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ABSTRACT

Title of Document: THREE PAPERS EXAMINING THE EXPERIENCE, VALUE FRAMEWORKS AND VALUE-BASED PURCHASING OF NOVEL DRUGS

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Directed By: Professor Nancy Miller, School of Public Policy

This dissertation explores real-world experience, value assessment frameworks, and value-based purchasing arrangements for novel medications. The first paper is a systematic literature review of outcomes of these novel therapies, where I show that the real-world experience with these medications—with never-before-seen mechanisms of action or those that address unmet medical needs for serious conditions—have high costs and do not often align with the outcomes reported in clinical trials. The need to increase access to these novel therapies is often hindered by questions about the cost and value these innovative medications. Advocates of value-based purchasing promote it as a potential solution to concerns that drug prices are increasingly misaligned with their therapeutic benefits. However, defining drug value is not easy. The second paper explores seven value-assessment frameworks developed by U.S-based organizations. These frameworks vary by the elements of a medication's value taken into account, how elements are measured and valued, how elements are combined into an overall assessment of a medicine's value and how that could then be linked to the reimbursement price. In response to increasing costs of these novel medications, state Medicaid programs have experimented with a variety of models for value-based purchasing arrangements (VBAs) to contain spending and achieve value in prescription drugs. The third paper is from in-depth, semi-structured,

qualitative interviews conducted with representatives from four state Medicaid programs that are currently implementing VBAs with drug manufacturers. While interest in Medicaid VBAs grows and states experience some success, there are challenges with the negotiation process, selecting and monitoring patient outcomes, and concerns with high launch prices persist.

THREE PAPERS EXAMINING THE EXPERIENCE, VALUE FRAMEWORKS AND VALUE-BASED PURCHASING OF NOVEL DRUGS

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Chapter 1: Dissertation Introduction

In May 2019, an article by the National Public Radio had this headline: “At $2.1 Million, New Gene Therapy Is The Most Expensive Drug Ever” (Stein, 2019). This article discussed Zolgensma®, a medication recently approved for treatment of spinal muscular atrophy, a rare disorder caused by a defective gene. This disorder destroys the nerves that control muscles, and if left untreated, infants with the most severe form typically do not live past their second birthday. According to the manufacturer, the medication is given as a one-time-only dose which then works by replacing the function of the missing or non-working gene with a new, working copy of the gene. Its price tag, however, is $2.125 million per patient (Stein, 2019). Even aside from its cost, the approval of this medication heighted on-going conversations about the safety and effectiveness of such novel products, particularly because of the different ways such drugs work. In essence, parents, physicians and payers need to weigh the potential benefits and risks without necessarily knowing all the long-term outcomes of these novel medications. Of particular note, in the month prior to the approval of Zolgensma®, Dr. Price, a former Secretary of Health and Human Services, asserted that this treatment “should not be rushed to market unchecked.’’(Price, 2019). While acknowledging that novel medications such as gene therapies may in the long term become an effective form of treatment for many rare conditions, “American healthcare professionals must not take undue risks with patient's lives” (Price, 2019).

These two news articles, in my mind, highlight the conflict between three concepts: 1) the urgent need for patients’ access to medications, particularly for conditions that

currently have no or few alternatives; 2) concerns with the safety and effectiveness due to the novel nature medications, since many of them are “first-in-class” with never-before-seen mechanisms of action, or unique drug development processes, or special supply chain considerations; and 3) the associated high market price tag. Healthcare providers, payers, and states regularly confront these three concepts to make decisions about how best to take advantage of these innovative products. Similarly, with the growing public focus on the high cost of prescription drugs, there have been many initiatives designed to help physicians, payers, and patients understand the value of new therapies and make better choices about their use. The impetus to increase access to these innovative therapies often runs headlong into questions about the risks, value, and costs of new medications. This dissertation seeks to explore the evidence used to make these decisions. Specifically:

1. Given their novel nature, does the real-world experience of these innovative therapies align with the outcomes presented in clinical trials?
2. Given the criticisms of current reimbursement strategies what frameworks (including limitations) currently exist for assess the comprehensive value of novel therapies?
3. As a result of budgetary pressure that drug prices put on states, as well as the harm excessive prices have on residents’ health and finances, many states are using alternative reimbursement models such as value-based payment arrangements (VBAs) with drug manufacturers. What is the experience of Medicaid programs implementing these VBAs?

Background

Novel Medications for Unmet Medical Needs

Increasingly, more innovative products are being translated into therapeutic products in the United States. These ground-breaking medicines include novel innovative products that serve previously unmet medical needs for a serious condition (FDA et al., 2014). ‘Unmet medical need’ is typically defined in terms of availability and adequacy of medical treatments for serious conditions. Specifically, a condition where treatment may not exist for a certain disease, or when available therapy exists, a new treatment would be considered to address an unmet need if it provides meaningful therapeutic benefit over available therapies. For example, there is unmet medical need across a wide range of rare diseases worldwide, including "neglected" tropical diseases, genetic disorders, metabolic disorders, kidney disorders, skin conditions, rare cancers and epilepsies. The coronavirus disease 2019 (COVID-19), a novel respiratory disease, also has no available treatments and presents an unmet medical need. On the other hand, while numerous antibacterial agents are available, new agents to treat drug-resistant organisms has been identified as an important unmet need. Similarly, there is unmet need across multiple diseases that disproportionately impact women, including endometriosis, uterine fibroids and osteoporosis, as well as the need to address dementia in older adults with Alzheimer's disease.

Rare diseases, which are disorders affecting less than 200,000 people in the USA, have considerable unmet medical needs (Ollendorf et al., 2018)). While the numbers around rare diseases are imprecise, it’s estimated that the lives of nearly 30

million Americans, half of whom are children, are directly affected by approximately 7,000 rare diseases, with 85 percent of these considered life-threatening. Despite the successes of researchers, patients, and clinicians, only 5% of rare diseases have an approved treatment option[1].

Challenges with Novel Medications: Conflict Between Need, Safety Cost

Pharmaceutical companies and federal agencies (e.g., the National Institutes of Health, the National Science Foundation), spend billions of dollars annually on biomedical research (Davio, 2017). These investments are intended to catalyze innovation, development and dissemination of new forms of medical care, including those that address serious and previously unmet unmedical needs. Approximately 42% of the 59 new drugs approved in 2018 were 'first-in-class', meaning they had new mechanisms of action; this was an increase over the prior four years, when that proportion was between 32% and 36% (Jarvis, 2020). Similarly, the industry has, in the past 5 years, focused more on drugs for rare diseases, which now regularly account for at least 40% of new drug approvals. Notable approvals in 2018 include two new drugs for sickle cell anemia - a genetic condition that causes hemoglobin (the oxygen-carrying component of the red blood cells), to become sickle (i.e., crescent-shaped), leading to a reduced amount of oxygen the blood can supply to vital tissues and organs of the body (FDA, 2019b). Others include an antibiotic for treatment-resistant tuberculosis and a therapy for women experiencing postpartum depression.

[1] https://www.phrma.org/media/progress-in-fighting-rare-diseases

Examples of novel drug approvals in 2019 include those for treatment in spinal muscular atrophy, a new treatment for adults with depression who have tried other medications without success, as well as a new treatment for patients with Parkinson's disease who experience "off" episodes, during which medications are not working well, causing an increase in PD symptoms, such as tremor and difficulty walking (FDA, 2020b). The number of novel medications - many of them being first-in-class with never-before-seen mechanisms of action, or unique drug development processes, or special supply chain considerations, is expected to increase dramatically over time. For example, by 2025, the FDA anticipates approving 10-20 gene therapy products per year, many of which are intended to be one-time curative treatments (FDA, 2019a). Further, sometimes, the approval of these novel products relies on surrogate endpoints (Lathia et al., 2009); meaning that instead of measuring the clinical outcome (whether people in a trial feel or function better, or live longer), researchers measured an effect that may correlate with a real clinical endpoint. While the FDA has published surrogate measures that may be acceptable to support drug approval (FDA, 2018a), some studies have found weak or missing correlations of treatment effects on these surrogates with treatment effects on clinical outcome (Gyawali et al., 2020). Similarly, although the FDA requires post market approval (PMA) confirmatory clinical studies for those approved using surrogate markets, one study found that these confirmatory trials and preapproval trials had similar design elements, including reliance on surrogate measures as outcomes (Naci et al., 2017).

While these novel medications carry the potential to cure intractable diseases or address previously unmet medical needs, these novel breakthroughs often come at

a steep price. For example, in 2018, spending on these novel medicines increased by 5.8% and accounted for $517 out of the $1,044 total per person medicine costs (IQVIA, 2019). With the high-costs, use of these medications by patients is also expected to increase over times – in 2018, their use grew by more than twice the rate of other traditional/non-novel drugs (IQVIA, 2019). Similarly, the restrictive eligibility criteria for participation in clinical trials may exclude patients such as older adults and lead to trial results that do not fully represent treatment effects in the patient population that will ultimately receive the drug (Zulman et al., 2011).

While cost issues present challenges for all payers, they are especially relevant for State-funded programs. First, States are health care payers for a range of populations, including Medicaid, inmates in correctional facilities, and public workers - state employees and retirees, legislators, judicial employees, and public university employees. Some unmet medical needs or rare diseases are disproportionately represented in these populations. For example, as the largest single insurer of children in the United States, Medicaid bears the burden of coverage and reimbursement for many medications for treatment of any childhood rare conditions, particularly those that are hereditary in nature.

Second, spending on State health programs must be considered as part of the overall annual State budget. These health programs therefore face more substantial budget constraints than do other payers, which can particularly limit their ability to manage the use of high-cost novel medications among large populations of patients who are clinically eligible to receive them. For example, the recent availability of novel medications that cure hepatitis C virus (HCV) infections enables the avoidance

of significant healthcare costs previously associated with treating the disease year after year (Roebuck & Liberman, 2019). While the high costs of these HCV treatments are declining over time (Loftus, 2018), federal laws require Medicaid to not deny access to any medically necessary drug whose manufacturer participates in the Medicaid drug rebate program. Further, chronic HCV infection disproportionately affects poorer populations who tend to be enrolled in Medicaid, or are incarcerated; prevalence in Medicaid has been estimated at 7.5 times that in commercially insured populations (Johnson et al., 2017). Expansions of Medicaid stemming from the Affordable Care Act may have also increased the number of individuals in need to these treatments, as more than 30% of people with Hepatitis C fall below 150% of the federal poverty line (Henry, 2018). State health programs therefore expressed concerns over allowing universal access to these new therapies because of the unique dual challenge of having both the financial constraints of annual public budgets and high numbers of HCV-infected enrollees (Roebuck & Liberman, 2019).

The Approval Process, Value Assessment and State Regulation

By acting as the gateway for access to novel medications for unmet medical needs, drug approval processes, and State laws are the focal point for the conflicts need, safety and cost. The FDA encourages drug development for unmet medical needs for serious conditions by reducing premarket study time. Unlike the FDA, State governments, in their role as a purchasers of healthcare services, must balance other goals and priorities. When they allow access to new medications, States must pay for

them; states work within a budget that may not accommodate unrestrained growth in the use of expensive medications.

In the U.S, where there is no regulation of medicines' prices at market launch, drug manufacturers can freely set the price at market launch and negotiate the actual price with insurance companies and other payers. to call for setting prices to reflect research, development, and production costs for drug firms. Concerns over rising drug prices has led some observers to instead focus on a drug's benefits, where value-based approaches can encourage firms to produce more of what people want — products that improve health — and thereby further stimulate innovation. In the last few years, several efforts have focused on methods to determine prices for drugs that are commensurate with their value.

Drug Approval

The FDA requires all new medications available in the country to have their safety and efficacy established through adequate and well-controlled clinical trials. These studies must include a design that permits a valid comparison with a control such as a placebo, or other active treatment (Kesselheim & Gagne, 2014). To incentivize the development of medicines to address an unmet medical need for a serious condition, the FDA developed programs to expedite drug development and review. For example, Section 506(b) of the Federal Food, Drug, and Cosmetic Act provides for the following designations to expedite access: fast track, accelerated approval, priority review and breakthrough therapy. Drugs qualifying for the "fast track" or "accelerated approval" pathways are allowed an abbreviated development process. In the former case the drugs may be approved after a single phase 2 trial and

in the latter case they are based on surrogate measures that are only “reasonably likely” to predict actual clinical benefit (Lathia et al., 2009). These “fast track” or “accelerated approval” pathways are increasing common - a recent study of medications approved between 1987 and 2014 showed that there was a 2.6% yearly increase in the number of therapies approved using FDA’s expedited review and approval programs (Kesselheim et al., 2015). Further, the 21st Century Cures Act provides for a process of accelerated approval for newer treatment modalities , including regenerative medicine therapies such as cell therapy, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products (Law, 2016). Once accelerated approval medications are granted marketing authorization, the FDA requires that the manufacturer complete confirmatory trials to describe and verify the clinical efficacy. However, studies show that manufacturers rarely conduct trials and report results monitoring safety or efficacy after approval. Among 600 trials, only 12.0% exclusively evaluated the originally approved indication (Skydel J et al., 2019).
In response to concerns that the small numbers of patients affected by each rare disease would not sufficiently encourage investment by pharmaceutical manufacturers in finding treatments for that condition, the US Orphan Drug Act of 1983 included grants to perform clinical trials, a 50% tax credit for clinical testing costs, and an exclusive right to market the drug for 7 years after regulatory approval (Food and Drug Administration, 2014).

Value Assessment of Prescription Drugs

In October of 2012, just two months after ziv-aflibercept (brand name Zaltrap®) had received FDA-approval for treating metastatic colorectal cancer, doctors at the Memorial Sloan-Kettering cancer center published an op-ed on the New York Times stating that they would not prescribe the new drug to their patients.[2] The reason? The drug cost about twice as much as its competitors, while offering roughly the same improvement in outcomes. Almost 10 years later in 2021, Aduhelm®, with an initial drug price at $56,000, was FDA-approved for the management of Alzheimer's disease. Almost immediately, major medical centers declined to offer Aduhelm®, citing a lack of clear evidence that the drug helps Alzheimer's patients.[3] Researchers determined that there was a "mismatch between the announced price and value-based estimates" for Aduhelm® and that the drug's manufacturer would need to lower the price by 85 percent to 95 percent from its initial list price because the price is "not in reasonable alignment with its clinical benefits."(ICER, 2022)

Value-based pricing (VBP) is a well-established pricing method for goods and services. VBP dictates that the price of the commodity should reflect the value to the buyer rather than the actual costs of production augmented by the profit margin (Kaltenboeck & Bach, 2018). In the U.S., a number of professional and private organizations have developed value assessment frameworks to define and measure the value of drugs. A framework to assess value of medications is one approach to assess the evidence and value of new novel medications (Garrison et al., 2018). These frameworks provide a way to measure and communicate the value of medications for

[2] Bach et al. (2012), available at http://nyti.ms/OA0x88.
[3] https://www.statnews.com/2022/01/06/top-hospitals-arent-offering-aduhelm/

decision-making purposes. It aims to ensure that the prices paid for drugs reflect the benefits they provide, either in terms of longer life or better quality of life. In some countries—Australia, Canada, Sweden, England—the government (or an agency of the government) develops and applies economic analyses to measure the value of a prescription medication, which then determines the price of that medication nationally. Here, the goal is to ensure that the value of a medication is well understood so that the society can spend the available resources that they have on them in a sensible manner.

Value-based Purchasing Arrangements by State Medicaid Programs

Rising prescription drug costs are consuming a growing proportion of state budgets. In response, states have experimented with a variety of policies to contain spending and achieve value in prescription drugs. Over the past decade, States are increasingly seeking to develop alternative payment arrangements that emphasize the value of the services provided instead of the quantity (Tompkins et al., 2009). These value-based strategies tie payment to outcome metrics. For example, several states have rolled out outcomes-based or population-based models for drug pricing in Medicaid. These include Oklahoma, with value-based payment strategies for four drugs: two long-acting antipsychotics, one intravenous antibiotic and one medication that manages epilepsy. Expected outcomes include reducing costly hospitalizations and improving medication adherence. Louisiana and Washington states are implementing models under which their Medicaid programs will pay a fixed annual amount to drug manufacturers for an unlimited supply of drugs that treat low-income beneficiaries with hepatitis C virus.

Conclusion

The favored form of evidence has been RCTs, which serves as the gold standard for clinical research, with rigorous scientific design and prespecified endpoints. Decisions about whether or not to adopt a new novel medication usually hinge first on the availability and quality of experimental evidence from trials. Novel medications, such as Zolgensma®, offer treatments that can greatly improve outcomes to patients with serious or unmet health conditions. However, many of these therapies are associated with significant costs that create barriers to access and affordability. Further, the increased use and rising drug costs have put prescription medications on the public agenda, necessitating individual States to intervene. However, given the limited data on these novel therapies, how do policy makers use the available evidence to measure value of these medications and acquisition decisions?

This dissertation will include three papers. The first paper will use available literature to systematically review and evaluate whether the favorable outcomes from the clinical trials of novel medications used for FDA-approval are bearing out in the real world. Similarly, using published literature, the second paper will explore value assessment frameworks developed by U.S-based organizations, including their limitations. The third paper will use semi-structured, qualitative interviews to understand value-based payment arrangements currently implemented by state Medicaid programs with drug manufacturers to mitigate the high costs associated with novel medications.

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Chapter 2 : Paper 1 - Real-World Experience with Novel Medications for Unmet Medical Needs – A Systematic Literature Review

Background

The Federal Food, Drug, and Cosmetic Act requires new drugs to show "substantial evidence" of efficacy before approval by the Food and Drug Administration (FDA) ((FDA, 2018b)). Historically, the FDA has interpreted that standard to encourage at least two rigorous clinical trials (preferably randomized, double-blind, placebo-controlled studies) that independently show a statistically and clinically meaningful benefit. The FDA however has made exceptions in cases of serious, unmet need; the FDA has several pathways aimed at expediting the development and approval of medications that address serious or life-threatening conditions. These include fast track, accelerated approval, priority review and breakthrough therapy as well as the orphan drug designation, where the FDA shortens the time spent on clinical trials and novel drugs receive faster review ((Kesselheim et al., 2011)). For example, in 1992, during the human immunodeficiency viruses (HIV) crisis, the FDA provided faster access to medications that addressed this 'unmet medical need' though an accelerated approval pathway and priority review designation.

A recent study of medications approved between 1987 and 2014 showed that there was a 2.6% yearly increase in the number of therapies approved using FDA's expedited review and approval programs (Kesselheim et al., 2015). Under the standard approval pathway, the FDA may also grant market approval based on surrogate endpoints, if the agency believes that the connection between the surrogate

endpoint and the desired clinical outcome is well established (FDA, 2018a). For example, the FDA routinely approves hypertension therapies that lower blood pressure (the surrogate endpoint) without requiring evidence that the therapies reduce cardiovascular disease (the desired clinical outcome).While the FDA has published surrogate measures that may be acceptable to support drug approval (FDA, 2018a), one study have found weak or missing correlations of treatment effects on these surrogates with treatment effects on clinical outcome in cancer care (Gyawali et al., 2020). Similarly, although the FDA requires post market approval (PMA) confirmatory clinical studies for those approved using surrogate markets, one study found that these confirmatory trials and preapproval trials had similar design elements, including reliance on surrogate measures as outcomes ((Naci et al., 2017)). Therefore, although these FDA programs bring to market much needed therapies for unmet medical needs or serious medical conditions, it is possible that the expedited development or review may raise concerns with risks from safety issues that may not be identified prior to marketing.

One concern is that drugs that have greater therapeutic innovation may also have more risk or uncertainty about drug safety, which could have negative health consequences for patients. For example, in an earlier study, Olson (2002) finds that faster drug reviews is associated with increased adverse drug reactions ((Olson, 2002)). One reason for greater sense of awareness of potential risks associated with these drugs among physicians, patients and insurers is that the FDA may assume greater risk or uncertainty to help accelerate the approval of novel drugs, particularly when no other therapy exists for a serious condition. Greater uncertainty about a

drug's safety profile prior to approval may translate into greater risk of adverse drug effects after approval. For example, Olson (2002) finds that faster drug reviews and therapeutic novelty are associated with increased adverse drug reactions (Olson, 2002).

Real-World Evidence (RWE) is the clinical evidence about the use and potential benefits or risks of a medical product derived from analysis of real-world data (RWD)[4]. RWD are defined as "routinely collected data relating to a patient's health status or the delivery of health care from a variety of sources other than traditional clinical trials" (Whatley & Malone, 2017). Examples of RWD include data derived from electronic health records (EHRs); medical claims and billing data; data from product and disease registries; patient-generated data, including from in-home-use settings. While clinical trials play a critical role in evaluating the safety and efficacy of drugs, observational studies using real-world evidence (RWE) provide significant opportunities to gain insight into treatment patterns and outcomes in clinical practice outside randomized controlled trials (Kuehn, 2016).

Research Questions

The broader idea is that real-word evidence of effects of medications (e.g., benefit, risk, and resource use), including gaps, that are not collected in the context of conventional clinical trials (Ollendorf et al., 2018). Identifying these effects and gaps points future innovators at these opportunities, gives them a target to hit, and reminds stakeholders of the real- world needs experienced by patients of these much-needed medicines. The purpose of this study, therefore, is to systematically examine the

[4] The definition of RWE provided by section 3022 of the Cures Act was subsequently revised by a technical amendment in Section 901 of the FDA Reauthorization Act of 2017 (Public law 115-52)

literature to identify the real-world experience of patients, providers and payers with novel products. Specifically,

1. Are the outcomes obtained in the clinical trials evident in the real world?
2. Are the characteristics of patients exposed in the premarket drug trials comparable to those in the real-world?
3. How do insurers and payers balance the limited pre-approval clinical information that may be unconfirmed or does not justify the high cost of these novel therapies?

Conceptual Framework

FDA regulators must balance two competing goals in making approval decisions for novel drugs: ensuring drug safety and facilitating access to new medicines for unmet needs. When doing so, FDA regulators must also confront uncertainty in drug approval decisions since all of a drug's effects are not fully known at the time of approval (Olson, 2008).

There are several sources of uncertainty about drug safety at the time of FDA approval of these novel drugs. The first source is the limitations of clinical trials. These limitations include small numbers of patients, eligibility restrictions on clinical trial participants, understudied patient populations, and a short duration for learning about a drug's effects (Zulman et al., 2011). Since clinical trials are conducted on a carefully screened, relatively small group of patients under the highly controlled circumstances, little information is revealed about moderately rare side effects and risks among understudied populations such as women, minorities, and patients who have multiple health problems or chronic illnesses. Drug interactions are often not

detected until a drug is sold in the general patient population because the sickest individuals (who may also be taking several different drugs) are not selected to participate in these trials (Kesselheim & Gagne, 2014). These limitations suggest that a drug's complete safety profile may not be fully known until that drug is more widely used.

