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Improving Evidence Developed from Population-Level Experience with Targeted Agents

Mark McClellan, Director, Health Care Innovation and Value Initiative
and Senior Fellow, Economic Studies, The Brookings Institution

Richard L. Schilsky, Chief Medical Officer, American Society of Clinical Oncology

Dane Dickson, Director of Clinical Science, MolDX, Palmetto GBA

Samuel Nussbaum, Executive Vice President, Clinical Health Policy
and Chief Medical Officer, WellPoint, Inc.

Dietmar Berger, Senior Vice President and Global Head – Clinical Hematology/Oncology, Genentech

Jane Perlmutter, Founder and President, Gemini Group

Vincent Miller, Chief Medical Officer, Foundation Medicine, Inc.

Jennifer Malin, Medical Director, Oncology for Care Management, WellPoint, Inc.

Gregory Daniel, Fellow and Managing Director, Engelberg Center for Health Care Reform,
The Brookings Institution

Richard Pazdur, Director, Office of Hematology and Oncology Products,
U.S. Food and Drug Administration

Janet Woodcock, Director, Center for Drug Evaluation and Research,
U.S. Food and Drug Administration

Introduction

The prescription and use of medical products outside of regulator-approved indications – so-called “off – label” use – is common in U. S. health care and supported by varying degrees of evidence. As providers work to characterize and diagnose a patient’s illness, they are able to draw on medical literature, trials information, practice guidelines and standardized therapeutic pathways to develop treatment plans they deem most likely to achieve the best possible clinical outcome for each patient. In the routine practice of medicine the prescribing physician may choose a therapy that may not be approved by the U.S. Food and Drug Administration (FDA) for the patient’s particular condition but has some clinical evidence supporting its use by the patient. Such off-label use is especially prevalent in the field of oncology, where significant unmet medical need, the diversity of the patient population and a constellation of rare cancer types combine to make the traditional process of treatment decision-making more difficult to apply. Some patients may suffer from a malignancy with distinct biomarker signatures that do not align with the abnormalities found in other cancers of the same histologic type. Still other patients may have exhausted multiple lines of treatment or approved treatment options but maintain adequate functional status. In these cases and others, the ability to harness additional resources to treat a patient is an important part of the physician’s toolbox.

As the science underpinning cancer treatments continues to improve, so too does the potential precision with which oncologists can choose to apply a drug. For example, it is biologically plausible that a targeted anti-cancer agent that has efficacy in a biomarker-defined population in one cancer type may also have activity in another cancer type expressing the same biomarker. Matching patients with treatments based on these criteria is further improved through advancements in rigorously-validated, comprehensive next generation sequencing (NGS) and other sophisticated laboratory-developed tests. In short, an increasing

number of targeted cancer treatments may mean that off-label use will become even more important as a means to offer patients the chance to receive a potentially effective therapy.

Although off-label prescribing is often necessary in oncology, it is not without its challenges. Data providing clinical support for use of an off-label treatment is sometimes limited. With questions about actual benefits and side effects and the high costs of many therapies, a decision to pursue off-label treatment may not be optimal in many cases. In addition, insurers may be reluctant to provide coverage if the off-label indication being treated is also not included in one of the major drug compendia. Given the extremely low participation rate of cancer patients in therapeutic clinical trials (generally recognized as 3-5%) and the large number of targeted therapeutic options becoming available, it is not feasible to perform randomized trials for every drug in every indication. A systematic approach to routinely capture the outcomes of patients who receive off-label treatments is needed. Such systems could provide better evidence to support treatment decisions as well as provide evidence and/or infrastructure that could support the design of more rigorous and efficient studies needed for labeling or compendia changes.

A range of proposals have sought to generate better evidence to guide cancer care. Reflecting the growing importance of treatment decisions based on genomic tests, recent proposals have focused both on the process by which off-label treatment decisions are made and the evidence development mechanisms that would allow further progress. In this issue brief, we describe the key features of proposals from the American Society of Clinical Oncology (ASCO) and Palmetto GBA, intended to provide evidence on off-label use and facilitate patient access to potentially effective treatments. We use these proposals to illustrate the key data and operational issues that proposals for improving off-label evidence will need to address to succeed, and describe potential solutions to accelerate progress.

