
PERSONALIZED MEDICINE AND VALUE ASSESSMENT FRAMEWORKS

Context, Considerations, and Next Steps

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The Personalized Medicine Coalition would like to thank Jennifer Snow, Kristen Migliaccio-Walle, and Ann Cameron, who served as the principal authors of this report on behalf of Xcenda, as well as those of our members who took the time to read and comment on this paper's drafts.

INTRODUCTION

Amidst growing concerns over the rising cost of health care in the United States, several stakeholders have developed novel value assessment frameworks (VAFs) that attempt to consistently quantify which treatments provide the most benefits for patients and the health system. By identifying the most valuable treatments, VAFs are designed to help maximize the value of dollars spent on health care.

Personalized medicine, also called precision or individualized medicine, is an evolving field in which physicians use diagnostic tests to identify specific biological markers, often genetic, that help determine which medical treatments and procedures will work best for each patient. By combining this information with an individual's medical records, circumstances, and values, personalized medicine allows doctors and patients to develop targeted treatment plans and utilize targeted medicines.¹ As with VAFs, the field aims, in part, to maximize the value of every dollar spent by identifying with more precision which medical treatments and procedures will work best for each patient.

Despite the shared objectives of VAFs and personalized medicine, most VAFs do not sufficiently capture the value of personalized medicine, focusing instead on population health, thereby overlooking efficiencies in patient-level health care. By not accounting for heterogeneity of treatment effects across patients and not sufficiently acknowledging elements of personalized medicine such as diagnostic testing, genetic counseling, and a patient's values and circumstances, these VAFs neglect to adequately consider the fundamental element that comprises value in health — namely, the patient. As such, VAFs could unintentionally set back the country's drive toward a new era in which health care decisions are informed by our evolving knowledge of how individuals respond to specific therapies.

In that context, this report (1) describes the intersection of personalized medicine and VAFs; (2) provides an overview of U.S.-centered VAFs; (3) identifies areas of consideration related to personalized medicine that need to be accounted for in VAF methodology; and (4) provides a synopsis of how VAFs may incorporate these considerations. Finally, the report offers recommendations for refining VAF methodologies so that they will be more useful for delineating the value of personalized treatments to both patients and the health care system.

PART I

CONTEXT

“Personalized medicine has become a critical component in the discovery of new treatments that improve outcomes.”

Intersection of Personalized Medicine and Value Assessment Frameworks

Personalized medicine has become a critical component in the discovery of new treatments that improve outcomes, especially within certain therapeutic areas such as oncology, in which the emergence of mutation-specific indications has extended survival for many patients across diagnoses. In 2006, there were six personalized medicine drugs, treatments, and diagnostic products available, whereas there were 132 available in 2016.¹ In 2014 and 2015, over 20 percent of medicines approved by FDA were personalized medicines.² This number rose to 27 percent in 2016. Half of the personalized medicine approvals in 2016 were oncology drugs.

A recent study by the Tufts Center for the Study of Drug Development, meanwhile, showed that almost half (42 percent) of all compounds and the vast majority (73 percent) of oncology compounds in development could lead to future personalized medicines.³ Significant increases anticipated in research and development investments by biopharmaceutical companies for personalized medicines are predicted to result in an almost 70 percent increase in the number of personalized medicines on the market by 2022.¹

The uptake and integration of personalized medicine in clinical practice, however, has lagged behind the science due to several sets of barriers (see Table 1) — some of which involve the under-recognition of and a lack of evidence to demonstrate its value to patients and the health care system.^{1,4}

Novel value frameworks have emerged in parallel with the field of personalized medicine. This has given rise to the question of whether value frameworks (some of which are rooted in conventional, 20th-century methods of value assessment) are aligned with the state of biomedical science. Existing health care technology assessments and emerging VAFs have been designed primarily around an examination of a treatment that emphasizes traditional components of value (e.g., efficacy, safety, and cost). As such, there are no established paradigms for assessing the value of other technologies and services within a full treatment regimen, such as diagnostic testing. In addition, lack of coverage for many diagnostic tests and services, current pricing and reimbursement policies, alternative payment models that do not adequately account for the cost and value of novel targeted therapies, and uncertain evidence requirements that would convince payers and providers of the benefits of personalized medicine have contributed to the lack of access to and use of personalized medicine.⁴

TABLE 1. CHALLENGES TO THE UPTAKE AND INTEGRATION OF PERSONALIZED MEDICINE IN CLINICAL PRACTICE INCLUDE BARRIERS RELATED TO VALUE DEMONSTRATION

| | |
|----------------------------------|---|
| Knowledge and Empowerment | Lack of education and awareness among patients and health care professionals |
| | Lack of patient empowerment |
| Value Demonstration | Lack of value recognition (both clinical and economic) and evidence requirements for coverage |
| | Uncertain evidence requirements for coverage/ reimbursement and other access hurdles |
| | Access and reimbursement hurdles |
| Infrastructure | Lack of effective health care delivery infrastructure and information management systems |

The History of Value Assessment Frameworks

The lack of cohesion between VAFs and personalized medicine may stem in part from the fact that the emergence of value assessments for the comparison of treatment options preceded many of the major scientific developments in personalized medicine. Value assessment for quality assurance purposes has been the foundation of health technology assessment around the world for more than 20 years. The establishment of the modern “quality era,” however, is often marked by the creation of the National Institute for Clinical Excellence, now the National Institute for Health and Care Excellence (NICE), in the United Kingdom, which was established in 1999 — still four years before the drive toward personalized medicine began in earnest with the first complete sequencing of the human genome.¹

A new era of value assessment in the U.S. has evolved in recent years spurred in part by the passage of the Affordable Care Act (ACA) and the creation of the Patient-Centered Outcomes Research Institute (PCORI), which was tasked with conducting patient-centered comparative effectiveness research (CER). CER is the foundation of many of the value frameworks that currently exist. During this time, an increased focus on the limitations of cost-per-quality adjusted life year (C/QALY)-based cost effectiveness analysis to form coverage or payment decisions has developed. The ACA contained a provision that prevents reliance on C/QALY based on a broad recognition from policymakers, patients, and other stakeholders that such analyses have significant limitations and often overlook important differences among patients. Such limitations in C/QALY-based research can be even more apparent in their application to personalized medicines.

