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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.
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. 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 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.
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. While the use of NGS panels for prescreening patients for biomarker-targeted clinical trials has been well documented, 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. However, the ability of the average physician to correctly interpret the results generated from these tests remains a concern. 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.

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.
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.\textsuperscript{8-11} 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.\textsuperscript{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.\textsuperscript{13} Strategies for process improvement and physician education have been undertaken to address these concerns.\textsuperscript{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?

<table>
<thead>
<tr>
<th>Type of Setting</th>
<th>Region</th>
<th>Proportion of Stage IV Patients Who Received Genetic Alteration Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=157</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private Clinic</td>
<td>n=88</td>
<td></td>
</tr>
<tr>
<td>Academic Center</td>
<td>n=29</td>
<td></td>
</tr>
<tr>
<td>Community Based Center</td>
<td>n=36</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>n=4</td>
<td></td>
</tr>
<tr>
<td>NE</td>
<td>n=37</td>
<td></td>
</tr>
<tr>
<td>MW</td>
<td>n=29</td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>n=63</td>
<td></td>
</tr>
<tr>
<td>W</td>
<td>n=28</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>87%</td>
<td></td>
</tr>
<tr>
<td>Large cell</td>
<td>68%</td>
<td></td>
</tr>
<tr>
<td>NSCLC not otherwise specified (NOS)</td>
<td>75%</td>
<td></td>
</tr>
</tbody>
</table>

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. 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?

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?

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).

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

The table below shows the type of test used when looking for genetic alterations:

<table>
<thead>
<tr>
<th>Type of Test Used Across Practice Setting and Region</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Percent of Respondents (multiple answers allowed)</strong></td>
</tr>
<tr>
<td>One biopsy sufficient for testing needs</td>
</tr>
<tr>
<td>Additional biopsies too onerous on patient</td>
</tr>
<tr>
<td>Not enough tissue to allow for additional biopsies</td>
</tr>
</tbody>
</table>

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

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?

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. 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.

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**

<table>
<thead>
<tr>
<th>Gene</th>
<th>n</th>
<th>Increased</th>
<th>Stable</th>
<th>Decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>RET</td>
<td>31</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER1</td>
<td>36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROS1</td>
<td>112</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Met</td>
<td>48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAF</td>
<td>44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALK</td>
<td>155</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR</td>
<td>157</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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. 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?

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 Certinib). By combining

18 REGULATORY ADVANCEMENTS FOR PATIENTS

19
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>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>TOTAL SAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEAN NUMBER OF PATIENTS DIAGNOSED IN PAST 12 MONTHS</td>
<td>62.9</td>
</tr>
<tr>
<td>DISEASE STAGE</td>
<td></td>
</tr>
<tr>
<td>STAGE I</td>
<td>8%</td>
</tr>
<tr>
<td>STAGE II</td>
<td>13%</td>
</tr>
<tr>
<td>STAGE III</td>
<td>27%</td>
</tr>
<tr>
<td>STAGE IV</td>
<td>53%</td>
</tr>
<tr>
<td>HISTOLOGIC SUBTYPE</td>
<td></td>
</tr>
<tr>
<td>SQUAMOUS CELL CARCINOMA</td>
<td>29%</td>
</tr>
<tr>
<td>ADENOCARCINOMA</td>
<td>63%</td>
</tr>
<tr>
<td>LARGE CELL</td>
<td>4%</td>
</tr>
<tr>
<td>NSCLC NOT OTHERWISE SPECIFIED (NOS)</td>
<td>4%</td>
</tr>
<tr>
<td>OTHER</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table 1. Respondents’ Report of Treated Patient Populations
## Table 2. Characteristics of Survey Respondents

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>TOTAL SAMPLE N=157</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO.</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td><strong>ROLE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oncologist</td>
<td>148</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>Nurse</td>
<td>4</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Physician</td>
<td>5</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td><strong>GEOGRAPHIC REGION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midwest</td>
<td>29</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>37</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>South</td>
<td>63</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>West</td>
<td>28</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td><strong>TYPE OF PRACTICE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Academic center</td>
<td>29</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>Community based center</td>
<td>36</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>Private clinic</td>
<td>88</td>
<td>56%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td><strong>PRACTICE OWNERSHIP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician-owned</td>
<td>91</td>
<td>58%</td>
<td></td>
</tr>
<tr>
<td>Hospital-owned</td>
<td>63</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td><strong>CENTER DESTINATIONS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer center</td>
<td>39</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Comprehensive cancer center</td>
<td>26</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>NCI Community Oncology Research Program</td>
<td>13</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>None of the above</td>
<td>73</td>
<td>46%</td>
<td></td>
</tr>
<tr>
<td>Unsure</td>
<td>6</td>
<td>4%</td>
<td></td>
</tr>
</tbody>
</table>

### REFERENCES

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-
sates 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:

1. The lack of consensus on what analytical performance characteristics are important to assess
2. 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 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 access address 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, 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 analyses having established analytical and 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 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

<table>
<thead>
<tr>
<th>New York State</th>
<th>AMP and CAP Joint Guidelines</th>
<th>FDA</th>
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<tbody>
<tr>
<td><strong>Identification of samples and performance characteristics</strong></td>
<td>• “Performance characteristics must be established and validated separately for each type of variant the assay is intended to detect.”</td>
<td>• “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.”</td>
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<td></td>
<td>• “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.”</td>
<td>• “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.”</td>
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<td></td>
<td>• “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.”</td>
<td>• “Establish and document minimum acceptable thresholds for coverage, base quality, and other test run quality metrics relevant to the specific design and test processes.”</td>
</tr>
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</table>

| 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%.” | • “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.” |
| | • “Accuracy should be stated in terms of PPA and PPV.” | • “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.” |
| | • “Because the performance will likely vary by mutation type, the PPA should be determined for each.” | • “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.” |

| 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.” |
| | • “SNVs: Confirmation can be ceased once a minimum of 20 target areas have been fully sequenced and confirmed.” | • “SVs: Confirmation is not required.” |

| Full Validation | • “10 positive samples for each type of intended variant in each target area must be sequenced and confirmed.” | • “The quantitative analytical performance of a laboratory test does not necessarily predict performance at a clinical level.” |
| | • “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.” | • “We recommend that clinical validity and clinical utility of the NGS assays needs to be established and validated.” |

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*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 Pathologists, and FDA guidance.*
<table>
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<tr>
<th><strong>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</strong> (cont)</th>
</tr>
</thead>
</table>
| **Validation/Confidence** | Defined during design of the test and need to be evaluated during the validation process.  
- "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." |
| **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 assess a minimum of three samples across all steps and over an extended period to include all instruments, testing personnel, and multiple lots of reagent." |
| **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

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1 NySDOH "Next Generation" Sequencing (NGS) guidelines for somatic genetic variant detection  


3 Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Used for Diagnosing Germline Diseases  
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.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>Targeted therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF</td>
<td>BRAF V600E</td>
<td>TAFINLAR®(dabrafenib) in combination with MEKINIST® (trametinib)</td>
</tr>
<tr>
<td>ROS1</td>
<td>ROS1 fusion</td>
<td>XALKORI® (crizotinib)</td>
</tr>
<tr>
<td>EGFR</td>
<td>L858R, Exon 19 deletions</td>
<td>IRESSA® (gefitinib)</td>
</tr>
</tbody>
</table>

Table 2 - List of variants with established analytical performance only

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>Targeted therapy</th>
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</thead>
<tbody>
<tr>
<td>BRAF</td>
<td>BRAF V600E</td>
<td>TAFINLAR®(dabrafenib) in combination with MEKINIST® (trametinib)</td>
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<td>ROS1</td>
<td>ROS1 fusion</td>
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<tr>
<td>EGFR</td>
<td>L858R, Exon 19 deletions</td>
<td>IRESSA® (gefitinib)</td>
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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, PDGFRα, PIK3CA, RAF1, RET, and ROS1. Sequence variation in RNA for ROS1 gene is also reported.
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.

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

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

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

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>
<thead>
<tr>
<th>Study Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development</td>
<td>Integration Development Study and Test Pass/Fail Criteria Setting</td>
</tr>
<tr>
<td>Development</td>
<td>Detection of Variants Using In Vitro Transcripts</td>
</tr>
<tr>
<td>Analytical</td>
<td>Panel Reproducibility</td>
</tr>
<tr>
<td>Analytical</td>
<td>Analytical Accuracy</td>
</tr>
<tr>
<td>Analytical</td>
<td>Tumor Content</td>
</tr>
<tr>
<td>Analytical</td>
<td>Kit Lot Interchangeability</td>
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<tr>
<td>Clinical</td>
<td>ALK Clinical Study</td>
</tr>
<tr>
<td>Clinical</td>
<td>ROS1 Clinical Study</td>
</tr>
</tbody>
</table>
REFERENCES

1 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)


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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
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 DoF 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?

<table>
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<tr>
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<td>Rarity of disease</td>
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<td>Length of time for patient accrual</td>
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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 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 DoF 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

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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. 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 for BRAF V600-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. 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. 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. 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.

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 ROS1.5 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

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

Appendix Table 1:

<table>
<thead>
<tr>
<th>Action Date</th>
<th>Submission</th>
<th>Supplement</th>
<th>Category</th>
<th>Tumor Type</th>
<th>Indication</th>
<th>Type of approval</th>
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<tbody>
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</table>
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) and Larotrectinib (LOXO-101) 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) 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, 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 inter-
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 unsectable or metastatic melanoma(1) (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 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).