The Importance of Evidence Development Proposals

Proposals to improve the manner in which providers apply and learn from use of targeted agents have complementary goals. The ultimate goal is to improve patient access to the most appropriate, efficacious treatment for their particular cancer. To accomplish this, evidence generated on the outcomes of off-label drug use should ideally be used to better inform clinical and shared-decision making by patients and providers, safety and effectiveness of treatments in clinical practice, and the evidentiary basis for coverage of highly-targeted treatments used off-label. In essence, successfully implemented evidence collection efforts will help to bring “order out of chaos:” as the number of targeted therapies and availability of genomic profiling in advanced cancer continue to increase, so too do the possibilities of prescribing and providing access to drugs off-label without a strong evidentiary basis for the decision.

An infrastructure built to support the development of better evidence on off-label drug use dovetails with other, ongoing efforts to improve the body of clinical outcomes information and move stakeholders toward a truly learning health care system. The FDA’s Sentinel Initiative, for example, is an important post-market safety surveillance tool for monitoring adverse events in the real-world patient population. The Patient Centered Outcomes Research Institute’s PCORnet is establishing a nationwide infrastructure for comparative effectiveness and patient-centered outcomes studies. A number of registries exist for tracking patient data and outcomes within specific diseases or product categories. Prospective clinical trials form the basis of drug development and regulatory approval, underpinning much of the post-market research outlined above. These are all important and worthy pieces of the same overarching research continuum, and finding ways to collect data on treatments used off-label and maximize its compatibility with other modes of evidence development will be key.

It is important to note that these efforts exist on a spectrum, from “real world evidence” (RWE) developed from observational studies using data captured through routine practice to prospective, complex randomized controlled trials (RCTs). As such, each effort has unique characteristics and requirements.

The potential exists to develop better evidence throughout this spectrum with thoughtful attention to the protocol, the type and amount of data to be collected, the level of human subjects research protections required, external stakeholder interactions, and the potential downstream uses of the evidence generated. While considerations of the intended uses of the data collected should dictate the design of such a system, programs should also be flexible enough to support evidence development across a range of uses and provide incentives for clinicians and health systems to implement more rigorous and structured programs when needed. For example, an all-comers-type registry with minimal study requirements could capture information on clinical use already happening and expand participation of clinicians and patients to expedite hypothesis generation based on efficacy signals; this could occur across multiple cancer types and provide important evidence to guide the development of more efficient RCTs to test those hypotheses when feasible. Such a program and its infrastructure could then potentially support “plug-and-play” studies with more rigorous parameters; these could be used to develop more robust evidence to support new clinical pathway or guideline development, movement of an off-label use from “off” to “on” compendia, or even potentially support label changes by FDA. A more restrictive or structured program might generate better evidence but might also be harder to implement and face more resistance from clinicians. Positioning an evidence development program at various points along the RWE-RCT spectrum will therefore require having the appropriate methods and incentives in place to ensure the effort is meaningful for all.

Application of Evidence Developed from Off-Label Drug Use

Exploring the potential uses for evidence developed from off-label treatment will help to position any proposed collection effort on the RWE-RCT spectrum and to further elucidate program specifics. Toward that end, it is helpful to outline how various stakeholder groups could harness off-label use data and how those applications should inform the goals of the program:

- *Informing clinical decision-making*
Better outcomes information on off-label use of drug products could have multiple positive impacts on the clinical decision-making process. The data helps to create a stronger evidentiary basis for future treatment decisions; as greater evidence accrues on patient response and experiences with the off-label treatment, oncologists and patients gain more confidence in predicting response and appropriateness for a wider range of clinical scenarios.
- *Informing coverage decisions*
In order to serve their members, payers typically base coverage decisions on clinical evidence and outcomes data available for a treatment, published scientific literature, and expert input reflected in clinical guidelines and compendia; this in turn may sometimes aid payers in defining treatment pathways. Off-label indications that have enough supporting evidence to be listed in the major drug compendia are covered by law by Medicare, and often covered by private payers. Typically, those uses that are not supported by the compendia are not covered, although health plans have developed approaches to support oncology drug therapy when proven treatment options have been exhausted and there are no alternatives. A robust off-label evidence collection system could help bolster the data underpinning these resources, either by generating stronger evidence to improve clinical pathways or by generating enough evidence to effectively move a use from off to on-compendia. This allows for more confidence in off-label coverage policy and raises the possibility of better identifying those off-label treatments that fail to produce clinical benefit. A clearer understanding of how certain drugs are performing off-label could also help payers cover care that has a positive impact on patients; it may also serve a secondary function in helping payers design and implement provider incentives or rewards to drive prescribers toward more efficient, effective treatment decisions. Finally, the inclusion of off-label outcomes in determining coverage could lessen potential barriers to patient access if the prescribed treatment would not

have been covered previously, and could potentially help support modifications to the drug label as described below.