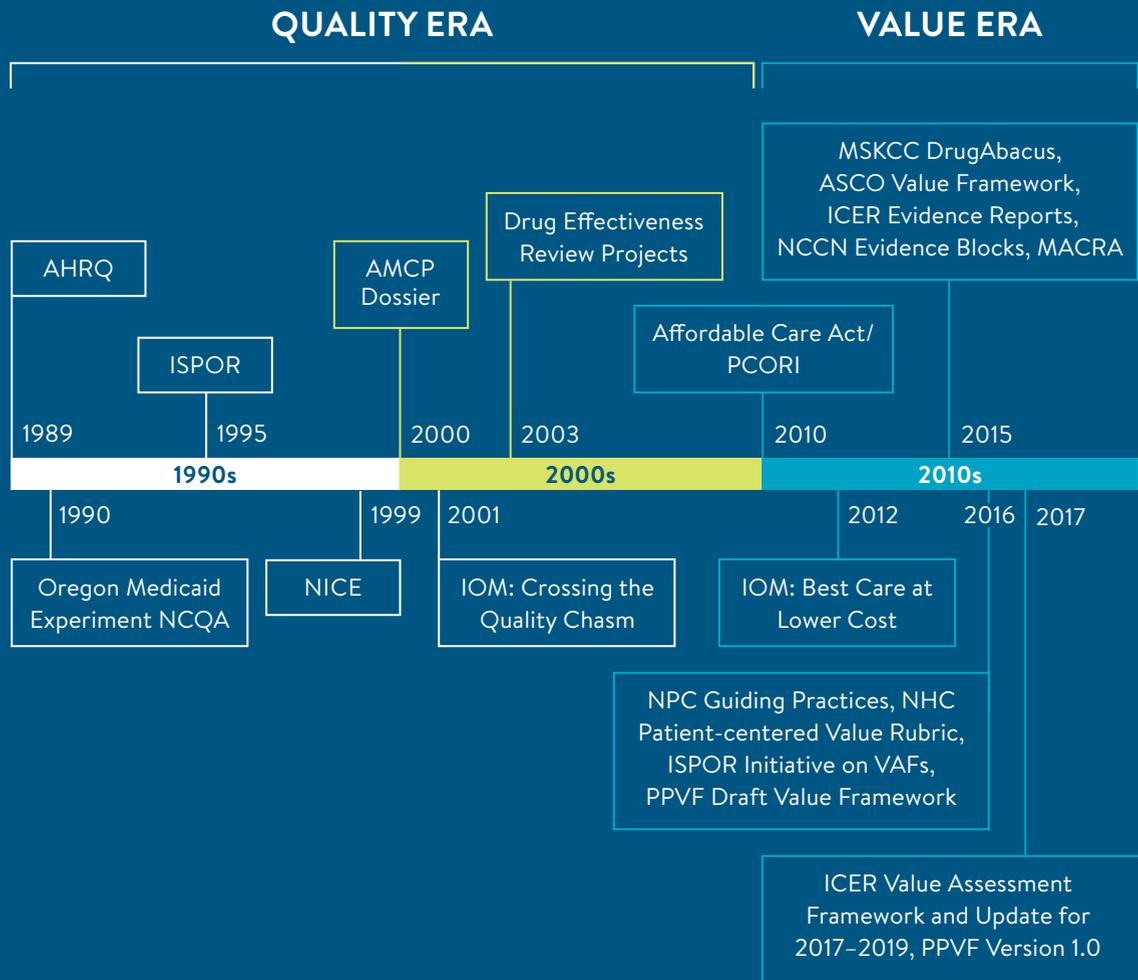
Continued cost pressures, price sensitivity, and perceived budget constraints then gave rise in 2015 to frameworks that sought to apply the principles of value assessment to address the increasing costs of health care. As VAFs were developed to reflect specific and often separate stakeholder perspectives and were used to determine the comparative value of various treatments, some stakeholder groups (primarily payers and providers) began to view them as potentially useful tools for informing health care policies. Patient advocates, medical product manufacturers, policymakers, and other stakeholders began to take note of the growing number of VAFs, giving rise to myriad initiatives, collaborations, and discussion documents offering new perspectives on value. The evolution of the value assessment debate in U.S. health care is shown in Figure 1.

Several VAFs have gained prominence in the latter part of the “value era.” The American Society of Clinical Oncology (ASCO) introduced its Value Framework in 2015.⁵ The Memorial Sloan Kettering Cancer Center (MSKCC) DrugAbacus was then released,⁶ followed by the

Institute for Clinical and Economic Review's (ICER's) receipt of grants from the Laura and John Arnold Foundation to initially conduct up to 20 comparative evaluations in 2016 and 2017 and then to support their continued efforts moving forward,^{7,8} and the launch of the National Comprehensive Cancer Network (NCCN) Evidence Blocks framework.⁹ Avalere also partnered with FasterCures to put forth a Patient-Perspective Value Framework (PPVF) in 2016.¹⁰ Each of these VAFs have gained familiarity and prominence with U.S. stakeholders since their inception¹¹ and are presently among the most often referenced (see Appendix A for examples of other organizations offering perspectives on value).