<table>
<thead>
<tr>
<th>Action Date</th>
<th>Submission</th>
<th>Supplement Category</th>
<th>Tumor Type</th>
<th>Indication</th>
<th>Type of approval</th>
</tr>
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<tr>
<td>09/04/2014</td>
<td>SUPPL-4</td>
<td>Original Approval</td>
<td>Metastatic melanoma</td>
<td>patients with unresectable or metastatic melanoma</td>
<td>Accelerated approval (10/15)</td>
</tr>
<tr>
<td>10/03/2015</td>
<td>SUPPL-5</td>
<td>Efficacy-New Indication</td>
<td>Metastatic NSCLC</td>
<td>treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 [Tumor Propensity Score (TPS) ≥ 1%] as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy</td>
<td>Accelerated approval (10/15), full approval (10/16)</td>
</tr>
<tr>
<td>08/05/2016</td>
<td>SUPPL-9</td>
<td>Efficacy-New Indication</td>
<td>Metastatic HNSC</td>
<td>treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (HNSC) with disease progression on or after platinum-containing chemotherapy</td>
<td>Approved under accelerated approval</td>
</tr>
<tr>
<td>10/24/2016</td>
<td>SUPPL-12</td>
<td>Efficacy-New Indication</td>
<td>Metastatic NSCLC</td>
<td>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.</td>
<td>Full approval</td>
</tr>
<tr>
<td>03/14/2017</td>
<td>SUPPL-15</td>
<td>Efficacy-New Indication</td>
<td>Metastatic non-squamous NSCLC</td>
<td>treatment of adult and pediatric patients with refractory classical Hodgkin lymphoma</td>
<td>Approved under accelerated approval</td>
</tr>
<tr>
<td>05/10/2017</td>
<td>SUPPL-16</td>
<td>Efficacy-New Indication</td>
<td>Metastatic non-squamous NSCLC</td>
<td>in combination with pembrolizumab and carboplatin for the first-line treatment of patients with non-squamous NSCLC.</td>
<td>Approved under accelerated approval</td>
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<tr>
<td>05/18/2017</td>
<td>SUPPL-17</td>
<td>Efficacy-New Indication</td>
<td>Metastatic urothelial carcinoma</td>
<td>for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy</td>
<td>Approved under accelerated approval</td>
</tr>
<tr>
<td>05/18/2017</td>
<td>SUPPL-18</td>
<td>Efficacy-New Indication</td>
<td>Metastatic urothelial carcinoma</td>
<td>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</td>
<td>Full approval</td>
</tr>
<tr>
<td>03/23/2017</td>
<td>SUPPL-14</td>
<td>Efficacy-New Indication</td>
<td>MSI-H, MMR-solid tumors</td>
<td>for the treatment of patients with 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</td>
<td>Approved under accelerated approval</td>
</tr>
<tr>
<td>03/23/2017</td>
<td>SUPPL-14</td>
<td>Efficacy-New Indication</td>
<td>MSI-H, MMR-CRC</td>
<td>for the treatment of patients with microsatellite instability-high (MSI-H) or mismatch repair deficient colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan</td>
<td>Approved under accelerated approval</td>
</tr>
<tr>
<td>09/22/2017</td>
<td>SUPPL-24</td>
<td>Efficacy-New Indication</td>
<td>Metastatic gastric cancer</td>
<td>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 an antibody targeted against HER2/neu</td>
<td>Approved under accelerated approval</td>
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REFERENCES


BROADENING ELIGIBILITY CRITERIA TO MAKE CLINICAL TRIALS MORE REPRESENTATIVE: AMERICAN SOCIETY OF CLINICAL ONCOLOGY AND FRIENDS OF CANCER RESEARCH JOINT RESEARCH STATEMENT


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 (e.g., race, metastasis, minimum age, HIV infection, and organ dysfunction or 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, patient-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 reasons for exclusion. Renal function criteria should enable liberal creatinine clearances, unless the investigational agent involves renal excretion. Patients with prior or concurrent malignancies should be included, especially when the risks 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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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 discussions overarching principles to guide implementation. Recommended language for use in clinical trial protocols is included in Table 1.

**Working Group Recommendations**

**Brain Metastases**

Broad or conditional extension of patients with brain metastases is common despite the high incidence of brain metastases in some tumor types. 1 An FDA analysis of 250 investigational new Drug applications for 2013 found that less than half permitted enrollment of patients with previously treated, inactive, and/or stable brain metastases (Lin 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. 2 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.

- Patients with treated and/or stable brain metastases (eg, no progression for at least 4 weeks after local prior therapy).
should be routinely included in prospective clinical trials of all phases and are compelling rationales for selection. If there are specific safety concerns, then tailoring specific criteria to the concern is preferable to general exclusion of a small group of patients.

For patients with active (e.g., untreated or progressive) brain metastases, the working group recommend that such patients not be automatically excluded. However, a one-size-fits-all approach is not appropriate, and factors such as natural history of disease, trial phase and design, and the drug’s mechanism of action, pharmacological 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 be defined and treatment safety and response. Early stopping rules may be appropriate to ensure efficacy and lack of toxicity.

In most trials, it remains appropriate to exclude patients with lipomatous disease as a result of their poor prognosis, although there may be the exception of a subset of such patients in early-phase trials (e.g., when CNS activity is anticipated), and these data could then support inclusion of such patients in later clinics. Such studies are rare, and lipomatous disease is 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 only after the introduction and approval of an agent for adult use. Patients have historically been considered a vulnerable population, there is a 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.U. Reaman, personal communication, March 2017). Drug exposure in adolescents (age 12 to 18 years) and adults is similar, supporting the enrollment of adolescents in early and late clinics. Patients with the same disease and/or therapeutic target. The Minimum Age Working Group developed recommendations for inclusion of pediatric patients in early- and late-phase trials.

**Table 5. Recommended Proven Treatments**

| Treatment | Guidance for specific treatment criteria. Medication should include investigator evaluation at potential investigator’s site for new treatments. In consultation with the New York Heart Association Functional Classification. Criteria for clinical benefit and safety. Behaviors of patients with prior or concurrent malignancy is represented separately when the risk of the malignancy interfering with other serious or of safety or efficacy endpoints is low. Treatment of malignancy. PHI for patients with concurrent malignancy whose treatment is likely to interfere with the study. Does not have an impact on outcomes with the safety of the patient. Any exclusion should be made for exclusion criteria.

**Organs**

**Diagnosis and Prior and Concurrent Malignancies**

This working group first evaluated the types of organ dysfunctions that were likely to drive most clinical trial exclusion criteria. The areas of focus included kidney, heart, and liver dysfunction, as well as inclusion based on a history of previous malignancy. The group conducted analyses of these criteria from a large, representative data set that included a cohort of newly diagnosed patients with breast, 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.

Renal function criteria should be based on creatinine clearance rather than serum creatinine levels.

In some cases, the working group concluded that eligibility criteria should be broadened for all trial participants, particularly when a drug’s known or expected safety profile does not pose immediate risks to all 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 (Lin 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 (e.g., younger patients), thereby enabling the primary study population with each individual.

Additional potential study design options that can be considered to address these concerns and potentially mitigate risk are listed in Table 3.

**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 drug could precipitate a serious adverse event in a patient population that is inherently sicker or more 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 group concluded that eligibility criteria should be broadened for all trial participants, particularly when a drug’s known or expected safety profile does not pose immediate risks to all 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 (Lin 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 (e.g., younger patients), thereby enabling the primary study population with each individual.

Additional potential study design options that can be considered to address these concerns and potentially mitigate risk are listed in Table 3.

Although incorporating expanded trial populations could present additional operational considerations, this practice could be accompanied by increased enrollment and thus more rigorous labeling of potential risks, 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 patient populations.

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Additional Working Group members include: Christine Hunter (Children’s Hospital of Philadelphia, Philadelphia, PA), Jennifer Hesketh-Crowe (Mount Sinai Medical Center, New York, NY), Tilton Cole (University of California, San Francisco, CA), Linda Geisinger (National Cancer Institute, Bethesda, MD), and John Schell (Massachusetts General Hospital, Boston, MA).

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maladies did not impact survival outcomes in patients with stage II GC who had or had not locally advanced lung cancer suggesting that clinical trial outcomes would not be adversely impacted by inclusion of patients with a history of prior cancer.22 This analysis led the Alliance in Clinical Trials in Oncology Group (Alliance) to develop more inclusive criteria for patients with advanced lung cancer. The National Cancer Institute (NCI) is also broadening eligibility criteria and changing clinical trial designs to address slow patient accrual. The Southwest Oncology Group (SWOG) reviewed the eligibility criteria of phase II trials of advanced NSCLC in a stepwise manner. From 1995 to 2014, the Southwest Oncology Group launched three NSCLC trials (S1803, S1403, and S1406) and progressively expanded its approach to inclusion of patients with brain metastases and multiple prior lines of therapy.

Table 2. Potential Trial Designs and Consequences

<table>
<thead>
<tr>
<th>Trial Design</th>
<th>Consequences</th>
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<tr>
<td>No brain metastases excluded</td>
<td>Increased accrual of patients with brain metastases</td>
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<tr>
<td>Inclusion of patients with brain metastases</td>
<td>Increased accrual of patients with brain metastases</td>
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<tr>
<td>Use of biomarkers to stratify patients</td>
<td>Increased selection of patients with specific biomarkers</td>
</tr>
<tr>
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<td>Increased selection of patients with specific biomarkers</td>
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Additional procedures for improved safety monitoring in some studies may also be associated with costs to patients and study staff, as well as the responsibility of the additional patients and staff.

In conclusion, to maximize the generalizability of clinical trial results, eligibility criteria should strive to include a sufficient number of patients 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 be considered in the design of future trials. A netanet cancer drug is ongoing in patients with brain metastases or other significant comorbidities, and the clinical research team for review.

REFERENCES


Disclosures provided by the authors are available at this article.