- *Validating diagnostics*

The process of generating evidence related to diagnostic test results, off-label treatment use, and clinical outcomes may also help evaluate the diagnostic tests as well as the drugs. In some cases, analytic and clinical validation of comprehensive NGS tests may have been published.¹ However, for “hot spot” NGS tests or certain in-house developed tests, data on analytic and clinical validation may not be available. In the latter case, the off-label program provides a vehicle for validating the test and its performance, though this may require a “gold standard” reference test and tumor sample storage for retrospective analyses. Such efforts to discern the impact of diagnostic tests from observational analysis would likely raise the same type of issues as described above. That is, a more structured evaluation could require additional data collection on test controls, test characteristics, laboratory procedures, and other parameters which would generate more robust evidence. This scenario is likely to be more difficult to implement, however, because it would require extensive data collection about test characteristics and information that is not readily available to oncology practitioners.

- *Informing regulatory discussions*

The downstream potential for using off-label evidence developed through a registry or other real-world methods to initiate or inform regulatory interactions is of great interest to manufacturers. While not a regulatory decision per se, one of the most important applications might be in expanding information about the safety and efficacy of the drug in populations that would not have qualified to participate in the original clinical trials, which in turn could inform revisions to a drug’s label. Taken further, a more tightly-controlled off-label program (i.e., closer to RCTs) could potentially generate a body of evidence that could be used to expand a drug’s approved list of indications. Designing a system capable of such an end, though, will most likely require FDA approval of an IND for the study design and data collection effort; this increases the data and analytical requirements of the program as well as the likely financial costs, and, again, moves the proposed system toward the clinical trial end of the research spectrum.

- *Informing full-scale clinical trials*

A more immediate potential benefit of collecting off-label evidence, and another of importance for drug sponsors, may be in its application as a hypothesis-generating tool. As strong signals in specific patient populations begin to appear, manufacturers could initiate follow-on clinical trials within the patient population that received the off-label treatment. Indeed, an approach similar to the recently-established Lung Cancer Master Protocol may be feasible, where decision-making regarding follow-on trials is enabled within the framework of the program itself. An off-label program might also be informative for trials that are in planning stages but ultimately might prove futile; that is, data on off-label use could be of potential benefit to sponsors if they provide early signals of inefficacy, allowing sponsors to allocate resources to other drugs or trials with greater clinical potential. Most importantly, early signals indicating lack of efficacy would also help patients avoid unnecessary toxicities, as well as financial expenditures across the health care system. Competition between the simplified off-label studies highlighted here and more robust clinical trials should be avoided if it is possible for the patient to participate on the clinical trial.

¹ Frampton GM et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. *Nature Biotechnology*. 2013;(31):1023-31. Epub 2013/10/20.

Potential Pathways to Better Evidence Development

As outlined above, improved clinical evidence on the real-world application of treatments used off-label could bring better evidence to care of cancer patients and thus could have great value to patient, clinician, payer, and regulator decision-making. The ASCO and Palmetto GBA proposals, and their historical antecedents, are illustrative of the types of approaches needed to realize such value. These proposals have some features in common with previous initiatives in Medicare and private insurance to generate better evidence through data collection and analysis as part of coverage of treatments where the evidence is limited.

Coverage with Evidence Development

Medicare's Coverage with Evidence Development (CED) serves as an important case study for exploring hurdles to successful implementation. The Centers for Medicare & Medicaid Services (CMS) codified CED into policy in order to provide Medicare beneficiaries with access to treatments and procedures for which little clinical evidence existed within the senior population, which is typically underrepresented in clinical trials. Physician payment under a provisional coverage determination for the medical product or procedure is provided conditional on participation in a registry designed to capture the outcomes of treatment. As evidence accrues CMS can choose to either discontinue provisional coverage, to apply a National Coverage Determination (NCD) and expand full coverage to the entire Medicare population, or to potentially grant coverage for a subset of patients in which the treatment is shown to be effective. An example is CMS' CED policy for the use of fluorodeoxyglucose positron emission tomography (FDG-PET) in initial diagnosis of solid tumors. Initiated in 2005, the FDG-PET CED decision established the National Oncology PET Registry (NOPR), which collected prospective data on Medicare beneficiaries receiving FDG-PET scans for diagnosing and staging their tumor; based in part on evidence collected through CED, coverage was expanded through a full NCD in 2013.