A second source of uncertainty about risks of novel medications is the lack of physician and patient experience with these new agents (Lexchin, 2012). Introduction of any new product involves learning. Physicians need to acquire some experience with a drug before they have a good sense of the factors such as appropriate doses, degree of differential response in sub-populations, range of side effects, and early warning of side effects (Olson, 2008). Among novel drugs, which may represent the first of their kind, there is a greater role for learning because physicians and patients have less experience, information, and familiarity with the risks among these drugs. Among new non-novel drugs, physicians and patients may be able to draw from their experiences with similar drugs already used in the marketplace. Previous experience with similar drugs can facilitate learning about the side effects or potential interactions involving non-novel drugs. The lack of experience with newly approved novel drugs suggests that physicians and patients confront greater uncertainty about ADR risks for such drugs relative to less novel drugs.

A third source of uncertainty about drug risks is the FDA review process. Regulators may be willing to assume more risk in the review process to help accelerate the approval of novel drugs, especially for novel diseases where there are no treatments available. Less time spent reviewing the application or seeking new

information about drug effects may result in less information about new-drug risks and more uncertainty about drug safety (Olson, 2002).

Methods

Search Criteria

The literature was systematically searched on real-world use of novel medications using the following databases: MEDLINE via the EBSCO interface and Web of Science. Search strategies used subject heading terms appropriate for each database and key words relevant to novel drugs, impact and outcome. The search strategy was adopted for each of the two databases. As an example, Table 2.1 presents the full search strategy for EBSCO Medline and Web of Science.

Table 2.1: Search Strategy on Databases

Key words	**Search Terms**	**EBSCO MEDLINE**	**WEB OF SCIENCE**
Approval through expedited program	Accelerated OR Breakthrough Therapy OR unmet need OR Novel drug OR innovative product OR first-in-class OR rare disease OR orphan disease	AB (Accelerated OR Breakthrough Therapy OR Novel drug OR innovative product OR first-in-class OR rare disease OR orphan drug) AND AB (impact or effect or influence or outcome or result or consequence OR experience) AND AB (clinical care OR treatment OR guidelines OR safety OR effectiveness OR side-effect OR adverse drug event OR toxicity OR response OR efficacy OR survival OR quality of life OR Cost OR utilization OR Use)	TS=(Accelerated OR Breakthrough Therapy OR Novel drug OR innovative product OR first-in-class OR rare disease OR orphan drug) AND TS=(impact or effect or influence or outcome or result or consequence OR experience) AND TS=(clinical care OR treatment OR guidelines OR safety OR effectiveness OR side-effect OR adverse drug event OR toxicity OR response OR efficacy OR survival OR quality of life OR Cost OR utilization OR Use)
impact	impact or effect or influence or outcome or result or consequence		
outcome	clinical care OR treatment OR guidelines OR safety OR effectiveness OR side-effect OR toxicity OR response OR efficacy OR cost Or Use		

AB: abstract; TS: Topic

Inclusion Criteria

Inclusion criteria were defined *a priori* to searching for articles.

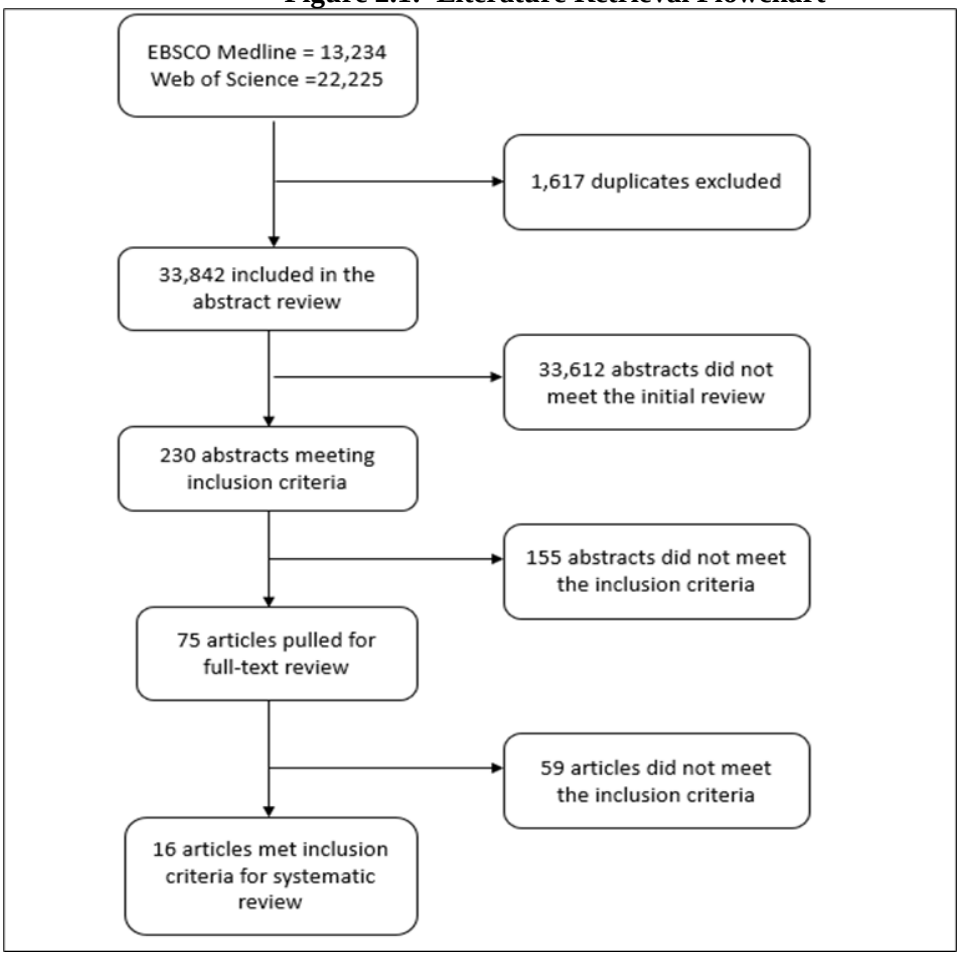
- Articles published in English
- US setting
- Published 2009 – present
- Published in a peer-reviewed journal
- Have one of the following study designs: retrospective cohort study; retrospective case-control study; before-and-after design
- Has one of the following data sources: electronic health records (EHRs); medical claims and billing data; data from product and disease registries; patient-generated data
- Only evaluates novel drugs approved using one of the 4 FDA accelerated programs

Results

Data Extraction and Analysis

The author identified and screened a total of 235,459 citations and abstracts through the electronic database searches and manual review of articles. Figure 2.1 presents the flow of articles through the ensuing levels of review. A total of 16 studies were included in this review. Table 2.4 provides a summary of some of the data extracted from the eligible studies.

Figure 2.1: Literature Retrieval Flowchart



Outcomes from Studies

Results from the review of the studies included in the systematic review were grouped by the following outcomes: patient experience, healthcare utilization, cost, and payer experience. A study could have more than one outcome. Table 2.2 presents the included studies by outcome.

Table 2.2: Summary Table of Number of Studies by Outcomes

Outcome	Number of Studies	Included Studies
Patient experience	10	Chang, J et al., 2011
		Ali, AK ,2011
		Kish, JK et al., 2018
		Lakshmi, S et al., 2016
		O'Connor, JM et al., 2018
		Sanchez, Y et al., 2012
		Wang, AA et al., 2020
		Weisshof, R et al., 2019
		Varella et al., 2019
		Zhou, M et al., 2015
Healthcare utilization	3	Chang, J et al., 2011
		Ali, AK ,2011
		Klink, AJ et al., 2019
Cost	5	Chang, J et al., 2011
		Deshpande, CG et al., 2011
		Guo, J et al., 2012
		Klink, AJ et al., 2019
		Penington, R et al., 2016
Payer	3	Handfield, R et al., 2013
		Robinson, SW et al., 2014
		Shaw, DL et al., 2018

1. Patient Experience

Typically, physicians and patients lack experience with novel drugs and initial real-world use involves learning, such as the extent to which there is a differential response among sub-populations and the range of side effects. Findings are discussed within four patient factors: patient characteristics; patient outcomes; patient side-effects; patient costs.

a) Patient characteristics:

Two studies found that in real-world use, patients have characteristics that differ from those in controlled environment of clinical studies. Kish et al. followed 763 female patients who received palbociclib (a novel, first-in-class anti-cancer agent) one-year

after its approval (Kish et al., 2018). Real world use of this drug included a more heterogeneous patient population compared to that in clinical trials and were sicker. Similarly, O'Connor et al. found that, within 4 months of FDA approval, novel cancer therapeutics may have rapidly changed clinical practice, with patients treated in real-world being significantly older (median age, 66 compared with 57) than those studied in the pivotal clinical trials (O'Connor et al., 2018).

b) *Patient outcomes*

Findings from five studies were not consistent when comparing treatment outcomes from real-world use to those from clinical trials. Patient treatment outcomes were similar to those from trial data in two studies, one study showed worse outcomes and another study showed mixed results in real life compared to the controlled environment of clinical studies.

Specifically, Chang et al. found that hypertensive patients whose treatment included aliskiren (a first-in-class antihypertensive agent) demonstrated significantly better adherence to treatment compared with those initiated on other similar therapies (Chang et al., 2011). Weisshoff et al. had similar finding among patients treated with tofacinib – a first-in-class treatment for ulcerative colitis where, tofacitinib led to a clinical response in 69% of the patients, with 27% patients in remission 1 year of treatment (Weisshof et al., 2019). These rates were consistent with the rates reported in recent clinical trials. Conversely, Lakshmi et al found that the real-world hepatitis C virus (HCV) infection cure rates with novel directly acting antiviral agents (DAAs) in 84 patients with HCV/HIV coinfection are lower than those seen in clinical trials ((Lakshmi et al., 2016)). Varella et al however found mixed results. Compared to the 24-month progression-free survival (PFS) observed in the clinical trials of palbociclib

real-world use showed mixed findings - PFS in patients using one palbociclib treatment combination was comparable to that reported in clinical trial, but shorter for another treatment combination (Varella et al., 2019).

c) *Patient side-effects*

One study comparing side-effects in real-world vis-à-vis clinical trials, found that outcomes in both scenarios were comparable. Since clinical trials are conducted on a carefully screened, relatively small group of patients under the highly controlled circumstances, there is typically little information about rare side effects. In their study of 1,592 adverse event reports for aliskiren, Ali et al found that this novel first-in-class drug was associated with a large number of reports of rare and serious side effects – which was consistent with the clinical trials and safety reports received by the European Medicines Agency and the Medicines and Healthcare Products Regulatory Agency in the United Kingdom in 2009 (Ali, 2011).

d) *Patient costs and access*

Many novel therapies in the U.S are launched with costly price tags, and the question remains whether the price of these new medications confers additional value. Two studies examined value and access to novel cancer agents. Sanchez et al. quantified the optional value of a novel cancer drug, defined as the additional value patients receive when innovative treatments enable them to survive until the advent of even more effective future treatments (Sanchez et al., 2012). For a recently diagnosed patient with chronic myeloid leukemia, the option value of novel medications amounts to 0.76 life-years. This option value is worth $63,000, which equivalent to 9% of the average survival gains from existing treatments (Sanchez et al., 2012).

While novel cancer agents have become the standard of care and first-line therapies for many malignancies, issues impacting access to these drugs persist. Wang et al found that a patient's insurance has a significant effect on the time-to-receipt of newly prescribed novel oral cancer agents, with Medicare experienced longer time-to-receipt (9.1±13.1 days) compared to patients with commercial insurance (4.4±3.3). Uninsured patients experienced the longest time-to-receipt (15.7±7.8 days) (Wang et al., 2020).

2. Healthcare Utilization

Three studies found lower healthcare utilization among patients using novel medications. First, the improved treatment compliance with aliskiren therapy (a novel blood pressure-lowering agent) may have contributed to the lower utilization of healthcare resources (Chang et al., 2011). Also, Ali et al. showed that use of the same drug was associated with lower rates of hospitalizations and emergency room (ER) visits. Similarly, among patients with melanoma treated with various first-line novel cancer therapies, Klink et al. found that the likelihood of hospitalization and ER visits was not consistent but varied across these novel therapies, with higher rates of healthcare utilization for therapies than others (Klink et al., 2019).

3. Cost

Five studies showed that novel therapies are available at high costs. One study showed that use of aliskiren (a novel blood pressure-lowering agent) in combination with others was associated with significantly greater increases in prescription drug costs (Ali, 2011). Klink et al found that total monthly costs varied substantially across first-line therapies for metastatic melanoma varied across these novel therapies, with

higher costs for some therapies than others (Klink et al., 2019). Finally, An 11-year analysis of pricing of specialty drugs (primarily those used for rare illnesses) also found that the annual increase in price of the average of 44 specialty drugs was greater than general inflation rate (Penington & Stubbings, 2016).

At the payer level, Guo et al. found that spending on Medicaid increased proportionately between 2006 and 2011 with the introduction of two novel therapies for rare diseases (Guo et al., 2012). Further, Deshpande et al determined that that patients' adherence to novel anticoagulant treatment protocol led to a reduction in overall healthcare cost as higher drug costs were offset by lower medical (inpatient and outpatient) costs among adherent patients (Deshpande et al., 2018).

4. Payer Experience

Shaw et al identified features of these novel drugs under Medicare plans (Shaw et al., 2018). Characteristics of these novel drugs included having CMS-protected drug status, those that underwent FDA priority review, or FDA-accelerated approval were each associated with higher rates of coverage, whereas year of approval, drug type, and orphan drug status were not (Shaw et al., 2018). With their high price tag, novel therapies especially those for rare diseases, are of increasing concern to private and public healthcare insurance plans. Three studies identified some strategies used by payers to mitigate the high costs of these drugs. The Handfield et al survey with commercial US payers found that while 67% were concerned about these novel therapies, only 17% have developed meaningful strategies for addressing the cost of these medications. While cost effective analyses serve as a strategy for payers to determine access and coverage decision-making for many drugs, the lack of the

availability of medicines to comparisons, limits the application of this tool to orphan drugs for rare diseases (Handfield et al., 2013). Coverage limitations, tier placement, cost sharing, and utilization management applied for the selected medications were also identified as potential strategies (Robinson et al., 2014).

Assessment of Quality

The GRADE methodology was used to assess the quality of the body of retrieved evidence, and thus, the assessment of quality for the selected studies was done by outcome reported. As presented earlier, there are four outcomes reported in the selected studies: patient experience, healthcare utilization, healthcare costs, payer experience. No two studies used the same measure for the outcomes for the same novel medications. For example, while both Kish et al and O'Connor et al examined patient characteristics, Kish et al reported patient comorbidities while O'Connor reported on patient's age. Thus, the approach used in this assessment was to rate the quality of evidence of each outcome in each article, not across the body of evidence. Tables 4 presents the overall scoring and quality grade for each of the outcomes reported. Per the study inclusion criteria, randomized clinical trials were excluded from the study. In line with the GRADE approach, observational studies start as LOW quality evidence to support estimates of intervention effects. Some factors may lead to rating up the quality of evidence —for instance, when an effect size is very large, a dose-response gradient is shown, or possible confounding is adequately addressed. Except for confounding, all of these factors were not overwhelmingly met and thus not included in Table 2.3. Some studies employed techniques to control for heterogeneity; it was therefore decided to start all these observational studies at the

VERY LOW level and upgrade from there. Thus, studies that utilize statistical techniques to address confounding were upgraded to a LOW level. Only 3 of the 16 studies made attempts to reduce confounding (by stratification) . these studies were upgraded to a LOW level.

Table 2.3: GRADE - Assessment of Quality by Outcome and Risk of Bias

Outcome (# of studies)	Specific Type Outcome (# of studies)	Included Studies	Confounding	Overall quality of evidence
Patient experience (10)	Patient characteristics (2)	Kish, JK et al., 2018	No technique	Very low
		O'Connor, JM et al., 2018	No technique	Very low
	Patient outcomes (4)	Chang, J et al., 2011	Stratification used	low
		Weisshof, R et al., 2019	No technique	Very low
		Lakshmi, S et al., 2016	No technique	Very low
		Varella et al., 2019	No technique	Very low
	Patient cost (2)	Sanchez, Y et al., 2012	No technique	Very low
		Wang, AA et al., 2020	No technique	Very low
	Patient side-effects (1)	Ali, AK ,2011	No technique	Very low
	Patient adherence (1)	Zhou, M et al., 2015	No technique	Very low
Healthcare utilization (3)	Hospitalization and ED visits (3)	Chang, J et al., 2011	No technique	Very low
		Ali, AK ,2011	No technique	Very low
		Klink, AJ et al., 2019	No technique	Very low
Cost (5)	Prescription cost (1)	Penington, R et al., 2016	No technique	Very low
	Overall healthcare costs (1)	Deshpande, CG et al., 2011	Stratification used	low
	Payer costs (1)	Guo, J et al., 2012	No technique	Very low
	Monthly drug costs (1)	Klink, AJ et al., 2019	Stratification used	low
	Annual prescription drug costs (1)	Ali, AK ,2011	No technique	Very low
Payer strategies (3)	Commercial (1)	Handfield, R et al., 2013	No technique	Very low
	All payers (1)	Robinson, SW et al., 2014	No technique	Very low
	Medicare (1)	Shaw, DL et al., 2018	No technique	Very low

Discussion

This study reviewed the available evidence for novel medications published over the last 10 years. In total, 16 studies were included in the review. The vast majority of these studies (63%) focused on patient experience. Often, patients treated in practice will be clinically distinct from patients included in clinical trials. Understanding patient characteristics and safety outcomes for novel treatments is important to practitioners who may be prescribing a new agent with little or no practical experience. Real-world population was found to be more heterogeneous and sicker than in clinical trials. There were however mixed treatment outcomes from real-world use when compared to those from clinical trials; with studies showing worse, better or mixed results in real life compared to the controlled environment of clinical studies.

Hospitalizations and ED visits represent important health care resources; this study mixed healthcare utilization among patients using novel medications. Thus, differences in resource use and costs should be considered by health care decision makers particularly in value-based care framework, where cost is weighed alongside clinical effectiveness to inform the selection of the optimal therapy for patients. As expected, novel medications had high costs. Further, the study found that a patient's insurance has a significant effect on the time-to-receipt of newly prescribed novel medications. Payers used various strategies to manage these costs, including coverage limitations, tier placement, cost sharing, and utilization management applied for the selected medications were also identified as potential strategies.

Physician, payer and patient decisions regarding use of novel medications requires knowledge and evidence of how the population of interest interact with the prescribed treatment and the impact on healthcare utilization. However, the analysis of the GRADE quality assessment could not be applied across studies due to the absence of studies on the novel medication with measures of the same outcome. To this end, further work could expand the inclusion criteria to include other study designs, which may expand the number of studies, thus identify studies with similar outcome measures and novel medications.

Implications of Findings

The evolving science is likely to lead to even greater number of new technologies for medicines that may pose additional questions about their affordability and sustainability of public programs such as Medicare and Medicaid. While the high costs of these novel therapies are evident in real-world, the benefits from real-world use are not always clear. One limitation is that data to evaluate real-world use of these medications are more prone to data bias and confounding than evidence provided through randomized clinical trials due to lack of randomization. However, examination of real-world experience has greater external validity by including patients who are often not represented in clinical trials, such as older adults, smokers and patients with comorbidities.

As shown in this study, evidence from real-world use may be of a low quality. However, findings may be beneficial. For example, information from real-world experience with novel medications can provide valuable insights on drugs for rare diseases that typically have few therapeutic alternatives. Also, results from these

studies can be used by the FDA and payers (e.g., Medicaid) to negotiate with drug manufacturers, including establishing post-market requirements, conditional approvals or reimbursement and risk-sharing agreements.

