAS) or a Changes Being Effected (CBE) supplement. The type of supplement that should be submitted depends on the magnitude of the intended labeling change. The FDA defines a "major" change as one "that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product." The Agency defines a "moderate" change as one that has "a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product."

- **Major changes to labeling are required to be submitted to the FDA through a PAS.** The FDA must review the changes requested in a PAS before the applicant can implement the requested changes. The following changes to labeling are considered major changes: the addition of new indications; the addition of clinical pharmacology data; the addition of pharmacoeconomic claims; or the addition of claims of superiority to another drug product.

- **Moderate changes to labeling are required to be submitted to the FDA through a CBE supplement.** Unlike a PAS, a CBE supplement does not require prior approval from the FDA before a change can be implemented. Moderate changes to labeling that may be submitted through a CBE include: the addition of an adverse event; the addition of a precaution arising out of a post-marketing study; or the clarification of the administration statement to ensure proper administration of the drug product.

The 505(b)(2) Pathway–"Literature-based" 505(b)(2)s
A 505(b)(2) application is a type of new drug application "where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference."[24] Both innovator and generic companies can avail themselves of this type of application. The 505(b)(2) pathway originated in the 1984 Hatch-Waxman Amendments, which also created the 505(j) pathway for ANDAs. The central component of the 505(b)(2) pathway is that it permits the FDA to rely for approval of an NDA on data not developed by the applicant. This is in direct contrast to the traditional 505(b)(1) pathway, which is used by manufacturers that have full right of reference to the underlying data in the application.

In some cases, a manufacturer can add new information to product labeling by submitting a 505(b)(2) new drug application. The manufacturer can do this by submitting a "literature-based 505(b)(2)," which relies in part on clinical evidence from published literature to which the manufacturer does not have a right of reference. A manufacturer may submit a literature-based 505(b)(2) to support a number of aspects of the application, including any of the following: a new dosing regimen, a new combination product, or a new indication for a previously approved drug. In the same manner, a generic drug applicant can add information to its labeling by submitting a 505(b)(2) supplement to its ANDA.

LIMITATIONS OF EXISTING PATHWAYS

Despite the mechanisms that currently exist for drug manufacturers to revise product labeling, sponsors do not always keep the labeling for many drugs up to date. In particular, existing pathways rely on sponsors to incorporate new information onto the labeling of older products, but those sponsors have either lost interest in maintaining product labeling or have exited the market altogether.

- **Current pathways may be too resource intensive for sponsors of older drug products.** Sponsors of older drug products who lack incentives to update labeling may view existing pathways to update labeling as too burdensome to warrant expenditure of the substantial resources needed to submit supplements.

- **Published literature is rarely used to support new drug applications.** The 505(b)(2) pathway exists to allow manufacturers to add indications and other information to product labels using published literature. However, it is rarely used; a recent study found that approximately 3% of 505(b)(2) applications are literature based.[25]

- **No clear pathway exists to update the labeling of drugs with withdrawn NDAs.** When a drug product has been withdrawn, the product's manufacturer no longer has any mechanism for maintaining product labeling. Generic products relying for approval on an NDA that has been withdrawn are generally required under current law to have the same labeling as the reference product, despite the fact that the reference product's labeling has become static. In many cases, no clear pathway exists for these generic products to undergo the steps necessary to bring their labeling up to date. While the 505(b)(2) pathway is available to generic applicants it may be outside of their business model and come with additional responsibilities that are unpalatable.

PROPOSED APPROACH TO UPDATE LABELING

The following proposal seeks to facilitate timely labeling updates by lowering the barriers to supplemental new drug applications. Since one of the primary reasons labeling becomes outdated is limited incentives for manufacturers to update labels once innovator exclusivity either has expired or is close to expiring, this proposal seeks to provide manufacturers with the raw materials to submit supplemental applications and thereby make the submission of such applications less burdensome. In addition, this proposal provides a novel method of enabling generic manufacturers to update product labeling in cases where the brand name reference listed drug that the generic product relies upon has been withdrawn from the market. In such circumstances, it is essential that FDA manage the review of new clinical data and maintain the sameness requirement, whereby all generic labeling changes at once after an FDA order.

STEP 1
FDA IDENTIFIES PRODUCTS THAT MAY HAVE OUTDATED LABELS

The FDA may identify one or more drug products whose labeling is missing critical information about drug safety or effectiveness or includes outmoded prescribing instructions.

STEP 2:
SPONSOR AGREEMENT

The FDA will notify the sponsor(s) of drugs identified in Step 1 and proceed if agreement to pursue revised labeling is obtained. Where drugs identified in Step 1 have an active or discontinued NDA, the sponsor referred to in this step is the holder of the RLD NDA; where the RLD has been withdrawn, the sponsor(s) referred to in this step is/are one or more ANDA holder(s).

STEP 3:
FDA WORKS WITH STAKEHOLDERS TO REVIEW AVAILABLE POST-MARKET EVIDENCE

The FDA may enter into cooperative agreements or contracts with private entities to review the available evidence concerning drugs identified in Step 1. The Agency may seek public input concerning such evidence (including, as determined appropriate by the Secretary, holding public meetings), and should seek input from each sponsor of the approved application for such drug.

STEP 4:
FDA DETERMINES WHETHER AVAILABLE EVIDENCE MEETS EXISTING STANDARDS

The FDA may determine, with respect to a drug identified in Step 1, whether the evidence reviewed in Step 3 is sufficient to meet existing regulatory standards for revising the labeling of the drug.

STEP 5:
INITIATION OF UPDATE PROCESS PER FEDERAL REGISTER NOTICE OR OTHER COMMUNICATION

The FDA publishes a Federal Register notice or other communication that:

- Summarizes the findings supporting the determination of the Agency that the available evidence is sufficient to meet the standards under section 505 of the FDCA for amending the labeling of the drug as an additional indication for the drug;
- States the modifications to the labeling that should be made;
- Describes the process under Step 6 for approving modifications to the labeling of the drug.

STEP 6:
SUBMISSION OF SUPPLEMENTAL DRUG APPLICATION PER FEDERAL REGISTER NOTICE OR OTHER COMMUNICATION

The sponsor of a selected drug in Step 1 may submit a supplemental application to the FDA that includes a statement that such application is submitted in response to a notice referred to in Step 5; and which also states that it seeks to modify the labeling of the drug in accordance with the statement of the FDA in the relevant notice. The following three scenarios involving supplemental applications are envisioned:

❶ If the NDA for a drug identified in Step 1 has not been withdrawn and the manufacturing of such drug has not been discontinued, a supplemental new drug application may be submitted by the holder of the NDA.

