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Title: State Legislative Trends Related to Biomarker Testing

Running Title: Biomarker Testing State Legislations

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Precise:

Incorporation of comprehensive biomarker testing into clinical practice lags behind guideline recommendations with coverage policy differences across insurance health remaining as an important barrier.

Although recent legislation in Illinois, Louisiana, and California aim at improving access to biomarker testing, there remains variability between these laws in the population impacted,

cancer stage, and whether the coverage of testing is mandated, or the legislation only addresses prior authorization.

Abstract

Comprehensive biomarker testing has become the standard of care to inform the choice of the most appropriate targeted therapy for many patients with advanced cancer. Despite evidence demonstrating the need for comprehensive biomarker testing to enable the selection of appropriate targeted therapies and immunotherapy, incorporation of biomarker testing into clinical practice lags behind recommendations in NCCN guidelines. Coverage policy differences across insurance health plans have limited the accessibility of comprehensive biomarker testing largely to patients whose insurance covers the recommended testing or those who can pay for the testing, contributing to health disparities. Furthermore, even when insurance coverage exists for recommended biomarker testing, patients may incur burdensome out-of-pocket costs depending on their insurance plan benefits which may also create barriers to testing. Prior authorization for biomarker testing for some patients can add administrative burden and may delay testing and thus treatment if not carried out in a timely manner. Recently, three states (Illinois, Louisiana, and California) passed laws designed to improve access to biomarker testing at the state level. However, there is variability between these laws in terms of the population impacted, stage of cancer, and whether the coverage of testing is mandated, or the legislation only addresses prior authorization. Advocacy efforts by patient advocates, health care professionals, and professional societies are imperative at the state level to further improve coverage for and access to appropriate biomarker testing.

Keywords: Biomarker testing; Legislations; Insurance; Coverage; Prior authorization

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Introduction

The knowledge and practice of precision medicine in cancer have been progressing rapidly, with advances in targeted cancer therapies and immunotherapy that can prolong patient survival and quality of life in patients who harbor specific driver mutations or markers predictive of response to immunotherapy identified through comprehensive biomarker testing (CBT).[1-4] Eligibility for treatment with these novel therapies requires CBT to determine if the patient is a candidate for a specific treatment. Failure to determine candidacy through CBT can mean a missed opportunity for the patient to receive more effective targeted treatment and results in either mistreatment with a less effective therapy (e.g., they never discover actionable mutations that would allow them to receive the most appropriate therapy), or delayed treatment in case of a failed response to initial less effective therapy and a later switch to the more effective targeted therapy. Conversely, immunotherapy may not be effective in patients with lung cancer and an *EGFR* mutation or *ALK* rearrangement. The presence of these two oncogenic drivers have been exclusion criteria for immunotherapy trials in patients with lung cancer.[5, 6] Indeed, consideration of CBT has become the standard of care for many cancers, with more to follow, and today CBT is often required to determine patient eligibility for clinical trials.[7] Further, a large proportion of driver mutations identified by CBT are actionable and can be treated with a US Food and Drug Administration (FDA)-approved agent. For example, 78% of mutations in patients who currently smoke and 47% of mutations in patients who have never smoked with lung adenocarcinoma were actionable.[8] Similarly, 54% of in Korean cancer patients were actionable.[9] These examples confirm the importance of CBT in appropriate patients prior to initiation of therapy.[10]

Currently, there are different approaches to test for genetic alterations that can potentially guide treatment. Multiple single gene assays, each of which identifies a single analyte, are

needed to select the appropriate targeted agent or immunotherapy; but if done in sequence, can result in significant delays in initiating either novel or conventional therapy depending on testing outcomes. In contrast, a next-generation sequencing (NGS) panel can identify multiple genetic alterations using a single test which identifies several to hundreds of genetic alterations.[11] There is increased clinical interest in incorporating NGS into clinical practice, with 75% of oncologists nationally reporting use of NGS testing in 2017, and 27% reporting incorporating NGS results into their treatment decisions.[12] However, significant variability exists between practice type, setting, and presence of institutional policy as well as the healthcare provider sub-specialization in the rate of CBT.[10, 13] Further, there is significant variation in the coordination of CBT between subspecialty services across institutions.[10]