Table 2.4: Summary of Findings From Literature Review

Author	Citation	Objective	Drug	Medical condition	Exposure	Results	Findings category
Ali, AK ,2011	Pharmacovigilance analysis of adverse event reports for aliskiren hemifumarate, a first-in-class direct renin inhibitor	to examine the postmarketing safety profile of aliskiren hemifumarate, a first-in-class direct renin inhibitor	aliskiren hemifumarate	Hypertension	Use of Aliskiren (brand names, Tekturna, Tekturna HCT and Rasilez)	Aliskiren was associated with angioedema (EBGM 3.9, 95% confidence interval [CI] 3.2–4.7) and renal dysfunction (EBGM 3.4, 95% CI 2.6–4.5). Hyperkalemia, dry cough, and diarrhea were also linked to aliskiren (EBGM 7.4, 95% CI 3.4–13.0, EBGM 11.0, 95% CI 7.8–14.2, EBGM 4.3, 95% CI 3.2–5.8, respectively).	patient experience
Chang, J et al., 2011	Compliance, Persistence, Healthcare Resource Use, and Treatment Costs Associated with Aliskiren plus ARB versus ACE Inhibitor plus ARB Combination Therapy In US Patients with Hypertension	To compare the compliance, persistence, healthcare resource utilization, and healthcare costs associated with aliskiren plus ARB versus ACEI plus ARB combination therapies among adult patients diagnosed with hypertension.	aliskiren hemifumarate	Hypertension	Use of Aliskiren	aliskiren plus ARB patients (n = 1395) demonstrated a significantly higher PDC (67.0% vs 54.3%; difference 12.7%; 95% CI 10.6, 14.7) and a significantly lower discontinuation rate (50.4% vs 68.6%; odds ratio 0.46; 95% CI 0.40, 0.54) than ACEI plus ARB patients (n = 16 507). Aliskiren plus ARB patients had significantly fewer all-cause hospitalizations (adjusted incidence rate ratio [IRR] 0.73; 95% CI 0.61, 0.86) and significantly fewer all-cause emergency room (ER) visits (adjusted IRR 0.72; 95% CI 0.61, 0.85) than ACEI plus ARB patients. Compared with ACEI plus ARB therapy, aliskiren plus ARB therapy was associated with significantly larger increases in prescription costs by $US264 post therapy initiation (95% CI 153, 375), but with non-significantly greater reductions in total healthcare costs by -$583 (95% CI -2409, 1242) [2008 values].	patient outcome; Cost; Healthcare utilization

Author	Citation	Objective	Drug	Medical condition	Exposure	Results	Findings category
Deshpande, CG et al., 2011	Real-World Health Care Costs Based on Medication Adherence and Risk of Stroke and Bleeding in Patients Treated with Novel Anticoagulant Therapy	To examine the association of cost with adherence, comorbidity, and risk of stroke and bleeding in patients taking novel oral anticoagulants (rivaroxaban and dabigatran).	rivaroxaban and dabigatran	atrial fibrillation	rivaroxaban and dabigatran	adherence rates over 3, 6 and 12 months were 72%, 65%, and 54%, respectively. For all time periods, the level of adherence significantly (P<0.001) increased with an increase in stroke risk and risk of bleeding. Adjusted all-cause total cost calculated for 12-month period was significantly lower ($29,742 vs $33,609) among adherent vs nonadherent users. Drug cost was higher ($5,595 vs. $2,233) among adherent vs nonadherent patients but was offset by lower medical costs ($23,544 vs $30,485) costs	Cost
Guo, J et al., 2012	Recent Developments, Utilization, and Spending Trends for Pompe Disease Therapies	To review recent developments in therapies for Pompe disease, including the US Food and Drug Administration (FDA) approval of 2 biologic drugs, and to describe the associated drug utilization and spending trends in the US Medicaid program for patients with this disease.		Pompe disease is a rare condition, with an incidence rate estimated to be between 1 in 40,000 and 1 in 300,000 live births worldwide	Myozyme (alglucosidase alfa, recombinant human GAA) and Lumizyme (alglucosidase alfa),	expenditures rose from $9450 to $930,459 for Myozyme and from $119,691 to $1.16 million for Lumizyme. The average price per prescription was approximately $10,000 for Myozyme and approximately $20,000 for Lumizyme over the study period	cost
Handfield, R et al., 2013	Insurance Companies' Perspectives on the Orphan Drug Pipeline	To determine the views of leading commercial US	orphan drugs	rare disease	perspective on orphan drugs: access to and	67% of US private insurance companies are concerned about orphan drugs, but only appr 17% have developed meaningful	payer experience

Author	Citation	Objective	Drug	Medical condition	Exposure	Results	Findings category
		payers regarding providing access to and coverage for orphan drugs; to assess whether and to what degree cost-effectiveness analysis (CEA) is viewed by payers as relevant to rare disease coverage			coverage for orphan drugs	strategies for addressing the cost of orphan drugs. Of those with such a strategy, 100% are unsure how to determine the best economic assessment tools to control orphan drug costs, and two thirds are relying on PA as a means to control costs. More than 80% of the companies are not using cost-effectiveness methodologies with regard to rare diseases, generally because of a lack of the availability of medicines to facilitate such comparisons. CEA is used by less than 20% of our study sample of payers in dealing with orphan drug policies.	
Kish, JK et al., 2018	Real-world evidence analysis of palbociclib prescribing patterns for patients with advanced/metastatic breast cancer treated in community oncology practice in the USA one year post approval	examined real-world evidence in the first year post approval to understand the clinical and demographic characteristics of patients treated with palbociclib in community oncology practices and the dosing, treatment, and complete blood count (CBC) monitoring patterns.	palbociclib	novel, first-in-class cyclin-dependent kinase (CDK) 4/6 inhibitor was approved in the USA in February 2015 for the treatment of advanced/metastatic breast cancer		Of those, 612 (80.2%) receivedpalbociclib concomitantly with letrozole. Mean mean age at palbociclib initiation was 64 years. Of patients with a known starting dose (n = 417), 79.9% started on palbociclib 125 mg. Dose reductions were observed in 20.1% of patients. Percentages of patients according to line of therapy at initiation of palbociclib were first-line, 39.5%; second-line, 15.7%; third-line, 13.1%; and fourth-line therapy or later, 31.7%. On average, two CBC tests were conducted during the first cycle of palbociclib treatment. Overall, 74.6% of patients had a neutropenic event during follow up including 47.3% and 8.0% of patients with a grade 3 or 4 occurrence, respectively	patient experience/SE
Klink, AJ et al., 2019	Health Care Resource Utilization and Costs in First-Line Treatments for Patients with	To examine healthcare resource utilization (HCRU) and total cost of care among U.S.	1) Ipilimumab, an anti-cytotoxic T-lymphocyte antigen-4 (anti-	metastatic melanoma		Adjusted total monthly costs varied substantially across first-line therapies for metastatic melanoma and were significantly lower in PD-1-treated patients compared with patients treated	Costs; Healthcare utilization

Author	Citation	Objective	Drug	Medical condition	Exposure	Results	Findings category
	Metastatic Melanoma in the United States	metastatic melanoma patients treated with first-line systemic therapies, including	CTLA-4); 2) antiprogrammed cell death-1 (PD-1) antibodies pembrolizumab and nivolumab; 3) Targeted therapies include the BRAF inhibitors vemurafenib, dabrafenib, and encorafenib, and the MEK inhibitors trametinib, cobimetinib, and binimetinib,			with a CTLA-4 inhibitor, CTLA-4 + PD-1 combination, and BRAF/MEK combination.	
Lakshmi, S et al., 2016	Improving HCV Cure Rates in HIV-Coinfected Patients-A Real-World Perspective	To study rates and predictors of HCV cure among HIV/HCV coinfected patients; to evaluate the effect of attendance to clinic visits on HCV cure		hepatitis C virus (HCV	attendance to follow up clinic visits	Most commonly used regimen was Sofosbuvir/ledipasvir (40%) followed by simeprevir/sofosbuvir (30%). Cure was achieved in 83.3%, 11.9% relapsed and 2.3% experienced virological breakthrough. Two patients (2.3%) had not completed treatment based on pills counts and follow up visit documentation. cure was associated with attendance to follow up clinic visits (OR=9.0, 95% CI=2.91–163) and use of an integrase based HIV regimen vs. other non integrase regimens such as non nucleoside analogues or protease inhibitors (OR=6.22, 95% CI 1.81–141). Age, race, genotype, presence of cirrhosis, prior HCV treatment, HCV	patient experience/SE

Author	Citation	Objective	Drug	Medical condition	Exposure	Results	Findings category
						regimen and pre treatment CD4 counts were not associated with cure.	
O'Connor, JM et al., 2018	Speed of Adoption of Immune Checkpoint Inhibitors of Programmed Cell Death 1 Protein and Comparison of Patient Ages in Clinical Practice vs Pivotal Clinical Trials	To assess the speed with which anti–PD-1 agents reached eligible patients in practice and to compare the ages of patients treated in clinical practice with the ages of those treated in pivotal clinical trials.	nivolumab or pembrolizumab	melanoma, non–small cell lung cancer (NSCLC), and renal cell carcinoma (RCC).	eligible for anti–PD-1 agents treatment by cancer types	2123 (68.7%) received anti–PD-1 agents treatment, including 439 eligible patients with melanoma (79.1%), 1417 eligible patients with NSCLC (65.6%), and 267 eligible patients with RCC (71.2%). Within 4 months after FDA approval, greater than 60% of eligible patients in each cohort had received anti–PD-1 agents treatment. Overall, similar proportions of older and younger patients received anti–PD-1 agents treatment during the first 9 months after FDA approval. However, there were significant differences in age between clinical trial participants and patients receiving anti–PD-1 agents treatment in clinical practice, with more patients being older than 65 years in clinical practice (range, 327 of 1365 [60.6%] to 46 of 72 [63.9%]) than in pivotal clinical trials (range, 38 of 120 [31.7%] to 223 of 544 [41.0%]; all P < .001).	patient experience/SE
Penington, R et al., 2016	Evaluation of Specialty Drug Price Trends Using Data from Retrospective Pharmacy Sales Transactions	To analyze the annual change in wholesale acquisition cost (WAC) pricing of specialty drugs sold over a period of 11 years.	orphan drugs	immune disorders, cancer, multiple sclerosis, and hepatitis C		The price of the specialty drugs studied has generally shown a greater rate of increase since experiencing a trough rate increase in 2009 of 4.08%. The economic crisis of 2008 created a short pause in this overall trend, but increases in the rate of price growth have since rebounded. WACs increased at a rate of 7.03% or greater from 2010 through the end of the study period. There was a clear increase over the last few years of the study in the number of drugs with more than 10% annual increases in WAC, which has also shown a	cost

Author	Citation	Objective	Drug	Medical condition	Exposure	Results	Findings category
						rebound after the economic crisis at the end of the last decade.	
Robinson, SW et al., 2014	An Early Examination of Access to Select Orphan Drugs Treating Rare Diseases in Health Insurance Exchange Plans	evaluate the degree of access to medications in a subset of exchange plans based on coverage, tier placement, associated cost sharing, and utilization management (UM) applied	11 orphan drugs across 7 rare diseases	7 rare diseases: Huntington disease, hydatidosis, parathyroid carcinoma, atypical hemolytic uremic syndrome, sickle cell anemia, advanced soft tissue sarcoma, and Gaucher disease type 1.		for a certain rare disease experienced relatively robust coverage (at least 65% of plans) but often included some form of UM. more than 70% of plans in this study use coinsurance for the highest tiers of their formularies. Rates of coinsurance for medications on highest tiers range from 10% to 50% in silver plans and 15% to 50% in bronze plans. Among those plans utilizing copayments rather than coinsurance, ranges of copayments for these select products vary between $20 and $250 per prescription across both silver plans and bronze plans.	payer experience
Sanchez, Y et al., 2012	The Option Value of Innovative Treatments in the Context of Chronic Myeloid Leukemia	To quantify in the context of chronic myeloid leukemia (CML) the additional value patients receive when innovative treatments enable them to survive until the advent of even more effective future treatments (ie, the "option value")	tyrosine kinase inhibitors (dasatinib and nilotinib)	chronic myeloid leukemia		For a recently diagnosed CML patient, the option value of innovative therapies from future medical innovation amounts to 0.76 life-years. This option value is worth $63,000, equivalent to 9% of the average survival gains from existing treatments.	patient experience/SE
Shaw, DL et al., 2018	Coverage of Novel Therapeutic Agents by Medicare Prescription Drug Plans Following FDA Approval	To characterize Medicare prescription drug plan coverage of novel therapeutic	novel therapies approved between 2006 and 2012		novel therapies approved between 2006 and 2012	While 90% of novel therapeutic agents were covered by at least 1 plan in the year after FDA approval, coverage patterns were heterogeneous and often used prior authorization or step therapy restrictions..	payer experience

Author	Citation	Objective	Drug	Medical condition	Exposure	Results	Findings category
		agents approved by the FDA between 2006 and 2012.				The median proportion of plans providing unrestrictive coverage was 29% at 3 years, and few therapeutics (4%) were covered by all plans without restrictions at 3 years	
Wang, AA et al., 2020	Barriers to receipt of novel oral oncolytics: A single-institution quality improvement investigation	to describe patients' wait times for novel oral oncolytics at our institution and to identify barriers that delayed or prevented access to these medications.	29 novel oral oncolytics: targeted therapies (i.e., tyrosine kinase inhibitors,small molecule inhibitors) or novel formulations (i.e., trifluridine/tipiracil combination), characterized most frequently by high cost and requirement for prior authorization by payers	cancer	n/a	Of the 270 successfully filled prescriptions, the mean time-to-receipt was 7.310.3 days (range: 0–109 days). Patients with Medicare experienced longer time-to-receipt (9.113.1 days) compared to patients with commercial insurance (4.43.3). Uninsured patients experienced the longest time-to-receipt (15.77.8 days) overall.	Patient experience
Weisshof, R et al., 2019	Real-World Experience with Tofacitinib in IBD at a Tertiary Center	report our experience with tofacitinib for medically resistant Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a chronic	Tofacitinib is a first-in-class, partially selective inhibitor of Janus kinase	ulcerative colitis	treatent with oral 5 mg or 10 mg tolfacinib twice daily	In this cohort of patients with moderate-to-severe, anti-TNF resistant IBD, tofacitinib induced clinical response in 69% of the patients. 27% were in clinical, steroid-free remission by 1 year of treatment	patient experience/SE

Author	Citation	Objective	Drug	Medical condition	Exposure	Results	Findings category
		inflammatory condition affecting 3.1 million Americans with an increasing incidence worldwide					
Zhou, M et al., 2015	Adherence to a Novel Oral Anticoagulant Among Patients with Atrial Fibrillation	To examine adherence and persistence to dabigatran among adults with atrial fibrillation	dabigatrin	nonvalvular atrial fibrillation		Among those using dabigatran alone (n=2,713), the mean MPR was 0.73 (standard error=0.30), 41% were nonadherent with therapy, and 32% had gaps of 60 days or greater. Among those observed for 9 (or 12) months who used dabigatran alone, rates of nonadherence were 47% (49%), whereas 48% (49%) discontinued therapy during follow-up. Rates of adherence and persistence were similar for patients with incident atrial fibrillation	patient experience

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Chapter 3 : Paper 2 - Comparison of U.S. Value Assessment Frameworks and Implications for Novel Medications

Background

A major contributing component to the rise in healthcare expenditure is the higher costs of novel therapies, many of which cost upwards of $100,000 annually (Mailankody & Prasad, 2015; Saluja et al., 2018). Since many of these novel therapies are associated with only modest improvements in survival, a careful consideration of the incremental cost per health outcome gained of these novel treatments is required prior to investment (Barnes et al., 2017). Given the increasing number of high-cost medications, and the criticisms of current reimbursement strategies, healthcare systems need to explore alternative methods to incorporate value assessment into drug coverage or reimbursement decision making.

Value-based pricing (VBP) is a well-established pricing method for goods and services. VBP dictates that the price of the commodity should reflect the value to the buyer rather than the actual costs of production augmented by the profit margin (Kaltenboeck & Bach, 2018). Value-based pricing offers a method to provide the best estimate for the price of a drug as it relates to the benefits it provides for the individual patients it is applied to. In principle, VBP for drugs means that prices charged to payers are mainly linked to the drug's value, and that a drug’s impact on budget is a secondary driver of pricing strategies (Webster, 2018).

Value Assessment Frameworks

A framework to assess value of medications is one approach to assess the evidence and value of new novel medications (Garrison et al., 2018). These

frameworks provide a way to measure and communicate the value of medications for decision-making purposes. It aims to ensure that the prices paid for drugs reflect the benefits they provide, either in terms of longer life or better quality of life. In some countries—Australia, Canada, Sweden, England—the government (or an agency of the government) develops and applies economic analyses to measure the value of a prescription medication, which then determines the price of that medication nationally. Here, the goal is to ensure that the value of a medication is well understood so that the society can spend the available resources that they have on them in a sensible manner.

In the United States the government does not examine and compare value of medications to determine the allocation of resources. However, this has not removed the need for this information, since a number of professional and private organizations have developed value assessment frameworks to define and measure the value of drugs. The aims of these frameworks differ—some seek to help physicians and patients make more informed, evidence-based treatment decisions, whereas others are intended to aid payer coverage determinations or price negotiations between payers and manufacturers (Kaltenboeck & Bach, 2018). However, although value-based pricing for pharmaceuticals has been for years considered superior compared with cost-plus methods of price determination, there are differences in understanding on its meaning (what is value?) and how value is translated into price models (Jommi et al., 2020; Kaltenboeck & Bach, 2018; Webster, 2018).

Objective

The purpose of this study was to review the elements of a medication's value taken into account by current value assessment frameworks, how they are measured and valued, how these are combined into an overall assessment of a medicine's value and how that could then be linked to the reimbursement price. Specifically, the study aimed to (1) describe U.S-based value assessment frameworks and describe the means by which 'value' is measured and valued, describe the options available for aggregating the different components of value to establish a price; 2) compare the value frameworks and their ability to assess value of novel medications; and (3) identify the limitations associated with use of value frameworks.

Conceptual Framework

A common strategy to determine value of a medication is the quality adjusted life year (QALY) methodology. Some countries—Australia, Canada, Sweden, England—incorporate use of QALYs to measure health gain and make reimbursement decisions. The QALY standard assigns a monetary value to the quality of life and survival length for patients and then assesses the cost effectiveness of a drug based upon the drug's potential ability to both improve a patient's quality of life and to extend that life (Pettitt et al., 2016). Drugs that do not offer a full year of life, or that offer less-than-full quality of life, are rated lower on the QALY scale and may not qualify for reimbursement when QALYs are used for such decision-making.

While QALY is a practical tool for measuring health benefits on medications, is not without challenges in valuing medications. The QALY measure disadvantages patients with disabilities, seniors, and those with chronic conditions (Pettitt et al.,

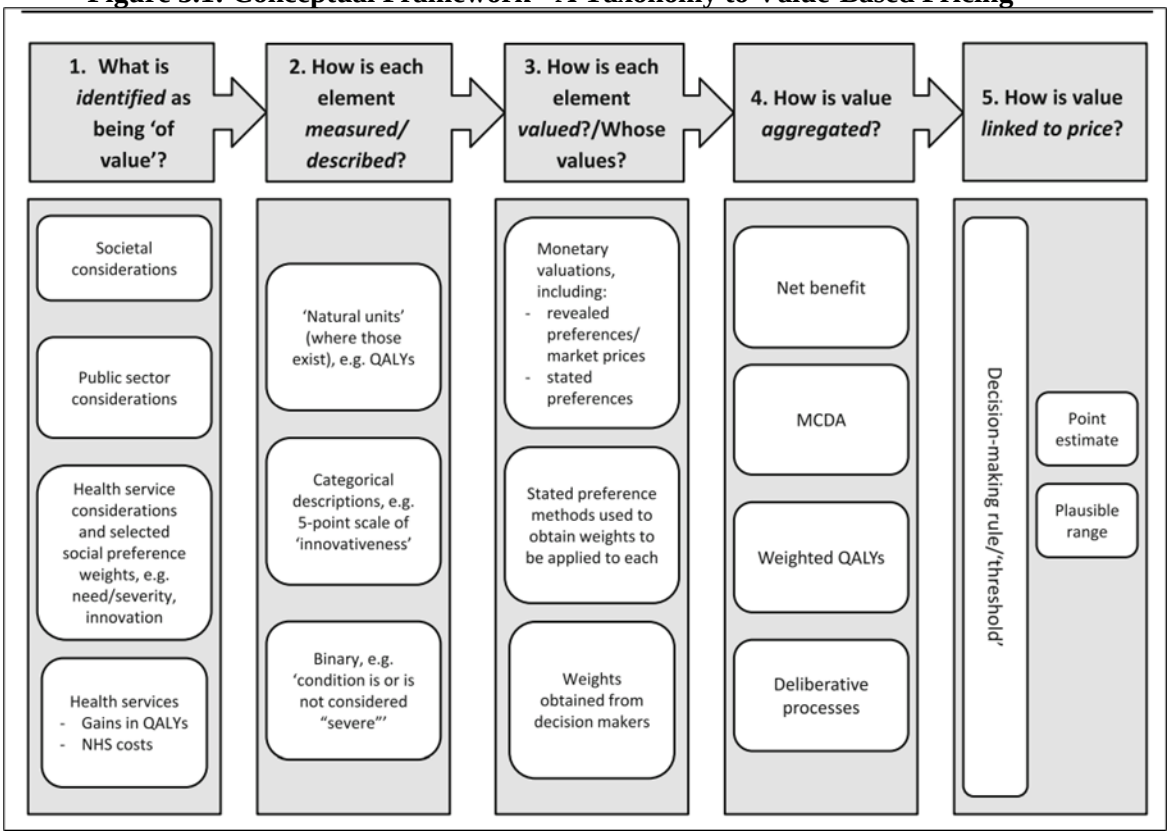
2016; Smith, 2019). Since these patients may experience a potential for health that is less than their 'healthier' counterparts, a medication that extends or improves their lives may result in lower rating of QALYs than a medication developed for a non-disabled or younger population, where the drug is able to return the patient to normal health. Similarly, the QALYs methodology is particularly ill-suited to assess the value of medications for rare diseases. These new medications for rare diseases can be labelled by QALYs as 'cost-ineffective', and lack long-term data on safety and effectiveness relative to more researched conditions because these rare conditions have often not benefited from decades of research (Hyry et al., 2014; Smith, 2019).

The United Kingdom's National Institute for Health and Care Excellence (NICE) uses QALYs to recommend how to prioritize treatments within and between patient groups. In 2010, announced plans to replace the existing model with 'value-based pricing' for branded medicines, where the prices the government would reflect the "clinical and therapeutic value to patients and the broader NHS [National Health System]"(Office of Fair Trading, 2007). To the best knowledge of the author, there is no national value-based pricing model launched in the United Kingdom to date. However, this proposal attracted discussions by academics, government agencies, payers, and manufacturers on how a national value-based pricing model could be operationalized at a national level.

This study applies a conceptual framework developed in responses to UK's value-based pricing proposal to examine value-based frameworks developed by private and professional societies in the United States. This study utilized a multi-criteria decision analysis framework developed for "value-based pricing" by Sussex

et al. (Sussex et al., 2013). In an attempt to go beyond QALYs, this framework identifies and describes the full set of possible means by which value-based pricing might be operationalized and categorized by developing a taxonomy of approaches. The developers describe the elements of value that could be considered and how these might be measured and valued, combined into an overall assessment of a medicine's value, and then linked to the maximum price the health system is willing to reimburse. Figure 3.1 identifies the elements of this framework.

Figure 3.1: Conceptual Framework - A Taxonomy to Value-Based Pricing[5]



[5] Sussex, J., Towse, A., & Devlin, N. (2013). Operationalizing value-based pricing of medicines. *Pharmacoeconomics*, *31*(1), 1-10.

This conceptual framework, displayed in Figure 3.1 has five main dimensions:

What is identified as being of value? Instead of focusing on single or limited benefit, this framework recognizes that the value of medications is multi-dimensional. This may include:

- Societal value: This includes some or all of unrelated medical costs, productivity effects, costs incurred outside the healthcare sector, and benefits accruing to all stakeholders in society including the patient's family.
- Public considerations: significant innovation leading to distinct benefits; whether the treated population is a socially disadvantaged group (e.g., children, ethnic minority);
- Health service considerations and selected preferences: evidence that the impact of a treatment has aspects not adequately covered by other treatments; innovative attributes of a drug leading to distinct benefit may be deemed to have value independently of the health gain generated; reduction in fear of the risk of death and/or illness and impact on dignity (i.e., being treated in a way that the patient finds less unpleasant, e.g. taking a medicine once a week rather than three times a day).
- Health services: health improvement as measured by gains in QALYs, survival; cost savings to other publicly funded services; cost savings to patients and their caregivers

How each element is measured/described? After identifying the relevant benefits of value, the next step involves describing and measuring each. Some benefits (e.g., QALYs) have existing scale of measurement, where health improvement is measured

on a continuous scale. For other benefits, measures will need to be developed: for example, there are no ready-made measures of innovativeness, burden of disease or severity. To be incorporated, the value framework needs an explicit measurement of benefits via either a scale of effect (e.g., to describe the magnitude of severity, burden of disease or innovativeness) or a finite number of discrete categories for each value component (e.g., high, medium, low). Whichever approach is used, the framework requires clarity over the benefits being measured and the definitions that underpin each measure.