❷ If the NDA for a drug identified in Step 1 has not been withdrawn, but the manufacturing of such drug has been discontinued for other than safety or effectiveness reasons, a supplemental new drug application may be submitted by the holder of the NDA.

❸ If the NDA for a drug identified in Step 1 has been withdrawn for other than safety or effectiveness reasons, a supplemental new drug application may be submitted under Section 505(b)(2) by the sponsor of a generic version of such drug. Following the submission of the supplement, the FDA would request that any other generic products relying on the same withdrawn RLD amend their labeling to conform to the changes made in supplement.

CONSIDERATIONS FOR POLICYMAKERS

As mentioned in the introduction to this white paper, the proposal outlined in this document is intended to serve as a "straw man" to generate discussion around the topic of outdated labeling. There are existing unanswered questions regarding the proposal, which policymakers should contemplate moving forward.

- **Avoid undercutting the current sNDA process.** How can a program to facilitate updated product labeling avoid the unintended consequence of undercutting the current sNDA process? In other words, if the FDA facilitates labeling updates for certain older drugs, will it lower the incentive for manufactures of newer products to submit labeling updates through sNDAs?
- **Decrease the regulatory burdens for sponsors to participate in labeling updates.** To what degree would the sponsors of brand name drugs nearing the end of exclusivity or generic drugs be willing to submit supplements to update product labeling? What impediments exist? Could a new incentive structure for supplements remove these impediments?

- **Establish guardrails to protect reimbursement of off-label use.** In order to be successful, a program to update outdated labeling will need to avoid the unintended consequence of motivating payers to end compendia-based reimbursement. What guardrails can be established to safeguard the payment of off-label use?

- **Maintain the same labeling for the RLD and all versions of the generic drug.** The Hatch-Waxman Amendments require the labeling of all generic drugs to be the same as the RLD. How will FDA ensure that the RLD and all versions of the generic drug remain the same at all times in order to avoid prescriber confusion?

- **Consideration of additional policy options.** In the event that the proposal outlined in this white paper is infeasible, alternative policy proposals need to be developed. In addition to labeling updates, FDA could partner with evidence-based practitioner groups and medical journals to serve as a consolidator and validator of high quality clinical trials and real-world evidence. This would allow the FDA to evaluate clinical evidence in cases where sponsors choose not to update the non-safety portions of the labeling. Policymakers could also consider options to allow the FDA to publish, through the Federal Register or otherwise, corrections to outdated labeling that could then be communicated directly to clinicians.

APPENDIX
OUTDATED LABELING CASE STUDY: CISPLATIN

Cisplatin is a platinum-based chemotherapy originally approved in 1978. It is now off patent and is marketed widely by a number of separate generic manufacturers. The new drug application (NDA) for the reference listed drug (RLD) has been discontinued. As a result, generic cisplatin, which is used in dozens of treatment regimens for both solid tumors and hematologic malignancies, has outdated labeling that is unlikely to be revised. A comparison of the current labeling for generic cisplatin and recommended preferred uses in clinical practice guidelines highlights the divergence between current labeling and real-world practice.

Appendix Figure 1. Comparison of Most Recent Cisplatin Labeling and NCCN Category 1 Uses of Cisplatin

Tumor setting	FDA-Approved Uses on Labeling	NCCN-Recommended Preferred Category 1 Uses	Number of NCCN Preferred Category 1 Uses
Bladder	✓	✓	5
Bone		✓	1
Cervical		✓	3
Esophageal and Esophagogastric Junction		✓	6
Gastric		✓	4
Head and Neck		✓	31
Hepatobiliary		✓	3
Malignant Pleural Mesothelioma		✓	3
NSCLC		✓	3
Ovarian	✓	✓	1
Small Cell Lung Cancer		✓	1
Testicular	✓	✓	5
Sources FDA-approved labeling for cisplatin available on FDA's website, ANDA: 018057; Company: HQ SPCLT PHARMA; Link: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/018057s079lbl.pdf. NCCN Drugs and Biologics Compendium, entry for cisplatin.			

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FRIENDS of CANCER RESEARCH

A Friends of Cancer Research White Paper

DATA GENERATION TO SUPPORT CROSS-LABELING OF INDICATIONS FOR COMBINATION PRODUCTS

INTRODUCTION

The field of oncology is increasingly shifting from use of single agent, broad spectrum chemotherapies to more targeted treatments that can require combination strategies to overcome redundant and evolving oncogenic pathways in cancers. This is particularly common for hematologic cancers such as multiple myeloma and non-Hodgkin's lymphoma where combination therapies are quickly becoming the standard of care and extending patients' lives. Yet, as two-drug combinations replace monotherapies as standard of care, combination regimens that include 3 or more drugs and novel-novel drug combinations are already being developed. Continued progress in this area will require parallel advances in both clinical and regulatory science.

Traditional clinical trials often utilize factorial study designs to identify the contributions of individual drugs in a combination with a high level of rigor and statistical power. In cases where a new combination includes an approved monotherapy, the traditional approach may result in inclusion of irrelevant, and sometimes unethical, trial arms and repetitive data generation. For example, when a monotherapy is being tested in combination with standard of care (SOC), only the trial arms that assessed the SOC and SOC + monotherapy would be relevant, not the monotherapy alone. Risk/benefit approaches which utilize available knowledge regarding approved oncology treatments, including toxicology, mechanism of action, and efficacy of monotherapies, will be needed to enable greater flexibility of clinical trials designed to extract adequate safety and efficacy data without impeding development. Streamlined approaches to clinical trials (see Appendix, Table 1) will become increasingly important as combination therapies evolve from double and triple combinations to include quadruplet, or larger, combinations.

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ABOUT FRIENDS OF CANCER RESEARCH

Friends of Cancer Research drives collaboration among partners from every healthcare sector to power advances in science, policy, and regulation that speed life-saving treatments to patients.

