Resource
Genetic Biomarker Testing and Prior Authorization

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GENETIC BIOMARKER TESTING AND PRIOR AUTHORIZATION

In the spring of 2020, CHBRP began compiling information on genetic biomarker testing and prior authorization for Californians enrolled in state-regulated health insurance plans or policies that have metastatic or advanced stage 3 or 4 cancer. This research was done in response to the Legislature's request to analyze AB 2640 (Gonzalez): Genetic biomarker testing. The introduced legislation was withdrawn from consideration before CHBRP completed its full analysis.

CHBRP has compiled this resource for policymakers to use when considering future legislation related to the topic. This resource includes background information on genetic biomarker testing for Californians with advanced cancer, and, where possible, the presence and impact of prior authorization on such testing.

Background

This section of the brief provides background information on genetic biomarker testing as it is used to treat patients with metastatic or advanced stage 3 or 4 cancer.

Cancer Prevalence in California

In 2019, 186,920 Californians were newly diagnosed with cancer, a set of diseases characterized by abnormal cell growth (ACS, 2019). The rate of cancer cases per 100,000 people has decreased over the past 30 years. In 2016, the rate of cancer diagnosis was 381 cases per 100,000 people, down from about 451 in 1988 when statewide cancer reporting began (CDPH, 2019).

The ten most common types of cancer among California males and females accounted for 77.8 percent of all new diagnoses, and 74.4 percent of all cancer related deaths (CDPH, 2019). The most common types of cancer among California males and females is described in Table 1 below.

Table 1. Ten most common types of cancer among California males and females, 2016

Females	*Males*
Breast	*Prostate*
Lung and bronchus	*Lung and bronchus*
Colon and rectum	*Colon and rectum*
Corpus and uterus NOS	*Melanoma of the skin*
Thyroid	*Urinary bladder*
Melanoma of the skin	*Non-Hodgkin lymphoma*
Non-Hodgkin lymphoma	*Kidney and renal pelvis*
Ovary	*Oral cavity and pharynx*
Pancreas	*Leukemia*
Kidney and renal pelvis	*Liver and intrahepatic bile duct*

Source: California Health Benefits Review Program, 2020. Adapted from CDPH, 2019.

Metastatic and Advanced Stage 3 or 4 Cancer

The assignment of cancer "stages," or "staging," is a process by which medical providers determine the extent of cancer growth in the body (NCCN, 2020). Most often, physicians use the TNM staging system developed and maintained by the American Joint Committee on Cancer and Union for International Cancer Control. The letters describe different aspects of cancer growth. The TNM system is used for the majority of cancers, but not for all of them; one common exception to the TNM staging system is Hodgkin lymphoma (NCCN, 2020).

In the TNM staging system, the "T" denotes the extent of the primary tumor, or first mass of cancer cells in the body. The N refers to lymph nodes and denotes the extent of cancer in those nodes that are close to the origin of the cancer. "M" refers to "metastatis," or spread to distant sites in the body. TNM values, if used, are then combined to assign an overall stage to the cancer (ACS, 2015). Stage groups are determined based on where the cancer has grown and spread, and patients in the same stage group tend to have similar prognoses (NCCN, 2020).

Stage 3 cancer generally denotes that the cancer is larger than lower stages (stages 0-2), and has possibly spread to surrounding tissues and/or lymph nodes. Stage 4 cancer denotes that cancer has spread from its origin to at least one other organ (also known as "secondary" or "metastatic" cancer) (NHS, 2018).

The overall prevalence of metastatic or stage 3 or 4 cancer is unknown.

Genetic Biomarker Testing

Genetic biomarker testing exemplifies the shift towards "personalized medicine," which tailors individuals' prevention, diagnosis, and treatment according to their genetic profile (NIH, 2020). Genetic biomarker testing is used in clinical care to tailor treatment.

For instance, it can be used to identify which individuals are likely to respond positively to certain prescription medications (Jorgensen, 2009). Conversely, it can identify individuals at risk of having a toxic response to a prescription medication to minimize drug-related adverse events and associated costs, such as hospitalizations (Armstrong, 2012). Genetic biomarker tests are also commonly referred to as "single gene tests" because they test for the presence or absence of specific molecular markers than can predict how a person will respond to a particular medication.

Biomarkers, which can be found in blood, other bodily fluids, or tissue, can help detect or diagnose cancer, assess prognosis, guide anticancer therapies or understand recurrence (Tainsky, 2009). Because AB 2640 would have pertained to health insurance enrollees with metastatic or stage 3 or 4 cancer, CHBRP has focused this resource on biomarker testing as a means to treat active cancer in a patient.

There is consensus among clinical guidelines about the cancers for which genetic biomarker tests should be performed. Results from these tests are then used to inform cancer treatment recommendations. In addition to single gene tests, multi-gene testing is also available, but clinical guidelines regarding multi-gene tests are much more varied.