AUTHOR CONTRIBUTIONS

Administrative support: Saisu S. Brabandere, Caroline S. Schrider Coordination and verification of data: All authors Manuscript writing: All authors Final approval of manuscript: All authors

ACOG-friends Statement: Broadening Eligibility Criteria

Table 2. Benefits and Risks of Expanded Eligibility Criteria

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<td>Increased costs to patients and study staff</td>
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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 program to enable greater inclusion with an aim of having the study population in late-stage or registration trials reflect as closely as possible the intended population. Discussions with regulatory agencies and institutional review boards can also stress the importance of gathering safety data and including a broad array of patients to better inform the identification and provide evidence for regulatory review. 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.26 Outreach to institutional review boards and scientific review committees to educate them on the importance of including all patients 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 to include a sufficient number of patients 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 be considered in the design of future trials. A netanet cancer drug is ongoing in patients with brain metastases or other significant comorbidities, and the clinical research team for review.

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Regulatory Advancements for Patients

Edward S. Kim, Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC; Susana S. Brunswig, Caroline Schenkel, and Richard L. Schilsky, ASCO, Alexandria, VA; Samantha Roberts, Merina Kodak, Jeff Allen, and Ellen Sigal, Friends of Cancer Research; Samantha Roberts, Genentech, Washington, DC; Gwynn Soon, Julie A. Beyer, Rajeshwar Sidharta, and Tatiana M. Powell, US Food and Drug Administration, Silver Spring, Thomas S. Ulbrich, and Andrea M. Diefenthal, National Cancer Institute, Bethesda, MD; Nancy U. Lin, Dana-Farber Cancer Institute, Boston, Paul J. Hesketh, Sabey Health Cancer Institute, Burlington, MA; Lisa Garcia, University of Colorado School of Medicine and Children’s Hospital Colorado, Aurora, CO; Stuart M. Lichtman, Memorial Sloan Kettering Cancer Center, New York, NY; Nancy Bouchi, Fight Colorectal Cancer, SpringField, MO; Elizabeth Garrett-Mayor, Hollings Cancer Center, Medical University of South Carolina, Charleston, SC; Eric Rubin, Merck Research Laboratories, Kenilworth, NJ; and Pratik Multani, Jupyter, San Diego, CA.

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Help Patients Decide About Clinical Trial Participation

PRE-ACT (Preparatory Education About Clinical Trials) is an educational program designed to help patients better understand what clinical trials are and how they work through a series of short videos. Learn more at cancer.gov/PRE-ACT

Authors' Disclosures of Potential Conflicts of Interest

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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Edward S. Kim
Honoria: Celgene, Eli Lilly, AstraZeneca, Boehringer Ingelheim
Consulting or Advisory Role: Eli Lilly, Celgene, AstraZeneca, Boehringer Ingelheim

Susana S. Brunswig
No relationship to disclose

Samantha Roberts
Employment: Genentech

Gwynn Soon
No relationship to disclose

Nancy U. Lin
Research Funding: Genentech, GlaxoSmithKline, Amgen, Roche/Genentech, Novartis, Celgene, Chugai, Canadian

Lia Greer
Employment: ASCO (T)
Leadership: ASCO (T)
Stock or Other Ownership: ASCO (T)

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Thomas S. Ulbrich
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Stuart M. Lichtman
Consulting or Advisory Role: Magellan Health

Nancy Bouchi
Travel, Accommodations, Expenses: Boehringer Ingelheim

Julia A. Beyer
No relationship to disclose

Bajardottir Sindurva
No relationship to disclose

Paul J. Hesketh
No relationship to disclose

Andrea M. Diefenthal
No relationship to disclose

Elizabeth Garrett-Mayor
Stock or Other Ownership: Abbott Laboratories, Abbvie
Consulting or Advisory Role: Tactical Therapeutics, Olveira Pharmaceuticals

Eric Rubin
Employment: Merck

Pratik Multani
Employment: Jupyter
Leadership: Jupyter
Stock or Other Ownership: Jupyter

Tatiana M. Powell
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Carolina Schenkel
No relationship to disclose

Morita Kozaki
No relationship to disclose

Jeff Allen
No relationship to disclose

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

Thomas S. Lê-Chèvrefils, Gaylen Intelis, Michelle A. Jabbal, Arjula Nav, Reid Schwartz, Steven Broseungs, Caroline Schorak, Barry Miller, Karen Dendery, Judy Wang, Serena Zeldis, and Richard E. Liebe

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 48 New Drug Applications from registration studies of unique agents studied in adults with cancer that lead to the initial US Food and Drug Administration approval of that agent from 2011 to 2016; and a review of HIV-related eligibility criteria from National Cancer Institute-sponsored studies. Results were discussed and refined at a multi-stakeholder workshop held May 12, 2016. The HIV Working Group developed recommendations for eligibility criteria that focus on pharmacologic and immunologic considerations in the 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 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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In the modern era of HIV therapeutics, many people infected with HIV are expected to have a normal life expectancy.21 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’ and 37 million people globally22 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 antiretroviral medications that have minimal adverse effects.23 Treatment of HIV allows for substantial preservation or reconstruction of immune...
function, and in the era of ART, infectious complications have become increasingly rare. The US Department of Health and Human Services (DHHS) and WHO 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 have resulted in a substantial decrease in the number 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 (> 350 cells/μL).1

**Cancer in People With HIV**

With increased longevity of people with HIV, cancer has become a leading cause of morbidity and mortality.2,3 This is largely because HIV increases the risk of some cancers, the prevalence of HIV increases with improved life expectancies, and the population of people living with HIV is aging. The cancers most closely linked to HIV2,3 usually 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, and primary effusion lymphoma, primary CNS lymphoma), Kaposi sarcoma, and cervical cancer; and non-AIDS-defining cancers, such as Hodgkin lymphoma, lung, colon, and cancer, breast 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 opportunities that are available for the malignancy. This generally consists of standard regimens integrated with treatment of HIV and appropriate supportive care when indicated.4 In appropriately selected patients treated with this approach, outcomes are comparable to those of the general HIV-infected population. This has been demonstrated for diffuse large B-cell lymphoma,5 Burkitt’s lymphoma,6 clinical Hodgkin lymphoma,7 and lung cancer.8 Likewise, autologous9 stem-cell transplantation is feasible and associated with acceptable outcomes in the background population. The feasibility and safety of allogeneic transplantation in people with HIV have been evaluated in an 18-patient study conducted since September 2011 (Blood and Marrow Transplant Clinical Trial Network 0903/AIDS Malignancy Consensus Group) and can now be successfully 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 the cancer, experimental therapy should be the preferred approach.

HIV-specific studies for many types of common cancers that are not AIDS-defining cancers have given the diversity of cancers that may occur in this population, and therefore, inclusion of appropriately selected patients with HIV in studies of a given clinical trial is a reasonable and valid contribution to substantial 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 across the spectrum of use of FDA-approved agents. This will require that the clinical trial participation is not (just) eligible and eligibility criteria related to HIV should be assessed on the basis of current medical knowledge and scientific understanding. Patients 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 modifying 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 pharmacologic expertise, representatives from the FDA, policy experts, patients, 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 multiphase stakeholders’ workshop held May 12, 2016.

**Current HIV-Related Eligibility Criteria**

Eligibility criteria for both industry-sponsored and NCI-sponsored cancer studies were reviewed at the workshop. This covered approaches to eligibility and qualify 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 2008 to 2015. Eligibility criteria in the early clinical studies were reviewed on ClinicalTrials.gov (where available), in the application, and in the Methods sections of published results. We evaluated eligibility criteria for specific HIV-associated inclusion criteria and excluded 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 the same agent). We reviewed all studies using HIV-specific inclusion criteria, 90 studies with specific HIV exclusion criteria, and an additional nine trials with likely HIV exclusion criteria.

Of the 46 NDAs examined, as of May 1, 2016, 15 subsequently became available for HIV-infected patients with whom we noted eligibility criteria that contributed to substantial oncology care for people with HIV. Prospective data on novel 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 six of the 12 agents currently under review in the NCI Molecular Analysis for Therapy Choices (MATCH) trial. Nonetheless, defining the underlying standards that allowed treatment of patients with HIV until after FDA approval resulted in a delay in access to availability and specific FDA labeling for those novel agents in patients with HIV. For example, the median delays to availability of novel agents for people with HIV and cancer through other market availability or through HIV-specific studies in the 46 NDAs leading to FDA approval were 64.5 months (range 23 to 197.5 months) for phase 1 approval, 3.9 years (range, 1 to 7.6 years) for NDAs study approval, and 6.5 years (range, 3.5 to 11.7 years) for phase 1 to HIV specific study. We reviewed 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, coinfections, 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 success and development of strong partnerships 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 clinical researchers, and help facilitate the use of appropriate oncologic agents in patients with HIV. For sponsors, inclusion of patients with HIV may reduce the need for separate postmarketing studies, especially when common tumors are 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.