How is each element valued? Whose values? The next step is to value the benefits, which involves deciding on whose values are to be taken into account and how those values are elicited. Determining whose values count/are preferred is closely related to what elements of value are identified as relevant. Frameworks can elicit values from patients (or their caregivers, e.g., for children or groups of patients not in a position to express preferences), the general public, or decision makers such as politicians, clinicians/experts or the managers of payer organizations. Various methods exist to measure how patients and other stakeholders prioritize or apply preferences to determine value. These methods include stated preference methods (rating or ranking approaches, self-explicated methods to determine how much they are willing to pay for each element), or by revealed preferences, by studying the actual value.

How the different elements of value are aggregated? Value based-pricing requires that the disparate elements of value to be aggregated. This may include:

- Net-benefit (NB) approach: converting all values into money terms

- Multi-criteria decision analysis (MCDA) approach: considering each element of benefit in terms of its own 'units', and applying a set of weights to each benefit to represent the rates at which different elements may be traded-off with each other, and scores to indicate how well each benefit type is achieved by the medicine in question.
- Selecting one measure of benefit, e.g., using QALYs for each element, and then using a series of weights to up-rate or down-rate the element to reflect the magnitudes of other elements of benefit.
- Deliberative process

How is value linked to price? As a final step, the conceptual framework requires that aggregate value be converted into a price, where a decision rule for converting the overall measure of value into the maximum price the payer would reimburse, given its budget constraint. The maximum price may exist as a point estimate or a range.

Methods

An initial literature search was conducted using MEDLINE to identify articles of value assessment frameworks for prescription drugs. Different combinations of key words were used, including: *value framework*, value-based framework*, value-based framework AND drugs, value-based assessments, value-based decision making, and value-based health care.*

A manual review of titles was conducted to examine the suitability of key words and to exclude irrelevant articles. Articles were excluded for three main reasons: 1) language other than English, 2) irrelevant content (e.g., similar keywords but different content, such as computer sciences) and 3) the absence of an abstract or full text. This

manual review identified two recent peer-reviewed articles—by Buscolo et al. and the work of Neumann and Cohen that relied on a comprehensive systematic literature review to identify dimensions of value assessment frameworks in the US (Boscolo et al., 2020) (Neumann & Cohen, 2015). Rather than replicate existing work, this study expanded on the work by these authors to implement a structured search using the snowball method.

Search Strategy

The snowball method and reference tracking were used in conjunction with a systematic search of academic databases. The snowballing literature review method was used, rather than a database search review because it is suitable for expanding existing literature reviews with new aspects. This study also assumed that influential ideas on value assessment frameworks from older literature were sufficiently incorporated in the literature published by Buscolo et al (Boscolo et al., 2020) and the work of Neumann and Cohen (Neumann & Cohen, 2015). The principle benefits of utilizing snowballing are that it focuses on the cited or referenced papers, which in comparison with the database approach reduces the noise (Wohlin, 2014). Moreover, it is usually true that new studies cite one article among the previous pertinent studies or a systematic literature review study already done in a specific area. The snowball method included checking references of relevant papers and citation tracking. Studies identified in this manner up until May 30, 2021 were included for analysis.

Snowballing involves deriving the tentative start article and conducting forward and backward snowballing. Instead of a keyword search, a citation network was built through a snowball sampling technique that started with the ‘seed’ articles,

i.e., the articles published by Boscolo et al. and the work of Neumann and Cohen. Earlier publications (cited publications) from the reference list in the 'seed' articles show the publications that the authors consulted. New articles that cite the 'seed' articles (citing publications) lead to more recent publications on the same subject. This technique produces a network of relevant articles built around the "seeds" and facilitates insights into the broad context of the research instead of the narrow set of publications that are returned in keyword searches.

Study Selection

All articles were screened for eligibility based on their titles and inclusion criteria. After excluding duplicates, articles were included if they discussed value-based pricing for medications. Articles were limited to a US-based study setting.

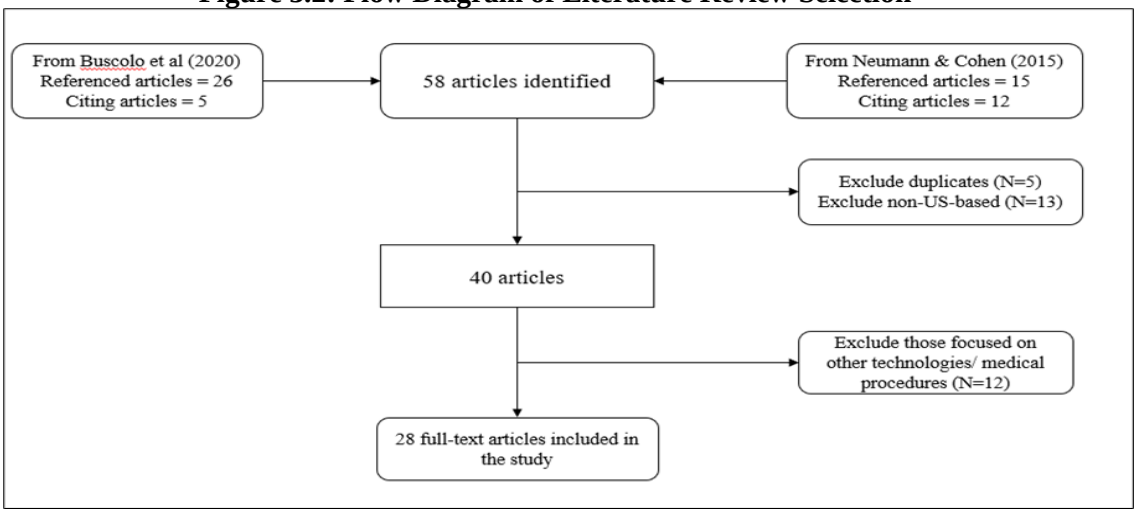
Data Analysis: Identifying Dimensions of Value-based Frameworks

Based on the five main dimensions identified by the conceptual framework, an extraction template was developed to collect and contrast information on the five features: 1) What is of value? 2) How is each element of value measured/described? 3) How is each element valued? Or whose values? 4) how is value aggregated? 5) how is value linked to price?

Findings

After applying the inclusion criteria, a total of 28 articles were included in the study. Figure 3.2 shows a flow diagram of the literature selection process. The final selection of publications was then subjected to a qualitative review and use the template to extract the name of the framework and the five features.

Figure 3.2: Flow Diagram of Literature Review Selection



Overview of Value-Assessment Frameworks

The study identified following five U.S. value assessment frameworks were also included in the original landscape analysis by Boscolo et al. and the work of Neumann and Cohen: The American College of Cardiology and the American Heart Association (ACC-AHA), the American Society of Clinical Oncology (ASCO), the Institute for Clinical and Economic Review (ICER), Memorial Sloan Kettering Cancer Center (DrugAbacus), and the National Comprehensive Cancer Network (NCCN). The following two new frameworks emerged from this analysis that were not previously included by those authors: the Innovation and Value Initiative's (IVI) and the Patient-Perspective Value Framework (PPFV) developed jointly by Avalere and FasterCures. These seven frameworks are discussed below. Table 1 presents the summary of their features, including intended user, target items, and disease conditions addressed.

Table 3.1: Summary Features of Value Assessment Frameworks for Drugs in U.S

Framework	Targeted items	Intended user	Disease conditions targeted
ACC-AHA	Drugs, devices, other interventions	Clinicians/ patients	Cardiovascular
ASCO	Drugs	Clinicians/ patients	Oncology
ICER	Primarily drugs, limited extension to other medical services	Primarily payers; secondarily policy makers, clinicians, patients	All conditions, particular focus on new drugs anticipated to be high impact
DrugAbacus	Drugs	Primarily payers; secondarily policy makers, clinicians, patients	Oncology
NCCN	Treatment regimens, primarily drugs	Clinicians, patients	Oncology
IVI	Drugs	Payers, policy makers, clinicians, patients	All conditions
PPFV	Drugs	Payers, policy makers, clinicians, patients	All conditions

ACC-AHA: American College of Cardiology and the American Heart Association; ASCO: American Society of Clinical Oncology; ICER: Institute for Clinical and Economic Review; DrugAbacus: Memorial Sloan Kettering Cancer Center; NCCN: National Comprehensive Cancer Network; IVI: Innovation and Value Initiative; PPFV: Patient-Perspective Value Framework

The intended users of each value framework generally reflecting the interests and expertise of the developing organizations. As such, those that comprise professional societies with physician members, ACC-AHA, ASCO and NCCN, are designed to assist with the decision-making between patients and physicians. Those developed by ICER, IVI, PPFV, and DrugAbacus are intended for broader audiences — payers, policy makers, physicians and patients. The organizational mission also appears to guide the targeted drugs. The ACC-AHA focuses on cardiovascular interventions, while ASCO and NCCN are focused specifically on cancer treatments, mainly cancer drugs and biologics. The frameworks by ICER, IVI and PPVF have no limitations on the types of medications that could be assessed.

Value frameworks attempt to process and integrate various clinical benefits and cost metrics to arrive at a drug's value**.** This section also provides a summary description of each of the seven frameworks and assessment across these 5 dimensions.

1. American Society of Clinical Oncology (ASCO)

The American Society of Clinical Oncology (ASCO), a professional organization representing more than 40,000 oncologists, launched its ASCO Value Framework in June 2015 (Schnipper et al., 2015). ASCO states that this value framework is intended "to provide medical oncologists with the information and physician-guided tools necessary to assess the relative value of cancer therapies as an element of shared decision making with their patients".

What Is of Value? For each medication, the ASCO framework generates a net health benefit (NHB) score; the NHB score and drug cost are then used to assess the value of a proposed cancer treatment. Because oncologists are the target audience, the framework is tailored to how oncologists think about cancer care. To calculate the NHB score, ASCO aggregates scores across three elements: clinical benefit, toxicity, and a bonus category (Santos et al., 2021).

How Each Element Is Measured/ Described: Data to generate the key elements of the framework are collected from the pivotal randomized clinical trial, where for each treatment, ASCO assigns a score across three categories: clinical benefit (e.g., overall survival, progression-free survival, disease-free survival, or response rate), toxicity (i.e., safety), and a bonus category (symptom palliation, and improvement in quality of life - QoL) (Santos et al., 2021).

- Clinical benefit is determined by evaluating survival endpoints (or surrogate endpoints for survival) according to a set hierarchy: hazard ratio (HR) for death, median overall survival (OS), HR for disease progression, median progression free survival (PFS), and response rate (Meropol et al., 2009; Schnipper et al., 2016). OS is the length of time from the start of treatment for a disease that half the patients are still alive when comparing a new regimen to the standard-of-care. PFS is the length of time where half of the patients live with the disease but it does not get worse. ASCO uses a step-wise approach to identify and incorporate these survival endpoints into a score. Clinical benefit is assigned a categorical score between 1 to 5 based on the fractional improvement to the patient.
- Toxicity is evaluated as the relative toxicity of the new agent against standard-of-care, that is improvement in toxicity over the comparator is represented by calculating the percentage difference in total toxicity points. ASCO uses the relative frequency of grade 1 through 4 for each toxicity, with an adjustment for unresolved treatment-related (symptomatic) toxicities one year after treatment completion. Depending on the level of potential harm to the patient, the toxicity category can change the NHB score by 20 points.
- Finally, bonus points are awarded based on palliation, QoL, and treatment-free interval criteria. A new treatment can gain bonus points in two ways: palliation points and treatment-free interval points. Palliation points are awarded if there is a statistically significant improvement in cancer-related symptoms. Treatment-free interval points are earned when the patient's disease is not progressing and they are spared treatment-related toxicities.

- NHB Score: The clinical benefit and toxicity scores, as well as the bonus points, are combined to yield an NHB score. The maximum score is 130 for the advanced disease framework and 100 for the curative framework.

Assigning Values, and Who's Values: The ASCO framework was developed by the "ASCO Value in Cancer Care Task Force," composed of physicians. They sought input from an advisory committee that included oncologists, patient advocates, payers and the biopharmaceutical industry, and followed that input with a public comment period. According to the ASCO statement, the value framework is intended to be used by the physician and the patient to facilitate a discussion and shared decision-making regarding the benefits of a treatment option within the context of cost.

How Is Value Aggregated? The ASCO value framework seeks to quantify the NHB of a cancer treatment via a single summary score, where clinical benefit and toxicity scores, as well as the bonus points, are summed up to yield an NHB score. The maximum score is 130 for the advanced disease framework and 100 for the curative framework.. The ASCO framework produces NHB scores ranging from −20 (worst) to +180 (best). In 2018, ASCO defined threshold scores of ≤40, ≥45, and between 40 and 45 as low, substantial, and intermediate NHB, respectively (Cherny et al., 2019).

How is value linked to price? Under the ASCO framework, two cost estimates are considered: the drug acquisition cost (DAC), which is the price listed by the drug manufacturer, and patient costs, which depend on the patient's insurance. Also, included in these calculations are costs associated with supportive care drugs that are required to administer the treatment.

2. National Comprehensive Cancer Network (NCCN)

The National Comprehensive Cancer Network (NCCN), a nonprofit alliance of 26 cancer centers throughout the United States, launched its evidence block framework in October 2015. Similar to the ASCO Value Framework, the NCCN framework seeks to give "the healthcare provider and the patient information to make informed choices when selecting systemic therapies based upon measures related to treatment, supporting data and cost" (Network., 2021).

What Is of Value? NCCN uses a standardized scale to provide consensus-based scoring of the 5 measures: efficacy (E), safety (S), quality and quantity of evidence (Q), consistency of evidence (C), and affordability (A) associated with that drug or regimen. (National Comprehensive Cancer Network - Evidence Blocks, 2017).

How Each Element Is Measured/ Described: Each of the 5 measures in the NCCN's approach is displayed as a solid block using a scale from 1 to 5, where 1 is considered least favorable and 5 is most favorable (Network., 2021)

- Efficacy: This measure examines the extent to which the intervention is useful in prolonging life, slowing disease progression, or reducing the symptoms of a medical condition.
- Safety: This refers to the relative likelihood of side effects from an intervention.
- Quality and quantity of evidence: This is the number and types of clinical trials that are relevant to an intervention.
- Consistency. This is the degree to which the clinical trials for the intervention have consistent results.

- Affordability. This category is the overall cost of the intervention including the drug cost, required supportive care, infusions, toxicity monitoring management of toxicity, and inpatient stays with lower cost being assigned a higher score.

Assigning Values, and Who's Values: The NCCN Evidence Blocks framework is relatively subjective as it is created and scored by a panel of experts and then disseminated to clinicians. Guided by staff from the NCCN, in consultation with the group's members, the framework uses a standardized scale to provide consensus-based scoring of the efficacy, safety, and affordability of a drug or a regimen and the quality and consistency of the evidence associated with that drug or regimen. NCCN uses the average of panel members' quantitative assessment of effectiveness in prolonging life, arresting disease progression or reducing symptoms.

How Is Value Aggregated?: The NCCN framework produces scores from 1 (worst) to 5 (best) for each of the four health benefit measures, where scores for each are presented separately with no explicit synthesis. The final score for each measure is based on all responding panel members, rounding to the nearest whole number. The compiled results are used to build a 5 x 5 table that represents the NCCN Evidence Block for the treatment. Physicians can condense the information of different cancer treatments into an easy-to-understand format and work with patients to choose the best option. Discussing the benefits and drawbacks of each of the therapies can help patients identify the treatment that best matches their goals and preferences.

How is value linked to price? the NCCN defines its affordability measure as the overall cost of an intervention, including the drug, infusions, supportive care, toxicity monitoring and management, and the probability of care being delivered in the

hospital. Affordability scores, like all other measures, are presented separately with no aggregation or explicit synthesis.

3. Institute for Clinical and Economic Review (ICER)

The Institute for Clinical and Economic Review (ICER), an independent nonprofit organization founded in 2005 by Harvard physician-researcher Steven D. Pearson, MD, MSc, launched its assessment program in July 2015, with guidance from an advisory committee of payers, patient organizations, physician organizations, and the biopharmaceutical industry (ICER, 2022). Targeting payers and policymakers, ICER generates a value-based price benchmark anchored in the real benefits that a specific drug brings to patients.

What Is of Value? In February of 2017, ICER proposed a new structure of the framework that examines two general concepts: "long-term value for money" and "short-term affordability." Long-term value for money serves as the anchor for the ICER value framework and is comprised of 4 domains: 1) comparative clinical effectiveness, 2) incremental cost-effectiveness, 3) other benefits and advantages, and 4) contextual considerations. Short-term affordability is obtained by analyzing the potential budget impact of new treatments changes on health expenditures, which acts as a complementary consideration to the "long-term value for money" concept when measuring value.

How Each Element Is Measured/ Described? Long-term value for money serves as the anchor for the ICER value framework, and is comprised of 4 domains:

- Comparative clinical effectiveness: this element uses systemic literature reviews/meta-analyses to examine the body of evidence for the effectiveness

of the new treatment including randomized controlled trials and other sources such as cohort studies and patient-reported data. Additionally, ICER attempts to include an evaluation of the heterogeneity of treatment effect for key clinical outcomes to address variations between individuals within treatment groups. Following synthesis of the evidence by quantitative and qualitative techniques, ICER generates the "Integrated Evidence Rating Matrix". The evidence rating reflects a qualitative judgement of two critical components: 1) The magnitude of the difference between a therapeutic agent and its comparator in "net health benefit", which is the balance between benefits and risks and/or adverse effects; and 2) The level of certainty in the best point estimate of net health benefit (ICER, 2022).

- Incremental cost-effective analysis: using simulated computer models, ICER assess whether a drug is a good value for money in the long run by considering its cost in relation to the clinical benefits provided and comparing one treatment and its associated care pathway to another. ICER compares different treatment options with the cost per quality-adjusted life year (QALY).
- Other Benefits and Disadvantages: this element explores benefits and disadvantages of the treatment to the patient, caregivers, delivery system or public that is not evident from comparative clinical effectiveness evidence. Benefits can include public health benefits, increased productivity, and treatment outcomes that reduce disparities across patient groups. Disadvantages can include increased burden on the family or caregiver and

inability to return to work or other negative effects on productivity. This element is measured qualitatively on a Likert scale of 1-3: 1 (Suggests Lower Value), 2 (Intermediate) or 3 (Suggests Higher Value).

- Contextual Considerations. This element examines ethical, legal and other issues that influence the relative priority of illnesses and interventions. Factors considered include the likelihood of similar treatments being introduced, societal values, and the severity of the illness. Similar to the "other benefits and disadvantages" domain, these factors are judged by an independent appraisal committee. This element is measured qualitatively on a Likert scale of 1-3: 1 (Suggests Lower Value), 2 (Intermediate) or 3 (Suggests Higher Value).

The "short-term affordability" component examines the potential budget impact as the net impact across all elements of the health system, where ICER currently uses a "short-term" time frame of 5 years. Doing so allows for the incorporation of potential clinical benefits and cost offsets that may not happen immediately after the adoption of a new treatment.

Assigning Values, and Who's Values? The ICER framework was developed by ICER staff, who also sought input from an advisory committee consisting of payers, patient organizations, physician organizations and biopharmaceutical manufacturers. Updates to the framework have been informed by ICER's Methods Advisory Group, a public meeting and broad stakeholder input via public comment.

How Is Value Aggregated? Unlike the other frameworks, the ICER framework does not produce scores that can be ranked. Instead, it comprises multiple components,

including comparative clinical effectiveness, cost-effectiveness, and budget impact, each of which requires specific methodology and in-depth analysis.

How is value linked to price? For new treatment options, ICER calculates "value-based price benchmarks" based on how much better they are at improving patients' lives. To guide deliberation on affordability, ICER performs a potential budget impact analysis at the national level with a suggested threshold that, if exceeded, signals to policymakers that the amount of added health care costs associated with a new treatment may be difficult for the health system to absorb over the short-term without displacing other needed services or contributing to unsustainable growth in health care insurance costs (Pearson, 2018). ICER's value-based price benchmark is set at $100 000 to $150 000 per QALY.

4. Memorial Sloan Kettering Cancer Center (MSKCC) DrugAbacus

The Memorial Sloan Kettering Cancer Center (MSKCC) DrugAbacus tool, conceived by Peter B. Bach, MD, MAPP, Director of the Center for Health Policy and Outcomes at MSKCC and launched in June 2015, targets physicians and policymakers with an "interactive tool [that] takes more than 50 cancer drugs and lets you compare the company's price to one based on value."

What Is of Value? This system delivers a value-based price for a drug that graphically represents the user's weighted preferences and estimated monthly costs relative to 52 cancer drugs. The framework identifies eight elements for value: Efficacy; Toxicity, Novelty, Research and development cost; Rarity; and Population health burden

How Each Element Is Measured/ Described? The framework assigns values to each of the eight elements.

- Efficacy is assessed as improvement in overall survival, if available. Efficacy score also reflects evidence quality.
- Toxicity is a drug's impact on probability of severe side effects and treatment discontinuation.
- Novelty is scored as 1 (novel mechanism of action), 0.5 ("known target but different mechanism of targeting"), or 0 ("next-in-class").
- Research and development cost corresponds to the "number of human subjects enrolled in the approval trials for the first indication."
- Rarity is the 2015 projected disease incidence.
- Population health burden is the annual years of life lost to the targeted disease in the United States.

Assigning Values, and Who's Values? MSKCC provides an online, interactive tool that allows users to adjust the weights for various dimensions, such as a drug's efficacy and toxicity, and derive a "fair" price in accordance with their own preferences. The MSKCC DrugAbacus is a physician and payer focused value framework that uses weighted value metrics to calculate theoretical prices for drugs. These prices are compared to the market value of drugs to generate conversations about overall benefit and value between manufacturers and payers.

How Is Value Aggregated? "Fair price" is the product of the scores, each of which is scaled by a user-adjusted weight. The methodology for calculating the Abacus theoretical price is a two-step process with user-assigned weights to each of the eight domains of the MSKCC DrugAbacus. These prices are relevant for a treatment period that is required to achieve the reported benefit in FDA approval trials. Model-

calculated prices are for the duration of the treatment used in clinical trials and then adjusted to achieve a monthly price as shown in

How is value linked to price? The Abacus theoretical price is calculated using a formula that weighs elements such as efficacy, toxicity, population health burden, research and development, rarity, and novelty (DrugAbacus – FAQ, 2017). The generated theoretical price is compared to the actual market price to illustrate price deficits or surpluses for a given treatment.