Despite evidence demonstrating the effectiveness of CBT and targeted therapies or immunotherapy, incorporation of biomarkers into clinical practice is lagging behind recommendations in clinical guidelines. Currently, challenges to clinical adoption include inadequate or poor quality tissue specimens, delay in ordering the test, assay variability and inadequate analytic validation and delay in treatment due to long turnaround time to return results.[2, 7, 13] In addition to these testing challenges, financial and logistical factors including the need for prior authorization, high out-of-pocket costs and variability in insurance coverage can all pose significant barriers. In a 2022 landscape study of biomarker testing, the average allowed unit cost per test (i.e., negotiated rate between payers and providers before member cost sharing) for biomarker testing (single gene and panel tests) was $224 for commercial payers and $78.80 for Medicaid.[14] Between 2016-2019, the average allowed amount for NGS tests varied from $1,269 to $2,058 per test for all payes.[15] Between 2013-2015, the average commercial payer reimbursed amounts for single genes in patients with lung cancer ranged between $406 and

$1,127.[16] Using the average reimbursement of individual mutation tests, the total reimbursement for sequential testing comprising KRAS, EGFR, ALK, ROS1, and BRAF tests was $3,763 while the cost of NGS was $2,860.[16] In a 2020 American Cancer Society Cancer Action Network (ACS CAN) survey of 933 cancer patients, among the 44% who reported an out-of-pocket cost for biomarker testing, approximately a third paid over $500.[17] However, for patients whose insurance does not cover NGS, the out-of-pocket costs may exceed $10,000. The uncertainty of coverage policies and differences across insurance health plan can also limit access to CBT for patients.[18-20] In the 2020 ACS CAN survey, 29% of patients who discussed treatment plans with their providers decided to forgo biomarker testing because of its cost.[21] Finally, while biomarker testing for cancer targeted therapy in metastatic colorectal cancer and metastatic NSCLC is mostly cost-effective,[22, 23] a recent study showed use of upfront NGS testing in patients with metastatic NSCLC was associated with substantial cost savings and shorter time-to-test results compared to sequential testing of single analytes for both CMS and commercial payers.[24]

Studies show that currently only half of cancer patients in the U.S. for whom biomarker testing is recommended are receiving the tests.[25] Further, patients who are older, Black, and uninsured or Medicaid-insured patients are less likely to receive biomarker testing.[26-29] In another study, more than a quarter of patients who did not receive recommended biomarker testing reported it was because insurance was not covering the test at all and/or they would incur high out-of-pocket costs.[30] The existing racial, ethnic, and socioeconomic disparities in access to and utilization of guideline-indicated CBT and appropriate treatment with targeted therapies or immunotherapy contributes to disparities in patient outcomes.[27]

Insurance Coverage

Currently, commercial payers and Medicare typically cover the majority of oncology single analyte companion diagnostic biomarker tests when they meet the criteria for clinical utility by the Food and Drug Administration (FDA).[31] For biomarker tests that have not yet received FDA approval, additional materials for payer consideration includes clinical practice guidelines from entities such as the NCCN, American Society of Clinical Oncology (ASCO), Technology Assessment organizations, and peer-reviewed published evidence on clinical utility.[31]

Recently, there has been an increase in the number of large multi-gene NGS panels, which are offered by institutions and commercial providers and make more efficient use of tissue samples by providing more information compared to single gene tests. However, insurance coverage policies make it a challenge to cover the costs of the testing. The reimbursement for panel testing continues to lag substantially and may only cover single gene tests alone or in combination with multiple single gene tests that have established clinical utility. A recent analysis showed many commercial health plan coverage policies were more restrictive than clinical guidelines for multi-gene panel tests, with coverage varying among different states.[32] While multi-gene panels are also used to identify patients eligible for clinical trials, the mandate to cover routine costs of clinical trials does not extend this testing to the majority of payers aside from Medicare.[31] The main justifications for the lack of coverage are high costs and belief that the panels are for investigational purposes.[31] However, the precision treatments that result from this testing may be less costly and more effective than traditional treatments involving chemotherapy, or multiple sequenced rounds of traditional therapeutics before reaching the treatment most effective for an individual which could have been identified based on information

from a genomic change on an NGS panel or assessment of biomarkers associated with the efficacy of immunotherapy. For example, immunotherapy has been recently approved as a first-line treatment for patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer, with studies showing significantly longer progression free survival compared to standard chemotherapy regimens (5-fluorouracil–based therapy with or without bevacizumab or cetuximab).[33-35]