These VAFs, however, have different intended uses and structures. ASCO, NCCN, and the Avalere/FasterCures initiatives are primarily intended for use by patients and physicians in the context of shared decision making about treatment options, whereas the tools from ICER and MSKCC evaluate therapies at the population level to inform policies and payer coverage decisions. Each VAF is defined by stakeholder-specific elements and considerations that reflect the overall perspective of value represented in the resulting evidence. Of these, only the PPVF formally takes the patient perspective.¹⁰ As a result, different VAFs measure value in different ways, and each has strengths and limitations relative to different audiences and circumstances — especially in the context of personalized medicine (see Appendix B).

FIGURE 1. EVOLUTION OF VALUE-BASED HEALTH CARE IN THE UNITED STATES



AHRQ – Agency for Health Care Research and Quality; AMCP – Academy of Managed Care Pharmacy; ASCO – American Society of Clinical Oncology; ICER – Institute for Clinical and Economic Review; IOM – Institute of Medicine; ISPOR – International Society for Pharmacoeconomics and Outcomes Research; MACRA – Medicare Access and CHIP Reauthorization Act of 2015; MSKCC – Memorial Sloan Kettering Cancer Center; NCCN – National Comprehensive Cancer Network; NCQA – National Committee for Quality Assurance; NHC – National Health Council; NPC – National Pharmaceutical Council; PCORI – Patient-Centered Outcomes Research Institute; NICE – National Institute for Health and Care Excellence; PPVF – Patient-Perspective Value Framework

PART II

CONSIDERATIONS

“VAFs have the potential to encourage the use of personalized medicine, but that can only happen if frameworks incorporate the elements of personalized medicine that demonstrate its value.”

Necessary Considerations for Personalized Medicine in Value Assessment

With the development of these modern VAFs, there has been debate among the various stakeholders about what components and measures of health care interventions should be considered in the assessment of value (e.g., treatment cost, QALY gained) and what weights should be given to them.¹² Because VAFs and personalized medicine are aligned in seeking to improve patient care by providing information to aid in decision making, they should also be aligned in consideration of the components and measures of health care that ensure appropriately informed decision making at the individual and population levels.

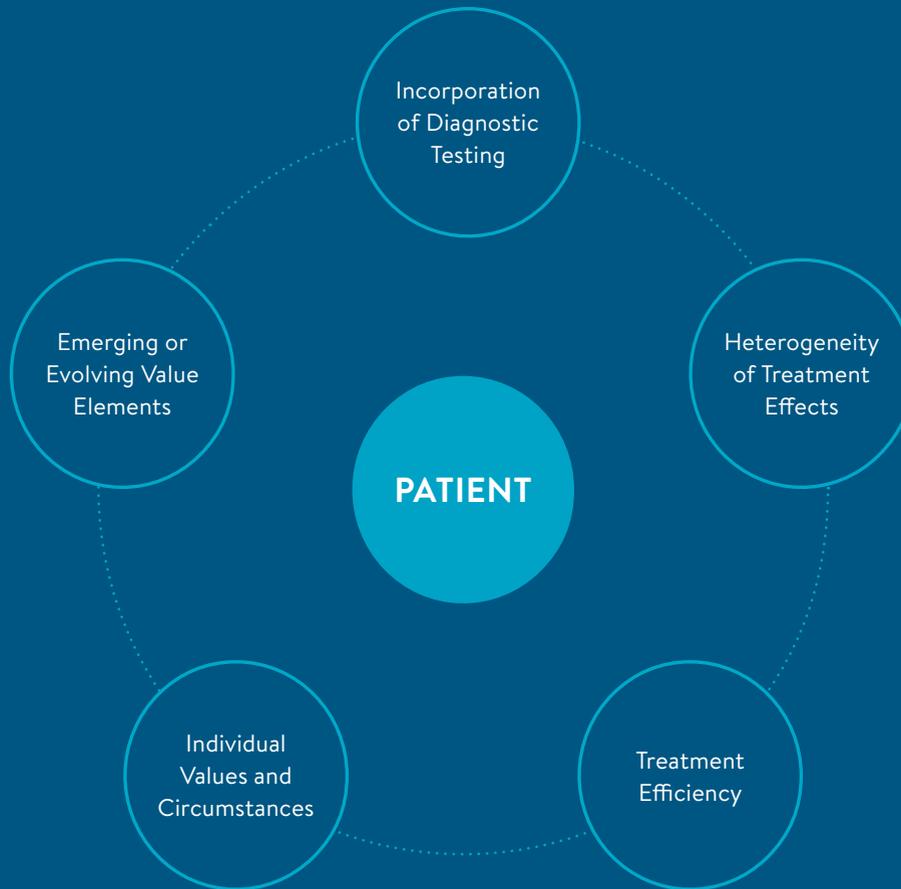
Decisions about how best to consider different health care components when assessing value — while instrumental for the usefulness of a particular VAF — also affect the development and integration of new technologies and products into health care practice. VAFs have the potential to encourage the use of personalized medicine, but that can only happen if frameworks incorporate the elements of personalized medicine that demonstrate its value.¹

The personalized medicine considerations presented in Figure 2 are multifaceted but fundamental for ensuring that patients are the focus of the debate that determines their access to new technologies and optimal care.

INCORPORATION OF DIAGNOSTIC TESTING

A patient's molecular characteristics as determined by diagnostic testing must be considered an integral part of the value assessment of a personalized treatment. Diagnostic testing forms the basis of personalized medicine, allowing for earlier and more accurate diagnoses and for targeted therapies that provide safer and more effective treatment options. Diagnostic testing in personalized medicine is a key part of a full treatment regimen and, as such, is instrumental to realizing the value of a targeted treatment. Further, it is important that VAFs consider aspects of the validation, utility, and economic impact of all relevant diagnostic tests when assessing the value of personalized treatment strategies. The use of diagnostics to detect or measure various biomarkers may play an important role across numerous clinical scenarios. The significance of all clinically useful biomarkers within these scenarios must therefore be figured into the methodology utilized to assess the value of personalized medicines.