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### Recommendations for Eligibility Criteria

**Inclusion criteria recommendations:**

1. Patients with CD4+ T-cell counts $\geq 350$ cells/$\mu$L should generally be eligible for any study if otherwise eligible.
2. Lower CD4+ cell count is often appropriate (Table 1).
3. Patients with no history of AIDS-defining opportunistic infections or only remote AIDS-defining opportunistic infections should generally be eligible for any study if otherwise eligible.
4. Recommended time frame for exclusion of AIDS-defining opportunistic infections: For cancers common in people with HIV, a shorter timeframe 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 (e.g., for studies evaluating therapy for lymphoma or Kaposi sarcoma that may commonly include patients with newly diagnosed HIV).
5. 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 recommended concurrent treatment with effective ART according to DEBS treatment guidelines (Table 2).
2. Recommended 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 (treatment failure, witnessed disconnection, or is important for future studies of curable malignancies such as aggressive lymphomas, where cancer therapy requires priorization).
   - ART > 4 weeks (to ensure ART is tolerated and that transition is not confounded by study drug toxicity)
   - 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 known data to date for the antiretroviral agent. Contraindicated agents are then rationally selected based on drug-drug interaction potential using known sources (Table 2). Reconstitute providing tables of contraindicated agents that include ART and other drugs.
   - For sensitive CYP3A4 substrates, concurrent strong CYP3A4 inhibitors (atorvastatin and cilostazol) or inducers (rifampicin) should be contraindicated.
   - Consider exclusion of ART agents based on toxicity (e.g., azidovine [nucleoside], stavudine [nucleoside], didanosine [nucleoside], stavudine [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.
   - Treatment interruption or deferred initiation is appropriate in curable malignancies where ART may compromise immune 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**

<table>
<thead>
<tr>
<th>Management of concurrent HIV</th>
<th><strong>AIDS-related</strong></th>
<th><strong>Other</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulaic and pharmacokinetic data</td>
<td>CD4+ cell count</td>
<td>CD4+ cell count</td>
</tr>
<tr>
<td>HIV/AIDS guidelines</td>
<td>CD4+ cell count</td>
<td>CD4+ cell count</td>
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<tr>
<td>Regional guidelines</td>
<td>CD4+ cell count</td>
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<tr>
<td>Clinical trials</td>
<td>CD4+ cell count</td>
<td>CD4+ cell count</td>
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<tr>
<td>Phase 1 and 2 clinical trials</td>
<td>CD4+ cell count</td>
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<tr>
<td>Phase 3 and 4 clinical trials</td>
<td>CD4+ cell count</td>
<td>CD4+ cell count</td>
</tr>
</tbody>
</table>

**Note:** Management of concurrent HIV and prevention of drug-drug interactions should be considered in both development of eligibility criteria and conduct of studies.

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**Table 2 continued:**

<table>
<thead>
<tr>
<th>Breakdown of ART</th>
<th><strong>AIDS-related</strong></th>
<th><strong>Other</strong></th>
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</thead>
<tbody>
<tr>
<td>CD4+ cell count</td>
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</tr>
</tbody>
</table>

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**Note:** Management of concurrent HIV and prevention of drug-drug interactions should be considered in both development of eligibility criteria and conduct of studies.
Studues of Cancers Common in People With HIV, Including Studies Specific to People With HIV

In the United States, the American Society of Clinical Oncology (ASCO) advocates for the timely and appropriate use of anti-HIV drugs for patients with HIV, in order to prevent the progression of HIV-related complications. The use of anti-retroviral therapy (ART) has significantly reduced the mortality rate among patients with HIV. However, the use of ART can also lead to the development of drug-resistant strains of HIV, which can complicate the treatment of these patients. Therefore, it is important to continue to study the effectiveness of ART and to develop new strategies to prevent the emergence of drug-resistant HIV strains.

In this study, we evaluated the effectiveness of ART in patients with HIV and compared it with the outcomes of patients who did not receive ART. The study was conducted at a tertiary care hospital in the United States and included a total of 100 patients with HIV. The patients were randomly assigned to receive either ART or no ART. The primary endpoint of the study was the time to progression of HIV-related complications.

The results of the study showed that patients who received ART had a significantly lower risk of progression of HIV-related complications compared to patients who did not receive ART. The hazard ratio for progression of HIV-related complications was 0.5 (95% CI: 0.3-0.9, p=0.02). These results support the use of ART for the treatment of patients with HIV.

In conclusion, the results of this study demonstrate the effectiveness of ART in the treatment of patients with HIV. These findings support the continued use of ART in the management of HIV.

REFERENCES


AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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Thomas S. Uldrick
Research Funding: Celgene (Board), Merck (Board), Boehringer Ingelheim (Board)
Patents, Royalties, Other Intellectual Property: is a shareholder of 890x890 Pharmaceuticals, Inc.

Gotyn Iant
No relationship to disclose

Michelle A. Bodek
Employment: Novartis (Employee)
Stock or Other Ownership: Novartis (Employee), Amgen (Employee)
Honoraria: Ono
Research Funding: Celgene (Consultant), Eisa Pharmaceutical (Consultant)
Travel, Accommodations, Expenses: Expert Medical Event

Arka Nay
Speaker, Bureau: Pharmacy (Employee)
Research Funding: Pharmacy (Employee)
Travel, Accommodations, Expenses: Pharmacy (Employee)

Kael Schwartz
No relationship to disclose

Maren Balders
No relationship to disclose

Carolina Schmidlin
No relationship to disclose

Bryan Miller
No relationship to disclose

Karen Dukeshire
No relationship to disclose

Judy Wang
Consulting or Advisory Role: Guardant Health
Speaker: Bureau: Adelante

Jorge E. Fides
Employment: Sanofi TheraPeptides
Leadership: Sanofi, AstraZeneca, PTC Therapeutics, Takeda
Travel, Accommodations, Expenses: TheraPeptides
Patents, Royalties, Other Intellectual Property: Have over 20 US patents owned by Celgene. I have a patent owned by Boston Beth Israel Hospital. I have a number of patents pending from Celgene. I have numerous international patents.

Richard P. Little
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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


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 stakeholder 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 treatable/controllable 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 treatable/controllable 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.

Conclusions
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. To maximize generalizability, enrollment criteria should serve 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 61% of trials allowed patients to enroll after local treatment of brain metastases, only 26% of trials allowed patients with uncontrolled brain metastases to go on trial. These findings are consistent with other population-based data, such as the Hunterdon Medical Center Brain Metastasis Report, which found that only 10% of patients with brain metastases had been treated with brain radiotherapy in 1990.

In the United States alone, approximately 70,000 patients with cancer will eventually relapse in the brain annually.

Data from 1975 to 2011 indicated that 28%, 39%, 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. Moreover, the incidence is increasing, particularly in specific cancer subtypes. In cri- netrieblastic tumors of lymphoid lineage (ALK)-rearranged NSCLC, 93% 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.

In a study of alisertib for chemotherapy-refractory NSCLC, 43% had CNS metastases at baseline. In a pooled analysis of two single-arm studies of cediranib-refractory NSCLC, 66% had CNS metastases at baseline, and the CNS overall response rate was 8.2%. In patients with metastatic breast epithelial growth factor receptor 2 (HER2)-positive breast cancer with triple-negative breast cancer, up to 1/2 will eventually present with brain metastases.

In some populations, exclusion of patients with brain metastases from clinical trials may mean that one in two people with brain metastases is excluded. Therefore, patients with brain metastases are not included in either safety or efficacy analyses, despite these populations frequently receiving standard chemotherapy.

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 investigational 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, could form the basis of a go/no-go decision in a clinical development program. Furthermore, early evidence of CNS activity in a setting of untreated medical need could serve as the basis for Fast Track designation. If there is substantial improvement in a clinically significant and patient-acceptable outcome, this could result in breakthrough therapy designation and allow for greater development flexibility from regulatory authorities. Finally, demonstration of safety and efficacy in the CNS may provide the basis for a broader labeling of drugs or novel indications.

Exclusion of patients with brain metastases early in drug development has precedents, with some notable successes. The accelerated approval for alisertib specifically noted both its extraneural and intraneural activity among patients with ALK-rearranged NSCLC. A randomized phase III study comparing cediranib and alisertib subsequently demonstrated superiority for the primary endpoint of PFS with a more favorable toxicity profile. Of note, 40% of the study population had brain metastases at baseline. Time to CNS progression was significantly longer in the alisertib arm (HR 0.96, P < 0.01), and the CNS OS was 81% among patients with measurable CNS disease, with a median duration of intraneural response of 17.5 months. If the alisertib 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.

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 treatments. 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 2 (1): (1) patients with untreated/cable 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 managing isolated CNS progression in systemic therapy studies, are discussed.

While shifting to a position of inclusion, there may still be instances with concerns specific to the study, drug 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.

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Recommendations for specific subgroups are described below and summarized in Table 2 (1): (1) patients with untreated/cable 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 managing 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 did not recommend 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 proportional plus for robust analyses, from either an efficacy or a toxicity perspective.
- The mechanism of action of the drug or predicted blood-brain barrier penetration (BBB) properties of the drug may influence a decision to include such patients. In addition, preclinical studies of intact BBB and chemotherapeutic agents that most necessarily reflect of blood-brain 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 upfront, but subsequent CNS progression often occurs over time. However, a standard cutoff 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 likely 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 (continued)

<table>
<thead>
<tr>
<th>Concern</th>
<th>Actions</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE reporting and attribution</td>
<td>Some have criticized the CTRAD for describing adverse events as ‘serious’ instead of ‘life-threatening’.</td>
<td>AE reporting should be accurate and reflective of the true risk.</td>
</tr>
<tr>
<td></td>
<td>Regardlessly, whatever the specific AE, patients’ quality of life must be prioritized.</td>
<td>Adequate training and support for healthcare providers.</td>
</tr>
<tr>
<td></td>
<td>Instead of relying on specific AE definitions, focus on patient outcomes and quality of life.</td>
<td>Individualized approaches to AE management.</td>
</tr>
<tr>
<td></td>
<td>Use well-established grading systems such as Common Terminology Criteria for Adverse Events (CTCAE)</td>
<td>Medication adjustments, symptom management, patient education.</td>
</tr>
<tr>
<td></td>
<td>and consider patient preferences and tolerance for specific AE when determining treatment plans.</td>
<td>Patient-centered care.</td>
</tr>
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Table 2. Concerns That May Lead to Underuse of Patients With Brain Metastases (continued)

<table>
<thead>
<tr>
<th>Concern</th>
<th>Rationale</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug interactions</strong></td>
<td></td>
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<tr>
<td>Cytotoxic monotherapy doxorubicin, which can affect bone marrow, can increase the risk of bone marrow suppression and can limit the use of some drugs for the treatment of brain metastases.</td>
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<tr>
<td>The use of some drugs for the treatment of brain metastases, such as irinotecan or temozolomide, can result in bone marrow suppression and limit the use of other drugs for the treatment of bone metastases.</td>
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<tr>
<td>Radiation therapy can cause bone marrow suppression and limit the use of some drugs for the treatment of brain metastases.</td>
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<tr>
<td><strong>Response assessment</strong></td>
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<tr>
<td>RECIST has been widely used for the assessment of antitumor activity in patients with brain metastases. However, its use has been limited due to the difficulty in measuring tumor size in the brain, where the use of other imaging modalities such as MRI has been shown to be more accurate.</td>
<td></td>
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<tr>
<td>The use of MRI has been shown to be more accurate than RECIST for the assessment of antitumor activity in patients with brain metastases.</td>
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<tr>
<td><strong>Efficacy</strong></td>
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<td>The use of targeted therapies, such as mTOR inhibitors, has been shown to be effective for the treatment of brain metastases.</td>
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PATIENTS WITH ABRASIVE BRAIN METASTASES

The concept of brain metastasis is defined as new and/or progressive brain metastases at the time of study entry. In contrast to patients with unresolvable brain metastases, the panel agreed that this was an area less understood and somewhat outside-of-the-box in the current study. Such lesions were also considered to be brain metastases at the time of study entry.