The Centers for Medicare & Medicaid Services (CMS) issued a national coverage determination for NGS[36] effective in March 2018 for patients with either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV somatic (acquired) cancers not previously tested using an FDA-approved or cleared NGS for an FDA-approved or -cleared indication. Subsequently, CMS approved NGS national coverage for patients with germline (inherited) cancers including breast or ovarian, who have not been tested before with the same germline test using NGS[36] in January 2020. The April 2022 CMS updated local coverage determination (LCD) for NGS comprehensive genomic profile testing for solid tumors [37] will improve access to comprehensive biomarker testing. The LCD is expected to facilitate comprehensive genomic profile testing, an NGS approach that uses a single assay to assess hundreds of genes including relevant cancer biomarkers, with evidentiary support for clinical utility in guidelines and clinical trials.[37] Although the 2018 and 2020 national coverage determinations subsequently affected private payer decisions to similarly cover NGS testing,[20, 38, 39] many payers who cover the testing negotiate payment only for those medically necessary biomarkers and not full NGS.[31] In contrast, Medicaid is not bound by either Medicare national coverage determinations or commercial payer policy, with coverage varying significantly state to state.[40]

In addition to variable coverage across insurance plans, there is also variability among payers regarding prior authorization specifications. While prior authorizations are intended to ensure medical necessity, these additional requirements can add administrative burden and may delay testing if not carried out in a timely manner. Additionally, the time required for labs to process tests can also delay the initiation of appropriate treatment. A recent survey of oncologists showed that clinical decision making for non-small cell lung carcinoma is influenced by the range of wait times for biomarker testing from the time of ordering to receipt of results with more experienced clinicians being more likely to defer treatment with non-targeted therapies while waiting for results, and most oncologists finding 2 weeks an acceptable wait time, but only 37% willing to wait longer.[13]

Recent State Biomarker Legislation

Three states (Illinois, Louisiana, and California) passed laws intended to improve access to CBT in 2021 and vary in design (Table 1). Given these laws take effect in 2022, it is not yet possible to assess their impact on CBT rates. Arizona, California, Massachusetts, New Hampshire, New York, Rhode Island, and Washington are considering additional bills this year that are designed to address barriers to CBT.

1) Coverage of Biomarker Testing – Illinois H.B. 1779

Effective January 1, 2022, Illinois House bill 1779 requires coverage of CBT under state-regulated insurance policies and managed care plans for the purposes of diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee's disease or condition when the test is supported by medical and scientific evidence (i.e., approved by FDA or being recognized by nationally-recognized medical guidelines).[41] The new law also improves access to CBT for Medicaid and state employee plans. This law is not limited to cancer patients, and requires

coverage of CBT for any medical condition when supported by medical and scientific evidence, including FDA-approved or deemed tests, Medicare coverage determinations and nationally recognized clinical practice guidelines.[42] The law is silent on the requirement for prior authorization; while testing must be covered, insurers may require prior authorization. Lastly, the law is silent on patients' financial responsibilities for biomarker testing, which therefore remain subject to annual deductibles, coinsurance and copayment provisions established under the health plan.

2) Coverage of Biomarker Testing - Louisiana S.B. 84

Effective January 1, 2022, Louisiana Senate bill 84 requires broad insurance coverage for genetic and molecular testing for cancer patients including but not limited to tumor mutation testing, NGS, hereditary germline mutation testing, pharmacogenomic testing, and CBT. Coverage applies to any state-regulated health plan and is subject to annual deductibles, coinsurance and copayment provisions established under the health plan. The coverage is also subject to applicable evidence-based medical necessity criteria under the plan[43] and does not specify the sources of evidence to determinate medical necessity. Further, the law remains silent on the requirement for prior authorization.

3) Prior Authorization for Biomarker Testing - California S.B. 535

Effective July 1, 2022, California Senate bill 535 prohibits state-regulated health insurance plans, including Medi-Cal managed care plans, from requiring prior authorization for CBT for an enrollee or insured individual with advanced or metastatic stage 3 or 4 cancer (initial diagnosis, progression or recurrence).[44] This law addresses prior authorization for plans that already cover CBT and does not mandate any other plan to cover CBT. It only applies to CBT for FDA-approved therapies, which could limit the impact of this legislation as testing is

necessary to then select the appropriate therapy. Therefore, if the choice of therapy is not determined at the time that the test is being ordered, the insurance plan can still require prior authorization or deny coverage. The provisions limiting application to advanced or metastatic cancer patients is also a barrier to widespread impact. Lastly, the law is silent on patients' financial responsibilities for biomarker testing, which therefore remain subject to annual deductibles, coinsurance and copayment provisions established under the health plan.