FIGURE 2. NECESSARY PERSONALIZED MEDICINE CONSIDERATIONS FOR VAFS



HETEROGENEITY OF TREATMENT EFFECTS

It had been readily assumed and accepted that evidence obtained from a clinical trial — the “gold standard” for drug assessment and approval — would be equally sufficient and applicable for informing value-based decisions; however, many stakeholders have noted the importance of considering real-world evidence when assessing value. Some patients will experience more or less benefit from treatment than suggested by the averages reported from clinical trials. VAFs must therefore account for the heterogeneity of treatment effects in order to maximize their utility and application at the individual patient level. Advances in personalized medicine have led to a greater understanding of some of the genetic and molecular underpinnings of the heterogeneity of treatment effects, and value frameworks need to reflect the state of science.

Addressing uncertainty in value assessments poses a methodological challenge, especially with consideration of the heterogeneous outcomes data that are available for personalized medicine interventions. Where applicable, sensitivity analyses must be universally and consistently incorporated into existing VAFs. For personalized medicines, doing so is even more relevant and imperative than in other areas due to the ability to define small subpopulations of patients who may benefit more or less from a treatment through the use of companion diagnostics. Without proper consideration of the range of potential outcomes, personalized medicines may be misjudged or undervalued early simply because the data required for value-based decision making are not yet robust when dealing with a smaller patient population.

INDIVIDUAL VALUES AND CIRCUMSTANCES

An important point where personalized medicine and VAFs diverge is the difference in perspective for making treatment decisions between patients/caregivers and other stakeholders. Personalized medicine depends not only on the consideration of a patient’s molecular characteristics but also on individual values, clinical and economic circumstances, and the potential impact of a therapy for that patient over the long term. Fundamental patient values and preferences, including the impact of treatment on quality of life, quantity vs. quality of time, functional ability related to illness or treatments, cost of supportive care, and other patient costs of treatment are weighed by patients and their caregivers when deciding on a treatment in consultation with health care providers.^{10, 13} These considerations should therefore be formally recognized in the methodologies of VAFs to appropriately value personalized medicines.

TREATMENT EFFICIENCY

One of the benefits of personalized medicine is that it can shift the focus of health care from reaction to prevention/early intervention through the identification of markers that suggest risk or presence of a disease much earlier in its progression or predict an increased risk of harmful side effects.¹ Thus, it can potentially avoid or reduce direct, indirect, and out-of-pocket costs downstream that are associated with rapid disease progression or adverse events. Treatment efficiency involves avoiding trial-and-error treatment strategies and ensuring that a patient receives the treatment that is the safest and most effective for him or her at the best time. In turn, a targeted treatment plan can potentially reduce the downstream expenses associated with ineffective or harmful treatment options. Efficiency requires a broader perspective that is not typically captured through standard clinical studies, often for pragmatic reasons, and involves avoiding the use of treatments that would not be effective for a given patient or matching the safest medications and doses to a patient based on his or her genetic profile.¹ VAFs, which seek to capture economic as well as clinical value, need to consider total health care costs — and greater treatment efficiency gained by personalized medicine strategies will have a significant impact.

EMERGING OR EVOLVING VALUE ELEMENTS

It is imperative that any assessment of the value of a treatment be updated routinely and rapidly enough to account for new information gained through real-world evidence and use of treatments. Indeed, a key element of personalized medicine involves the benefit of clinical practice experience to continuously gain knowledge about the patient characteristics, values, and circumstances that are associated with better outcomes. Thus, the application of evidence obtained at a discreet point in time (most frequently in the context of clinical trials) to estimate the impact of a health care intervention over years and sometimes decades is not sufficient to assess its full value.

To appropriately capture the benefits of personalized medicine, methods for assessing value must formally consider emerging or evolving value elements. Frequently, stakeholders must make clinical, coverage, or policy decisions based on evidence consisting of relatively short-term follow-up and outcomes. This initial constraint should not preclude criteria and methods for assessing evolving value elements over time within a VAF construct, nor should it provide justification for not doing so.

Although methods that are often employed to evaluate outcomes over time, such as post-marketing surveillance studies, open-label extension studies, and retrospective analyses, have a different level of rigor compared to randomized controlled trials, they are no less important in informing value and decision making when implemented properly.

Personalized Medicine in Current Value Frameworks

Existing VAFs largely fail to account for personalized medicine considerations and thereby may not provide an adequate assessment of value. It is critical, therefore, that those who wish to determine the value of personalized medicines within the current environment understand the components, limitations, and perspectives of different VAFs in the context of these criteria.

INCORPORATION OF DIAGNOSTIC TESTING

Current frameworks do not explicitly define formal or consistent approaches for the consideration of diagnostic testing intended to guide treatment decisions where appropriate. However, the use of diagnostic tests to help determine which treatments will be most effective and safest to use in any given patient is a crucial element of the complete personalized treatment regimen.