5. The American College of Cardiology and the American Heart Association

The American College of Cardiology and the American Heart Association (ACC-AHA) Statement on Cost/Value Methodology in Clinical Practice Guidelines and Performance Measures, aims "to include cost-effectiveness/value assessments and recommendations in practice guidelines and performance measures."

What Is of Value? Clinical benefit vs. risks Magnitude of net benefit; Precision of estimate based on quality of evidence; Value (cost-effectiveness)

How Each Element Is Measured/ Described?: Magnitude of treatment effect ranges from class I ("benefit [greatly exceeds] risk," "procedure or treatment is useful or effective") to class III ("no benefit, or harm," "procedure or treatment is not useful or effective and may be harmful"). Precision of treatment effect ranges from level A ("data derived from multiple randomized trials or meta-analyses") to level C ("only consensus opinion of experts, case studies, or standard of care").

Assigning Values, and Who's Values?: While full details on the development of the ACC-AHA framework are unknown, the framework is developed by a writing committee composed primarily of physicians.

How Is Value Aggregated?: ACC-AHA is based on previously conducted health economic assessments from a literature search, making them both transparent and replicable. When ACC-AHA is updating guidelines, an independent literature review for relevant health economic studies is conducted. Quality and potential for bias is assessed before the evidence is synthesized. When high-quality evidence exists that allows for the classification of value based on cost/QALY thresholds for specific treatments, a value statement for those treatments is included in the guidelines. A discussion of the evidence base is included in a separate section in the guidelines titled, "Cost and Value Considerations." As of August 2019, five guidelines include this discussion section, and two of those guidelines include value statements for some of the treatment recommendations**.** ACC-AHA assigns one of four value levels to a treatment — high, medium, low, uncertain.

How is value linked to price? Value corresponds to cost-effectiveness thresholds (high: less than $50,000 per QALY; intermediate: $50,000 to $100,000 per QALY; low: more than $150,000 per QALY. The framework lists the clinical benefit and value designations without combining them

6. Innovation and Value Initiative (IVI)

The Innovation and Value Initiative (IVI) is a collaboration of scientists, patient organizations, payers, life sciences companies, providers and delivery systems dedicated to finding scientifically credible approaches to measuring value in healthcare. Inspired by the open-source software process, IVI established the Open-Source Value Project, a platform for the development of dynamic, transparent and flexible scientific models that allows diverse health care stakeholders to measure

value in health care treatments or services. IVI's first two open-source models focus on the value of treatments for moderate to severe rheumatoid arthritis and non-small cell lung cancer (Innovation & Initiative, 2019). IVI does not promote a specific framework or a singular method of assessing value, but rather provides a testing ground for new methods and model design. The customizable nature of their models enables the user to adapt the framework design and inputs.

What Is of Value? IVI's individual patient simulation model for rheumatoid arthritis (the IVI-RA model) (Linthicum et al., 2020). The model simulates the costs, health outcomes, and risks associated with specific medications for patients with moderate to severe rheumatoid arthritis (RA) who have previously failed treatment with cDMARDs. The model is intended to help decision-makers assess the value of treatments for a population of patients with RA.

How Each Element Is Measured/ Described? IVI uses real-world data to inform patient preference, costs and baseline events rates (e.g., rate of disease progression, the rate at which patients discontinue treatment) in its OSVP models. In addition, to enhance the validity of the model, relative treatment effects are based on randomized controlled trial data when possible.

Assigning Values, and Who's Values? IVI's assessment topics are selected by IVI and its board of directors, informed by available evidence, multi-stakeholder input and IVI's Scientific Advisory Panel. The development of the OSVP models is characterized by a four-step iterative process (Weil et al., 2017): Step (1) release of the initial version of the model; Step (2) obtain public feedback, which can range from high-level comments to proposed changes to the source code; Step (3) review of

feedback by a technical expert panel (TEP) and prioritize recommendations for model revision according to a modified Delphi process; and Step (4) revise model and re-release. In principle, this four-step process will be repeated over time to refine the model based on new evidence and insights.

How Is Value Aggregated? To date, 2 models, rheumatoid arthritis (RA) and non-small cell lung cancer (NSCLC), have been developed, with a third model for MDD underway.

How is value linked to price? IVI relies on existing health economic literature to inform its estimates of hospitalization costs and productivity loss. Drug acquisition and administrative costs are based on wholesale acquisition cost (WAC) data less an estimated rebate.

7. Patient-Perspective Value Framework (PPVF)

The PPVF was developed by Avalere and FasterCures to ensure that patients' perspectives of value were better considered in value assessments. PPVF offers a new way to "assess the value of health care services that considers factors that matter to patients — such as functional and cognitive status, symptom relief, complexity of regimen and medical as well as non-medical out-of-pocket costs to the patient and family — and weights them in accordance with assessed patient preferences."(Josh Seidman et al., 2019)

What Is of Value? The PPFV framework uses patient preferences (needs, values, expectations, and financial trade-offs) as its lens through which patient value is understood. The model considers benefits—patient-centered outcomes (e.g., effectiveness, efficacy, side effects, complications, quality of life, and complexity of

regimen) (Willke et al., 2019). Costs considered in the PPVF reflect patient and family financial obligations (out-of-pocket medical costs and nonmedical costs) rather than systemwide costs. Quality and applicability of existing evidence, including the extent to which data exist on the heterogeneity of effects, address the individual-level question "What does the available evidence mean for someone like me?" And finally, usability and transparency form the foundation upon which the model rests.

Assigning Values, and Who's Values? The PPVF has completed the first 2 phases of its development process (Josh Seidman et al., 2019). In phase 1, a condition-agnostic framework for patient-centered value assessment was developed through broad public input. Phase 2 focused on testing and refining the framework, quantifying a scoring methodology, and developing a prototype for a preparation for shared decision-making tool. Phase 3 (launched in June 2018) involves the application of the PPVF scoring methodology to other value assessment methods (e.g., ASCO and the NCCN) and validation of the upstream shared decision-making tool developed in phase 2.

How Is Value Aggregated? The PPVF scoring methodology combines evidence from different study designs, such as randomized clinical trials (RCTs), including meta-analyses of RCTs, as well as several types of real-world data studies. The scoring methodology uses weights on the basis of the rigor of the study design and adjusts for various biases known to occur in these studies, such as confounding bias in real-world evidence studies and performance bias in RCTs.

How is value linked to price? The PPVF shared decision-making tool differs from traditional decision aids in that it prepares patients to engage in shared decision

making. It involves the application of the PPVF scoring methodology to other value assessment methods (eg, ASCO and the NCCN) and validation of the upstream shared decision-making tool (Josh Seidman et al., 2019; Willke et al., 2019)

Table 3.2 presents the seven value-based frameworks developed by private and professional societies in the United States when assessed across the following five main dimensions:

- What is identified as being of value?
- How each element is measured/described?
- How is each element valued? Whose values?
- How is value aggregated?
- How is value linked to price?

Table 3.2: Summary of Value Assessment Frameworks Across 5 Study Dimensions

Value Framework	what is identified as being of value?	how each element is measured/ described	how is each element valued? / Whose values?	How is value aggregated?	How is value linked to price?
ACC-AHA	1) Clinical benefit vs. risks 2) value	1) magnitude of net benefit, precision of estimate based on quality of evidence 2) cost-effectiveness	Magnitude of treatment effect ranges from class I ("benefit risk,") to class III ("no benefit, or harm,"). Precision of treatment effect ranges from level A ("data derived from multiple randomized trials or meta-analyses") to level C ("only consensus opinion of experts, case studies, or standard of care"). Three cost-effectiveness thresholds are applied (high: < $50,000 per QALY; intermediate: $50,000 to $100,000 per QALY; low: > $150,000 per QALY)	Assigns one of four value levels to a treatment (high, medium, low, or uncertain) Framework reports clinical benefit and cost effectiveness separately (not combined)	
ASCO	1)Clinical benefit: overall survival, progression-free survival, response rate 2) toxicity 3) Bonus factors: palliation, time off all treatment 4)Cost per month	1)Clinical benefit (≤80 points) reflects end point and magnitude of benefit, with preference given to evidence on overall survival if available. Toxicity (±20 points) reflects the rate of grade 3 to 5 toxic effects with treatment relative to standard of care 2)Bonus point score reflects palliation (10 points if drug improves symptoms) and increased time off all treatment (≤20 points).	User's weighted scores for clinical benefit and bonus factors; monetary valuation for cost per month	Calculates a "net health benefit score". A therapy can be awarded up to 130 points. The framework doesn't combine each drug's point score and cost. Costs are reported separately	
ICER	1) cost-effectiveness analysis 2)value-based price benchmark (VBPB) 3)Budget impact 4)modifications to account for other factors (comparative clinical effectiveness,	1) QALY: incremental cost for an additional QALY relative to a comparator 2) VBPB is the monetary price that would be needed for a treatment to meet a specific cost/QALY threshold 3) Budget impact is estimated as potential national budget	QALYs; Budget impact is based on panel opinion	QALY and as part of a scenario tool to estimate national budget impact	Cost-effectiveness ratio must not exceed a threshold ranging from $100,000 to $150,000 per QALY 2)Budget impact is acceptable if a

Value Framework	what is identified as being of value?	how each element is measured/ described	how is each element valued? / Whose values?	How is value aggregated?	How is value linked to price?
	other benefits/ disadvantages, contextual considerations- condition's severity, availability of alternatives)	impact for a treatment (assigned a value of high, medium, low or uncertain) 4) contextual considerations are included qualitatively			drug's introduction is compatible with an annual health care budget increase of GDP growth plus 1%.
DrugAbacus	Efficacy (survival) Toxicity Novelty R&D cost Rarity Population health burden	Efficacy is assessed as improvement in overall survival, if available. Efficacy score also reflects evidence quality. Toxicity is a drug's impact on probability of severe side effects and treatment discontinuation. Novelty is scored as 1 (novel mechanism of action), 0.5 ("known target but different mechanism of targeting"), or 0 ("next-in-class"). R&D cost corresponds to the "number of human subjects enrolled in the approval trials for the first indication." Rarity is the 2015 projected disease incidence. Population health burden is the annual years of life lost to the targeted disease in the US.	user's preference to obtain weights	weighted preferences and estimated monthly costs	calculates a preference-weighted price/"Fair price" that is the product of the scores, each of which is scaled by a user-adjusted weight.
NCCN	Efficacy Safety Evidence quality Evidence consistency Affordability	Each area (i.e., Evidence Block-EB) is scored on a scale of 1 to 5, with 1 indicating least favorable and 5 most favorable.	"Categories of Preference" are presented for each EB, user hierarchically categorizes drug as "preferred intervention," "other recommended intervention" and "useful in certain circumstances."	Scores for each are presented separately with no explicit synthesis	
IVI	1) Summary of patient outcomes 2) cost per QALY	an assessment of incremental QALYs, incremental costs, an incremental cost-effectiveness ratio	user's weighted preferences for a treatment relative to a comparator; QALY	1)multi-criteria decision analysis (MCDA), which reflects overall value	Cost-effectiveness ratio and willingness to pay per QALY;

Value Framework	what is identified as being of value?	how each element is measured/ described	how is each element valued? / Whose values?	How is value aggregated?	How is value linked to price?
				of a treatment on a 0-100 scale based on user-generated MCDA weights 2) cost-effective based on the user's weighted preferences and reported willingness to pay per QALY	Price is included in CEA and MCDA for user-generated value assessment
PPFV	1)patient preferences, 2)patient centered outcomes, 3)patient and family cost considerations 4)quality and applicability of evidence 5)usability and transparency	addresses frequency, severity, duration of side effects/ complications, discontinuation rates	weighs patient preferences to generate preference-weighted scores within each of five domains		Costs are reported separately as one of five domains

ACC-AHA: American College of Cardiology and the American Heart Association; ASCO: American Society of Clinical Oncology; ICER: Institute for Clinical and Economic Review; DrugAbacus: Memorial Sloan Kettering Cancer Center; NCCN: National Comprehensive Cancer Network; IVI: Innovation and Value Initiative; -OSVP: Open-Source Value Project; PPFV: Patient-Perspective Value Framework

Utility of Frameworks to Assess Value of Novel Drugs

This section compares the seven frameworks across the approaches used for identifying, measuring and valuing relevant benefits and costs, the explicit means of aggregating these, and a decision rule for converting the overall measure of value into the maximum price.

No Consensus on Elements of Value and How to Measure Value

Prior to the emergence of the values frameworks approach, it was difficult to quantitatively define the additional value of novel therapies. With value frameworks, both patients and physicians can make more informed decisions because there is greater clarity regarding the perceived value of new drugs relative to existing treatment options. However, these frameworks highlight the challenge of identifying "value" for prescription drugs. Value is an elusive target, and, as shown by these frameworks, there's no consensus about what dimensions of a medication should be taken into account.

While all frameworks each include some measure of drug effect, some elements that maybe important for novel medications are differentially considered (Cohen et al., 2017; Longacre et al., 2015). For example, ''unmet need'' may be an element of a new medicine's value in addition to other health effects (Anderson et al., 2014). Patients may also care about factors such as their QoL and ability to work productively. For example, ACC-AHA includes "unmet need" as a value factor, albeit in a qualitative manner, while ASCO includes bonus points for QoL. The DrugAbacus framework includes unmet need, burden of illness and innovation, all in a quantitative manner. ICER includes QoL, which is embedded in its CEA output.

Other benefits/disadvantages and contextual considerations are included qualitatively, which means the quantitative assessment outputs (CEA results and value-based price benchmark) are unchanged by their inclusion.

Should value frameworks that assess the value generated by medications focus exclusively on the demonstrated clinical benefits of these drugs or also consider their innovativeness (such as those offered by novel drugs)? Should value frameworks also consider the benefits of novel medications to the society rather than those of individual patients only? The response to this question may depend on the "perspective" or viewpoint of the value assessment frameworks (Jena et al., 2018). As demonstrated in this review, value assessment frameworks for medications have different objectives and intended audiences, which in turn dictate the perspective. Some frameworks (e.g., those by ASCO, NCCN, PPVF) aim to inform shared decision making between patients and physicians, and are thus oriented toward a patient-provider perspective. Here, whether a medication is innovative/novel or not may be irrelevant. Instead, a medication's survival, morbidity, side effects, or treatment convenience are the value elements of interest. On the other hand, a policy maker may be interested in the societal perspective, and want to assess innovation that reflects the value society places on progress against unmet health needs, particularly if this innovative therapy opens up the possibility that successful drugs will be available in the future (Weil et al., 2017). Societal perspective highlights the fact that scientific discovery is incremental, and that future innovations either directly use or indirectly benefit from a "failed" initial innovation that may deliver clinical benefits. ICER includes a population-based approach that resonates more with payers

and health systems. In addition to the cost-per-QALY calculation, there is a budget impact analysis where ICER estimates potential national budget impact (Ronquest et al., 2021).

The lack of consensus about what dimensions of a medication's value should be taken into account may reflect differences in patient's perspective of value. While some patients care about how well a treatment works and what side effects, they also care about factors such as their quality of life and ability to work productively (Mandelblatt et al., 2017). Some patients will value unmet need — a treatment for a condition that previously had none. Some will value reduced caregiver burden (Gould, 2013; Lakdawalla et al., 2018; Perfetto et al., 2017). High burden of illness is another factor for consideration. The inclusion of these patient-centric factors varies across the frameworks.

A broad range of the factors that patients care about are also not quantitatively included in several of the frameworks (Westrich, 2016). Perfetto et al (2017) also argue that a comprehensive measure of patient-centered value would incorporate factors beyond effectiveness and side effects, such as quality of life, work productivity, caregiver burden, unmet need and burden of illness (Perfetto et al., 2017). Further, differences in patient preferences for specific health outcomes that can result in treatments with similar summary scores being perceived as having different value to patients (Perfetto et al., 2017). Specifically, individual patients will respond to treatments differently — the average effectiveness and side effect response only represents the average patient. Including sensitivity analyses to capture the range of responses is important for a patient-centered value assessment. Although more

emphasis on the patient perspective is required to improve the precision of value estimates, these frameworks serve as a first step to understanding and addressing the burden of oncology drugs on patients.

Uncertainty From Method of Aggregating Values

Value determination requires disparate types of 'value' to be aggregated (Sussex et al., 2013). Most of the frameworks have created novel methodologies for assessing value or are using an untested combination of new and established methodologies (Garrison et al., 2018). According to Sussex et al (2013), this could via three options: Net-benefit approach, which converts all values into money terms; the multi-criteria decision analysis (MCDA) approach (discussed below); selecting one measure of benefit, e.g., using QALYs for each element, and then using a series of weights to up-rate or down-rate the element to reflect the magnitudes of other elements of benefit (weighted QALY approach); or a deliberative process. The key difference between the alternative approaches to aggregation is the chosen measure of value, and how different aspects of value are 'traded-off' (Sussex et al., 2013).

DrugAbacus, IVI and the PPVF incorporate weights into their methodologies through the MCDA approach, which enable users to customize the assessment to represent their personal preferences. Here, the framework considers each element of value in terms of its own 'units', and applying a set of weights to each value to represent the rates at which different values may be traded-off with each other, and scores to indicate how well each value element is achieved by the medicine in question (Kanavos et al., 2018). ASCO includes weights in the tool to allow for a similar type of preference customization by the user (e.g., preference for length of

survival over avoidance of adverse events). The NCCN includes scores for five different factors; users could choose to give preference to specific factors in their decision-making, implicitly creating customization. While offering a more transparent means of addressing multiple criteria for value, this MCDA however has the methodological challenges such as those arising from 'framing effects', i.e. the way questions are asked influences the preferences stated (Sussex et al., 2018).

ACC-AHA and ICER do not include customization. Instead, ICER selects one principal measure of benefit, (in this case, QALYs,) and then up-rating or down-rating that using a series of weights to reflect the magnitudes of other types of benefit. Thus, ICER assesses a drug's value on the basis of its budget impact and cost per QALY, then makes modifications to account for factors such as clinical effectiveness, other benefits and disadvantages, and contextual considerations, such as the treated condition's severity and the availability of alternative treatments.

Although some of these approaches are designed to incorporate user preferences, the overall score or recommended price produced may be inconsistent with those preferences. For example, ASCO's approach awards up to 80 points for a drug's effect on survival (or, in the absence of that information, its effect on surrogate end points such as response rate). On the basis of the drug's toxicity, it adds or subtracts up to 20 more points, and then adds up to 30 more points depending on the drug's palliative benefits and whether it statistically increases the time that patients can remain off all therapy. But summing arbitrarily derived values associated with different dimensions does not necessarily produce a coherent overall score. Results from the aggregation of value elements can also be confusing and even misleading to

end users in two ways. On one end of the spectrum, it may be unclear how to interpret and use an output, such as ASCO's net health benefit point system that cannot be compared across assessments (Neumann & Cohen, 2015). On the other end of the spectrum are outputs that suggest a false sense of precision and can be misused, such as ICER's value-based price benchmark or NCCN's EB scores (Longacre et al., 2015; Mandelblatt et al., 2017). If health care decision-makers use this output without understanding the underlying uncertainty and potential range of valid value estimates, their decisions could be misinformed and erroneous at best, and harmful to the patient at worst.

Limited Ability to Link Value to Price

As a final step, the conceptual framework requires that aggregate value be converted into a price through models (Sussex et al., 2013). The conversion method depends on the drivers identified in the value framework. If cost-effectiveness is the driver, the price will be calculated by using the incremental cost-effectiveness ratio and the relevant willingness-to-pay (WTP) thresholds or the net monetary benefit (Jommi et al., 2020). Otherwise, a premium price over the active comparator is identified in proportion to the additional value.

Approaches to value-based pricing ultimately require the conversion of value, however assessed, into a monetary price (Sussex et al., 2013). Some types of benefits can be readily expressed financially—time and cost savings to patients and carers and cost savings to other sectors (e.g. social care)—and can be combined with the costs of treatment to provide a net cost measure. But there are difficulties with assigning monetary values to all types of benefits, as such, not all frameworks evaluated in the

study covert elements of value to a price. For example, ACC-AHA only assigns one of 4 value levels to a treatment — high, medium, low, uncertain, while ASCO calculates a "net health benefit score" and separately reports cost. DrugAbacus calculates a preference-weighted price that represents the user's weighted preferences and estimated monthly costs. ICER's assessments have three value outputs: a CEA output, a value-based price benchmark (VBPB), and an assessment of long-term value for money. The CEA output estimates the incremental cost for an additional QALY relative to a comparator. The VBPB represents the price that would be needed for a treatment to meet a specific cost/QALY threshold. Long-term value for money is assigned a value of high, medium, low or uncertain based on panel opinion. Reports also include an inventory list of other benefits/ disadvantages and contextual considerations. ICER also estimates potential national budget impact.

Overall, value frameworks either ignore a drug's overall budget impact (ACC–AHA) or appear handle it inadequately. NCCN rates "affordability" on a scale of 1 to 5 without explaining the basis for those scores. ASCO lists cost as one of the factors considered but does not combine it with its point score. ICER adjusts a drug's price benchmark to meet cost-effectiveness of $100,000 and $150,000 per QALY. It also limits each drug's budget impact to no more than $777 million annually (an amount that ICER estimates would hold growth of total drug costs below the growth rate of the gross domestic product plus 1%, taking into account the number of new drugs approved each year) (ICER, 2022).

Limitations of Value Assessment Frameworks

A reflection on the review of the seven value assessments frameworks raises several areas of caution where there is room for improvement: 1) Varying Definitions of Value; 2) Confusing Output; 3) Varying Levels of Transparency; and 4) Limited Evidence Base.

Varying Levels of Transparency: To ensure the validity and credibility of value assessments, framework methodologies and models should be transparent and reproducible. While some frameworks provide full transparency, others rely on proprietary methods, which prevent end-users and researchers from replicating and validating an assessment's output. The inability to verify an assessment of value may ultimately undermine its credibility and utility (Sussex et al., 2013). For example, one report summarizes that assessments from new framework by IVI are fully transparent (Dubois & Westrich, 2019). IVI's models can be downloaded and customized by anyone, and the release of the models and source code demonstrates to both the public and the value assessment community that introducing a fully transparent and reproducible assessment can be done. On the other hand, NCCN's evidence block scores and COP are assigned by a multidisciplinary panel who are subspecialists in their disease area. Even though this panel consists of experts, it is not possible for an outsider to reproduce their findings (Jommi et al., 2020). Additionally, the driving factors behind COP categorization are not transparent. Although the panel relies on their clinical expertise to assign categories and cost is often not a factor in categorization, it is not possible to tell which categorizations are driven at least in part by cost. Similarly, other frameworks have sought to increase transparency but still fall

short. Recently, ICER introduced a pilot program to share models with manufacturers (Dubois & Westrich, 2019). However, authors have noted several limitations to ICER's: models should be available to all stakeholders rather than subject to restricted access; models should be fully available for use and customization rather than only available for review; and model sharing should not include confidentiality agreements that restrict the ability to share and discuss the models freely with all stakeholders (Lakdawalla et al., 2018; Sanders et al., 2016).