Though there are examples of CED arrangements that were pursued for certain off-label, off-compendium treatments, to date the policy has been hampered by a number of challenges that have significantly limited its success. In general, there has been limited infrastructure for collecting the additional data needed to develop better evidence. Individual CED programs have had to be bootstrapped to other existing efforts in order to be implemented and have faced difficulty in assembling a coalition for supporting the effort; without leveraging existing resources, they impose significant additional costs on the manufacturers and providers involved to set up and sustain the infrastructure. There have also been challenges in clearly outlining CMS' statutory authority for pursuing CED arrangements. For CED programs that involve multiple health systems and payers, comparability of results can be complicated without common study designs and leveling of out-of-pocket expenses. Still, CED is an important example of using coverage and reimbursement policy as a lever for collecting additional clinical data while providing access to treatments, and continues to hold potential as a mechanism for improving the evidence underlying treatment decisions.

ASCO's TAPUR Study

The proposal from ASCO, first described in "Implementing personalized cancer care", outlines a specific approach to the development of better evidence through the creation of a national "facilitated access program" and study of cancer patients receiving off-label use of targeted anti-cancer drugs². This led to the creation of the Targeted Agent and Profiling Utilization Registry (TAPUR) Study, which will enroll patients with advanced cancer for whom standard treatment options have been exploited and who have an "actionable" genomic alteration that can be targeted with an FDA-approved drug. The genomic variants must be identified by an analytically-validated test with a McKesson Z Code Identifier and performed in a

² Schilsky, RL. Implementing personalized cancer care. *Nat Rev Clin Oncol*. 2014 Jul;11(7):432-8. Epub 2014 Apr 1.

CLIA-approved, CAP-accredited lab. Treating physicians will use molecular data to select the drug from among those drug-variant matches specified in the program's protocol and begin treatment once any additional drug-specific eligibility criteria are confirmed. For cases in which the oncologist's preferred drug is included in the protocol but the specific drug-variant match is *not*, the physician may submit a proposal to treat with the drug and a clinical case summary to the program's molecular tumor board for review and approval; if approved, the patient can begin treatment. All drugs will be commercially available and provided free of charge by the drug manufacturer. Drugs included in the protocol will have a sufficient scientific and clinical rationale from available data to be reasonably likely to affect specific genomic variants that will also be listed in the protocol. They will also exhibit an adequate safety profile for the selected patient population. An IRB-approved protocol would be implemented to collect data on test results, patient characteristics, treatments, and patient outcomes to be recorded in the program's registry, thus enabling physicians, regulators, and payers to learn about the utility of different targeted therapies in specific off-label settings. The primary efficacy measure in the protocol is intended to be response rate, assessed using conventional RECIST. The unit of evaluation will be a "group" defined as a drug-variant match in a particular tumor histology, e.g., BRAF inhibitor-BRAF mutation-transitional cell cancer of the bladder. Eight patients will be enrolled in each group and evaluated for response after 2 cycles of treatment. If no responses are observed, accrual to that group will be terminated. If at least 1 response is observed then 16 additional patients will be enrolled in that group and evaluated for response. If there are fewer than 5 responses observed in 24 evaluable patients, the drug will be declared to have insufficient activity in that group and further enrollment will be terminated. If 5 or more responses are observed in 24 patients, the drug will be considered to have activity in that group. An independent data monitoring committee will periodically evaluate outcomes in each group of patients and determine when and to which parties the treatment results should be reported. It is anticipated a number of clinically relevant genomic alterations will occur in a gene of interest. Results for such will be annotated separately unless deemed by a stakeholder selected tumor board to represent similar function.