As oncology shifts to large combination therapies some uncertainty regarding the regulatory and legal implications of cross-labeling (listing of information regarding a new combination therapy on labels of all treatments included in a combination) and public health have been created. The composition of a combination therapy often includes monotherapies developed by different sponsors, sometimes with active market exclusivity or patent protection, which contribute to disparity in cross-labeling for drugs used in combinations. Although labels are not the only source of prescribing information used by physicians, inadequate cross-labeling may limit sharing of product information with patients and providers, potentially affecting patient care. Clarity in cross-labeling guidelines, which support maintenance of up-to-date labels for combination therapies and enhance information sharing on safety and effectiveness, will better promote appropriate use of the most effective combination therapies. More robust development of combination therapies can be achieved by updating regulatory pathways to address the challenges presented by cross-labeling.

The objective of this whitepaper is to develop a framework that will help inform the level of evidence to consider for combination therapies, alternative trial designs to generate that data, and suggest regulatory modifications to better facilitate up-to-date labeling of combination therapies without compromising FDA standards that protect the safety of patients. The framework will help trial sponsors to streamline clinical trials that more efficiently identify the contribution of each drug in a combination while minimizing redundancy of data generation and the number of patients required for enrollment in new clinical trials. The whitepaper will also discuss approaches in which streamlined trial designs can be used to provide evidence of contribution for each agent in a combination therapy that supports cross-labeling. Combinations of approved therapies, but not fixed-dose combination drugs which are regulated under a different framework,[1] indicated for hematologic cancers will serve as case studies to inform the framework development with the intent to direct future expansion of guidance to address other cancer types and novel-novel drug combinations. Further, it will be discussed how the proposed framework can generate the necessary evidence needed for cross-labeling and regulatory and legal challenges associated with cross-labeling.

CLINICAL TRIAL DESIGN

With greater number of and more diverse components incorporated into combination therapies, traditional clinical trials will require increasingly complex designs to accommodate more trial arms and accrual of an extensive number of patients. Trial sponsors and regulators, alike, will need to balance the level of evidence needed for approval with the speed of development to maintain equipoise. This is particularly important for therapies which benefit from the breakthrough therapy designation and accelerated approval where expedited approval is meant to enhance patient access. Innovative methods for assessing contribution of components in combination therapies are necessary to facilitate expedited approval.

Innovation in clinical trial design in oncology/hematology, especially in early stages of product development (e.g., I-SPY, BATTLE) has led to more adaptive trials that minimize redundant and expensive data collection while maintaining statistical rigor. These models have enabled sponsors to tease out contribution of therapies in a combination while avoiding large randomized trials, which can lead to a shortened development process and reduced number of patient accruals. Regulatory agency and stakeholder emphasis on collaboration and shared data collection between sponsors of clinical trials could considerably advance these goals. Further, FDA guidance "Adaptive Design Clinical Trials for Drugs and Biologics" specifically highlighted that there can be multiple prespecified timepoints within a clinical trial to evaluate the contribution of a drug such that the development pathway can be streamlined without requiring a factorial trial.[2] This will be particularly beneficial in immuno-oncology, where unique development challenges associated with kinetics of response and the types and timing of associated toxicity are often encountered. Add-on trials can also be a more efficient method to identify contribution while allowing quick advancement to phase III clinical trials. This, however, is dependent upon prior agreement of appropriate endpoints, inclusion of a heterogeneous population, and pre-specified level of evidence to support clinical trial flexibility. As the mechanism of action for immuno-oncology therapies is more thoroughly elucidated, a more adaptive framework will be possible that will better facilitate clinical trial design.

Another important consideration for clinical trial design is to minimize redundancy in data generation. Streamlined trial designs such as single arm trials have already been employed to expedite monotherapy development for cancer. Of the thirty most recent oncology therapies to receive accelerated approval, nineteen were based on results from single arm trials. This approach should be used prospectively to streamline the clinical trial process of combinations therapies as well.[3] Depending upon the potential risk/benefits and pharmacologic understanding of a new therapy, use of historical data is often an appropriate replacement for an active control arm in support of a combination therapy, particularly when evaluating non-inferiority in response rate of a new treatment or for applying inclusion/exclusion criteria based upon patient level demographics and risk factors to the single arm trial. For example, daratumumab was approved in 2016 for combination with pomalidomide and dexamethasone in multiple myeloma using only a single arm trial after the FDA determined that a previous randomized trial for pomalidomide and dexamethasone combination could appropriately be used as a control for the three-drug combination study. When such data exist, sponsors should consider use of historical data as the control in a n+1 trial or for trial designs including adaptive, umbrella, basket, or common control trials. Another opportunity to generate data without impacting clinical trial size or complexity is to use sources of real-world evidence, such as the American Society of Clinical Oncologist's CancerLinQ. Provided that adequate standards are established for quality of data and guidelines formed for collection, real-world evidence can enhance, although not replace, safety and efficacy data. Last, surrogate endpoints offer an accepted mechanism to reduce the length of clinical trials necessary for approval. Overall survival is the typical endpoint assessed in clinical trials for oncology despite that many novel therapeutics extending overall survival up to years beyond previous therapies, making it a difficult endpoint to measure. Surrogate endpoints such as response rate and progression free survival offer opportunities to balance evidence gathered in clinical trials with access to new therapeutics. Increasingly complicated combination therapies will benefit from consideration of appropriate endpoints that promote streamlined data collection.

Box 1: Select Master Protocols in Cancer

Innovative trials that established the "proof of concept" for adaptive trial designs such as umbrella and basket trials include the Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) program, the Lung Master Protocol (LUNG-MAP), and National Cancer Institute-Molecular Analysis for Therapy Choice (MATCH) Trial.[4] Neither BATTLE nor MATCH were developed with the intention of, nor did they lead to, a pharmaceutical registration, however, the proof of concept realized by completion of these groundbreaking approaches to clinical trials can be leveraged to translate to pivotal studies.

The **BATTLE program** was an umbrella trial that used adaptive randomization to assign patients with a single cancer type, advanced non-small cell lung cancer, to a trial arm for a targeted therapy based upon the presence of one of several tumor biomarkers detected by real-time biopsies. Completion of the BATTLE program signaled a pivotal shift to innovation in streamlining clinical trials.