Limited Evidence Base: Walton et al. (2017) observe that a fundamental limitation of all the frameworks is the absence of any well-defined theoretical basis for how to measure value (Walton et al., 2017). This requires estimating the rate at which stakeholders are willing to forgo one domain of value with another, or any related empirical analyses regarding how payers, physicians, or patients would or should make decisions based on the available metrics. Neuman & Cohen (2015) also note that even a well-designed value assessment framework will be derailed if the evidence that feeds into the assessment framework is sub-optimal (Neumann & Cohen, 2015). Many of the assessments do not use the full range of available evidence, limiting their evidence base to clinical trials, and sometimes only a single clinical trial (Jommi et al., 2020). All high-quality evidence, including real-world evidence, should be incorporated into assessments, and assessments should be updated regularly as new evidence becomes available (Boscolo et al., 2020).

Limited Assessment of Health Disparities and Equity: A critical aspect of treatment in the real world largely neglected by existing value frameworks is the impact on disparities in care. Previous research has demonstrated that non-clinical

characteristics, such as education level, can affect adherence behaviors, which ultimately affect outcomes (Goldman et al.,2018). Socially disadvantaged individuals are more likely to experience disease, at greater severity and with a higher likelihood of adverse effects (Goldman et al.,2018; Williams et al., 2019). Combined with poorer adherence behaviors, disparities in healthcare can be compounded in chronic disease, where long-term consistent adherence to treatment is necessary for achieving positive outcomes. Included in ICER's assessments is the selection and aggregation of any relevant "other benefits or disadvantages" and "contextual considerations,". Here, relative weights can be assigned to a drug's ability to likely reduce important health disparities across racial, ethnic, gender, socioeconomic, or regional categories of importance. Explicitly evaluating how a new treatment can affect adherence and otherwise improve existing disparities in care would be an important element in determining the social impacts of therapeutic use.

Discussion

In the U.S, where there is no regulation of medicines' prices at market launch, drug manufacturers can freely set the price at market launch and negotiate the actual price with insurance companies and other payers. In the last few years however, several efforts (such as the seven value assessment frameworks discussed in the study) have focused on methods to determine prices for drugs that are commensurate with their value. In-line with other authors, two potential models for applying value assessment frameworks emerge from this analysis: (1) models in which cost-effectiveness is a driver; and (2) multi-domain models, where there is greater integration between the different elements of value (Jommi et al., 2020). In the multi-

domain models, cost-effectiveness is not a driver and it is harder to identify the way added value domains are measured and aggregated, as well as how to link the added value to the price. As described in this study, value frameworks have different purposes, methods, inputs and outputs. Some have a narrower scope, focusing only on certain types of treatments; some are intended for insurers to use; and others are meant as shared decision-making tools to be used between patients and their physicians.

Identifying the value of a medicine involves identifying the health gain and other benefits of the drug, measuring and valuing those for each particular medicine, aggregating them, and applying a decision rule to convert the overall measure of value into a price (Sussex et.al, 2013). As shown by this study, frameworks vary in measurement, valuation and aggregation of a drug's value, and each stage entails a value judgement about what to do. There are no simple 'right or wrong' solutions. While some standardization is necessary, this lack of consensus is beneficial because it incorporates the views of different stakeholders (physician, patient and payer) and leads to an iterative process. Each of these frameworks are constantly being refined to meet the needs of the end users and provide an adequate measure of value. As these models evolve over time, they have the potential to not only affect the value of a drug but also the price of a drug. The measurement, valuation and aggregation of a drug's value will unavoidably be associated with significant uncertainty. Further research could reduce uncertainty but would not remove it entirely. Alternatively, the value measurement and aggregation process can provide an opportunity for price negotiation with drug manufacturers. For example, State Medicaid programs

implementing alternative payment arrangements, could apply these processes in an attempt to measure the value of a medicine as a guide to its value-based arrangement with drug manufacturers.

Study Limitations

While this study relied a comprehensive literature review to identify drug value assessment frameworks, it may have missed additional frameworks due to the lack of standard definitions and terminology in use to refer to what are intended to be value frameworks by this review. The application of these frameworks was not investigated and compared, as this study was designed for reviewing the structure, utility and purpose of different frameworks, rather than for empirically evaluating the success/failure from use.

Future Research

There is a general agreement that therapies that offer little clinical benefit—as defined by the framework—should have a lower value than that those offer larger clinical benefit. This study highlights additional opportunities for future research. First, while these emerging approaches for assessing drug value are welcome in a health system, there is little information about the extent to which decision-makers (e.g., physicians, payers) use these frameworks. Further research could explore their use in practice, and to identify specific elements for refinement before they're ready to be broadly applied. If paying for value is critical to the evolving pharmaceutical industry but each framework has limitations, how can the field of value assessment progress to advance decision-making? Specifically, the question remains of whether

innovativeness provides societal value and how the societal value created can be captured by value assessment frameworks. This dissertation focuses on novel medications, which are introduced to the market with high launch prices. Do these medications that address previously unmet medical needs warrant the high market prices?

Conclusion

Along with patients and payers, who bear the burden of treatment costs, physicians and policymakers have attempted to define value for prescription drugs. While there is agreement that medications that offer little clinical benefit—as defined by the framework—should have lower value than therapies that offer larger clinical benefit, each of the seven value assessment frameworks reviewed in this study provides a different approach to evaluating novel drug value, with strength and limitations. Also, U.S. value frameworks have been proposed as a method to analyze and identify value in novel drugs, they are still limited in their ability to impact the cost of these innovative drugs. Notably, none of these frameworks were developed by payers, who have authority over drug prices or drug coverage. As such, these frameworks serve to inform the ongoing debate about the value, price, and payer reimbursement of novel medications. Instead of looking to one framework to inform health care decisions, decision-makers should leverage multiple approaches in measuring value, thus providing a more robust understanding of a treatment and its implications for patient health.

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Chapter 4 : Paper 3—Implementing Value-based Arrangements for Prescription Drugs: The Perspectives of State Medicaid Programs

Introduction

State Medicaid programs are experiencing an increase in the cost of prescription drugs. In 2019, Medicaid had net drug spending of $29.6 billion, which was about 5 percent of benefit spending that year (MACPAC, 2020). Recent projections are that Medicaid drug spending will increase between 5 and 6 percent annually over the next several years. Of particular concern is the rise in spending on newer high-cost drugs, where growth of spending on prescription drugs continues to outpace growth in the rest of the market (Tichy et al., 2021). Many of the newly approved therapies are for patients with rare diseases (FDA, 2020a). These therapies provide new options for patients with life-limiting and life-threatening rare diseases, but their high costs create challenges for health systems. Given that Medicaid finances health coverage for high-need populations, the program pays for a disproportionate share of some of these high-cost specialty drugs.

State Medicaid administrators have expressed concerns about their ability to manage these newly approved therapies, which are often in treatment areas with expensive options, and may not have a verified clinical benefit (MACPAC, 2021a). In response to rising prescription drug costs, value-based arrangements (VBAs) have emerged as a mechanism for transforming how Medicaid programs pay for these high-cost therapies. VBAs aim to promote greater patient access to effective, but often costly, pharmaceutical therapies by linking reimbursement, coverage, or

payment to a clinical or utilization outcome or set of outcomes (Dubois & Westrich, 2019; Dworkowitz et al., 2019). Despite this increasing interest, relatively little is known about the extent to which VBAs are being pursued and implemented by Medicaid programs. This study seeks to explore state Medicaid VBAs. The goal of this study was to gain insights on the design of VBAs, negotiations between manufacturers and Medicaid programs, barrier encountered and how successful strategies that may have led to improving patient outcomes or containing costs.

Medicaid Reimbursement for Prescription Drugs

State Medicaid programs are administered and funded jointly by states and the federal government. To reduce expenditures for Medicaid prescription drugs, states and the federal government have implemented certain cost-containment measures:

Federally-mandated rebates under the Medicaid Drug Rebate Program (MDRP): For federal payment to be available for covered outpatient drugs provided under Medicaid, drug manufacturers are required to enter into rebate agreements with the Secretary of Health and Human Services and pay quarterly rebates to states (CMS, 2021). In exchange for the rebates, state Medicaid programs must cover all of a participating manufacturer's drugs when prescribed for a medically accepted indication. For most brand-name drugs, this rebate amounts to approximately a discount of 23 percent of the average manufacturer's price for the drug or the 'best price' offered to other payers, whichever is lower (CMS, 2021). All state Medicaid programs receive this standard rebate. While all state Medicaid programs must cover their drugs once a manufacturer joins the MDRP, state programs retain some

flexibility around the conditions of coverage—Medicaid programs may limit the use of some drugs through preferred drug lists, prior authorization, and quantity limits.

CMS-approved supplemental rebates. State Medicaid programs may also submit a request to the CMS through a State Plan Amendments to enter into supplemental drug rebate agreements with manufacturers that generate additional rebates. CMS has the authority to approve requests from state Medicaid programs to negotiate "supplemental rebates", which states receive in addition to those rebates that manufacturers are required to pay to participate in Medicaid (i.e., federally mandated rebates under MDRP). States may negotiate individually for supplemental rebates with specific manufacturer(s), or together with other states. States must continue to cover the manufacturer's drugs under the MDRP. States usually only have the leverage to negotiate rebates when there is more than one drug with the same clinical effect and safety profile. To prompt a manufacturer to offer a rebate, states can propose placing a drug on the "preferred" list. Drugs on the preferred list are not subject to prior authorization, which results in an increase in utilization and a shift in market share to the preferred drugs. Most states have negotiated supplemental rebates with drug manufacturers on top of the federal rebates (MACPAC, 2021b).

States and Value-based Arrangements

In some cases, the discounts from the MDRP are insufficient to align reimbursement to a drug's value, especially with new high-cost cell and gene therapies, which may be approved by the Food and Drug Administration based on surrogate endpoints that are likely to predict a clinical benefit but before the clinical benefit has been demonstrated (MACPAC, 2021b). As a result, some states are using

alternative payment methods to increase supplemental rebates through "value-based arrangements" (VBAs) negotiated with individual pharmaceutical manufacturers. Their reasons include the possibility of achieving better value for tax dollars spent, improvements in health outcomes, increased quality of care, reduced waste, greater cost and spending predictability, and lower overall spending (Yu et al., 2017). VBAs are contracts that tie payment for a drug to agreed-upon measures. The manufacturer and payer share the risk that a drug might not be efficacious or that it could become overused, rather than the payer solely bearing the risk.

As at September 2022, 15 states have received CMS approval for a State Plan Amendment (SPA) to implement these VBAs (Medicaid.gov, 2022a). A few of these states have subsequently used their supplemental rebate authority to negotiate VBAs with manufacturers. These arrangements may be broadly described by one of three models (Dworkowitz et al., 2019; Vlaanderen et al., 2019):

- A "results-based" or "outcomes-based" arrangement: Outcomes-based contracts allow states to collect supplemental rebates based on a drug's performance, where a manufacturer pays a high rebate if the drug fails to meet certain clinical outcomes. Some examples of these outcomes are hospitalization visits, side-effects, numbers of life years extended, or other vital signs.
- A financing model, where a state sets a ceiling on the aggregate payment for a drug and receives unlimited access to such drugs. Here, spending on a manufacturer's drugs is capped in exchange for the manufacturer becoming the exclusive supplier of a specific treatment to the state's Medicaid program.

- A drug adherence model, in which the level of rebates paid by the manufacturer depends on patient adherence to a drug therapy regimen.

Table 4.1 identifies nine states that have implemented VBAs for their Medicaid programs using their supplemental rebate authority.

Table 4.1: Examples of States Implementing APM for Medicaid Programs

State	Effective Date of CMS-Approved SPA for VBA	VBA Model	Summary Description of VBA
Louisiana	1/20/2020	Financial/volume-based model.	Also known as "Netflix" subscription-based payment model
Washington	1/01/2019		
Alabama	12/01/2020	Outcomes-based model	These models allow states to negotiate supplemental rebates depending on a drug's performance.
Arizona	05/01/2022		
Colorado	10/01/2018		
Massachusetts	1/01/2019		
Michigan	7/31/2021		
Oklahoma	1/01/2018		
Massachusetts	N/A	Spending caps and enhanced negotiating authority	Medicaid program has authority to negotiate with drug companies for supplemental rebates if drug spending is projected to exceed certain annual spending limit
New York	N/A		
Sources: Medicaid.gov website: https://www.medicaid.gov/medicaid/prescription-drugs/downloads/medicaid-pharmacy-value-based-purchasing-spa-mapping-07082022.pdf The National Academy for State Health Policy (NASHP) website: https://www.nashp.org/policy/drug-pricing-center/administrative-actions/#toggle-id-6-closed			

Outcomes-based VBAs: In 2018, CMS issued its first-ever approval of a state plan amendment proposal that allowed Oklahoma to negotiate supplemental rebate agreements using VBAs with manufacturers (CMS, 2018). Since receiving CMS approval, Oklahoma has entered into four VBA contracts with manufacturers. Each contract is a unique, negotiated agreement and requires extensive data analysis to explore the relevant patient population characteristics and potential, measurable

outcomes. For example, one contract is with the manufacturer of the antibiotic Orbactiv®, a treatment for bacterial skin infections (Dworkowitz et al., 2019). Here, the manufacturer will pay higher rebates to the state if patients taking the medication are hospitalized for conditions the drug is intended to treat (NASHP, 2018). In exchange, the state is no longer subjected the drug to prior authorization. In another contract, the drug manufacturer paid lower rebates for the antipsychotic Aristada® if patients remain on the therapy. Here, the VBA is designed to encourage patients to remain adherent to taking the medication. The state currently has agreements on long-acting injectable antipsychotics, an epilepsy drug, and an antibiotic used mainly in the emergency room (Oklahoma Health Care Authority, 2022).

Both Michigan and Colorado have each received approvals from CMS for state plan amendments (SPAs), authorizing them to enter into outcome-based contracts with manufacturers where the drug manufacturer will pay greater supplemental rebates if patients taking those medications fail to achieve certain clinical measures (Medicaid.gov, 2022b). Massachusetts has strengthened its authority to seek supplemental rebates from drug manufacturers for drugs purchased through MassHealth, the state's Medicaid program. The Massachusetts Secretary of Health and Human Services may directly negotiate supplemental rebates with drug manufacturers for MassHealth through a private process. If that process fails, for drugs that cost MassHealth $25,000 or more per member per year, or $10 million in total state spending for the year, the Secretary may choose to hold a public hearing to establish a payment rate for the drug in question (Mass., 2020). If an agreement cannot be reached and the drug meets certain price thresholds, the drug can be

referred to the Massachusetts Health Policy Commission for further review (Mass., 2020).

Volume-based VBAs: Louisiana and Washington State have taken a different approach to VBP in proposing a capped financing model, soliciting proposals from manufacturers of hepatitis C virus (HCV) drugs. Both states use a 2-part pricing strategy. First, both states pay a reduced price per prescription through supplemental rebates up to a certain spending threshold (LA Department of Health, 2019; Washington State Healthcare Authority, 2019). Second, after hitting this threshold, the per-prescription price falls to near zero through additional supplemental rebates. The Louisiana Department of Health sought to eradicate hepatitis-C by assuring full access to medications for those incarcerated in state prisons and individuals enrolled in the Medicaid program at no greater cost than the state would otherwise have paid for those individuals (Bach, 2018). Rather than pay per-patient treatment prices, with initial list prices of $84,000 per course of treatment, the state would treat as many people as it could during a set time period for a fixed subscription rate from the drug manufacturer (Johnson., 2019) referred to as a "Netflix" model. This payment model is beneficial to manufacturers because it increases access to medications and provides a competitive space for curative drugs that typically have diminishing utilization over time. Additionally, a subscription model like this provides years of guaranteed "spend" for manufacturers (Trusheim et al., 2018). In 2019, Louisiana formally released a solicitation for offers to identify pharmaceutical partners (LA Department of Health, 2019). The department planned to treat over 10,000 Medicaid-enrolled and incarcerated individuals by the end of 2020, with the ultimate goal of eliminating

hepatitis C. The State of Washington has also implemented a subscription model but plans to leverage its purchasing power by using a winner-take-all contracting process (Washington State Healthcare Authority, 2019). In this case, Washington would pay a flat fee to the winning bidder to open up hepatitis C treatment for all of its Medicaid beneficiaries, as well as prisoners and state employees. The state recently issued a request for proposals from drug manufacturers.

Study Objective

Value-based contracts have emerged as an important step toward getting better value for money spent on prescription drugs (Dworkowitz et al., 2019). Despite this increasing interest, relatively little is known about the extent to which VBAs are being pursued and implemented by Medicaid programs. One survey of 11 drug manufacturers and 9 health insurers that found that VBAs are more prevalent than reported but are not publicized; nearly 75 percent of VBAs implemented between 2014 and 2017 were not publicly disclosed (Mahendraratnam et al., 2019). The lack of public knowledge of these arrangements could underestimate their use in the market and limit what could potentially be learned from current experience that would advance the successful design and implementation of future VBAs in Medicaid. This study aimed to better understand VBAs implemented by Medicaid programs, with a particular focus on the following research questions from the perspectives of the Medicaid program:

1. what are the motivations for, and drug/disease characteristics of current Medicaid VBAs?

2. how do Medicaid programs approach the design, negotiation with manufacturers, and monitoring of VBAs?
3. what factors impede or contribute to the successful negotiation with manufacturers and implementation of VBAs?

Methods

This study used key informant interviews with state Medicaid officials implementing these state Medicaid VBAs. Qualitative data were collected from key informants using a semi-structured questionnaire and interview format. The key informant interview methodology is well suited for qualitative research focused on understanding what does and does not work regarding design and implementation, and what constitutes a successful VBA program. These finds can then provide a credible baseline on which to build a more quantitative research methodology.

Data Collection Procedures

Key informant interviews were conducted in English and took between 45 minutes and 1 hour. A semi-structured guide for the key informant interviews was used to enable the exploration of a consistent set of questions while at the same time providing the flexibility to probe on themes specific to the key informant. Interview questions were developed through a review of published literature of similar studies exploring VBAs in the commercial markets (Garrison et al., 2018; Goodman et al., 2019; Michelsen et al., 2020; Neumann et al., 2011).

The interview guide included nine domains (Table 4.2) and interview questions were intended to encompass the full range of information relevant to state

Medicaid VBAs including identifying drug and disease characteristics and contract components that contribute to successful VBA experiences and the primary barriers to VBA execution, and explore solutions to facilitate negotiation and implementation of these models.

Table 4.2: Key Informant Interview Guide Domains and Specific Topics

Domain	Specific Question/Topic
1. Experience with Medicaid VBAs	• State/geographic location, training, number of years' experience in Medicaid and number of years' experience with Medicaid drug VBAs • Number of VBAs implemented in the past 5 years
2. Motivation for Medicaid VBA	What were your motivations for Medicaid VBAs (e.g., tightening budgets, uncertain evidence of drug effectiveness)
3. Disease areas & drug attributes for VBAs	• Current disease areas with VBAs • Previously pursued (and not implemented) disease areas for VBAs • Desired disease/drug VBAs that are currently not in place • Drug attributes for current & desired VBAs (e.g., specialty, novel mechanism of action) • Disease attributes for current & desired VBAs (e.g., top 15 disease by cost or prevalence, acute/chronic disease duration, orphan status)
4. Approaches to developing VBA framework with drug manufacturers/elements of current framework	• Does the agreement include data collection to assess performance? If so, who collects the data? Who pays for this? Who tracks the patient? • Does agreement include data collection costs, including research set up and analysis? If so, who pays for these costs? • Is the drug reimbursement linked (prospectively or retrospectively) to the results of the data collection? • Does reimbursement to manufacturer vary with outcome? • How important is it to have early involvement of health economics and outcomes research in the VBA design and implementation stages? E.g., to inform selection of meaningful outcome measures for contract development • Does the state have a public or private contractor that could help them assess the benefits of participating, such as a pharmacy school?
5. Outcomes	• What categories of primary outcomes are used in VBAs e.g., adherence, healthcare utilization, response to therapy (based on patient disease improvement/endpoints relevant to the particular therapeutic area) • How are cost savings calculated? • How do you track patients that may move out of Medicaid over time?
6. Accessibility to data	• Ease and cost of current data types and sources to measure drug performance (e.g., types of claims data, electronic medical records) • Desired types of data not currently available
7. Mechanisms for	• Types of payment made by drug manufacturers included in VBA (e.g.,

Domain	Specific Question/Topic
reimbursement & VBA negotiation process	reimbursement, or rebates) • Methods used to facilitate VBA negotiations (e.g., using a standardized contract template) • Number of stakeholders involved in the negotiations (from State Medicaid and from the manufacturer sides) • Number of rounds of negotiation in order to finalize VBA • Are there tools that could help with making VBA negotiation process more workable for payers (e.g., standard contract templates across manufacturers, transparent risk evaluation)
8. Satisfaction/ dissatisfaction with current VBA	• How satisfied are you with the current VBA? • What are areas of satisfaction/dissatisfaction? • What is your definition of a successful VBA?
9. Future of VBAs	• Do you expect VBA activity to increase over the next 5 years? If yes, for which drugs? • If yes, what would further increase longer-term VBA activity in the Medicaid drug program?

Prior to the data collection activities, one dissertation advisor reviewed the interview guide to ensure rigor and appropriateness for the study. Although the core questions remained consistent throughout the data collection activities, probes were modified as we gained understanding of the state-specific VBA implementation context and to follow-up on specific areas of that required clarity.

IRB Review

The research design and question guide were developed and submitted to the University of Maryland, Baltimore County Institutional Review Board (IRB Study #760) for approval and exemption was granted on February 7, 2022. The interview guide contained open-ended questions, with each key informant being asked the same questions. The interview guide and full set of interview questions and verbal consent process are available in Appendices 1 and 2.

Study Participants and Recruitment

The nine states that have implemented VBAs for their Medicaid programs in Table 4.1 were selected as potential interview participants. These subjects were contacted by email to request their participation, at which time a brief description of the study was shared using a standardized script in English. When participants agreed to be interviewed, an appointment was scheduled at a time convenient for the key informant. All sessions were recorded with participant permission. The investigator obtained verbal consent from the participant at the time of the interview. During the consent process, all participants were informed that the information they provided during the interview was confidential (i.e., not shared with anyone outside of the research team) and voluntary (i.e., they were not obligated to answer each question).