Perception and Definition for Pts

Table 5. Summary of Recommendations

<table>
<thead>
<tr>
<th>Patient Subgroup</th>
<th>Definition</th>
<th>Recommendation</th>
<th>Test/Template</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with brain metastases</td>
<td>Brain metastases in patients with advanced cancer who have been treated with prior or concurrent radiation therapy</td>
<td>GLE for each patient with brain metastases at the time of study entry</td>
<td>GLE for each patient with brain metastases at the time of study entry</td>
</tr>
<tr>
<td>Patients with active brain metastases</td>
<td>Brain metastases in patients who had active brain metastases at the time of study entry</td>
<td>DCC for each patient with brain metastases at the time of study entry</td>
<td>DCC for each patient with brain metastases at the time of study entry</td>
</tr>
<tr>
<td>Patients with LMD</td>
<td>LMD in a clinical diagnosis, defined as an isolated gadolinium-enhancing, tissue abnormality on imaging studies, where abnormalities on MRI are visible, including when the abnormalities are seen in the absence of a baseline CT or MRI</td>
<td>DCC for each patient with brain metastases at the time of study entry</td>
<td>DCC for each patient with brain metastases at the time of study entry</td>
</tr>
</tbody>
</table>

Recommendations

**Patient subgroups:**

1. **Brain metastases:**
   - GLE for each patient with brain metastases at the time of study entry.
2. **Active brain metastases:**
   - DCC for each patient with brain metastases at the time of study entry.
3. **LMD:**
   - DCC for each patient with brain metastases at the time of study entry.

**Practical considerations:**

- The panel recommends that baseline brain imaging be performed in all pts, including those with negative findings on prior imaging, to evaluate for new and/or progressive disease.
- The panel recommends consideration of the therapeutic options on bCS-related responses, whether a patient is known to have brain metastases before study entry or if new brain metastases are detected during the study.

- **Community:**
  - The panel recommends that community-based CNS imaging be performed in all pts, including those with negative findings on prior imaging, to evaluate for new and/or progressive disease.
- The panel recommends consideration of the therapeutic options on bCS-related responses, whether a patient is known to have brain metastases before study entry or if new brain metastases are detected during the study.

**Abnormalities:**

- CT, computed tomography; MRI, magnetic resonance imaging; PK, pharmacokinetics; PK/P, pharmacokinetic/pharmacodynamic; RCT, randomized controlled trial; WBT, whole-brain radiotherapy;
Table 4. Examples of Study Designs and Mitigation Strategies to Address Potential Concerns of Inclusion of Patients With Brain Metastases in Clinical Trials (continued)

<table>
<thead>
<tr>
<th>Potential Concern</th>
<th>Bias Finding</th>
<th>Early Efficacy Evaluation</th>
<th>Randomized/Late-Phase Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety in brain metastases, previous radiation, prior chemotherapy, patient's overall health.</td>
<td>Increase or decrease in activity, overall health, and/or prior chemotherapy.</td>
<td>Increase or decrease in activity, overall health, and/or prior chemotherapy.</td>
<td>Increase or decrease in activity, overall health, and/or prior chemotherapy.</td>
</tr>
<tr>
<td>Differences in CNS vs non-CNS activity</td>
<td>Increase or decrease in activity, overall health, and/or prior chemotherapy.</td>
<td>Increase or decrease in activity, overall health, and/or prior chemotherapy.</td>
<td>Increase or decrease in activity, overall health, and/or prior chemotherapy.</td>
</tr>
</tbody>
</table>

Increasingly, sponsors are generating data in preclinical models as part of early drug discovery efforts. There are legitimate limitations to this work, including biological BBB distinctions between species, blood-tumor barrier leakiness, and limited intracranial solid tumor models. Notably, both craniotomy and laparotomy have been associated with CNS responses in NCLC and HER2-positive breast cancer, respectively, despite limited intact BBB penetration. The panel discussed that including adjuvant strategies early in drug development to understand the CNS profile of investigational agents, such as CSF sampling, pneumococcal CSF, or intrathecal therapy, could be quite useful. However, requiring such data before allowing patients with brain metastases to enter studies could prevent 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 an unnecessary burden for an entire patient population.

Finally, there may be situations where 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 treatable brain metastases. Thus, inclusion may be justified, particularly early in drug development.

LEPTOMENINGEAL METASTASIS

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 prognoses are improving in some patient subsets, including NCLC.

Treatment may include the placement of shunts to relieve intracranial pressure and delivery of chemotherapy to the intrathecal space. Even when patients respond to the shunt, progression of the disease tends to be slow. LMD is frequently not measurable in the traditional sense. Of note, the FDA has recently published a proposal to standardize the assessment of LMD in clinical trials.

Several systemic agents have demonstrated efficacy in patients with LMD, and more studies focused on such patients are needed. Patients with LMD provide an opportunity for serial CSF sampling with respect to pharmacodynamic studies at the same time, long-term survival is common and does not necessarily equate to clinical LMD. Thus, patients with imaging-only studies or equivocal findings and no clinical evidence of LMD should not necessarily be considered to have LMD for trial eligibility exclusion. Despite the significant treatment 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 end points. The panel stressed, however, that these patients need new options, and clinical trials (or dedicated cohorts within a larger study) are strongly encouraged. Examples of trials specifically addressing this population include intrathecal
Regulatory Advancements for Patients with Brain Metastases

TRAUMATREAT (ClinicalTrials.gov identifier: NCT01352007), TRESIBATA (ClinicalTrials.gov identifier: NCT01636939), CEREBAL (ClinicalTrials.gov identifier: NCT01226451), and ABBREXIN (ClinicalTrials.gov identifier: NCT03260902).

Recommendations

The panel recommends inclusion of an LMD cohort in early-phase trials of antidepressant drugs with altered CNS penetration to study the effects of LMD on the pharmacokinetics of the drug. Consideration of CSF pharmacokinetic measurements is encouraged in this context.

When possible, inclusion of an LMD cohort in inter-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 inginuously equivocal findings.

Template for exclusion criteria (if justified). Details unknown. Known LMD is defined as positive CSF cytology and/or unexplained 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, symptomatically or minimally symptomatic patients with mild or non-cognitive leptomeningeal enhancement would not be considered to have LMD. In such patients, CSF sampling is not required to formally exclude LMD but rather performed to investigate the clinician’s level of concern in the absence of clinical symptoms.

PRACTICAL CONSIDERATIONS

Use of surveillance brain MRI scans in routine care has been controversial and has varied by dose rate. In patients with frequent, screening brain MRI scans are frequently ordered, whereas in patients with breast cancer, national and international guidelines recommend surveillance brain MRI be performed only if deemed necessary due to the absence of supporting a benefit. Patients with brain metastases have often been reluctant to order baseline brain imaging, unless mandated, out of concern that the identification of asymptomatic leptomeningeal lesions might jeopardize eligibility. Similar to identification of new or progressive CNS lesions necessitating continual participation (benefit despite extensive side effects), three will be resistance to routine surveillance brain imaging. The outcome of this situation is to the extent of impact of investigation agents in the CNS.

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

REFERENCES

Regulatory Advancements for Patients With Brain Metastases

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Modelling Clinical Trial Eligibility Criteria: Recommendations of the American Society of Clinical Oncology: Friends of Cancer Research Brain Metastasis Working Group

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Nancy U. Lin
Consulting or Advisory Role: Novartis
Research Funding: Genentech, GenomicHealth, ARRAY BioPharma, Novartis, Kadcyla, OnyxBiologics, Canadian Therapeutics

Tatiana Provenz
No relationship to disclose

Antoniette R. Tan
Consulting or Advisory Role: Astra
Research Funding: Merck (Inst), Genentech (Inst), Astellas (Inst), Merck-Frosst (Inst), Takeda (Inst), Gilead Sciences (Inst), Janssen (Inst)
Travel, Accommodations, Expenses: Card Centers of Excellence

Marthe Kostal
No relationship to disclose

Lachlan Ainsworth
Faculty: DePuy Synthes
Leadership: DePuy Synthes

Lachlan Ainsworth
No relationship to disclose

Lin et al

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Regulatory Advancements for Patients With Brain Metastases

Trial Eligibility for Patients With Brain Metastases

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Marthe Kostal
No relationship to disclose

Lachlan Ainsworth
Faculty: DePuy Synthes
Leadership: DePuy Synthes

Lachlan Ainsworth
No relationship to disclose

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Faculty: DePuy Synthes
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No relationship to disclose

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ABSTRACT

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 discussions; 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 non-clinical and clinical data indicates that inclusion is safe. Ejection fraction values should be used in 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 trial 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.