Palmetto GBA and MolDX's MED-C

As part of its role as a Medicare Administrative Contractor (MAC), Palmetto GBA is facilitating the development of an off-label evidence development proposal under its Molecular Diagnostic Services (MolDX) program. The proposed effort, called the Molecular Evidence Development Consortium (MED-C), is an independent, non-profit organization designed as a collaborative approach to cancer care that allows patients to potentially gain access to oncology products off-label while also collecting registry data on care and outcomes. A patient enters the MED-C program after being newly diagnosed with a malignancy (i.e. non-small cell lung cancer) and meeting other inclusion criteria; the patient then receives standardized molecular testing (defined by outside thought leaders and MED-C stakeholders), which would be covered by Medicare (and other payers if they participate). The testing would identify compendia mutations or other off-label mutations for which treatments exist in other disease states (e.g., BRAF mutations targeted by existing treatments in melanoma). Those meeting compendia or off-label mutation criteria, established by a board of independent leading experts, enter a centrally-prescribed treatment pathway in which there would be a number of treatment options for combinations of mutations and disease; patients with no actionable mutation receive standard care. Data on centrally-defined primary and secondary endpoints will then be collected through a registry system. The independent physician group will also help MolDX establish connections to high-impact, ongoing clinical trials that would be appropriate for the pre-screened patient population, thus allowing patients to be enrolled directly into trials following molecular testing. The program is being developed in direct collaboration and consultation with stakeholder groups (patients, physicians, payers, regulators, industry, laboratory, pharmaceutical), will be adaptive to advancements in science and accumulated registry data, and initially implemented at least within the Palmetto and Noridian Medicare regions. The MED-C registry data would be jointly owned and available to the stakeholders.

Comparison between proposals

	ASCO TAPUR	MED-C
Target Population	Patients who have advanced-stage cancer for which standard treatment options are no longer available	Newly-diagnosed cancer patients in defined clinical areas
Purpose	Provide patients with more treatment options and collect data on patient outcomes following treatment with commercially available targeted agents selected based on a genomic profile	Provide infrastructure and methods to allow advanced molecular testing to be introduced and to iteratively learn and modify treatments to the progressive unlocking or personalized medicine
Age	Adults 18 and older	≥ 65 (Medicare); others if additional payers participate
Eligible Tests	CLIA-approved, CAP accredited, NYS accredited (for NY labs or patients) McKesson Z code identifier assigned	Stakeholder-defined “standardized” molecular test
Test Payment	Outside of registry	Medicare, potentially other payers
Drugs	FDA approved for targeted cancer indication	FDA approved for targeted cancer indication
Drug Payment	Drug company partners	Medicare for disease-listed compendia, Drug company partners for non-compendia
Referral to Relevant Clinical Trial	Yes, if participation is possible	Yes
Algorithm Development	Yes, rules-based matching in protocol or molecular tumor board analysis	Yes
Algorithm Adaptation	Yes, regular updates based on new data and possibility for molecular tumor board approval of match not specified in the protocol	Yes
Infrastructure Support	Yes	Yes
Data Monitoring, Analysis and Reporting	Yes, independent data monitoring committee	Yes
Data Sharing	Yes, all stakeholders plus submission for peer-reviewed publication	Open to stakeholders
Anticipated Launch Date	Initial pilot at specified sites in Q2-3 2015	Early pilot Q 3 2015

Key Considerations for Evidence Development Efforts

These two proposals, and the various ways in which they might enable multiple downstream applications of the evidence they generate, highlight a number of key considerations that should be addressed. The two proposals currently occupy slightly different points on the RWE-RCT spectrum, with the Palmetto proposal imposing more structure than ASCO's study. Where these and other proposals ultimately sit on that spectrum, the reliability and usefulness of the data generated, and the burden of data collection and implementation will all be informed and guided by how the challenges below are addressed. How these considerations are taken into account will also help to establish clear value-add for all stakeholders and increase the likelihood of a collaborative effort.

Drug Selection

Off-label evidence development programs may wish to approach the issue of drug selection in two ways: to mimic real-world prescribing patterns as closely as possible and allow any treatment to be used, or to create a set list of drugs that more clearly delineate the treatment pathways open to physicians and patients. Through either approach, it must be plausible that the drug being used off-label is a medically viable option for the patient and it must exhibit an adequate safety profile for the selected patient population for it to be prescribed outside of its approved indication. If a proposed program pursues the latter approach, it should work collaboratively with representatives from multiple stakeholder groups to establish transparent, clearly-defined criteria justifying inclusion of drugs selected for a particular target. Programs with drug lists must also ensure that a sufficiently large and diverse number of drugs are contributed to the program given the large universe of potential genomic variants potentially present in enrolled patients.

There may be cases where a drug sponsor has ongoing clinical research development on an off-label indication that would have otherwise been part of an evidence development effort. In these instances, manufacturers may have concerns about providing access to the drugs for the off-label program. Off-label efforts should therefore work with sponsors to find ways in which their patients may be enrolled in ongoing clinical trials. Finding such synergies is an important part of reinforcing evidence collection at multiple stages of drug development and use. Widespread comprehensive testing should substantially increase available patients for both conventional clinical trials and the proposals outlined herein.