All interview data recorded during the interview were saved on *Box,* a secure storage system secured by UMBC. Once the data were transcribed, analyzed and the study results summarized, all recordings were destroyed to ensure that no responses would be linked to an individual. The results are presented by the state name and the names of the individuals have been kept confidential. Descriptors of key informants are included, but in order to maintain confidentiality of the respondent, the participants' names are not included.

Analysis

Each key informant interview was recorded, transcribed and transcripts of the interviews printed. Transcripts with the qualitative data were manually analyzed, pulling out key concepts and themes.

Limitations and Strengths

As with all research, this study is subject to limits and potential biases which can skew the results. First this is an exploratory, qualitative study of expert opinions on the experience and barriers to implementing VBAs for medications, and strategies used to overcome these barriers and facilitate successful models. The findings presented in this study are based on opinions and experiences of key informants involved in implementation of Medicaid VBAs, rather than on empirical data generated from implementation of these VBAs.

Generalizability of these results may be limited because potential interview participants were selected from a small sample with a low response rate, and interviews were conducted on a selection of this sample of Medicaid agency staff who agreed to participate. Although the states participating in the key informant interviews are distributed across the US geographically, they may not be representative of their geographic region—views on implementation of a VBA by one state in the southeast or southwest (for example) may not reflect those of this group of states. Additionally, the interview questions collected information only on prior or current VBAs administered by state Medicaid programs, whose SPA was approved by CMS in 2020 or before. It is likely that study may have not captured any unique experience of those states that failed to launch their VBAs, or those of newer VBAs currently in development by states with no prior experience with these models. Given these limitations, this study may be best viewed as a series of case studies rather than other qualitative studies that seek to achieve thematic saturation.

Although there are several limitations to this study there are some strengths. Much of Medicaid VBA activity for prescription drugs remains out of public view, with limited information on experiences with implementation in published literature. This study begins to fill this gap—interviews with a set of well-placed Medicaid officials actively implementing these models provided firsthand insights and experiences that were not apparent in the literature. This study was conducted in a context of significant national policy change where Medicare will now negotiate drug prices for the first time in program history after Congress passed the Inflation Reduction Act (IRA) of 2022. Therefore, information sharing about experiences negotiating and implementing these Medicaid VBAs with manufacturers will strengthen the knowledge base, identify best practices, and support decisions regarding implementation of the under the IRA.

Key Findings

Characteristics of Interview Participants and State Medicaid VBAs

Nine potential key informant interviewees were contacted; three did not respond to the recruitment e-mails and another two responded and declined to participate. Therefore, four interviews were conducted between March 3, and September 21, 2022. All interviews were conducted by telephone, where all key informants agreed to have their interview audio recorded. A summary of the key informants' backgrounds is provided in Table 4.3; state names are masked for blind review and are identified by a number in the subsequent sections of this paper.

Table 4.3: Summary Characteristics of the Key Informants

State Number	Total No. Years of Experience in Medicaid	Years Implementing Medicaid VBAs
1	>19	~10
2	>10	~6
3	>15	~6
4	>10	~5

All four key informants have spent the majority of their careers in the pharmaceutical industry, either as pharmacists (retail or clinical), jurist, academia or in pharma companies, with more than 5 years leading the design and implementation of state Medicaid VBAs.

Motivation for and Characteristics of Medicaid VBAs

Table 4.4 summarizes the features of VBAs implemented by these interviewees. The 4 interviewees have 14 currently active VBAs, 7 of which are implemented by one state (State No.4). The number of VBAs implemented by state Medicaid program interviewed varied, ranging from 1 to 10. State No.3, received CMS-approval for a State Plan Amendment (SPA) to implement VBAs in January 1, 2018. Since then, the state has implemented the greatest number of VBAs, with 4 of its 10 VBAs are currently in place. Although, State No.4 and State No.1 states received CMS-approval at the same time, they differ in the number of VBAs for prescription drugs implemented (7 versus 1 respectively).

Table 4.4: Summary of Motivation and Characteristics of Medicaid VBAs

State	No. of VBAs Implemented	Motivation for Selected VBAs	Disease/Drug Class of Current VBAs	Desired VBAs not implemented
State No. 1	Current VBAs:1	Legislative priority; concern about high cost of treatment for a disease with relatively high	Mavyret for Hepatitis-C	▪ Zolgensma (spinal muscular atrophy) ▪ PCSK9 inhibitors ▪ Anticonvulsants

State	No. of VBAs Implemented	Motivation for Selected VBAs	Disease/Drug Class of Current VBAs	Desired VBAs not implemented
		prevalence (Hepatitis C)		
State No.2	Current VBAs:2	Concerns about managing drug costs; concerns about drug's effectiveness	▪ Zolgensma (spinal muscular atrophy) ▪ Mavyret (Hepatitis-C)	▪ Insulin ▪ Anti-asthma drugs ▪ Antipsychotics
State No.3	VBAs ever implemented:10 Current VBAs:4	Concerns about drug effectiveness in real world relative to outcomes from clinical trials	▪ Antipsychotic ▪ Anti-hepatitis-C ▪ Rare disease ▪ Enbrel®	▪ Hemlibra (hemophilia) ▪ Spinranza ▪ Onmipod (diabetes)
State No.4	Current VBAs:8 (7 drug, 1 non-drug)	High cost of medications	[not shared]	[not shared]

Regarding the state's motivation for pursing VBA between manufacturers, states seek value for high-cost novel medications (cell and gene therapies); officials expressed concerns about paying high prices when these products do not have a verified of clinical efficacy and safety of novel medications drugs. State Medicaid programs seek real-world evidence of outcomes reported in clinical trials.

> "…we did also have concerns [about Zolgensma] because there was really just one trial of, I think, 12 patients. And it was not a large trial and yet the results seemed to be... It was difficult to direct conclusions from a trial that small and so we really weren't sure what the outcomes would look like." **State No.2**

> "…so when we would hear all of these discussions about their product, we would soon find out the cost of those products. And then, we got to thinking. Well, if you're telling me your product does A, B, and C, are you willing to stand behind that? Do you really think it's going to meet these outcomes?.. " **State No.3**

For another state, the decision to pursue VBA was motivated by a legislative priority of the state government, which was driven by the high cost of treating a Hepatitis-C, a prevalent condition among the population covered by state programs.

> "Our governor announced a directive to eliminate Hepatitis C in the state of State #1. He directed our Department of Health and the Healthcare Authority, to work together in that effort... that's where the Healthcare Authority comes in, on how can we afford, make it affordable, because the Hepatitis C drugs were quite expensive. **State #1**

The most common diseases/drug classes included in the 14 currently active VBAs are those for management of rare diseases and treatment of hepatitis-C. State Medicaid programs also identified a variety of drug classes that they desired to pursue but were unable or have yet to pursue.

Approach to Design of VBA and Negotiations with Drug Manufacturers

Table 4.5 summarizes interviewees state's approach to developing Medicaid VBA, including model design of VBA (outcomes-based vs financial), negotiations with drug manufacturers, , stakeholders involved in the negotiations with manufacturers, and level of expert involvement in the VBA design and evaluation.

Table 4.5: Summary of Approaches to VBA Development

State	VBA model for drug reimbursement	VBA negotiation process	Expert participation in VBA design and evaluation
State No.1	Volume-based; lower price after set threshold number of doses is dispensed to patients.	Multiple state agencies involved in the design (Department of Corrections, state mental hospital, public employees self-funded program, Medicaid); About 1 year to develop RFP for the VBA; 4-6 months for negotiations with selected manufacturer	Consulted with experts for VBA design: outcomes researchers (OSHU), financial/ business analyst on manufacturer's revenue from state; No external evaluation of VBA
State No.2	1 Outcome-based model, and 1 Volume-based	Only Medicaid agency involved; duration of	Consulted with experts for VBA design: outcomes

State	VBA model for drug reimbursement	VBA negotiation process	Expert participation in VBA design and evaluation
	model	negotiations varies, maybe >1 year	researchers (OSHU), No external evaluation of VBA
State No.3	Outcome-based; manufacturers provide additional rebates if certain outcomes are met	Only Medicaid agency involved; negotiations last between 2-3 months and 1 year, appears to vary with size of manufacturer	No external evaluation of VBA
State No.4	Outcome-based; manufacturers provide additional rebates if certain outcomes met. Rebate maybe adjusted to the proportion of patients who met the outcome	Only Medicaid agency involved; negotiations last at least 3-4 months	Pharmaco-economist (consultant); No external evaluation of VBA

Many of these steps involved in the VBA design—selecting the VBA model, evaluating proposals from manufacturers, negotiating arrangements, developing contract documents—vary by state. For example, both State No.1 and State No.2 use a volume-based design for its VBA between the Medicaid program and the manufacturer (AbbVie) for the anti-hepatitis C drug Myvret.

> "…we have a threshold; the amount of the threshold is confidential. It's the number of pills we have to buy in the year and then we get penny pricing. The pharmacy bills Medicaid.... then each quarter, we invoice to the manufacturer, a rebate…. So they do the calculation, figure out how much we should get back, based on the agreed upon rebate and then we get a check back every quarter." **State No.1**
>
> "And so our payment arrangement on Mavyret is volume based. So basically our price for the drug decreases when more patients are treated. So the more beneficiaries who are treated for hepatitis C, the lower the cost is for the Medicaid program." **State No.2**

Notably, State #1's VBA with the manufacturer includes additional features not reported by State No.2; in State No.1 the manufacturer also conducts hepatitis-C public awareness and screening campaigns.

> "Part of the contract is that they are sponsoring a bus, an awareness bus, that they fund, I think six events per year. It's been harder with the pandemic, but

> we would try to, in the first year, there were some fairs, or health fairs. We would take the bus there and people could come in and get screened for Hepatitis C for free." **State No.1**

Although both State No.3 and State No.4 use an outcome-based model to determine the additional rebates, they may vary in how the additional rebates are calculated. For State No.3, the outcome threshold is determined across all the eligible population (e.g., maintain adherence level of at least 80 percent among Medicaid beneficiaries prescribed drug X for disease Y).

> "…but if we set up one of these agreements, and then if we don't hit the outcomes that you expect to see or that you saw in your clinical trials, and we don't see those in the real world, then we tack an additional rebate onto the use of that product, the utilization of it overall, generally. And that would come back to the state." **State No.3**

In State No.4, however, some of the seven drug-related VBAs are designed to align the additional rebates collected by the state with the proportion of patients that met the threshold.

> "…They give us extra X amount and that might be, again it depends on how the value-based contract is structured.. …. If it [outcome] only happens 10% of the time, we collect but only on the limited amount, on the limited volume only for those patients when something didn't happen." **State No.4**

When asked about the negotiation process with drug manufacturers—duration, number of rounds, stakeholders involved—all participants described processes lasting months to years, with varying level of involvement by other state agencies. Findings from this study suggests that the VBA negotiation process with drug manufacturers is complex, varies by state, requiring different points of alignment to successfully progress throughout all the steps.

> …. So I would say it took four to six months of negotiating.. The amount of work that we put into it was much more than what was necessary, based on really what came out of the contract itself, , we also drafted the RFP, which was another year." **State No.1**

> "…We have two outcomes-based contracts right now. And for one, we were in negotiations with a drug manufacturer for over a year." **State No.2**
>
> "It's very intensive, that's one thing you should know about this…It takes a lot of time and energy to figure out from our perspective what is the good model for this. Probably 3-4 months, even longer. And then just as much time and energy, if not more, to negotiate this with the manufacturer ... **State No.4**

The duration of the negotiations varies, and appears to depend on the size of the manufacturer.

> "..The negotiations vary depending, I don't want to say a hundred percent on the size of the manufacturer, but it appears to be that. If it's a very large manufacturer, there are multiple layers of people to go through. If it's a very small manufacturer, we've been able to turn one around in two to three months. But if it's large, it's probably closer to a year.." **State No.3**

The number of state agencies involved in decision making of VBA design varied by state. For example, State No.1 state requested proposals from eligible manufacturers through a public procurement process. The development of this request for proposal (RFP) involved multiple agencies in the state: the Department of Corrections, state mental hospital, public employees self-funded program, and Medicaid.

> "… So we had like their pharmacy directors from each one of them, they were helping us, providing us data that was informing the requests for proposals. … Then once we selected the final bidder, HCA [Health Care Authority] took the lead in the negotiating and we negotiated a price for, a non-Medicaid price and a Medicaid price, because for our public employees and corrections, they're not Medicaid." **State No.1**

All participants agreed that it was important to have early involvement of experts (health economics, outcomes researchers, business analysts) in the VBA design stage. For some states, these experts were external consultants (State No.1, State No.2, State No.4), while other states primarily relied on internal Medicaid staff with relevant training and experience.

> "…. We participated in that exercise [with Oregon Health Sciences University - OHSU] and went through many different payment model options, that they presented and we kind of chose, we went through and looked at several disease states. …. ….we also had a consultant Mark Trusheim at MIT, who is a former drug company employee, who kind of knew what their rebate negotiating strategy was…" **State No.1**
> "So they [OHSU] helped us lead with those internal discussions that we had within our department and helped with the development of our contract template. And helped us identify the drugs that we wanted to prioritize..." **State No.2**

All participants have yet to engage a public or private contractor to support evaluation of the VBA and the benefits of participating in VBA(s). One participant however noted that they expect positive savings by the state Medicaid program when this assessment is done.

> "We have not been doing it. No we don't. And we have not been doing it [VBAs] long enough and we have not deployed sufficient resources to now have an external partner. We will have to do it at some point to see what is the value of these contracts. … I know even just one contract that's out of these eight, which by itself more than makes up several times over for any additional one or two team members that we added in order to be able to do this…whenever there is an evaluation done, I know that we will come on top." **State No.4**

Approach to Monitoring VBA Implementation

Table 4.6 summarizes interviewees responses to questions on categories of patient outcomes included in the VBAs, data used to monitor these outcomes, and discussions on costs for data analysis.

Patient Outcomes: Interview participants identified the following patient outcomes included in their state's Medicaid VBAs: measure of healthcare utilization (emergency room or hospitalization visits and costs), mortality, drug initiation or adherence, and disease progression.

Table 4.6: Summary of Patient Outcomes and Data for VBA Monitoring

State	Categories of patient Outcomes Included	Data used to monitor outcomes and patients	Patient tracking-Concerns with Medicaid 'churn'	Data analysis – who pays?
State No.1	N/A – VBA is based on volume; track patients eligible for drug and number of new prescription fills	Medicaid claims data	active patient tracking and care coordination; churning is not a concern	Partnership with University; funding from a non-profit
State No.2	ED visits, death	Medicaid claims data, vital records (death data)	No active patient tracking; churning is not a concern	Medicaid program, no additional support
State No.3	reduction in hospitalization and ED cost; adherence; disease progression; utilization/volume	Primarily Medicaid claims data; 1 VBA with additional data collection	No active patient tracking; churning may theoretically impact outcome	Primarily Medicaid program through MoU with OK University; 2 earlier VBAs where the manufacturer paid for these costs
State No.4	[not shared]	Primarily claims data; 2 VBAs with additional data collection	[not shared]	Medicaid program

Data Sources: The availability of measurable patient outcome(s) easily identifiable and linked to a drug in Medicaid claims data was identified as a factor in determining whether to pursue a VBA with a manufacturer. Pharmacy and medical utilization and cost data (e.g., claims and encounters data) are the primary data sources to monitor patient outcomes and therefore determine eligibility for additional rebates from manufacturers. Reasons given for reliance on these data are that claims data are easily accessible and relatively inexpensive for drug outcomes measurement.

> ".. we are on a monthly basis, looking to see how many new starts we've had. We're tracking how many units we're purchasing.. Then we send the quarterly files to AbbVie, so that they can, they have their data sources and they can compare our data to their data, because at the end of the day, we both have to agree that the threshold has been met… ..." **State No.1**

> "So we try to structure contracts in such a way that all the information we need in order to monitor and then establish whether or not rebates are above board, and then invoice for those rebates. We try to have the data needs that can be stemmed in the claims only." **State No.4**
> "…And so we have access to claims data like ED visits, and then we have access to vital records data, which would be death rates. And that's really the limit of what we have access to. Of course, we have access to other utilization data on the drug and then in medical services. But so we limit our outcomes to those that we can track using claims data. And so then that really does limit the types of arrangements that we're willing to enter into." **State No.2**

There are instances where the Medicaid program needs additional data to monitor patient outcomes. Medicaid programs may require a prior authorization to ensure that a drug is medically necessary or alignment with evidence-based treatment guidelines before approval of coverage. This process requires submission of appropriate clinical information (e.g., diagnoses, results from diagnostic or laboratory tests) or attestation from the prescriber. Here, the Medicaid program uses data already collected for other purposes—in this case, clinical data (e.g., laboratory markers) from physician that were submitted as part of the prior authorization process and used to inform VBA outcomes.

> "But I think one or two cases we have things that we need a claim is not enough. So it needs to be additional data. And at least one of those cases is that we collected additional data at the time of this drug's VBA needs to be re-certified I think every six months… So we have a subset of our team is the one that does the prior authorizations. we ask the physician to show us that outcome of that test…. So they provided information and then that feeds into the rebate calculation." **State No.4**

For three of the four state Medicaid programs interviewed, do not actively track patients included in the VBA, instead, patient outcomes are reviewed retrospectively at the end of the year. However, one state Medicaid program reported that that the VBA includes patient tracking and care coordination for patients taking the drug included in the VBA.

> "What we're doing internally to kind of identify individuals that are Hepatitis C positive, haven't been treated. ... Then we're tracking as people get treated, we are tracking how well the plans are doing care coordination and reaching out to either the provider, or the individual patients and getting them connected to treatment and then getting them actually into treatment." **State No.1**

Medicaid Enrollment: Participants were asked if changes to coverage where Medicaid enrollees move in and out of Medicaid coverage (sometimes called "churning") impeded patient monitoring of outcomes. While one interviewee discussed it as a potential concern when calculating patient outcomes, in general, interviewees reported that 'churning' in Medicaid does not appear to be a big problem.

> "..That is true. All of the agreements that we've have says the member has to have continuous eligibility for a certain period of time. So as someone started the drug, lost their eligibility, we would not be able to include them in the analysis. So we might start out with 300 members that use the product. And our analysis might end up being, we analyze 250 of them…" **State No.3**
> "Our population is generally pretty stable…eligibility is monthly, but I think the churn is less than what is made out to be…… I believe CMS has changed some of the regulations around re-certifying people... I think those rules have lifted and it's not so rigorous." **State No.1**
> "…so we find that beneficiaries who have these genetic conditions that are in need of these high-cost treatments, if they are Medicaid eligible, then they tend not to move out of the Medicaid program. At least until their treatment is complete." **State No.2**

Data Analysis: Responsibility for data analysis to assess outcomes from use of the medications was discussed with all interviewees. For two state all data analytics are done in-house by the Medicaid agency staff as part of administration of the Medicaid program.

> "…we collect the data in-house. I know some states may have a separate third-party drug aggregator or a data aggregator, but we do all the data aggregation internally within our department" **State No.2**

> ".. regularly we do the monitoring. Both because we want to know how it's performing obviously, but also because that's how we understand whether or not the manufacturer has to pay us the rebate…yes… It's done by my rebate team" **State No.4**

For the two other states, data analysis to monitor patient outcomes on the VBA is conducted through existing contracts with local state universities. For State No.1, the state has received additional grant funding to support this work.

> "So at the University of [XX] , we are partnering with them where they are conducting a research analysis, to evaluate the effectiveness of the project. … we were able to get a grant from the Arnold Ventures, in order to fund that work," **State No.1**
>
> "Part of that contract [with the School of Pharmacy], we support some graduate students that are on part of that contract. So they are available to dig deeper into our claims data and do some of the analysis. I would say, they probably do 80, maybe even close to 90% of the data analysis for us." **State No.3**

Implementation Challenges of State Medicaid VBAs

One interviewee had previous experience with six VBAs that were no longer in effect at the time of the interview. While all interviewees indicated that they were generally satisfied with current VBAs, Table 4.7 summarizes four categories of challenges expressed by interviewees.

Table 4.7: Summary of Challenges from VBA Implementation

Category	Specific Challenge Identified
Manufacturers	▪ Decision to negotiate a VBA is dependent on manufacturer's willingness ▪ Outcomes proposed by manufacturer are not aligned with those of Medicaid program ▪ Manufacturer owed rebates and declines to renew agreement
Data collection & Patient Outcomes	▪ Outcome of interest from using the drug may take too long to collect ▪ Access to electronic health records
VBA design	▪ Lower than expected patient enrollment ▪ Overestimated thresholds for number of patients initiating treatment, and therefore taking the drug
Federal regulations	Concerns with anti-kickback statutes

1. Manufacturer-specific challenges

Decision to negotiate APMs is dependent on manufacturer's willingness: Medicaid programs reported that they lack leverage with drug manufacturers to negotiate VBAs, and therefore may not be able to pursue and negotiate effectively with manufacturers of new, innovative gene and cell therapies brought to market at high cost that are target candidates for VBAs.

> "…. but we are beholden to the manufacturers. We can't force manufacturers to enter into these payment arrangements with us. And there are very few who are willing to enter into these payment arrangements. At first, we would approach every manufacturer of a high-cost drug, of high-cost gene therapy. And many of them said, no, thanks." **State No.2**
>
> "So targeting a specific disease state or drug class never did work, because the manufacturers were not all in. … we would approach a manufacturer after, say, a presentation and say, "What about our value-based agreements?" And then, some were interested. …so finally, we just backed off and said, "Look, you guys as a manufacturer, you talked to your higher ups. If there's an interest, you guys come up with a plan that you are comfortable with, that we can discuss." And that made the discussions a lot more productive when we put it on the manufacturer to come to us with something versus us laying out 50 options, and them just continually saying that it's not going to work." **State No.3**

This lack of leverage with drug manufacturers to negotiate VBAs is of greater challenge with manufacturers of brand-name drugs, where there are no alternative drugs, and therefore no competition for the market.

> "We've got manufacturers even today that we would be interested in doing a value-based agreement. And they are, let's say, the only product in the class or the only... So they have no competition. And then, no incentive to offer any additional rebates or have their product analyzed. So they just don't have an interest" **State No.3**

In other cases***, the outcomes proposed by the manufacturer are not meaningful to the Medicaid program:*** Even when a manufacturer is willing to negotiate, the manufacturer may propose risk-sharing agreements that do not reflect clinically

meaningful outcomes for the patient. All four Medicaid officials interviewed expressed that a considerable number (not quantified by study) of early dialogues ultimately did not lead to contract implementation between manufacturer and the Medicaid program, where some of the roadblocks are related to disagreement on the patient outcomes, particularly when there was uncertainty about their relationship to the value of high-cost products.