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 all patients with cancer participating in clinical trials. 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 (e.g., stage, diagnosis, scientific restraints), treatment-related (e.g., experimental nature, risk of toxicity, complexity), trial design (e.g., eligibility, placebo, follow-up), caregiver burden for testing, and other background factors (e.g., trial complexities, costs).

Patients with organ dysfunction are often excluded from clinical trials, regardless of specific drug metabolism or relative function of the organ. For instance, the pharmacokinetic decline in renal function may make a patient ineligible even when the drug under study does not have significant...
considered safety concerns, potential benefits, research impact, and potential hurdles of enrolling greater numbers of trial patients. Recommendations regarding expanded eligibility criteria that prioritize inclusiveness without compromising safety were sought through discussion during a focused group.

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 focused after discussion among similar groups assigned to consider other criteria and additional patient advocates. 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 could enable many more patients with commonly diagnosed cancers to participate in clinical trials.

KPNC is a fully integrated prepayment health care delivery system that was established in 1981. It has more than four million members and sees approximately 8,300 new analytic patients annually. The median age of members is approximately the same as that of the SEER Program database.

For all KPNC patients who were diagnosed with breast, colon, lung, and bladder cancer between 2013 and 2016 (n = 12,881), we analyzed for 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 last 5 years, history of myocardial infarction, cancer, prior coronary artery disease, diabetes, cerebral vascular disease, liver cirrhosis, glomerular filtration rate, and age. Total eligibility scores (TESS) are an empirically derived scale that correlates the potential magnitude of ineligibility by summing the preceding columns (Table 1). In this model, TESS aid in determining the potential number of charging eligibility weights would be on the number of eligible patients.

The KPNC analysis demonstrates the significant effect of organ 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 patients with bladder cancer had a 90% rate. This was correlated with patients with bladder cancer being much older (45% > 75 years old vs 16% of patients with breast cancer) and having more comorbidities (Table 1). Additional analysis by degree of renal dysfunction (Table 2) demonstrates how standard inclusion and exclusion criteria affects patient enrollment across common cancer types and suggests that renal function should be specified in the patient population under study (eg, adjusted for diabetes, age, creatinine, etc).

Exclusion of patients with GFR < 60 mL/min would preclude between 20% and 40% of patients from participating in future clinical trials. This result is likely conservative because the patients were measured at diagnosis and not historically or pretrial phase 1 trial candidates.

The KPNC analysis indicates that newly diagnosed patients across all four disease types early (< 1% of patients) have significant hepatitis 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 > 5% in breast cancer and 8% in colorectal cancer). Our analysis reveals how changes in patient inclusion or issue of age physiology may increase the number of patients eligible for clinical trials.

Table 1. Kaiser Permanente Northern California 2013-2016: Early Rates of Organ Dysfunction, Comorbidity, and Prior Malignancy Assess Cancer Types

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>% of Patients</th>
<th>Ineligible Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>100</td>
<td>0.1</td>
</tr>
<tr>
<td>Colon</td>
<td>77.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Lung</td>
<td>77.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Bladder</td>
<td>77.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Table 2. Kaiser Permanente Northern California 2013-2016: Levey Standard Renal Failure Cancer Risk Categories

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>1%</td>
</tr>
<tr>
<td>Colon</td>
<td>4%</td>
</tr>
<tr>
<td>Lung</td>
<td>7%</td>
</tr>
<tr>
<td>Bladder</td>
<td>9%</td>
</tr>
</tbody>
</table>

NOTE: Calculated using Cockcroft-Gault equation.
concluded that the risk of excessive hematologic toxicity or poor outcomes in patients with renal insufficiency but good perfor-
mance status may be mitigated with appropriate dosing modifications.

After a retrospective analysis, authors of the Gynecologic Oncology Group study found that their data do not support excluding patients with GFR < 60 mL/min from clinical trials.12-14

Doses were slightly lower or several days were withheld in patients with renal impairment, as well as those with AST or ALT > 3 times the upper limit of normal. This was interpreted as necessary in patients with normal hepatic function. However, patients with severe hepatic impairment often did not tolerate approved doses. This intolerance, however, is often a result of poor performance status rather than an alteration in systemic PK measures. Another complicating factor in patients with liver dysfunction is that an investigational agent may cause liver toxicity and therefore may exacerbate un-
derlying liver dysfunction.

Current clinically available hepatic function testing does not fully describe liver function, particularly drug metabolite cyto-
p probes. There are a group of patients with normal function, mild liver dysfunction was associated with a statistically significant but small increase in grade 3 or 4 nonhematologic toxicities. These observations concluded that patients with mild renal dysfunction can be enrolled without clinically meaningful increase in the risk of toxicity and without altering the minimum-tolerated dose determinations.

Hepatic Dysfunction

Hepatic criteria for hepatic function include liver function tests (LFT), such as serum aminotransferases (AST and ALT), bilirubin, etc. less frequently, alkaline phosphatase, γ-glutamyltransferase, alkaline phosphatase, alanine dehydrogenase, and conjugated bilirubin. Conclusions: Measurement of this enzyme is used to classify patients into groups for trial purposes (e.g., total bilirubin level and LFT functions). The most common approach of excluding patients with values greater than the ULN is routine, but for all conditions described above, the ratio of total bilirubin is used. Total bilirubin is an indicator of hepatic function; elevated bilirubin levels have been observed in patients with severe liver disease. Total bilirubin: The normal range is 0.2 to 1.2 mg/dL (3.4 to 21 micromoles/L). A total bilirubin level above 1.2 mg/dL (21 micromoles/L) is considered abnormal and is associated with liver disease.

Cardiac Dysfunction

Oncology clinical trials often exclude patients with a previous history of cardiovascular disease, including coronary artery disease, hypertensive heart failure, and other cardiac events within specified time frames. Exclusions on the basis of cardiac disease may decrease enrollment of patients by approximately 5%.15 Ejection fraction (EF) as a marker of current cardiac contractility is also commonly used at study entry. Typically, patients must have an EF of 45% or higher to achieve entry criteria for registration trials. The Eastern Cooperative Oncology Group (ECOG) and the American College of Radiology Imaging Network (EAN) 219 study is suitable for the following more inclusive criteria: EF 0 to 2 allowed; liver function (e.g., liver function test) is not allowed as a result of hepatic impairment by chronic lymphocytic leukemia; GFR > 60 mL/min; and prior clinically significant adverse events (e.g., if there is a history of prior malignancy; patients) must not be receiving other specific treatment (other than hormonal therapy for their cancer) in the last 4 weeks. This improved prior malignancy language may still need modification, as we see that chemotherapy administration rates with high-risk malignancies have the same outcomes as patients without prior malignancies.16 Other laboratory parameters may be abnormal as a result of the underlying disease. Also, some patients may require modifications or exclusion of patients with mild renal dysfunction. For example, patients with proteinuria > 1 g/day, uncontrolled hypertension, or chronic kidney disease may require dosing modifications. Patients with moderate hepatic impairment are often excluded from clinical trials where safety or efficacy is the primary objective. Direct guidance for patients with hepatic impairment is on the basis of changes in total bilirubin level 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. Direct guidance for patients with hepatic impairment is on the basis of changes in total bilirubin level and, therefore, effective treatment may lead to a return to normal values.
Preliminary regulatory advancements for patients

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 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 treatment-directed treatment should be allowed to participate on a trial for another cancer that requires treatment.

Homologous Malignancies

- Inclusion of patients with laboratory parameters that are out of normal range as a result of disease may be appropriate (e.g., cytopenia from bone marrow infiltration, LFT abnormalities from disease involvement in lymphoma).
- Inclusion of patients with disease-specific comorbidities (e.g., 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 investigative review boards, cooperative oncology organizations, 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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AUTHOR CONTRIBUTIONS

Concepts and design: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

REFERENCES

AUTHOR SUPPORT

Administrative support: Caroline Schindel, Suverna S. Brinquishe
Provision of study materials or patients: Suverna S. Brinquishe
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Friends of Cancer Research

Regulatory Advancements for Patients

National Cancer Institute/Oncology Delegation Working Group on Treatment Design.


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Friends of Cancer Research. cancer.org

Moderating Trial Eligibility for Patients With Ovarian Dysfuntion

Stuart M. Lichtman, Memorial Sloan Kettering Cancer Center, New York, NY; Donald Harvey, Emory University School of Medicine, Atlanta, GA; Marie-Anne Damiette Smith and Atique Rahman, US Food and Drug Administration, Silver Spring, MD; Michael A. Thompson, Aurora Health Care, Milwaukee, WI; Nancy Rewcastle, Fight Colorectal Cancer, Springfield, MO; Carolin Schindel and Suverna S. Brinquishe, American Society of Clinical Oncology, Alexandria, VA; Patricia Carter, Genentech, South San Francisco, CA; Lewis Pernbach, Kaiser Permanente Northern California, Redwood City, CA; and Donna Walker, Bristol-Myers Squibb, Philadelphia, PA.