LUNG-MAP is another umbrella trial that has harnessed the power of innovative designs to minimize patient screening and accruals for trials in advanced squamous cell lung cancer. Similar to BATTLE, LUNG-MAP assigns patients to trial arms based upon tumor biomarkers, but the trial arms in LUNG-MAP are more diverse, including drugs sponsored by different manufacturers or an immunotherapy for patients with unmatched tumor biomarkers. LUNG-MAP establishes a master protocol for phase 2-3 clinical trials that assigns all patients to a treatment and minimizes patient attrition at screening with the intention of supporting drug approval.

NCI-MATCH is an example of a pioneering basket trial, which studied targeted therapies in patients with specific biomarkers, whose cancers have progressed or did not respond to standard therapies. MATCH streamlined clinical trials by assessing treatment efficacy in patients with diverse cancer types that shared a biomarker in a single trial.

A NOTE OF CAUTION

A different dynamic is created in the clinical trial process as increasing numbers and complexity of combination therapies affect the extent of innovation achievable. Clinical trials can become consistently complex as combinations grow in number of components, making assessment of the independent value and side effects associated with additional components more difficult. The particular components and level of available information concerning those additions to a combination can also exacerbate an already complicated clinical trial. For components where the science and biology of a therapy is less well understood, as in novel or immunomodulatory therapies, different levels of data are needed to assess each component. Specifically, the unique challenges and unexpected drug interactions possible with use of immunomodulatory therapies in combinations require added caution. Accelerated development and innovation should be balanced with caution when considering these combinations, particularly in immune suppressed populations.

LABELING FRAMEWORK

Streamlining trials for combination therapies while still capturing necessary contributions of components to inform labeling is vitally important. However, beyond data collection, marketing exclusivity, patent life, and labeling updates should also be considered especially when combination therapies may involve drugs from different sponsors. Gaps in regulatory policy and uncertainty regarding legal implications have likely contributed to multiple practices for cross-labeling when approval of new combinations expands indications of an existing approved drug. Although labels do not comprise the sole source of information for physician prescribing, there is a potential that the resulting label disparities may cause uncertainty among patients and physicians about to find up-to-date safety and efficacy. Ultimately, this raises concern that some patients may not receive the most efficacious or safe treatment available. Regulatory requirements already mandate that a sponsor must update a label when it becomes inaccurate, false, or misleading but a framework that outlines the scenarios when cross-labeling may be appropriate is necessary to better promote consistency of labels in representation of new safety and efficacy information and ensure patient access. For example, the combination of Revlimid, Velcade, and dexamethasone was shown clinically superior to a combination of only Velcade and dexamethasone but the indication for Revlimid, Velcade, and dexamethasone is listed only on the label for Revlimid[5]. A provider or patient who searched only the Velcade or dexamethasone label could potentially miss information concerning a more efficacious treatment. Consistent representation of safety and effectiveness on all labels could ensure practitioners can locate relevant information and bolster optimal patient care.

In the interest of public health, a successful framework development will require regulators to consider the various stakeholders and scenarios in which labeling guidelines apply. Specifically, reasons for updating a label may include an effort to effectively communicate up-to-date information for patient care, expand the label's indications for marketing purposes, update the label with new safety information, or to ensure global access to the combination therapy in countries where the initial product label is used as the basis for coverage determinations. Guidance will need to consider the motivation of stakeholders when clarifying the regulatory process to encourage maintenance of comprehensive labels and incentivize innovation with combinations, particularly when incorporating approved monotherapies.

A well-defined framework for labeling combination therapies must address standards for the type and level of evidence necessary to contribute to a label. Specifically, what level of evidence will be sufficient to support a label change when, as for expedited regulatory pathways, the precise contribution of components may not be as thoroughly dissected. Different levels of evidence may be required to support label changes depending on the type of change specified and should be considered in a framework guidance.

Finally, additional legal and regulatory issues associated with cross-labeling need to be addressed. Currently, a drug's sponsor is responsible for maintenance of and updating the drug label; however, the drug sponsor may not necessarily have access to the proprietary data generated from a combination trial which would support a label change. In the event where a clinical trial is conducted by an entity other than the drug sponsor, the mechanism to obtain a right to reference proprietary data and update a label may be cumbersome and pose a disincentive to the drug sponsor. A framework to streamline this process may, at least in part, address some barriers to cross-labeling and encourage maintenance of up-to-date labels for combination therapies. Further, there are instances where the holder of an approved new drug application (NDA) ceases to manufacture a drug and withdraws the NDA, leaving only the generic manufacturer(s) on the market with no legislative language or legal precedent to clarify the entity responsible to update the label. The FDA has issued draft ANDA Labeling Guidance to provide insights on some circumstances where ANDA holders can update labeling[6]. In cases that are not addressed by the draft guidance, incentives to encourage the NDA holder to continue manufacturing the drug or to maintain an up-to-date label despite cessation of manufacturing may be helpful. Alternatively, a new mechanism to allow FDA or a generic drug manufacturer to update a label may be necessary.

Numerous examples of combination therapies for hematologic cancers can be found where disparity in labels exists, highlighting the need for a labeling framework. Darzalex (Janssen Biotech), a monotherapy for multiple myeloma with accelerated approval, received approval in 2016 for two new indications in multiple myeloma. These included combinations with Revlimid (Celgene) and dexamethasone and combination with Velcade (Millennium) and dexamethasone. The new indications are listed only on the Darzalex label. Further, Elotuzumab (PDL Biopharma) received its first NDA for multiple myeloma in combination with Revlimid and dexamethasone. Similar to Darzalex, the indication is listed only on the label of the new molecular entity. For each of these examples, a regulatory framework which accounted for various stakeholder incentives and standards for supporting evidence could facilitate a streamlined process to update labels and ensure parity in labels.