Diagnostic Test Selection

Each effort will also need to decide how it intends to design and operationalize the diagnostic testing phase. Similar to the considerations that must be made around drugs used in the program, the diagnostic component can be left to the discretion of the oncologist and site-specific laboratory or more clearly pre-defined through a list of qualified tests. There are a number of key questions each program will need to address if establishing a list of approved diagnostics: Will the program require NGS or other types of molecular testing? If NGS tests only, should the program name specific NGS tests or be open to all types of tests? If specific NGS tests only, what criteria should be used to include/exclude tests? If the program is open to all types of tests, what additional data elements should be collected about the test in order to learn about the performance characteristics of the test? Will a new test be required at the time of patient entry into the program? Can samples be stored for retrospective testing?

This is not just an issue of deciding upon use of the same or multiple tests, but also of potentially requiring testing for a set of specific, pre-defined markers across whichever tests or platforms are sanctioned for the program. Again, this will come down to the specific aims and design of the off-label program and proposed registry.

The decisions surrounding which diagnostic tests to include within a program closely align with the RWE-RCT considerations in establishing which data elements to collect. On one end of the spectrum, an

open protocol that allows for all “home brew” LDTs and testing platforms more closely resembles real world practice – and has the added benefit of allowing for data collection on the diagnostics themselves. On the other end is a protocol with a clearly defined list of tests deemed acceptable by the program – this requires more standardization, but has the added benefit of increased data quality and diagnostic rigor.

Validity and Reproducibility of Diagnostic Tests

The need to ensure the inter-laboratory reliability of test results and resultant treatment decisions will depend to a great extent on the objectives of the off-label program and the intended use of the data derived therefrom. The current standard is for CLIA to require only analytic validity for a test to go to market, so clinical validation will necessarily be a more rigorous process and may be outside the scope of some off-label programs. Using CLIA-certified labs will help to address some quality questions, but it will not provide a full readout on all of the quality parameters programs may wish to assess. For this reason, additional accreditations or mechanisms to ensure quality may be needed (e.g., CAP or NYS accreditation, MolDX TA process, etc.).

If results from inter-lab analyses lead to concern about a particular site or LDT, programs will also need to have in place a process through which diagnostic tests and results can be cross-checked or reevaluated. This may happen if certain results are seen with one type of test and not others or if a particular laboratory is suspected of consistently poor performance. If poor performing tests can be defined, they can be excluded from the program just as poor performing drugs might be excluded as data develop.

Data Elements and Data Quality

Where off-label evidence development efforts fall on the RWE-RCT spectrum will determine the type, amount, complexity, source and verification of the data collected. These data must span many aspects of patient treatment and be obtainable without being overly burdensome on those involved in the care process. The decision-making for what data to collect should be informed by all stakeholder groups to ensure that the evidence is useful to all parties as it begins to accrue. In the absence of a randomized control group, increased emphasis on sound study designs and statistical methods for reducing bias (e.g., selection bias, confounding) will also be critical for maximizing the value and utility of the data collected.

Information collected on patients entered into the off-label program should include basic demographics (e.g., race, age, gender, BMI), the histological diagnosis and genomics data for the patient’s malignancy, a list of prior therapies and best response data, and a description of patient comorbidities. Where possible, off-label evidence development systems could also provide a unique platform for collecting data on Patient Reported Outcomes (PROs), although the reason for doing so and the intended use of the PRO data should be clearly specified. This will require a program to define the specific PROs to collect and to establish a validated method for doing so. For a given tumor type, patient data on pre-specified, commonly-reported, disease-specific symptoms should then be routinely captured if such data will help inform clinical, regulatory, or reimbursement decisions or generate new hypotheses for future studies.

Data elements specific to the prescribed off-label treatment should include information on the drug regimen, number of cycles, dosing details, and the treatment’s clinical outcomes including efficacy and safety. Programs will need to specify how endpoints are assessed for the latter (e.g., RECIST, CTCAE); for a given tumor type, efficacy of the off-label therapy would then be assessed at a pre-specified time-point on the basis of endpoints and criteria relevant to that disease. Programs will need to collect information on treatment toxicity, which will require specifying a toxicity grading criteria like the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE).