Implications and Future Directions

The current variability in coverage for CBT contributes to the widening of insurance disparity gap. While the CMS national coverage determination increased NGS testing for Medicare and subsequently commercially insured patients,[20, 39] those covered by Medicaid and patient assistance programs have slower growth rates of NGS testing.[38] There is substantial variability in NGS coverage because Medicaid coverage determined at the state level. Given differences in the racial and ethnic composition of the insured population (Black individuals account for 20% of Medicaid enrollees and approximately 10% of Medicare or commercial enrollees) the variability in coverage contributes to the increasing racial and ethnic disparity gaps among cancer patients.[38] Finally, even for health plans with current coverage of CBT, patients may incur out-of-pocket costs that are dependent on their insurance benefits, which can be a barrier to testing if the cost-sharing amount is not affordable or may result in sticker shock or surprise bills and subsequent financial burden if patient is not aware of the cost-sharing until after they receive their bill.

Cancer care is associated with substantial medical out-of-pocket costs, which together with lost productivity and changes in employment, income, and insurance, result in financial hardship that can adversely impact patients' health outcomes.[45-48] Additionally, the direct and

indirect costs of navigating a complex health care system can place a disproportionate burden on households with fewer socioeconomic resources, those who are uninsured or underinsured, or of racial/ethnic minorities who are at higher risk of financial hardship.[17, 49, 50] Therefore, inconsistencies in coverage for CBT, as well as the amount of cost-sharing is more likely to impact those already at a higher risk of financial hardship.

The recently passed and implemented laws in Illinois, Louisiana and California demonstrate momentum and interest from lawmakers in expanding access to CBT – and the importance of coordination among stakeholders and policymakers to ensure legislation does indeed expand access to appropriate testing. However, barriers not addressed by assuring coverage may also contribute to persistent disparities in NGS testing among different geographic and socioeconomic groups. Following the national coverage determination in 2018, there was an increase in NGS testing among all racial and ethnic groups across all insurance types with estimates of proportion of patients tested across all covariates increasing from 3.5% to 16.6% prior to national determination coverage to 10.3% to 44.6% following it.[38] However, testing rates in the Black and Hispanic/Latino groups were lower than the White group during both pre- and post-national coverage determination periods regardless of insurance type suggesting a persistent racial/ethnic disparity gap.[38]

In summary, the studies thus far have demonstrated that variability in insurance coverage for CBT contributes to the widening of racial and ethnic disparity gaps in testing rates. Public policy measures need to be identified and deployed to bring appropriate biomarker testing to guide precision therapy to cancer patients for whom it is medically appropriate and to ameliorate the socioeconomic and ethnic barriers. The Medicare national coverage determination in 2018 was an important first step in this direction, by increasing NGS testing for Medicare enrollees

with subsequent adoption by many commercially insured plans. The proposed CMS LCD for comprehensive genomic profile testing effective since April 1, 2022, is an additional step towards CBT. However, Medicaid and other state-regulated plans remain unaddressed. The examples of the 3 states that recently passed laws designed to improve access to CBT point out opportunities which may guide other states contemplating legislation to expand access to CBT. Specifically, legislation requiring insurance coverage for all disease types and stages may be most beneficial to the patients. Coordinated advocacy efforts by all stakeholders are needed to further improve coverage across all states and health insurance plans. Providers, patient advocates, and professional societies have a valuable role to play – not only in advocating for legislative changes, but also in understanding these policy changes and ensuring their patients benefit from new legislations.

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Table 1. Characteristics of 2021 State Biomarker Legislations.

	California SB 535	Illinois HB 1779	Louisiana SB 84
Requires insurance plans cover biomarker testing	No	Yes (When supported by medical evidence) *	Yes (When it meets the insurers' medical necessity criteria)
Applies to all cancer patients	No	Yes	Yes
Disease agnostic	No	Yes	No
Addresses prior authorization	Yes (i.e., prohibits prior authorization for stage 3 or 4 cancer)	No	No
Addresses cost sharing	No (i.e., coverage is subject to annual deductible, coinsurance and co-payment provisions of health coverage plan)		

* FDA-approved test or indicated test for an FDA-approved drug, CMS national coverage determination, nationally recognized clinical practice guidelines, consensus statement, professional society recommendations, or peer-reviewed literature