EMERGING CHALLENGES

Standard of Care

It is becoming increasingly unsuitable for standard of care (SOC) to serve as controls in clinical trials amid a rapidly changing practice of medicine. SOC can change quickly, often in less time than it takes to complete the clinical trial process and regulatory approval which, in oncology, averages 8 years.[7] If the SOC for an indication in cancer changes during the clinical trial process, use of the investigational drug may no longer be appropriate in the clinical trial population, resulting in a different patient population ultimately receiving the treatment. Further, whether the indication for which SOC is used in the clinical trial is indicated for on-label use will impact global access to new therapies which are compared to the SOC. Substantial disagreement can also exist amongst the medical community regarding which therapies constitute SOC, as there is regarding the use of autologous stem cell transplantation as first or second line therapy for multiple myeloma. When rapid changes or disparity of SOC exists, comparisons with SOC and accrual to clinical trials become problematic and create discordance between the practice of medicine, clinical research and registration trials, and drug labeling. In multiple myeloma, the combination therapy of lenalidomide and dexamethasone is most frequently used as a first line therapy, despite its use in clinical trials and indication on the lenalidomide label as SOC for relapsed myeloma, not first-line therapy. Most patients with relapsed myeloma are likely already resistant to lenalidomide/dexamethasone therapy. Using lenalidomide/dexamethasone as SOC in clinical trials for relapsed multiple myeloma results in approval and labeling of novel therapies that have not been tested in the most common form of relapsed multiple myeloma, which is lenalidomide/dexamethasone resistant. These issues will continue to pose a barrier to drug development as combinations increase in complexity. Alternative strategies, including validation of trial designs that replace components of a treatment with add-on to SOC designs, may need to be employed to establish an appropriate control arm.

Regulatory and Legal Ramifications

The regulatory and legal ramifications of updating a label for an approved monotherapy when used in a combination remain largely uncharted by the pharmaceutical industry. The uncertainty created, particularly when market exclusivity or patent life exist for a component of the combination therapy, can pose additional challenges to cross-labeling and impede consistency of labeling between monotherapies used in combination.

The FDA has used its regulatory authority to facilitate and encourage cross-labeling, albeit in a case specific manner which was highly dependent upon the level of cooperation that existed between sponsors. For example, when both sponsors agree to coordinate efforts to cross-label, the FDA has, in the past, either negotiated language for an indication for use in each label or encouraged use of a Drug Master File (DMF). In the latter, the initial sponsor could file a DMF and permit the second sponsor a right of reference to amend its current label using a supplemental NDA. Conversely, the scenario in which sponsors do not agree to collaborate (this may occur for a variety of reasons), has presented greater difficulty and ambiguity as to the regulatory and legal mechanisms necessary to cross-label. In these cases, the result has most commonly meant that the level of information on the individual labels remained disproportionate. A new approach could be taken where the FDA, with the permission of the trial sponsor, allows the manufacturer of each component of the combination to independently update its label by referencing the new study that tested the monotherapies in combination.

While the FDA has authority to mediate cross-labeling of combination therapies, the disadvantage of these regulatory solutions rests upon the necessity for drug and trial sponsor cooperation. A legislative fix, similar to that which was recently enacted in the Food and Drug Administration Reauthorization Act of 2017 (FDARA) regarding labeling of medical imaging products, would likely provide a more effective solution for cross-labeling of combination therapies. Section 706 of the Food, Drug, and Cosmetics Act was amended in FDARA to allow imaging devices approved for a new indication, dosage, etc., to reference existing imaging agents that are labeled for use with other marketed devices. The legislative update now allows the imaging agent's label to be modified by referencing a device master file or through right of reference to research conducted by a device company through a supplemental NDA. A similar approach could be used to simplify cross-labeling for combinations. However, any of the preceding approaches would also need to consider any patent rights pertaining to the combination or any individual agent, as discussed below.

Whether regulatory or legislative, attempts to incentivize cross-labeling for combination therapies must consider the potential impact that cross-labeling could have on market access for follow-on products such as abbreviated new drug applications (ANDAs) and 505(b)(2) applications. ANDAs are particularly vulnerable to market delay when patents/exclusivities are extended because of the "same labeling" rule that requires the ANDA to incorporate the same information from the reference listed drug (RLD) label onto its own. Further, follow-on products are listed in the FDA "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange Book) and, when associated with an innovator drug with current patent life, must include certification that the applicant does not infringe on and will not seek market approval until all relevant innovator patents are expired or submit a "paragraph IV certification" to challenge the validity of the patent. It is possible that certain circumstances exist where an innovator label could be updated to include use in combination, thereby extending patent life or exclusivity, and subsequently block generic market entry. However, there is a regulatory mechanism that allows use of a "skinny label" that may mitigate this effect. In the event the innovator product is protected by exclusivity or method of use patents, which are still in effect after the initial exclusivity/patents expire, generic or 505(b)(2) application could still be filed but would have to account for the protected indication by "carving out" the indication under active exclusivity/method of use patent from the label. The skinny label would list only the non-protected information on the label but should not prevent market entry. It is important to note that this discussion pertains to drug-drug (or NDA-NDA) combinations and does not address potential regulatory or legal implications associated with drug-biologic (or NDA-BLA) combinations, which are approved via a separate regulatory pathway for combination products, and are outside the scope of this whitepaper. A thorough legal and regulatory examination regarding market exclusivity and patent life, including case study analysis of the potential outcomes of previous combination approvals, will be needed to inform future policy solutions.

CASE STUDIES TO INFORM LABELING POLICY

In each scenario below, consider the implications to patent life and market exclusivity of an innovator drug if that drug's label were updated to include an indication for use in a new combination therapy. Additionally, where possible, the economic incentives and implications of such cross-labeling would be of further interest to inform policy.

Issues to Consider
To best inform this analysis, it may be most helpful to consider the following questions:

- Would this impact regulatory exclusivity? How?
- Are there issues with sharing or giving rights to use combination study data with or to a manufacturer whose drug is used in the combination?
- Are there economic incentives or outcomes that would impact the sponsor's or the other manufacturer(s)' decision to update a label that should be considered in these scenarios?
- What impact would patent rights for a drug included in the combination, or for the combination, have?

Scenario 1: A novel therapeutic in combination with a drug that has existing exclusivity/patents and a generic.

Elotuzumab (PDL Biopharma) was approved for multiple myeloma in combination with lenalidomide (Revlimid, Celgene) and dexamethasone (generic)[8].

- Only the Elotuzumab label reflects this indication. This combination is also included in NCCN guidelines for previously treated multiple myeloma.
- This case study will address the implications that cross-labeling may have on market exclusivity and patent life because it includes a novel therapeutic (elotuzumab), a brand product with existing market exclusivity and patent life (Revlimid),[9,10] and a generic (dexamethasone) where the clinical trial led to approval of combination without a label change to the patented therapeutic.
- The compound patent for Revlimid (US 5,635,517) will expire in October 2019 and the polymorph patent (US 7,465,800) will expire in 2027.
- The compound, or composition of matter, patent for Revlimid (US 5,635,517) expires in October 2019. It also has two method of use patents (US 7,189,740 and US 7,968,569) expire in 2023. Market exclusivity will end in 2018 but several orphan drug exclusivities exist which will last through 2020, 2022, or 2024.[11]

Scenario 2: A monotherapy approved initially through accelerated approval and later regular approval receives an additional indication in combination with another therapy that has existing exclusivity/patents and a generic.