For example, ICER's *Non-Small Cell Lung Cancer: Evidence Report*, published in October of 2016, included an evaluation of the value associated with certain tyrosine kinase inhibitors (TKIs) and programmed death 1 receptor (PD-1) agents in the treatment of advanced non-small cell lung cancer. The evaluation estimated that the TKIs had reasonable value compared to generally accepted value ranges (\$110,840 to \$147,244 per QALY) but that PD-1 immunotherapy agents did not meet accepted value thresholds (\$219,179 to \$415,950 per QALY). As the report acknowledges, however, the use of diagnostic tests that detect the amount of programmed death ligand 1 (PD-L1) protein that an individual's tumor expresses, a crucial element for the molecular activity of PD-1 immunotherapy treatment, can help determine which subset of patients the immunotherapy is more likely to work for. Although ICER did evaluate the cost-effectiveness of the treatments in some stratified subgroups of patients, ICER did not explicitly account for diagnostic testing. Thus, ICER's evidence report did not consider PD-L1 diagnostic tests in the analysis of these treatments and missed a valuable component of the treatment regimen that can lead to improved outcomes and decreased downstream costs. In response to public comments about this oversight, ICER acknowledged differences in valuing diagnostic tests, but the organization has not indicated how the conceptual value framework approach would be revised to take those differences into account.¹⁴

A more consistent approach would consider (1) when diagnostics should/should not be included in assessment processes, (2) how (methodologically) diagnostics are included in the evidence review and economic evaluations, and (3) implications and standards for analyzing and reporting on patient subgroups (which the PPVF does aim to examine).

HETEROGENEITY OF TREATMENT EFFECTS

Most U.S.-based VAFs are focused on population averages and do not sufficiently acknowledge the importance of heterogeneity of treatment effects in distinguishing a treatment's value. Health care decision making that is focused on average treatment response can restrict patient access to the treatment option that is most effective for them.

For example, PD-1 immunotherapy treatments work well for some non-small cell lung cancer patients, but they are less effective for others. For a patient who expresses high levels of the PD-L1 protein, PD-1 immunotherapy agents may represent the safest and most effective treatment for them. However, the average response, as measured across the population of patients who participated in PD-1 agent clinical trials, including those with low PD-L1 expression, implies that these agents are less effective in general. If the latter conclusion were broadly applied to payment and care delivery policies, many patients would not receive or would be delayed in receiving PD-1 treatments, even if it was the best possible option for them. Non-small cell lung cancer, as with many diseases, involves a complex etiology and progression that requires a consideration of heterogeneous treatment response.

Restricted access greatly affects individual patient health and could have a substantial impact on downstream health care costs as patients' conditions progress in the absence of the most effective treatment and/or they suffer from increased adverse events. Therefore, as currently constructed, most value assessment frameworks have little utility or application at the individual patient level.

Some frameworks, including those developed by ICER and NCCN, do acknowledge the importance of considering alternative data sources in addition to randomized controlled clinical trials whose results are based on cohort average responses.¹⁴ The extent to which this will be considered in practice, however, remains to be determined, as there is no specific guidance on how and when to do so despite provisions in the 21st Century Cures Act intended to encourage the use of alternative data sources.¹⁵

INDIVIDUAL VALUES AND CIRCUMSTANCES

Most VAFs fall short of adequately addressing the patient perspective. ICER, and to a lesser extent the ASCO Value Framework, explicitly included quality adjustments for survival (i.e., quality of life) from their inception; ICER through the use of the QALY as a denominator for cost-effectiveness and ASCO by awarding bonus points for demonstrated improvement in quality of life. Until recently, however, this was the extent of formal consideration given to the patient perspective.

The NCCN Evidence Blocks and MSKCC DrugAbacus do not consider whether an outcome is patient-centered, whereas ICER and ASCO indicate that the patient perspective

is at least nominally addressed when assessing the value of a treatment. Still, ICER and the MSKCC DrugAbacus take a population-based perspective, thereby implicitly deprioritizing the individual patient in their assessments. ASCO and the NCCN Evidence Blocks are intended for shared decision making between the patient and provider; however, they are derived from population-based evidence that does not readily support individual outcomes or perspectives.

The emphasis on the consideration of data from clinical trials precludes the consideration of important elements of care related to a patient's individual experience. This has contributed to a public discussion on the increasing importance of including patient-centered perspectives of value and patient circumstances.^{16,17}

For example, a recent ICER evaluation of treatment options for relapsed or refractory multiple myeloma, *Treatment Options for Relapsed or Refractory Multiple Myeloma: Effectiveness, Value, and Value-Based Price Benchmarks*, published in June 2016, had a narrow scope and did not consider many realities of clinical practice.^{18,19} Multiple myeloma is a heterogeneous and complex disease that often requires several courses of treatment. A multiple myeloma patient, in consultation with his or her physician, will consider an array of individual circumstances when choosing among treatment options throughout the course of care, such as risk profile, response to previous treatments, tolerance and willingness to suffer side effects, the impact on a patient's family, and the value that an individual patient places on extending survival with hope of further advancement in science that may offer more curative value. Clinical judgment based on these factors has resulted in better clinical outcomes according to the American Society of Hematology.²⁰ Yet, if the ICER analysis is applied in isolation, it would constrain clinical practice and the consideration of these important circumstances and values, thereby setting back patient-centered care.

Recent updates to the ICER VAF assert that the patient experience and values are important and will be considered in the context of evaluations that primarily aim to inform health policies and decision making about delivery system interventions. ICER acknowledges the “inherent tension” between the two perspectives and intends to “create an explicit place and role” for aspects that are important to individuals. Ultimately, however, the VAF is not intended to inform patient-level choices or decision making and may overlook important patient subgroups as they pertain to personalized medicine.¹⁴ Only the recently introduced PPVF explicitly adopts the individual point of view as its primary perspective.¹⁰

TREATMENT EFFICIENCY

Although VAFs generally focus on improvements in effectiveness, which can be demonstrated through traditional clinical trials or prospective study designs and practices, they do not generally consider efficiency, which involves avoiding trial-and-error treatment by getting therapies to those who are most likely to benefit from them at the best time.

VAF developers must not underrate the impact a therapy may have on individual patient health outcomes when considering the potential budget impact to any individual stakeholder or stakeholder group. Indeed, value-based frameworks must consider how assessing the impact of different therapies on individual patients may, in turn, facilitate improvements and efficiencies at the population level by getting the right medicine to a patient as early as possible, thus creating system-level savings. These considerations are largely absent in the current environment.