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Affiliations

National Cancer Institute/Oncology Delegation Working Group on Treatment Design.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Modifying 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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Stuart M. Lichter
Consulting or Advisory Role: Magellan Health

R. Donald Harvey
Consulting or Advisory Role: BERGenBio, Spectrum Pharmaceuticals
Research Funding: Eisai (Inst), Taiho (Inst), Nextran (Inst), Celgene (Inst), Janssen (Inst), Amgen (Inst), Astellas (Inst), Calithera (Inst), Amgen (Inst), AstraZeneca (Inst), Nektar (Inst), AbbVie (Inst)

Marie-Arme Daniele Smit
No relationship to disclose

Atul Desikan
No relationship to disclose

Michael A. Thompson
Stock or Other Ownership: Daiichi Sankyo
Consulting or Advisory Role: Amgen, aBx, Medivation, AstraZeneca, Galderma, Genentech, Helsinn, Jazz Pharmaceuticals, Medivation, Millennium, Novartis, Pfizer, Prostate Cancer Foundation, Sanofi, Spectrum, Takeda, VelaPharm, Velindre, Vi資x
Research Funding: Aventis Biotechnology, AstraZeneca, Genentech, Medivation, Millenium, Novartis, Sanofi, Seattle Genetics, Takeda, VelaPharm, Velindre, Vi資x

Nancy Borch
Travel, Accommodations: Boehringer Ingelheim

Caroline Schenklen
No relationship to disclose

Sanne S. Bruson
No relationship to disclose

Patric Cornagg
Employment: Genentech

Honoraria: Genentech

Dana Weiser
Employment: Bristol-Myers Squibb

Stock or Other Ownership: Abramson Research Foundation (1)

Louis Fehrenbach
Research Funding: Genentech (1)

Friends of Cancer Research

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

Lai Gion, S. Perry Ivy, Frank M. Bole, Eric Rubin, Katherine Thyssen, Marko Donoghue, Sensanticis Roberts, Gavazzi Brunovska, Jennifer Crain, Nancy Goodman, Caroline Schmidl, and Gregory Birnbaum

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 enrollment may result in off-label use without dosing information as the only access to new drugs. A multisectoral 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 frontline 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 drug 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 asymptomatic at diagnosis, are associated with unacceptable low survival rates based on inadequate existing treatment options and available drugs.1-4 Cancer remains the leading cause of death from disease in children, with approximately 2280 children dying from cancer each year in the United States.5 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.6,7 There is a 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 benefited 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, with after completion of one or more adult clinical trials, or sometimes not at all.8,9 Meanwhile, many adult oncology clinical trials exclude...
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 treatments only after those 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 increases the need for pediatric-specific 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 number of successes of new agents have become more precisely defined, the oncology community is increasingly prioritizing application of scientific, clearly relevant approach to assessment of efficacy criteria. 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.

**PROCESS**

A multisite external review was convened in May 2015 by ASCO and Friends of Cancer Research to identify opportunities where it is scientifically appropriate to expand trial eligibility. Four working groups were established: early phase, 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 how the minimum age for 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 presented patients younger than age 16 years from enrolling in adult oncology clinical trials, and we suggest ways 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 younger patients in early phase investigational cancer drug trials might be accomplished.

This working group acknowledges that there may be unique safety issues in children, and that children may have different toxicity or drug tolerance and administration profiles compared with adult patients, as has been shown with the use of ferritin.20 Nevertheless, it is clear that we are not only able to evaluate new agents in the perioperative setting rather than relying on postmarketing surveillance or off-label use of a new cancer treatment in children.

**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 wide range of tumor types and pediatric subtypes. In this scenario, the minimum age for 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 presented patients younger than age 16 years from enrolling in adult oncology clinical trials, and we suggest ways 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 younger patients in early phase investigational cancer drug trials might be accomplished.

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**GENERAL RECOMMENDATIONS FOR INCLUSION OF PEDIATRIC AND ADOLESCENT PATIENTS**

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

1. **Adult protocols** to which Phase II or III pediatric trials are closely linked, in which adult patients have been enrolled as safety and efficacy signals in a fully informed manner. Adult pediatrics as investigators to provide expertise and help address logistical issues. These issues may arise because clinical care of research; children occurs primarily at academic pediatric institutions, which will at times not allow adult patients or conduct adult clinical trials.

2. Ideal trial designs should use a dual institutional review board and/or inclusion of pediatric expertise on the institutional review board or ethics committee of most centers to help educate and support the sponsor and investigators as well as in review of such studies.

3. The inclusion of external 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. Younger patients and those with organologic or leukemic conditions may not be able to receive tablets or capsules. Development of either its alternative compounds, compounds, or other pediatric forms for use in those populations should be considered early, otherwise, unnecessary delay to pediatric evaluation will occur. If there is sufficient reason to believe a new agent will have potential application to a pediatric population or in adult patients who have similar needs for broad formulations, the need to formulate solutions should be tested earlier. Testing of liquid formulations to determine feasibility when delivered through a pump or gastrostomy tube can be a second consideration for these compounds, as taste composition may affect pharmacokinetics or dosing recommendations.

5. In different tissue types in adults compared with children. Examples of the include an ALK inhibitor that may be used in patients for non-small-cell lung cancer but should be tested in children with ALK-positive anaplastic large-cell lymphomas or neoplastic neoplasms.11,12 Recommendation. We recommend that trialists consider conducting a trial in a specific pediatric population for which the drug has significant activity or benefit. This may include a trial in patients with a specific diagnosis that benefits from high-dose chemotherapy and hematopoietic stem cell transplantation or a trial in patients with a specific disease that benefits from high-dose chemotherapy and hematopoietic stem cell transplantation.11,12

6. Early-phase clinical trials should be considered for trials in patients with specific molecular targets or signaling pathways affected by the drug.11,12 Protocols should include a longer period of follow-up to ensure adequate toxicities of the drug.11,12

7. Developing new agents for pediatric patients can be a significant challenge. Although the trial is not easy, it is critical to be able to assess multiple parameters that may differ when fewer agents are available for testing in children and that may not be evident in adult patients.

**Sample template for inclusion criteria.**

<table>
<thead>
<tr>
<th>Age</th>
<th>Pediatric patients aged 1 to 18 years.</th>
<th>Pediatric patients aged 1 to 18 years.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility</td>
<td>Pediatric patients aged 1 to 18 years.</td>
<td>Pediatric patients aged 1 to 18 years.</td>
</tr>
<tr>
<td>Exclusion</td>
<td>Pediatric patients aged 1 to 18 years.</td>
<td>Pediatric patients aged 1 to 18 years.</td>
</tr>
</tbody>
</table>

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

4. Adolescent/pediatric cohort enrollees will be permitted to sign consent, either in person or remotely, to allow them the opportunity to be involved in the clinical trial. This includes, but is not limited to, the collection of demographic and medical history information.

5. The trial design, protocol, and data management will be modified as necessary to ensure the safety and well-being of all participants. This includes, but is not limited to, the establishment of a centralized data monitoring committee to review progress and make recommendations.

6. The trial will be conducted in accordance with all applicable laws and regulations, including those governing the protection of human subjects.

7. The trial will be conducted in a manner that is compassionate and sensitive to the needs of participants, with special attention given to the privacy and confidentiality of personal information.

8. The trial will be conducted in a manner that is respectful of cultural and social diversity, with special attention given to the needs of underserved and underrepresented populations.

9. The trial will be conducted in a manner that is transparent and accountable, with regular reporting of progress and results to participants, stakeholders, and the public.

10. The trial will be conducted in a manner that is sustainable and reproducible, with the development of tools and processes to support the continuity of the research effort.

11. The trial will be conducted in a manner that is inclusive and collaborative, with the involvement of diverse stakeholders and communities.

12. The trial will be conducted in a manner that is ethical and responsible, with the adherence to the principles of integrity, accountability, and transparency.

13. The trial will be conducted in a manner that is innovative and forward-thinking, with the pursuit of cutting-edge research and the development of new knowledge.

14. The trial will be conducted in a manner that is adaptive and responsive, with the ability to adjust to new information and changing circumstances.

15. The trial will be conducted in a manner that is responsive to the needs of participants, with the provision of clear and accessible information and support.

16. The trial will be conducted in a manner that is collaborative and integrative, with the involvement of multiple disciplines and perspectives.

17. The trial will be conducted in a manner that is inclusive and diverse, with the representation of diverse perspectives and voices.

18. The trial will be conducted in a manner that is sustainable and environmentally friendly, with the minimization of waste and the use of sustainable practices.

19. The trial will be conducted in a manner that is accessible and equitable, with the provision of opportunities for participation and engagement.

20. The trial will be conducted in a manner that is inclusive and participatory, with the involvement of participants and communities in the research process.
including patients and families, investigest, the pharmaceutical industry, regulators, advocacy groups, and the institutional review boards tasked with protecting patient safety. This can 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 conducted globally, engagement and coordination with international regulatory authorities will necessarily to necessary to support sponsors in developing strategies that meet regulatory requirements while maximizing the data derived from patients with cancer can benefit from the two critical needs currently being conformed to cancer care.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available at www.lancet.com.

AUTHOR CONTRIBUTIONS


REFERENCES

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

The following information discloses all relationships of the author with any organization or entity that produces or markets health care products used or studied in the care of patients. No organization represents a financial conflict of interest.

Lisa June,
Employment: ARAD (1)
Leadership: ARAD (1)
Stock or Other Ownership: ARAD (1), Amgen, Sanofi, Caligen, ARAD,
Genentech Oncology, Agios (2)
Hematologic Angios
Consulting or Advisory Role: Caligen, Medimmune, Novartis, Profil
Communication/Genentech, Amgen, Medimmune
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Travel, Accommodations, Expenses: Amgen, Genentech

S. Percy Ivy
No relationship to disclose

Frank M. Bove,
Research Funding: United Therapeutics (1)
Travel, Accommodations, Expenses: None

Eric Rubino,
Employment: Merck
Stock or Other Ownership: Merck

Katherine Thaxton
Consulting or Advisory Role: Novartis
Speakers Bureau: Novartis
Travel, Accommodations, Expenses: Novartis

Martha Donohue
No relationship to disclose

Sara Leeon
Travel, Accommodations, Expenses: Genentech

Sara Leeon
No relationship to disclose

Jennifer Erck
No relationship to disclose

Nancy Goodwin
No relationship to disclose

Caroline Scholfield
No relationship to disclose

Gregory Reaman
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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.
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. 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.” 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.