The data elements that should be collected on the diagnostic test used to arrive at a treatment decision are especially challenging given that the great majority of diagnostic tests are non-FDA-approved. In recent years, there has been a proliferation of Laboratory Developed Tests (LDTs) that are laboratory-specific,

raising potential issues surrounding the quality and comparability of the data. For these reasons, there are basic data elements that should be collected on each test used, including the reported results, the testing platform used, information on the completing laboratory and its CLIA certification, and details on the test protocol. The accessibility of information on the latter (e.g., reagents, order, timing, equipment) may prove a significant challenge, especially as these details are not generally available in laboratory reports as provided to an oncologist or care team. Indeed the laboratory results themselves present potentially significant logistical challenges depending on their form, content, and mode of delivery to physicians; as many reports are text-heavy, long-form, and paper-based, mining the documents for relevant information may prove difficult.

Payment Mechanisms

Payment for off-label treatment and accompanying care is a critical issue and important hurdle for establishing an off-label evidence collection program. In the ASCO and Palmetto proposals, these two costs are tightly linked. In both proposals it is intended that the drugs are provided by partnering pharmaceutical companies (all drugs in ASCO's proposal; non-compensia drugs in Palmetto's) or covered by Medicare (on-compensia treatment in Palmetto's program). In the context of the ASCO program, access is being provided in an IND-exempt clinical trial, so the Affordable Care Act (ACA) provision would require regulated health plans and insurers to provide coverage of associated clinical care costs. Palmetto's program applies Medicare fee-for-service coverage and may be followed by other insurers. While this removes potential reimbursement issues by removing the treatment cost itself from the equation, it does highlight that drug manufacturers would need to be willing to participate. Other proposals may encounter further challenges to covering care costs if the drugs are not provided by the manufacturer and the care does not take place in the context of a clinical trial covered by the ACA. This is especially true if the off-label use is not limited to the uses found in approved compendia, as payer groups are reticent to cover such off-label, off-compensia treatment; payer contracts generally exclude therapies considered investigational or experimental.

Payment for the diagnostic testing, then, is a secondary but no less important payment challenge. Diagnostic tests are typically covered only for specified disease settings by the payer and are likely covered by the trial sponsor when a patient is enrolled in an RCT, but there may not be a clear path to reimbursement when these costs are in conjunction with an off-label program. Further complicating this picture are individual state regulations and Medicare policies specific to diagnostics, which must be deemed reasonable and necessary to be covered. While Medicare and private payers may pay for the diagnostics involved in both evidence development proposals, patients may still be responsible for copays. There could also be costs associated with testing and screening for disease progression that are not covered as part of the off-label care. Because of these factors, ensuring that patients are not burdened with high costs in order to participate in any proposed program is a key concern; as evidence is generated that links response to drugs hallmarked by common molecular genomic mechanisms, this will become less of a consideration.

Patient Engagement

For any evidence development proposal, inclusion of the patient perspective and active engagement with patients and caregivers will be of paramount importance. At a fundamental level, patients will need to understand how access to the program and off-label treatment is provided and how costs of diagnostic testing and care are addressed. Proposed programs must develop clear education materials that help to convey this information, especially for use in typically underserved patient populations that might not have access to information on clinical trials. Every effort must also be made to provide patients with confidence in equitable access and coverage. This is especially true given the genomic profiling necessary to participate, as, depending on how genomic and diagnostic tests are covered, patient out-of-pocket expenses will be a determinant factor to access. Patients should be involved in the drug selection, diagnostics discussion, and considerations for what data to collect, as well as any governing bodies or

committees overseeing program operations and data analysis. In order to successfully interface with patients and bring them into the fabric of the program, off-label efforts would do well to find synergy with organizations already actively engaging patient communities. There is great opportunity, for example, to learn from groups such as PatientsLikeMe which are setting a high bar for robust, patient-generated data. In all, proposed programs need to make sure that they are *meaningful* for patients.

Governance

The governance of evidence development programs will likely require a number of standing bodies to be involved in overseeing operations. For example, a central group of expert stakeholders should be engaged in determining criteria for treatment, coverage, and patient inclusion in the program, as well as implementation and termination of specific treatment approaches. An independent board for approving day-to-day treatment decisions may also need to be established. This would most likely look and act like a tumor board – in which physicians and experts use test results and clinical evidence to aid an oncologist’s recommendations on patient treatment – and should be transparent, multi-stakeholder, and separate from the program’s governing structure. An Independent Review Board should also be utilized to approve the overall process, including a program’s plans for data collection and use. The ASCO and Palmetto proposals include a variety of these committees for overseeing governance, drug selection, and physician treatment decisions. Specifically, the ASCO TAPUR study will be overseen by a multi-stakeholder steering committee that will assess the overall organization and progress of the study, a multi-disciplinary molecular tumor board to assess proposed drug-variant matches that are not explicitly permitted by the protocol and an independent data monitoring committee that will regularly review study outcomes and recommend release of study data when protocol-specified endpoints are met. Moving forward, program sponsors will need to clearly establish how participants in these review boards are chosen and how standards and practices are codified. They may also wish to identify already established bodies or groups that could aid in governance, streamlining the process.