Most VAFs do not have a mechanism to consider the diagnostic tests that can help predict what medications will be most effective and at what doses they will be safest for individuals based on their genetic makeup. Although current VAFs do consider the clinical and economic consequences of therapy brought about by efficacy, adverse events, and toxicity as defined within a clinical trial, they do not go far enough in demonstrating the real-world value associated with reducing costs by helping to avoid ineffective or harmful treatment options and reducing the downstream expenses associated with rapid disease progression and/or adverse events.

For example, although the MSKCC DrugAbacus figures the toxicity of a certain drug into its determination of an estimated appropriate price, it does not consider if there is a pharmacogenomic test that can mediate that toxicity. So, if a diagnostic test could help determine which patients should have a lower dose of a drug or avoid taking it all together due to an increased risk of severe toxicity, the value of that drug would be much greater. Yet there is no mechanism for consideration of pharmacogenomic testing, and patients who would not suffer from toxicity or who would benefit from a lower dose of the drug could face losing that treatment option based on low value estimates within the full population.

EMERGING OR EVOLVING VALUE ELEMENTS

The evidence used for VAF evaluations, especially clinical trial data, is generally static in nature and may not be available for all relevant patient groups or accountable for individual patient circumstances and/or other emerging value factors. As a result, VAFs can discourage the use of treatment options that may prove beneficial for specific subgroups of patients.

For example, ICER's value assessment report on PD-1 immunotherapy treatments for non-small cell lung cancer patients did not consider the potential of these therapies in patients with tumors that express "microsatellite instability," which was still under study when the report was released. Just over six months after ICER's report was published, however, FDA approved an immunotherapy for the treatment of patients with any solid tumor expressing microsatellite instability — including those with non-small cell lung cancer.²¹ Until recently, ICER had no formal policy for updating its evaluations based on the availability of important new data. Thus, the organization's conclusion in 2016 that PD-1 immunotherapies are not cost-effective for the treatment of non-small cell lung cancer may continue to inadvertently discourage

the consideration of a treatment option that has since proven to be highly beneficial for a subgroup of patients. These kinds of consequences are of serious concern to patient advocacy groups such as the American Lung Association, which warns that ICER's assessment is "taking the precision out of precision medicine."²²

In order to accurately assess the full value of a treatment regimen, VAFs should thereby begin to incorporate specific methods for the consideration of emerging evidence that can inform outcomes. In some cases, it may not be possible to capture this evidence within the controlled environment of a clinical trial. As such, VAFs should also account for evidence that emerges over time through clinical practice and studies other than randomized controlled trials.

CONCLUSIONS

Shortcomings in value assessment methodologies may disrupt the advancement of personalized medicine.

In fact, the most influential VAF at this time, published by ICER, has fallen short on all five considerations outlined in Figure 2. Diagnostic testing is addressed only in the context of a summary of coverage policies and clinical guidelines. Consideration of the heterogeneity of treatment effects when valuing therapies is addressed through one-way sensitivity analyses over potential ranges of inputs. This neglects the associations between input parameters and the corresponding impact of heterogeneity among patients on outcomes. Consideration of individual values and circumstances was criticized as inadequate, lacking clarity, and disproportionately emphasizing price by a majority of those who submitted public comments to ICER in response to recent evidence reports. ICER's reliance on the cost per QALY also inherently ignores those aspects of value defined by patients, their family, and caregivers. Treatment efficiency is nominally considered in conclusions relating to which patients may benefit most from these therapies; what is missing is the impact on the broader context associated with negative consequences avoided through diagnostic testing and the use of personalized medicine. ICER is further critiqued for combining adverse events across therapeutic options, thereby "distorting" the impact these may have. Finally, the framework has been criticized for a failure to consider evidence and value elements as patients and clinicians gain more experience with treatment options as they emerge over time.²³

Revisions to current VAFs and those developed in the future will need to appropriately consider and account for the role of diagnostic testing, patient-centered values, therapeutic efficiencies, and improved outcomes, as well as evolving evidence over time.

Furthermore, a single VAF will not be sufficiently comprehensive to meet sometimes competing value assessment needs. Thus, the value assessment process may evolve such that VAFs designed for different audiences could be viewed as individual tools in a broader value toolbox.

Each of the commonly considered VAFs may have strengths and limitations relative to different stakeholder perspectives and circumstances that can bolster or undermine their usefulness and applicability to personalizing patient care. Table 2 highlights a few key personalized medicine-related strengths and limitations of each VAF.

Although many stakeholders, including payers and policymakers, are focused on population-level decision making and are the intended audience of many value assessments, VAFs should not discount or diminish other key perspectives of value. The final decision of which therapy or combination of therapies is most appropriate for a patient must (1) be left to the patient working with his or her provider, (2) involve consideration of the patient's clinical circumstances, and (3) involve consideration of a therapy's impact on a patient over the long term. By utilizing personalized medicine strategies, providers will be able to identify individuals within larger populations who are more or less likely to respond to certain therapies.