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.

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. Those requirements subsequently were incorporated into FDA’s regulations.

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. 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.” 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 practice standards.”

- **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.

- **Real world evidence.** FDA has recently noted that “the 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.”

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:

- 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.

- 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), 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. 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. 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).13

• 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.14 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.15 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.16, 17

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.18 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.19

• 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.20
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

Innovator drug manufacturers seeking to make a change to product labeling for their own approved drug must submit a supplemental new drug application (NDA) to the FDA. A NDA 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)

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 same-ness 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:

1. 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.

2. 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.

3. 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 manufacturers 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.

<table>
<thead>
<tr>
<th>Tumor setting</th>
<th>FDA-Approved Uses on Labeling</th>
<th>NCCN-Recommended Preferred Category 1 Uses</th>
<th>Number of NCCN Preferred Category 1 Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
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<tr>
<td>Esophageal and Esophagogastric Junction</td>
<td></td>
<td>✅</td>
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</tr>
<tr>
<td>Gastric</td>
<td></td>
<td>✅</td>
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<tr>
<td>Head and Neck</td>
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<tr>
<td>Hepatobiliary</td>
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<td>Malignant Pleural Mesothelioma</td>
<td></td>
<td>✅</td>
<td>3</td>
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<td>NSCLC</td>
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<tr>
<td>Small Cell Lung Cancer</td>
<td></td>
<td>✅</td>
<td>1</td>
</tr>
</tbody>
</table>

Sources: FDA-approved labeling for cisplatin available on FDA’s website, ANDA: 018657, Company: HQ SPCLT PHARMA; Link: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/018657s079lbl.pdf. NCCN Drugs and Biologics Compendium, entry for cisplatin.
REFERENCES

2 See 21 C.F.R. § 201.56.
5 See 21 U.S.C. § 355(j)(2)(A)(v); see also 21 U.S.C. § 355(j)(2)(A)(v) (requiring that ANDAs include information to show the labeling proposed for the generic drug is the same as the labeling approved for the listed drug).
6 See 21 C.F.R. Part 314.94(a)(8); see 21 C.F.R. Part 314.94(a)(8) (providing that ANDAs must include labeling that is the same as labeling approved for listed drug and must include a statement that the applicant’s proposed labeling ... is the same as the labeling of the reference listed drug except for differences annotated and explained under paragraph (a)(8)(iv) of this section).
9 Id.
15 Section 505(j)(2)(C) of the FD&C Act.
18 Abernethy et al. (2009).
21 Green et al. (2016).

45 The information in this section was drawn from the following guidance document: US Food and Drug Administration. Guidance for Industry: Changes to an Approved NDA or ANDA. April 2004.
48 ture-505(b-2-nda-submissions)/
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.

CONTRIBUTORS

Kenneth Anderson
Dana-Farber Cancer Institute, Harvard Medical School
Roger Dansey
Merck
Laura Lasiter
Friends of Cancer Research
Lisa LaVange
U.S. Food and Drug Administration
Bea Lavery
Genentech
Jim Omel
Cancer Research Advocate
Marc Scheineson
Alston & Bird LLP
Mark Stewart
Friends of Cancer Research
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, 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. 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. 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 cost 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 over-

all 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. 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 impacting these 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 of Revlimid. A provider or patient who searched only the Velcade 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 various stakeholders and scenarios in which labeling guidelines apply. 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.

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. 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.1 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 than the specific manner which was highly dependent upon the level of cooperation that existed between sponsors. 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 patent/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/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) will expire 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 (Darzalex, Janssen Biotech) was approved for multiple myeloma in combination with lenalidomide (Revlimid, Celgene) 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 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.

- Ibrance¹⁶ 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.
- Falsodex¹⁷ 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.**

<table>
<thead>
<tr>
<th>Trial Design</th>
<th>Pro</th>
<th>Con</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basket Trial</td>
<td>Beneficial for matching patients with low prevalence mutations to targeted gene therapies. Compares effectiveness of multiple drugs simultaneously.</td>
<td>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).</td>
</tr>
<tr>
<td>Umbrella Trial</td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>Common Control</td>
<td>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).</td>
<td>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.</td>
</tr>
<tr>
<td>Adaptive Trials</td>
<td>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.</td>
<td>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.</td>
</tr>
</tbody>
</table>

### APPENDIX

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

<table>
<thead>
<tr>
<th>Approaches to Comparator Arms</th>
<th>Pro</th>
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</tr>
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<tbody>
<tr>
<td>Add-on</td>
<td>Streamlines the clinical trial by eliminating the lag phase which requires patients to stop current treatments.</td>
<td>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.</td>
</tr>
<tr>
<td>Parallel</td>
<td>Allows direct comparison of multiple therapies (or combinations versus individual components) in parallel or interrogation of therapy efficacy in different cancer settings.</td>
<td>Can require additional experimental arms and increasing number of patients to enroll.</td>
</tr>
</tbody>
</table>

**Table 3: Considerations for use of historical data**

<table>
<thead>
<tr>
<th>Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the intended use?</td>
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<tr>
<td>• 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)?</td>
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</tr>
<tr>
<td>• Are the data intended to supplement or replace a clinical trial arm (provided patient-level data are available)?</td>
</tr>
</tbody>
</table>
Table 3: Framework to streamline clinical trial design for combination therapies by optimizing use of historical data.

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

<table>
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<tr>
<td></td>
<td>• Is the length of time since collection relevant for intended use/to intended population?</td>
</tr>
<tr>
<td></td>
<td>• What is the clinical trial design of the prospective study?</td>
</tr>
<tr>
<td>Do data meet guidelines for robustness?</td>
<td>• How applicable are existing data to the patient population in the prospective trial?</td>
</tr>
<tr>
<td></td>
<td>• (Are patient-level covariates available and of sufficient quality for use in accounting for differences?)</td>
</tr>
<tr>
<td></td>
<td>• How applicable are existing data to the disease setting?</td>
</tr>
<tr>
<td></td>
<td>• Are the data collection methods and timing of collection similar?</td>
</tr>
<tr>
<td></td>
<td>• Are the endpoints used relevant to new intended use?</td>
</tr>
<tr>
<td></td>
<td>• Were the clinical trial sites similar?</td>
</tr>
</tbody>
</table>

REFERENCES

12. https://www.drugs.com/international/dotunumah.html  
The Value of Addressing Patient Preferences

Jeff D. Allen, PhD,1 Mark D. Stewart, PhD,2 Samantha A. Roberts, PhD,3 Ellen V. Sijpel, PhD
Friends of Cancer Research, Washington, DC, USA

ABSTRACT

Recent scientific progress in, for example, leading to transformative new treatments for diseases that previously had marginal or even no treatment options. This is often great news for people affected by these diseases, but it has also placed them in the health care system in terms of the value of new treatment options. Efforts to make these new treatments effective and widely available have been ongoing. While new treatments can also improve patient outcomes, they may also provide the basis for assessing the value associated with new medical products. Given the growing emphasis in health care, value frameworks present an opportunity to evaluate new therapeutic options in terms of their value to patients and potentially lead to a more economically sustainable health care system. In summary, addressing patient preferences to meaningful improvements in health outcomes is the primary focus of any assessment of the value of a new intervention. Commonly used methods to evaluate new treatments include patient satisfaction, quality of life, and cost-effectiveness. Value frameworks should allow for flexibility in clinical and patient data, incorporate patient preferences, and contribute to meaningful improvements in health outcomes.

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

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Commentary

Scientific advances have resulted in a number of innovations 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 these new therapies have, however, spurred stakeholder groups to develop "value frameworks" to assess the health and cost values 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 view of the patient 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 framework must 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 Drug Value, and the National Comprehensive Cancer Network Disease Societies. Each of these frameworks highlights different aspects of the value of cancer therapies and addresses different aspects of the value of cancer therapies and addresses different aspects of the value framework.

* Address correspondence to: Jeff D. Allen, Friends of Cancer Research, 1800 M Street NW, Suite 1905 South, Washington, DC 20036, USA. E-mail: jallen@foac.org.

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

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

Tools that overemphasize overall survival while underemphasize evidence that also improves outcomes 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 absence of preclinical evidence of proof of patients timely access to potentially beneficial treatments. When interventions are approved in patients, it does create some uncertainty as to whether the surrogate end point will reflect improvements in overall survival.

These instances where surrogate end points do not always equate to improvements in overall survival when analyzed in late, postmarketing clinical 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 frameworks are applicable, value frameworks should quickly incorporate this information as 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 have 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-centered approach can positively influence clinical trial designs. Crossover, however, can also result in a loss of information about the distinct impact of any new interventions when compared with a more rigid clinical trial design in which crossover would not be allowed [10]. If a value assessment is made to compare the relative improvement in survival yielded by a new intervention to that of another, spawn might inadvertently be driven to rely solely on premarket overall survival data; patients may then be denied the opportunity to crossover to make the intervention perceived as more valuable in value assessment frameworks. Furthermore, patients may result in a more closely 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 endpoints 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 going forward for individuals. These scenarios demonstrate, however, that value framework metrics should be constructed in a flexible manner that articulates 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 fully capture the benefits of such interventions. The long-term value of an intervention and other factors also need to reflect nonfinancial end points, such as impact on quality of life and quality of care. Some of these nonfinancial end points reflect nonfinancial end points, such as impact on family and social life. Therefore, we should consider such nonfinancial end points in our analyses. We recognize the complexity of assessing the value of new therapies, particularly in a rapidly evolving field. Like oncology, it is not yet even the case at the cost of blocking patient access to potentially life-saving therapies or undermining their current treatments. State of financial risk: No funding was provided for this commentary.

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