Infrastructure

Outside of considerations about the structure and function of the delivery of off-label care itself, there are a great many operational issues that these programs will need to address. Tackling challenges in common data models and interoperability between registry sites, for example, will enable the data to be pulled together seamlessly as it is collected. Exploring the potential use of distributed data networks may help alleviate challenges associated with centralized data collection, as well as potentially allow programs to make use of already established research infrastructure. Programs will also need to tackle issues around data governance: how will data be collected, maintained, and accessed? These are not insignificant challenges, and moving from the current status quo to a reliable program with robust data collection is likely to be an iterative process. Identifying ways in which off-label evidence development programs can harness existing and emerging data infrastructures may help improve data collection and reduce the costs of that collection in the future. For example, health plans and large health systems routinely participate in developing safety and effectiveness evidence on technologies used in their populations through programs like the FDA’s Sentinel Initiative, PCORnet, and their own internal research programs. Identifying how these current practices and infrastructure can support off-label use registries would be worthwhile. Finally, infrastructure issues extend to potential coordination between programs to reduce competition, increase overall awareness, and allow for patient referral between programs.

Sustainability

Finally, concerns around the costs of administration and data collection, and ultimately who will be paying for it, should be addressed as soon as possible in order for proposed programs to be viable in the long-term. Ideally, these efforts will enable contributions from all stakeholder groups to share the costs and benefits for successful operation. For example, creating a system in which insurers are willing to cover the cost of tests and routine care, industry helps to provide drugs, patients consent to provide personal data on an ongoing basis, and physicians have the least-burdensome-possible mechanism for

entering and interfacing with data will go a long way toward establishing an off-label program that is realizing its full potential as part of a truly learning health care system. The best long-term business case for sustainability will likely involve data collection that is relatively low-cost, expands participation of clinicians and patients in reporting outcomes, addresses unresolved clinical benefit questions worthwhile to payers, and meets manufacturer interests in refining treatment use and identifying treatment areas where further clinical study is warranted.

Recommendations and Next Steps

Developing better evidence about oncology products used off label is an important and worthy part of improving patient care. As these and other proposals move toward implementation, the considerations outlined above will help to ensure that they are truly impactful and provide all stakeholder groups with the evidence they need to make informed treatment, coverage, and regulatory decisions. In the meantime, there are opportunities for stakeholders to bolster off-label programs by pursuing other initiatives in parallel:

- Identify opportunities to reduce and potentially cover upfront infrastructure costs. With national efforts and resources being increasingly used toward building a truly learning health care system with patient engagement and support, opportunities to design the off-label use registry to be synergistic with evolving efforts like Sentinel and PCORnet should be explored.
- Identify “pilot” examples that can be used to build support from manufacturers, payers, patients, and providers while testing, refining, and implementing the initiative. These pilots would benefit from a parallel effort to develop common infrastructure and data elements that would allow stakeholders to link or scale up pilots as necessary.
- Develop clearer guidance on how the evidence developed from an off-label use registry could be used to inform future research, clinical, coverage, and regulatory decisions. This could be done as a collaborative effort involving FDA, payers, product developers, patient groups, and other interested stakeholders. For example, the guidance could address how “signals” developed from this program could support the design of more efficient and targeted RCTs when practical, or more structured observational studies that could support regulatory and coverage decisions.
- Identify what next steps should be taken in order to get additional clarity on how evidence from these registries should be communicated to providers and patients to inform their shared decisions. Is published literature enough? Are there better ways to communicate the evidence?
- Identify what, if any, policy changes by CMS or private payers would be needed in order to increase the feasibility that such registries could be implemented in ways that would lead to meaningful and reliable evidence.
- Identify what efforts should be taken by all stakeholders to reduce overall cost of patient care through streamlining of testing and treatment.

These recommendations will not only begin to set the stage for greater generation and application of evidence developed on off-label uses in oncology, but will contribute to a more robust, coordinated effort to improve patient and clinician participation in health care quality improvement.