Daratumumab[12] (Darzalex, Janssen Biotech) was approved for multiple myeloma in combination with:[13]
a. lenalidomide[14] (Revlimid, Celgene) and dexamethasone (generic)
b. bortezomib[15] (Velcade, Takeda/Millennium) and dexamethasone (generic)

- Both combinations are listed as preferred regimens (class 1) in NCCN guidelines for patients previously treated multiple myeloma.
- Only the daratumumab label reflects this indication in either combination.
- There are many patents for Revlimid, an expanded indication exclusivity which ends in 2018, and orphan drug exclusivities which end in 2020, 2022, or 2024.
- Velcade has three patents (US 5,780,454; US 6,713,446; and US 6,958,319), pediatric exclusivities which expire in 2018, 2019, or 2022, and an orphan drug exclusivity which expires in 2021.

Scenario 3: Brand product combined with brand product.

A combination of palbociclib (Ibrance, Pfizer) and fulvestrant (Falsodex, AstraZeneca), both brand products with current patents and exclusivities, was approved for breast cancer following endocrine therapy after a single clinical trial. Both drug labels were approved independently.

a. Ibrance[16] received approval in combination with Falsodex in February, 2016. Ibrance has three patents (US 6,936,612; US 7,208,489; and US 7,456,168) and a new chemical entity exclusivity.
b. Falsodex[17] received approval in combination with Ibrance in March, 2016. Falsodex has four patents (US 6,774,122; US 7,456,160; Us 8,329,680; and US 8,466,139) and pediatric exclusivity.

In this example, both innovator drugs in the combination updated their labels to include the new indication. This will be an interesting case to study the economic incentives which influenced this decision and how patent life and exclusivity was impacted to inform cases in Scenarios 1 and 2.

APPENDIX

Table 1: Comparison of different clinical trial design for combination therapies.

Trial Design	Pro	Con
Basket Trial	Beneficial for matching patients with low prevalence mutations to targeted gene therapies. Compares effectiveness of multiple drugs simultaneously.	Measurement of genotype status is static and does not account for change in tumor composition over time. Can become increasingly complex as additional arms are added. There is also a risk of overlooking or failing to tease out impact of a mutation in different tumor types (e.g. BRAF in melanoma vs. BRAF in colorectal cancer).
Umbrella Trial	Streamlines clinical trials by testing multiple drugs in a single cancer type and targets patients to the most appropriate therapy based upon specific molecular aberrations. There are potentially less screen failures and more patients may benefit from a treatment under an umbrella design.	Measurement of genotype status is static and does not account for change in tumor composition over time. Can become increasingly complex as additional arms are added.
Common Control	Reduces clinical trial recruitment by comparing multiple trial arms to a single control. Enables faster time to data for multiple agents in a more rigorous statistical fashion (if randomized and in the same study).	Can be difficult to determine an appropriate control arm that is a suitable comparator for multiple experimental arms. There is the additional need to demonstrate "similarity" or relevance of patients to compare if done in separate trials or without direct randomization.
Adaptive Trials	Speeds the clinical trial by approving modification protocols before the trial starts and interim analyses gives the flexibility to adapt the trial in real-time and respond to unexpected events.	Adaptations or trial decisions based on highly uncertain data early in patient accrual can lead to erroneous conclusions and frequent interim analyses may jeopardize the integrity of a trial. Patient accrual sometimes occurs too quickly to allow time for impactful trial adaptations. Further, practical challenges of executing adaptive trials and complicated statistics may prove difficult for study investigators and sponsors.

APPENDIX

Table 2: Comparison of modifications to comparator arms for clinical trials of combination therapies.

Approaches to Comparator Arms	Pro	Con
Add-on	Streamlines the clinical trial by eliminating the lag phase which requires patients to stop current treatments.	Must consider possibility of developing drug resistance during the first phase, before addition of a second therapy. There is added difficulty in selection of an optimal endpoint(s) to demonstrate benefit/risk in the various phases.
Parallel	Allows direct comparison of multiple therapies (or combinations versus individual components) in parallel or interrogation of therapy efficacy in different cancer settings.	Can require additional experimental arms and increasing number of patients to enroll.

APPENDIX

Table 3: Framework to streamline clinical trial design for combination therapies by optimizing use of historical data.

- **Identify historical data sources.**
- **Determine intended use for data. Comparator or experimental arm?**
- **Determine if historical data meets guidelines for similarity to current clinical arms to provide for robust assessments.**

Considerations for use of historical data	Questions
What is the intended use?	• Are the data intended to provide an objective response rate for comparison, or are they intended to serve as a control group (requiring patient level data and covariates)? • Do the data support an evaluation of safety or efficacy? • Are the data intended to supplement or replace a clinical trial arm (provided patient-level data are available)? • Is the length of time since collection relevant for intended use/to intended population? • What is the clinical trial design of the prospective study?
Do data meet guidelines for robustness?	• How applicable are existing data to the patient population in the prospective trial? • (Are patient-level covariates available and of sufficient quality for use in accounting for differences?) • How applicable are existing data to the disease setting? • Are the data collection methods and timing of collection similar? • Are the endpoints used relevant to new intended use? • Were the clinical trial sites similar?

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The Value of Addressing Patient Preferences

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ABSTRACT

Recent scientific progress is, in some cases, leading to transformative new medicines for diseases that previously had marginal or even no treatment options. This offers great promise for people affected by these diseases, but it has also placed stress on the health care system in terms of the growing cost associated with some new interventions. Effort has been taken to create tools to help patients and health care providers assess the value of new medical innovations. These tools may also provide the basis for assessing the price associated with new medical products. Given the growing expenditures in health care, value frameworks present an opportunity to evaluate new therapeutic options in the context of other treatments and potentially lead to a more economically sustainable health care system. In summary, the contribution to meaningful improvements in health outcomes is the primary focus of any assessment of the value of a new intervention. A component of such evaluations, however, should factor in timely access to new products that address an unmet medical need, as well as the magnitude of that beneficial impact. To achieve these goals, value assessment tools should allow for flexibility in clinical end points and trial designs, incorporate patient preferences, and continually evolve as new evidence, practice patterns, and medical progress advance.