TABLE 2. STRENGTHS AND LIMITATIONS OF CURRENT VAFS FOR THE EVALUATION OF PERSONALIZED MEDICINES

| | |
|--------------|--|
| ASCO | <ul style="list-style-type: none"> • Clinical trial data averages may not represent the individual patient • Components of the framework may miss considerations important to patients or may have weights that do not represent patients' values • Requires user to seek out and assess the literature for the most relevant data • Does not take into account companion diagnostics |
| MSKCC | <ul style="list-style-type: none"> • The DrugAbacus tool includes data for drugs chosen for inclusion by MSKCC with a primary focus on efficacy outcomes associated with the first approved indication. Thus, it may underestimate product value and potential benefits associated with personalized medicine drugs • Does not take into account companion diagnostics • Does not explicitly account for combination drug regimens (particularly with regard to pricing) |
| ICER | <ul style="list-style-type: none"> • Not intended to inform patient-level choices and may overlook patient subgroups • May not capture value over the life cycle of the product (i.e., topics may only be evaluated once, with no explicit schedule for updating over time); although ICER recently released an update to the clinical and economic evidence on PCSK9 inhibitors for treating high cholesterol (September 9, 2017) • Process updates have been made to address several limitations of the ICER framework |
| NCCN | <ul style="list-style-type: none"> • Already aligned with personalized medicine in that some oncology agents are only recommended for use in patients with known mutations (BRCA1/2, KRAS, EGFR) • Quick-view format enhances approachability and ease of use, but may lack detail necessary for personalized medicine beyond what is contained in the NCCN guidelines |
| PPVF | <ul style="list-style-type: none"> • Includes many patient-centered issues identified through workshops and working groups that affect patient-level decision making • Incorporates costs other than drug costs (i.e., encompasses cost of diagnostic) • Specifically accounts for evidence on subpopulations, potentially opening up the discussion to outcomes achieved in the context of personalized medicine • Components are intended to be applied across VAFs to increase transparency and consistency in defining and capturing patient-centered values |

ASCO – American Society of Clinical Oncology; EGFR – epidermal growth factor receptor; KRAS – Kirsten rat sarcoma; ICER – Institute for Clinical and Economic Review; MSKCC – Memorial Sloan Kettering Cancer Center; NCCN – National Comprehensive Cancer Network; PCSK9 – proprotein convertase subtilisin/kexin type 9; PPVF – Patient-Perspective Value Framework; VAF – value assessment framework

PART III

NEXT STEPS

“Specific limitations and gaps must be addressed to update the value toolbox to ensure alignment with the value elements of personalized medicine in preparation for the increasingly predominant role it will have in patient treatment.”

Summary and Strategic Recommendations

Considerations related to personalized medicine can significantly affect value assessments and the direction of decisions made about patient care based on such assessments. Decision makers should closely examine genetic, clinical and other patient-level data to guide individualized understanding of value and develop approaches to apply them at the individual and population level. As the next generation of VAFs is introduced, it is critical to understand how existing constructs can and should contribute to the broader understanding of the value of personalized medicine — and where there are still needs to fill. The Avalere/FasterCures PPVF provides an important example of how that may be achieved. It provides a construct and methodological approach that is intended to be applied across multiple stakeholders and situations (i.e., in shared decision making, applied to existing frameworks, to support public health care programs, and for strategic, internal analyses).¹⁰

Furthermore, it may be appropriate to have multiple frameworks available for the assessment of health care value from which stakeholders can choose the most appropriate tool or tools for each circumstance. To do so effectively, all stakeholders must continue to be engaged, and multiple perspectives must be integrated throughout the value assessment process in order to truly encompass and reflect value to a health care system that is evolving to a more personalized paradigm. Specific limitations and gaps must be addressed to update the value toolbox to ensure alignment with the value elements of personalized medicine in preparation for the increasingly predominant role it will have in patient treatment.

Recommendations include:

1. Diagnostic testing must be considered an integral part of the assessment of the value of treatment options where efficacy and/or safety information can be obtained.
2. A formal mechanism for consideration of heterogeneity of treatment response needs to be appropriately balanced with population-based considerations.
3. Methods to assess value must consider emerging or evolving elements over time to elucidate the benefits of potentially useful treatments on an individual patient level.
 - Frameworks must be explicit in the patient population being evaluated.
 - Frameworks must frequently update or re-evaluate the treatment landscape in order to capture patient groups that may attain more value from treatments than others through factors associated with the practice of personalized medicine.
 - Value assessment results based on average response in clinical trials may, over time, yield to different, often higher value results in particular patient subsets in a real-world setting as patient characteristics and circumstances associated with better outcomes are elucidated.

4. Education and awareness of appropriate application and use of value assessment frameworks in personalized medicine, including approaches that provide greater transparency and capacity for disaggregation of results that are being applied at the population level, must be increased among payers to reduce the risk of inappropriate restrictions on reimbursement and access to medicines that lead to limited patient access to individualized care.
5. The perspectives of all personalized medicine community stakeholders, especially patients, must be considered in the development and refinement of VAFs and the assessment of therapies.

Value frameworks have the potential to highlight the benefits of personalized medicine, if modified and used appropriately, by demonstrating that some patient groups may attain greater value than others.

APPENDIX A

Organizations offering new perspectives on value include:

- Avalere/FasterCures — Patient Perspective Value Framework Version 1.0¹
- Biotechnology Innovation Organization — Principles on the Value of Biopharmaceuticals²
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) — Initiative on Value³
- National Health Council (NHC) — Patient-Centered Value Rubric⁴
- National Pharmaceutical Council (NPC) — Guiding Practices for Patient-Centered Value Assessment⁵
- PhRMA — Principles for Value Assessment Frameworks⁶

1 Avalere/FasterCures. Patient-Perspective Value Framework (PPVF). Version 1. FasterCures website. <http://www.fastercures.org/reports/view/66>. Accessed May 18, 2017.

2 Biotechnology Innovation Organization (BIO). BIO Principles on the Value of Biopharmaceuticals. BIO website. https://www.bio.org/sites/default/files/files/BIO_PRINCIPLES_ON_THE_VALUE_OF_BIOPHARMACEUTICALS.pdf. Accessed April 3, 2017.

3 International Society for Pharmacoeconomics and Outcomes Research (ISPOR). ISPOR announces establishment of new initiative on value assessment frameworks. ISPOR website. <http://press.ispor.org/index.php/new-initiative-on-value-assessment-frameworks/>. Accessed May 10, 2017.