> "…… so an example would be, this particular contract for Zolgensma with spinal muscular atrophy, was based on the child was still alive, at a certain point and time…… But the longer they lived, the larger amount of the cost of the drug you paid. But in their studies, they didn't even go out to five years, all of the individuals were alive. . So why would I think that your drug is going to keep kids alive for five years? I would be interested in the meaningful outcomes: are they [children] sitting? Are they moving their head? Are they meeting their regular childhood milestones, their motor function milestones?" **State No.1**

While outcomes proposed by manufacturers could reflect the relative importance of manufacturer's interest to enter into a VBA with the state Medicaid program, those outcomes are not always aligned with those of the Medicaid program. Manufacturers may be seeking to only serve their own interest to access patient data and may seek to limit their exposure in the risk-sharing agreement by offering limited additional rebates to the Medicaid program.

> "But in the beginning, some of them required a lot of data with very little investment from the manufacturer... And we didn't go down a path with a contract with a lot of manufacturers that wanted. They wanted the data…but they weren't willing to put up very much rebate, potential rebate. So one of the big challenges anybody that's going to do this or have to understand that the manufacturers are going to come to the table have interest. And initially, they're not going to want to put up a lot of investment." **State No.3**

Another manufacturer-related reason (shared via email) why prior VBA contracts with manufacturers were not renewed:

> "Manufacturer did owe rebates to the state Medicaid program and declined to renew. I think they thought the VBA would increase their market share and it did not or not enough for them to continue." **State No.3**

2. Data collection and patient outcomes

One interview participant reported that for some drugs, the outcome that would be of interest to patients and the state Medicaid program may not be measurable within the one-year contract of the state VBA model. Here, the follow-up for the desired outcome (prevention of stroke) requires a longer-time follow-up than that of the VBA.

> "Some of them, if the outcome, the real outcome of interest, like if it's a cardiovascular drug, like the PCSK9 inhibitors, you can look at, "Yeah, they are really good at lowering cholesterol. The data shows that. But are they preventing stroke, heart attack and all of that?" The timeline is so long, that the outcome of interest, it might be five or 10 years down the road and it just, as a state and how budgets are built, it's just not practical. "**State No.1**

Another interviewee noted the wish to have access clinical data from electronic health records, which would support implementation of specific VBAs where monitoring of these patient outcomes is crucial.

> "We would like to have some type of electronic medical record where we could see lab values. And we could do something in diabetes if we had A1C levels. Right now, all we can see is, we paid for the lab test, but we don't know what the results are." **State No.3**

3. VBA design

One state Medicaid program reported the failure to receive the additional rebates from the VBA due to the state's inability to get a sufficient number of patients into treatment using the drug included in the VBA (i.e., the state failed to meet the volume threshold agreed to with the manufacturer in the VBA). The interviewee thought that this threshold needed to receive additional rebate may have been set higher that what is feasible.

> "…we're halfway through our third year and we have yet to meet the threshold. ... So we definitely overestimated the threshold and each year, we continue to negotiate it down." **State No.1**

Another interviewee reported similar concerns, where a prior VBA was not renewed with the manufacturer due to the smaller than expected number of Medicaid enrollees eligible to use the drug included in the VBA.

> ".and we had one that we thought if we open up coverage for this product, we're going to see it [utilization] increase. And then, we're going to have enough people to analyze. And that didn't work. That was what I would consider not successful, because we had very little members. And we finally just had to agree with the manufacturer to not continue. **State No.3**

4. Federal regulations

One interviewee discussed concerns with current federal regulations, where setting up any additional services to support the VBA may be construed as extra value given potentially under anti-kickback statutes.

> "… what's really challenging is the federal regulations around these types of arrangements where, there is a fine line between a kickback and bona fide and the legal interpretation is a little challenging. It's AbbVie and the 340B rules, because our Department of Corrections is a 340B entity for infectious diseases, …." **State No.1**

Successful Strategies by State Medicaid VBAs

Interviewees were asked about their definition of a successful Medicaid VBAs, and whether they were satisfied with the current VBAs. Despite the challenges, state Medicaid programs expressed satisfaction in the following three areas: 1) development of a positive working relationship with manufacturer 2) improved patient outcomes from use of drugs included in the VBA, and 3) realizing cost-savings/ additional rebates from manufacturers.

> "So I'm very satisfied with the outcomes of our contract and the vendor [manufacturer- AbbVie] that we selected. They've been a great partner and it's been a really very positive experience…. I think we successfully negotiated a

> really, really good rate, for our Medicaid program and our non-Medicaid program, that we couldn't have gotten, had we not gone through this process." **State No.1**

> "we have had some program savings through these payment arrangements. So we have received rebates as a result of these arrangements. So that's great, that we were able to take advantage of those savings." **State No.2**

> "….But in this case, we had a one-year agreement, but we extended even for a second year just to make sure it wasn't a fluke. But both years, we saved the amount we agreed upon, and they did not have to pay a rebate. So we considered that a success, because it kept our members out of the hospital and the ER." **State No.3**

> "And then we have one contract alone that's generated more than $15 million**." State No.4**

Interviewees also identified the following four components that contributed to successful implementation of their current Medicaid VBAs for prescription drugs: 1) Leverage new state laws to support Medicaid VBA negotiations; 2) Engage a data partner to support analysis of patient outcomes; and 3) Preparedness to pursue a VBA with a manufacturer; and 4) Input from experts during the design of the Medicaid VBA.

1. Leverage new state laws in VBA negotiations with manufacturers

One Medicaid program requested and received additional legislative tools from the state's legislature that allow for more efficient or direct negotiations with manufacturers. First, this new law eliminates the requirement to follow the procurement laws when negotiating for additional rebates with manufactures.

> "…we have this authority which in short we call it direct negotiation authority. So, it did a few things, …it allowed us to negotiate with the drug manufacturers directly. Which means we don't have to follow the state procurement rules in order to talk to the drug manufacturer..." **State No.4**

The new law also provides additional leverage for negotiations, where if the Medicaid program is unable to reach an agreement with a manufacturer, the manufacturer

would be referred to another state agency, which may require the manufacturer to provide testimony on its drug pricing policy at a public hearing.

> "…we wanted to have more leverage….. and if we try to negotiate with the manufacturer in good faith and the negotiations were unsuccessful, we can then do two further steps. One, to post our proposed price for this drug publicly and get public comments. And then we can refer this drug to [name of state agency]" **State No.4**

The interviewee also described a recent case where the prospect of a referral to the second state agency was used as leverage to resume negotiations with an otherwise reluctant manufacturer.

> "..we sent a letter that gave a 30-day countdown to the manufacturer that, basically we said, okay we believe the negotiations have failed. If you do not come to our terms we will forward this [negotiations] to [name of other agency]. We sent the letter twice and that worked…we got what we wanted." **State No.4**

2. Engage a data partner to support analysis of patient outcomes

Because Medicaid programs primarily use Medicaid claims data to monitor patient outcomes in the VBA, data collection costs are relatively low because much of the infrastructure is already in place. One key question included in the study is who pays for data analysis. Based on these four interviews, the burden and cost of data analysis has typically been the Medicaid program's responsibility. Accurate and timely assessment of drug's performance is critical, given that the results from these outcome metrics determine whether or not the program receives additional rebates. One interviewee indicated that having a data partner to conduct these analyses contributed to successful implementation of their Medicaid VBAs.

> " …the biggest benefit we have, I think, is having the college that already has our claims in their normal daily work. I talked to a lot of states that have an interest, but they don't have the resources. They don't have that type of relationship. They would have to hire somebody to do the data work. So, if

> they couldn't get the manufacturer to pay for the data analysis, then the state would have to. And that's an additional investment that you would have to build into your agreement. So, you're going to ask the manufacturer for even more potential rebate dollars just to kind of cover that cost as well..” **State No.3**

3. Preparedness to pursue a VBA with a manufacturer

One interviewee observed that assessing the state’s risk readiness to implement a VBA for the Medicaid program contributed to successful implementation of their VBAs. This was done via internal data analysis to determine which drugs to pursue for a VBA, the market in which the drug exists in, and the potential patient population eligible to use the drug.

> “.., we have allocated resources to do this stuff [VBA design]. ... Which drugs to pursue? So we do the regular reviews of the drugs already on the market as well as drugs now coming to the market. For the VBA perspective, it needs to make sense clinically, it needs to make sense financially. for example, do we have anyone with a diagnosis of very rare disease?… does it occur maybe in 500 people in the entire United States with this disease? So I like to know where they are and know whether they want use this drug.” **State No.4**

4. *Input from experts during the VBA design*

From these interviews, some states have had external support from experts at a university in the VBA design phase. Another Medicaid program has received additional funds to support internal data analysis to determine readiness to pursue for a VBA. Three interviewees discussed the importance of input by health economists or outcome researchers when you're designing the VBA.

Two of these interviewees identified a team at Oregon Health Sciences University (through a grant-funded initiative) that facilitated discussions with states interested in VBA models. This team held multiple sessions with state Medicaid programs, where

they discussed different model options available and potential disease states for these models. Participants were asked if they thought that those experts helpful.

> "…State No.1 participated in that exercise [by Oregon Health Sciences University - OHSU] and we went through many different payment model options, that they presented and we kind of chose, we went through and looked at several disease states. …." **State No.1**
> "We thought it was very valuable, yes. Could we have done it without it? Yes. But I think it just really gave us a better understanding of kind of what you're up against. So, I thought it was extremely helpful." **State No.1**

> "So they [OHSU] helped lead those internal discussions that we had within our department and helped with the development of our contract template. And helped us identify the drugs that we wanted to prioritize…." **State No.2**

Future of State Medicaid VBAs

Overall, all four interviewees expect that there will be an increase in activity around VBAs in Medicaid over the next five years or so. Reasons for this increase include 1) Recent federal guidance on VBAs, which allow Medicaid programs to leverage VBAs in the commercial market; 2) Continued interest from manufacturers.

> ".. CMS just put out some guidelines or guidance on commercial value-based purchasing agreements and they then apply to the Medicaid program for the state, where that plan is. So as the commercial programs start to enter into more of them, it's possible that we'll see more traction in the Medicaid space" **State No.1**

> "…we're starting to receive a few more proposals. So we have the two contracts in place, but we are working with three drug manufacturers for additional ones, we are reviewing their proposals…. Most of them seem to be for orphan drugs,." **State No.2**

Interviewees identified the following drug classes or disease areas as potential candidates for future Medicaid VBAs with manufacturers: insulins, gene therapies for rare disease (e.g., sickle cell disease), genetic disorders (e.g., hemophilia, thalassemia).

> "If I had to pick another drug class right now, for this particular model, I would choose insulin." **State No.1**

> "They've got it [Bluebird Bio], for commercial plans, and we've been in talks with them. They are coming out to the market with their product, Zynteglo ... and with a type of value-based agreement tied to it. …. especially with the new products coming out in the next year for hemophilia A, B, sickle cell...." **State No.3**

> "The talks are still going on and the manufacturers now are in the high-cost specialty products, gene therapies, things like that. All of those manufacturers are considering some type of agreement." **State No.4**

Medicaid VBAs continue to gain traction as Medicaid programs acquire experience with the concepts. Despite this positive outlook, all four interviewees expressed concerns about the very high launch prices of new drugs as they enter the market.

> "..So I feel that that's how drug prices are starting to increase with this value-based, … we have to have value-based contracts, but they also have to be affordable and sustainable." **State No.1**

> "…. the solution would be for these drugs to cost less in the first place and for drug prices to be set based on the value at the outset, without making states enter into these novel payment arrangements and tracking data and outcomes. And so while I'm glad that this was an option and that State No.2 took advantage of it, it's not a solution to managing for cost in the long term." **State No.2**

One interviewee observed that information asymmetry on a drug's price often prevents manufacturers and Medicaid programs from reaching mutually beneficial agreements around VBAs, and the manufacturer is able to take advantage of Medicaid programs. As it stands today, Medicaid programs do not have access to the same information as drug manufacturers when negotiating contracts and that breeds distrust, making the negotiating process far more arduous than it needs to be**.**

> "People talk about this is what will solve the increasing drug prices. It won't solve the growing drug price problem. VBA is not the way to solve it. It's because of the information asymmetry between manufacturers and everyone else. Because they know their product price so they know they will only agree to the contract which are incremental. the price unilaterally…" **State No.4**

What more could be done to further increase longer-term VBA activity in the Medicaid program? Interviewees suggested additional federal support: 1) for states to develop contracts and negotiate with manufacturers, and 2) to compel manufacturers to negotiate with Medicaid programs.

> "The states would need support. They either have the knowledge and the staff and the skillset to do it, or they don't. So every state is different. So it would almost be nice if there was like a national, if we could have like a national group negotiate on behalf of all states for their Medicaid programs, what these might look like." **State No.1**

> "I think that some additional support for states that have.... And so that's a lot of resources that the state has to provide to administer these contracts. And it would be great if we had more federal support in just the administration." **State No.2**

> "And so it would be great if CMS could somehow compel these drug manufacturers really to work with Medicaid programs and other healthcare payers into negotiate in good faith." **State No.2**

Discussion

In response to rising prescription drug costs, value-based arrangements (VBAs) have emerged as a mechanism for transforming how Medicaid programs pay for high-cost therapies. VBAs aim to promote greater patient access to effective, but often costly, medications by linking reimbursement, coverage, or payment to a clinical or utilization outcome or set of outcomes (Dworkowitz et al., 2019). Despite this increasing interest, only a few Medicaid programs have approached manufacturers to engage in these types of agreements, and therefore, relatively little is known about the extent to which VBAs are being pursued and implemented by Medicaid programs. This study aimed to better understand VBAs implemented by Medicaid programs,

with a particular focus on gaining insights into their negotiation, operationalization, and impeding or success factors from the perspectives of Medicaid officials.

Interest in Medicaid VBAs grows, but little information on implementation

Interest in the concept of risk sharing for prescription drugs in Medicaid has been strong, as is evident from the large number of articles and conferences dedicated to the idea (Dolan & Tian, 2020; Dubois & Westrich, 2019; Hwang et al., 2017; NASHP, 2021). However, as of September, 2022, only 15 states have submitted and received CMS approval to implement a prescription drug VBA with manufacturers for the Medicaid program (Medicaid.gov, 2022a). Further, based on public sources, 9 of these 13 state Medicaid programs have entered into VBAs with drug manufacturers (Dworkowitz et al., 2019; NASHP, 2021). Officials from four of these nine states were interviewed for this study.

Medicaid officials included in this study have had over spent on average, seven years designing and implementing a total of 20 VBAs (14 currently ongoing). Variation in the number of contracts reported by each state Medicaid program was observed—of the 14 currently active VBAs, 7 are implemented by one state (State No.4). This variation suggests that some states may have more success than others in navigating the complexities of designing and implementing these arrangements. Also, gaining information on the status and performance of these VBAs is challenging, because, as discussed by the interviewees, little formal evaluation has occurred and because details of these agreements are not be in the public domain. Making public more content and terms in these VBA contracts and findings from patient outcomes can be beneficial, allowing a manufacturer to gesture to the public that they stand by

their ‘product’, that value is an important issue for them, that they are engaged in addressing drug prices, and that they have credibility and enough experience to advance VBA discussion and policies.

VBA Design and Negotiation Process

While VBAs may help to reduce the impact of initial high drug price, published literature also documents that their adoption has remained low due to challenges during the contracting and executing stage (Hou & Neely, 2018). State Medicaid programs interviewed highlighted the lack leverage to compel manufacturers to negotiate for additional rebates, and therefore may not be able to pursue and negotiate effectively with manufacturers for desired VBAs, particularly when the drug of interest does not have competition on the market.

CMS’ Final Rule issued on December 31, 2020 (Final Rule) allows Medicaid programs to leverage VBAs in the commercial market (CMS, 2022). Specifically, as stated in the regulation, “When a manufacturer offers a VBP arrangement on the commercial market, the final rule requires that the manufacturer offer that arrangement to all states (see 42 CFR § 447.505(a) best price defined) in order to opt to report multiple best prices associated with the VBP arrangement.” Although Medicaid programs can only make “minor adjustments to the arrangement”, states will not need to develop new VBA models, but rather direct resources to adapting already developed models to address the specific needs of the Medicaid program.

This Final rule also addresses prior concerns from manufacturers related to Medicaid best price requirements, where the manufacturer would have had to offer the same supplemental rebate to all states, regardless of whether the state had an

existing VBA with the manufacturer. To overcome this concern, this Final Rule allows manufacturers to report multiple best prices for VBAs, so long as the manufacturer makes the VBA available to state Medicaid programs. When a manufacturer enters into a VBA with a commercial payer, it must report (i) a non-VBA price, which is the best price offered absent a VBA; and (ii) the multiple prices tied to the various outcomes of the VBA. States then have the option to participate in that VBA. When a state Medicaid program enters into the VBA, it would receive a best price rebate based on the patient's outcome. If a state elects not to enter into a VBA, the best price used in the Medicaid rebate formula would mirror the lowest price available absent the VBA.

Selecting and Monitoring Patient Outcomes

The availability of measurable patient outcome(s) easily identifiable and linked to a drug in Medicaid claims data was identified as a factor in determining whether to pursue a VBA with a manufacturer. This requirement to have simple methods (e.g., from claims data) of measuring treatment effects and clearly defined outcomes appears to be supported in the literature (Stanley et al., 2012). Measuring value of prescription drugs requires the availability of real-world evidence as the source of outcomes data (Jommi et al., 2020; Seeley et al., 2018; Yu et al., 2017).

Outcomes definition is the process to analyze intermediate or final results of a drug or treatment in terms of efficacy, safety and clinical validity (Steinbrenner, 2020). The success of a VBA is dependent on defining the appropriate and specific values of the prescription drug (Cohen, 2020; Jommi et al., 2020). Only certain types of outcomes may prove suitable for value assessment. Ideally, they should be

objective, clearly defined, reproducible, and difficult to manipulate (Garber & McClellan, 2007). They should be valid measures of the desired treatment effect and should not be confounded by patients' characteristics or other therapies (Garber & McClellan, 2007). Surrogate endpoints will not work well unless they are valid predictors of patient outcomes.

One of the challenges to implementation reported by state Medicaid officials is the disagreement between states and drug manufacturers about which outcomes should be included in the agreement to determine additional supplemental rebates. Value frameworks could help convert the identified value to price. In addition, value frameworks can consider complex issues of disease severity, equity, patient's perception which may impact societal views about a drug's value (Parmar et al., 2020; Seeley et al., 2018).

While some interview participants expressed a wish for electronic medical records, state Medicaid information systems remain underdeveloped in their ability to collect clinical outcomes as electronic medical records. As such, this still remains a goal rather than a potential reality in the near future. One potential solution is use of clinical information collected as part of the prior authorization process. One interview participant has used the prior authorization process to access clinical outcomes from use of a medication included in a VBA. Medicaid programs may require a prior authorization to ensure that a drug is medically necessary or alignment with evidence-based treatment guidelines before approval of coverage. This process requires submission of appropriate clinical information (e.g., diagnoses, results from diagnostic or laboratory tests) or attestation from the prescriber (Forrester, 2020).

Clinical outcomes submitted as part of the prior authorization process can then be incorporated with claims data analysis to assess patient outcomes from use of drugs in the VBA.

Concerns with high Launch Prices Persist

While discussions from interviewees suggest that these VBAs may have slowed state spending growth, VBAs alone are not the solution to these high costs. Interview participants expressed concerns about the very high launch prices of new drugs as they enter the market. To compensate for the additional rebates that manufacturers may have to reimburse in the VBA contract, participants are concerned that manufacturers could inflate their drugs launch prices. While states continue to innovate with VBAs to address high costs of prescription drugs, Medicaid programs may need additional tools to address high launch prices.

Further Research

Future research could expand on this qualitative study to include more state Medicaid programs—those that have submitted a request and received approval for State Plan Amendment from CMS, as well as those that have yet to do so. Additional qualitative research with more states would further augment this study findings with understanding what does and does not work regarding design and implementation, which would be useful to those designing VBA programs.

There is also very limited published literature to inform what design and implementation features are associated with successful VBA programs. Features of interest may include VBA model (e.g., outcome-based vs volume-based), characteristic of drugs included in the VBA (indicated disease condition, type of

molecule), eligible Medicaid population (e.g., pediatric, older adults), type of outcomes, duration of VBA contract. Future studies should incorporate a broader sample of participants, and findings from these studies might also uncover new definitions of VBAs. The Medicaid prescription drug benefit is also undergoing changes. For example recent changes to the Medicaid Drug Rebate Program allows reimbursement for a medication to vary depending on its outcome in a particular patient or group (CMS, 2022). Congress is also considering "The Medicaid VBPs for Patients Act", which aims to decrease barriers to VBAs in Medicaid (H.R.7389, 2022). Other proposals call for CMS and state Medicaid programs to accelerate efforts to develop new reimbursement models, such as using installment approaches (NASEM, 2020). Future research could also explore how these policy efforts change how access to high-cost therapeutics are managed by Medicaid programs.

This paper is based on qualitative data and lacks empirical evaluation. Further research can be undertaken quantitative methods. For example, a Medicaid program may consider a VBA successful if a certain performance threshold is met and additional supplemental rebates are collected from manufacturer. Further research could also examine empirically if greater improvements in performance occurred with the VBA implementation as compared without the VBA (i.e., the comparison group). One study has shown that there are considerable differences between states in terms of Medicaid coverage for some gene therapies and how access is managed (Berry et al., 2022). Further research could examine whether these VBAs had an impact on Medicaid beneficiaries' access to these treatments.

Conclusion

A limitation of this study is the small sample size (only four states participated in the interviews), which may affect generalizability of these findings. To date, only nine of the 50 U.S states have developed VBA with manufacturers; it is possible that the low implementation of VBAs reflects issues with technical or administrative capacity, where states with VBAs have larger capacity. Medicaid officials from all nine states currently implementing VBAs were contacted; three did not respond to the recruitment e-mails and another two responded and declined to participate. However, the four states that participated in these interviews are considered leaders in innovating Medicaid VBAs with drug manufacturers. Given the limited public information, this study begins to fill this gap—interviews with a set of well-placed Medicaid officials actively implementing these models provided firsthand insights and experiences that were not apparent in the literature.

Although there are limited data about the components of current contracts (e.g., how much financial risk is involved, product and class specifications), VBAs will likely not be a singular solution for prescription drug cost containment. Instead, VBAs offer an opportunity for Medicaid programs to achieve higher value for dollars spent when implemented. As other states think about how VBAs fit into the larger effort by their Medicaid programs to use VBAs, it is important to consider lessons from prior or current VBAs and to set appropriate expectations for what VBAs can realistically achieve.

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