Keywords: assessment, breakthrough therapies, cancer, value framework.

Commentary

Scientific advances have resulted in a number of innovative and highly effective new options for cancer therapy within the last few years. Many of these therapies are targeted to those patients who are most likely to benefit, thus improving therapeutic effectiveness. The rising costs of many new therapies have, however, spurred stakeholder groups to develop "value frameworks" to assess the health care value of these therapies. Although it is clear that the cost of drugs is a growing concern, value frameworks that do not include all of the trade-offs involved in making a value assessment may provide an incomplete report to patients and could result in misuse of these frameworks. Therefore, the metrics included in value frameworks and how the metrics are measured must be transparent, and the end user of the value frameworks needs to be carefully considered as frameworks begin to evolve and mature. Five value frameworks are currently in development to assess the value of cancer therapies: The American Society of Clinical Oncology Value Framework, the European Society for Medical Oncology's Magnitude of Clinical Benefit Scale, the Institute for Clinical and Economic Review Value Assessment Framework, the Memorial Sloan Kettering Cancer Center's DrugAbacus, and the National Comprehensive Cancer Network Evidence Blocks [1–5].

Several recent review articles compare these frameworks and highlight several issues, including the need for increased patient input and improved patient-centeredness [6,7]. It is worth noting that these frameworks are being improved via incorporation of stakeholder feedback, and this perspective is meant to offer guiding considerations as they continue to evolve.

Patients with life-threatening illnesses, such as cancer, place a high value on prompt availability of new therapies. Value frameworks should recognize and account for the trade-offs inherent in drug development by ensuring that metrics, such as end points used to demonstrate safety and efficacy and clinical trial designs employed to evaluate new products, do not diminish patients' preferences in determining and receiving their optimal treatment or create unintended consequences in therapeutic research and development. For example, there may be increased tension between providing timely access to new treatments for patients and designing a drug development program to meet an arbitrary and population-based value standard rather than focusing on the benefits to defined individuals. In oncology, a traditional gold standard for demonstrating efficacy to justify FDA approval of a drug is an improvement in overall survival [8]. For drugs with the potential to fill an unmet medical need for a very serious, life-threatening disease (i.e., drugs that provide a treatment where none exists or that may be superior to existing therapy), however, the FDA can grant accelerated approval. This approval is based on effects on an end point that is reasonably likely to predict a clinical benefit, such as tumor shrinkage or other intermediate end points, and which can be measured earlier than overall survival (21 CFR Part 314, Subpart H). This approach can provide seriously ill patients with earlier access to new drugs while

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postmarket studies are conducted to confirm clinical benefit, as opposed to requiring significantly longer and more limited access to premarket studies to demonstrate an effect on overall survival before the treatment becomes available to patients.

In some proposed value frameworks, a drug would be determined to be more valuable, and consequently would likely command a higher price, if it showed a significant effect on overall survival. Although this seems logical, it may penalize some of the more effective drugs currently available to cancer patients (e.g., precision medicine or targeted therapies), many of which have demonstrated unprecedented effects on response rates and disease control rates in the premarket setting such that a randomized trial to assess survival might not be acceptable to patients.

Tools that overemphasize overall survival while underemphasizing other outcomes that also matter to patients, such as reduction of tumor or symptom burden or reduction in hospital admissions, may inadvertently create an incentive structure that prioritizes the development of long-term clinical benefit data in the premarket setting at the expense of providing patients timely access to potentially beneficial treatments. When interventions are approved based on surrogate end points, it does create some uncertainty as to whether the surrogate end point will reflect improvements in overall survival.

There are instances where surrogate end points do not always equate to improvements in overall survival when analyzed in later, postmarket confirmatory trials. Value frameworks, however, should ensure patients are able to designate the level of uncertainty they are willing to accept as they use these frameworks to potentially guide their therapy decisions. Importantly, when these confirmatory data are available, value frameworks should quickly incorporate this information so patients have the most up-to-date information.

When options have been exhausted, patients want access to experimental therapies provided through innovative clinical trial designs. In addition to end point selection, the experimental design of a clinical research trial plays a role in balancing the optimal evaluation of a new intervention with patient access. Patients who had been treated with the standard of care might be allowed access to the investigational intervention once the primary end point has been met in some clinical trials. This approach, referred to as crossover, allows more of the study participants to have access to the intervention under study and is an example of how a patient-centric approach can positively influence clinical trial designs.

Crossover, however, can also result in loss of information about the clinical impact of any new interventions when compared with a more rigid clinical trial design in which crossover would not be allowed [9,10]. If a value assessment is made by comparing the relative improvement in survival yielded by a new intervention to that of another, sponsors may inadvertently be driven to rely solely on premarket overall survival data; patients then may be denied the opportunity to crossover to make the intervention be perceived as more valuable in value assessment frameworks. Precluding crossover may result in a more clearly defined assessment of magnitude of benefit, but patients may also be less likely to participate in studies that prohibit crossover.

These examples are not intended to suggest that clinical end points, such as overall survival, should not be included as important components of value-based assessments of medical technologies. Understanding the long-term implications of providing and paying for new treatment options is necessary to improve health care for patients and ensure that it is accessible and affordable for society and for individuals. These scenarios demonstrate, however, that value framework metrics should be constructed in a flexible manner that ranks appropriate timely access as a component of value to encourage the development of treatments that address unmet medical needs and patient needs. To accomplish this goal, value frameworks should appraise the full spectrum of available evidence and employ appropriate methods to ensure they fairly capture the benefits of each therapy. The long-term value of an effective intervention also needs to reflect nonfinancial end points, such as impact on family and community, route of administration, and other functional elements, which may not easily be quantifiable in standard, short-term pecuniary terms. They should also evaluate the therapy's impact on the overall cost of care (e.g., physician visits, hospital care, surgery).

Some value frameworks do incorporate the use of the quality-adjusted life-years, which have become standard in economic evaluations that attempt to identify what is optimal for society. Quality-adjusted life-years may not, however, adequately capture what is important for individual decision making. Therefore, value frameworks directed toward patients should work to provide a tailored output based on the needs of the individual end user. Value frameworks could serve to promote the inclusion of these important patient-focused metrics in future trials to better accomplish this goal.