4 National Health Council (NHC). Patient centered value model rubric. NHC website. <http://www.nationalhealthcouncil.org/sites/default/files/Value-Rubric.pdf>. Accessed April 7, 2017.

5 National Pharmaceutical Council (NPC). Guiding practices for patient-centered value assessment. NPC website. <http://www.npcnow.org/guidingpractices>. Accessed April 3, 2017.

6 PhRMA. Principles for value assessment frameworks. PhRMA website. <http://www.phrma.org/codes-and-guidelines/principles-for-value-assessment-frameworks>. Accessed May 10, 2017.

APPENDIX B

| Framework | Perspective | Value Measures |
|---|--------------------|---|
| American Society of Clinical Oncology (ASCO) Value Framework¹ | Physician/Patient | Clinical benefit; toxicity; bonus points (i.e., survival, palliation, QoL, treatment-free interval); Costs Derived from population-based evidence |
| Memorial Sloan Kettering Cancer Center (MSKCC) DrugAbacus² | Payer/Policy maker | Life year gain; toxicity; novelty; development cost; rarity; burden, unmet need; prognosis Derived from population-based evidence |
| Institute for Clinical and Economic Review (ICER) Reports³ | Payer/Policy maker | Efficacy; harms; quality of evidence; “additional benefits/harm” “contextual considerations” Derived from population-based evidence |
| National Comprehensive Care Network (NCCN) Evidence Blocks⁴ | Physician/Patient | Efficacy; safety; quality of evidence; consistency of evidence; affordability Derived from population-based evidence |
| Avalere/FasterCures Patient-Perspective Value Framework (PPVF)⁵ | Patient/Physician | “Domains;”* patient preferences; patient-centered outcomes; patient & family costs; quality & applicability of evidence; usability & transparency *Each PPVF domain consists of 3 to 4 technical criteria that define the domain (e.g., quality of life, efficacy, and safety) |

1 Schnipper LE et al. Updating the American Society of Clinical Oncology value framework: revisions and reflections in response to comments received. *J Clin Oncol*. 2016;34(24):2925-2934.

2 Memorial Sloan Kettering Cancer Center (MSKCC). Evidence driven drug pricing project. DrugAbacus. MSKCC website. <http://www.drugabacus.org/>. Accessed March 17, 2017.

3 Institute for Clinical and Economic Review (ICER). Overview of the ICER value assessment framework and update for 2017-2019. ICER website. <https://icer-review.org/material/final-vaf-2017-2019/>. Accessed June 22, 2017.

| Strengths | Limitations | Potential Alignment with Personalized Medicine |
|---|---|--|
| <p>Reflects some aspects of care important to patients, but only at the population level; cost comparison includes drugs and supportive care</p> | <p>Primary measures of value are clinical benefit & toxicity; bonus points are conditional on population-level effects; focused on trial-based evidence; does not account for diagnostics, patient values, efficiency, or evolving evidence; oncology only</p> | <p>Insufficient for valuing personalized medicine</p> |
| <p>Captures value associated with unmet need, burden, and prognosis Enables users to determine what weights to assign to each value component</p> | <p>Willingness to pay for life years gained (LYG) signification driver of value; drug costs only; does not account for diagnosis, patient values, efficiency, or evolving evidence; oncology only</p> | <p>Insufficient for valuing personalized medicine</p> |
| <p>Takes into account some cost offsets; discounts, and rebates Diagnosis may be considered, but criteria for doing so lacks transparency; patient values are taken into account through formal engagement throughout the evaluation process, though remain a relatively minor aspect of overall value Nominally takes into account societal value of access to therapy</p> | <p>Limited patient perspective Highest level of evidence is from trials; other forms of evidence are “not limited”; does not sufficiently account for efficiency of therapy or evolving evidence Criteria and methods for inclusion of diagnostics, patient values, real-world evidence, efficiency, and evolving evidence require further transparency</p> | <p>Some elements of the framework have the potential for capturing the value of personalized medicine; however, as currently applied, the framework is insufficient for valuing personalized medicine</p> |
| <p>Affordability is a specific element of value; however, does not include diagnostics or reflect affordability for patient</p> | <p>Focused on trial-based evidence and expert opinion; does not account for diagnostics, patient values, efficiency, or evolving evidence; oncology only</p> | <p>Insufficient for valuing personalized medicine</p> |
| <p>Flexible approach allows multiple applications Intended to support shared decision making at the individual level Patient preferences and patient-centered outcomes are core domains of value Explicitly accounts for multiple cost perspectives and diagnostics</p> | <p>The flexibility of this framework could lead to inconsistent weighting of the domains and/or criteria across users As a result, application of the framework and reporting of outcomes may be variable or compatible The framework itself is transparent; however, the application of it remains to be seen</p> | <p>Promising for use in valuing personalized medicine therapies Inclusive of key patient-focused value elements aligned with the benefits of personalized medicine How this framework is applied and interpreted remains to be seen and may be ultimately contingent on the user</p> |

4 National Comprehensive Cancer Network (NCCN). NCCN unveils Evidence Blocks for CML and multiple myeloma. NCCN website. <https://www.nccn.org/about/news/newsinfo.aspx?NewsID=546>. Accessed March 1, 2017.

5 Avalere/FasterCures. Patient-Perspective Value Framework (PPVF). Version 1. FasterCures website. <http://www.fastercures.org/reports/view/66>. May 2017. Accessed May 18, 2017.

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- 10 Avalere/FasterCures. Patient-Perspective Value Framework (PPVF). Version 1. FasterCures website. <http://www.fastercures.org/reports/view/66>. Accessed May 18, 2017.
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MISSION

The Personalized Medicine Coalition (PMC), representing innovators, scientists, patients, providers, and payers, promotes the understanding and adoption of personalized medicine concepts, services, and products to benefit patients and the health system.