Until patient-reported outcomes are routinely captured in clinical trials, framework developers should consider other methods to collect this information. Methods could include less formalized, postmarket data collection to better understand if an intervention is having a positive impact on aspects of patients' lives that are not frequently collected in premarket clinical trials. The involvement of patients and their caregivers in identifying aspects of daily life that were undesirably interrupted by an illness could also help inform future value assessments of different interventions. For example, patients often note that a desired outcome of treatment is the ability to continue to work [11]. An intervention that consistently allows patients to return to work more quickly than an alternative may be more valuable to some patients and may positively inform their treatment decisions.

Frameworks should also be flexible in incorporating evolving information regarding the context of use, such as the future availability of additional treatments for the same condition, as well as in assessing the value associated with different uses of the product, such as in a different line of treatment, population subset, or indication [12]. Because the body of evidence on medical products continues to evolve after approval, the value of a treatment should not be a static measure that is assigned at a single time point but rather should be a dynamic measurement that incorporates new evidence collected in the postmarket setting through additional clinical trials or real-world use in clinical practice.

The incorporation of real-world evidence into value frameworks will facilitate the inclusion of long-term safety and effectiveness data and provide information as to how different products perform in patient populations that are typically excluded from clinical trials. Real-world evidence may also yield important insight into the tolerability of different products based on treatment adherence or dose modification patterns, information that is not always reflected on drug labels. Overall, real-world evidence can help ensure that value frameworks do not solely rely on the best average treatment effect by recognizing the heterogeneity that is associated with cancer. Conducting postmarket trials has challenges and limitations, but efforts are underway with the goal of uncovering long-term, longitudinal information that will help inform and optimize the use of new products [13,14].

As these value frameworks undergo improvements, developers should consider including patient input early and throughout the development process; incorporating molecular diagnostics into these frameworks to better integrate the concept of precision medicine; defining value and making it explicitly known to end users; developing methodology to incorporate new data as they are rapidly produced in oncology drug development; and ensuring that frameworks align with improved understanding and reliability of surrogate end points and innovative trial designs.

In addition, these frameworks may ultimately help improve the dialogue between the drug industry and society as they continue to be refined and utilized. We recognize the complexity of assessing the value of new therapies, particularly in a rapidly evolving field like oncology, but it should not come at the cost of blocking patient access to potentially life-saving therapies or undermining their current treatments.

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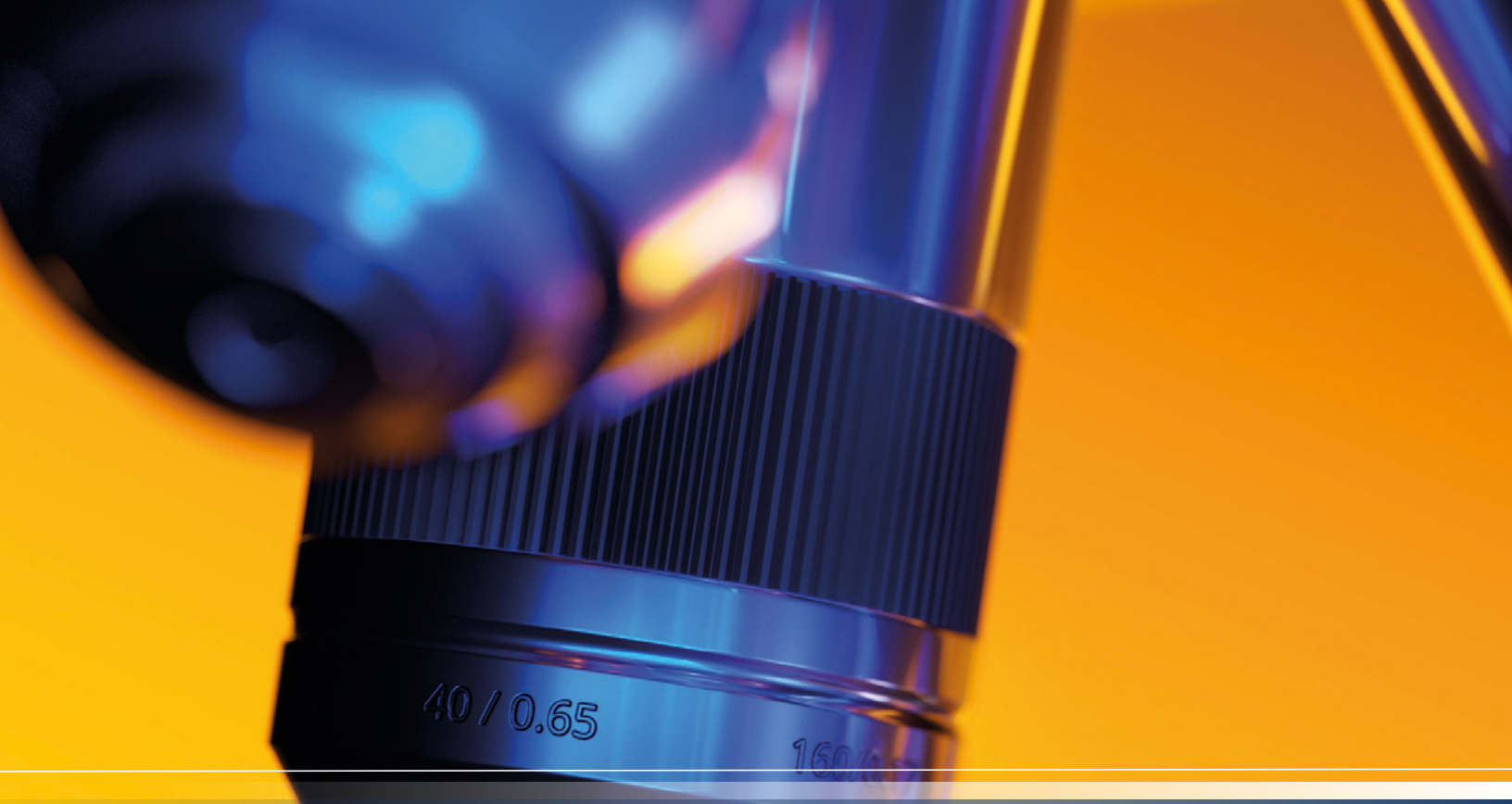

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