Disparities[1] and Social Determinants of Health[2] in Genetic Biomarker Testing

Disparities are differences between groups that are modifiable. CHBRP relies on the following definition of "health disparity': Health disparity is defined as the differences, whether unjust or not, in health status

[1]

[2] CHBRP defines social determinants of health as conditions in which people are born, grow, live, work, learn, and age. These social determinants of health (economic factors, social factors, education, physical environment) are shaped by the distribution of money, power, and resources and impacted by policy (adapted from: (CDC, 2014;

or outcomes within a population. (Wyatt et al., 2016). CHBRP found literature identifying disparities in genetic testing by race and ethnicity.[3]

Lynch et al. (2018) found discrepancies in testing for mutations in the epidermal growth factor receptor (EGFR) gene, the testing of which is indicated for all newly-diagnosed patients with metastatic lung cancer. Hispanic and Black people were less likely to be tested than white people and Asian/Pacific Islanders. This happened even as overall testing rates increased from 2011 to 2013 (by 19.7%).

Clinical Guidelines for Genetic Biomarker Testing

Table 2 summarizes current guidelines for clinically recommended biomarker tests for metastatic cancers and the targeted biologic medications which, depending on testing results, may be used to treat them. **Table 3** summarizes recommendations and guidelines for multigene testing in advanced metastatic cancers.

Table 2. Clinically Recommended Biomarker Tests for Metastatic Cancers

Biomarker	Condition(s)	Drug(s)	References
ALK	Metastatic non-small cell lung cancer	Crizotinib	(NCCN, 2017; NCCN, 2018)
BRAF	Metastatic non-small cell lung cancer, metastatic melanoma, metastatic colorectal cancer	Dabrafenib, encorafenib, trametinib, vemurafenib	(ASCO, 2018; ESMO, 2015; ESMO, 2019; NCCN, 2018; NICE, 2020)
EGFR	Metastatic non-small cell lung cancer	Afatinib, erlotinib	(NCCN, 2017; NICE, 2013)
HER2	Metastatic breast cancer, advanced/metastatic gastroesophaeal adenocarcinoma	Ado-trastuzumab emtansine, lapatinib, trastuzumab, pertuzumab	(ASCO, 2013; ASCO, 2017a)
KRAS	Metastatic colorectal cancer	Cetuximab, panitumumab	(ASCO, 2017b; NICE, 2020)
ROS1	Metastatic non-small cell lung cancer	Crizotinib, entrectnib	(NCCN, 2018; NCCN, 2019; Sequist and Neal, 2020)

Source: California Health Benefits Review Program, 2020.

Healthy People 2020, 2019)). See CHBRP's SDoH white paper for further information: http://chbrp.com/analysis_methodology/public_health_impact_analysis.php.

[3] CHBRP identified several studies that found that African American women are less likely to be tested for the BRCA 1 and BRCA 2 gene mutations, but because those mutations are identified to determine the likelihood that a person may develop cancer, and not to treat cancer once it's already been identified, those studies have been excluded from discussion.

Table 3. Recommendations and Guidelines for Multigene Testing in Advanced or Metastatic Cancers

Number of Genes	Criteria	References
Testing of 5 to 50 genes	Genes must be clinically relevant and cited in the label of an FDA-approved companion diagnostic. The test should not be more expensive than the cost of individual testing.	(CMTP, 2015)
Testing of 50 or more genes	Stage IV non-small cell lung cancer, rare or stage IV solid tumors (e.g., lung and pancreatic cancers), cancers that are unresponsive to treatment or exhausted other treatment options	(CMTP, 2015)
Number of genes unspecified	Genetically heterogeneous disorders and oncology applications, circumstances requiring evaluation of multiple high-penetrance genes of established clinical utility or association with cancer risks and mutations, or identifying rare driver mutations for which effective drugs may be available	(ACMG, 2013; ASCO, 2015; CMTP, 2015; NCCN, 2017)

Source: California Health Benefits Review Program, 2020.

Public and Private Coverage for Genetic Biomarker Tests for Cancer

Previous research has found that coverage for both single gene and multi-gene testing varies substantially across private health insurance plans and policies, and that there are discrepancies between coverage policies and clinical guidelines for such tests (Lu et al., 2018). Lu et al. also found that prior authorization was present in coverage for genetic biomarker tests for eight of the ten private insurance payers that they studied (Lu et al., 2018).

Prior Authorization

Prior authorization is a utilization management tool commonly used by health insurance carriers to ensure that a given medical intervention meets the insurance plan or policy's criteria for coverage (Newcomer et al., 2017). Prior authorization developed as a tool for insurers to assess the appropriateness of treatment that would result in a hospital admission or a high-cost procedure (Resneck, 2020). For California laws related to prior authorization, please see the *Policy Context* section of this resource.

Policy Context

CHBRP is not aware of any California law or regulations related to genetic biomarker testing. CHBRP is aware of requirements for state-regulated health insurance plans and policies to cover "all generally

medically accepted cancer screening tests." These tests must take place *before* cancer diagnosis, and thus are unrelated to genetic biomarker testing for enrollees with metastatic or advanced stage 3 or 4 cancer.

Under California law, if prior authorization is required for non-emergency medical services for an enrollee in a CDI-regulated health insurance policy, preauthorization must be given immediately, but no more than five calendar days after the request for preauthorization.[4] When an enrollee's condition is such that they face an imminent and serious threat to their health, an insurer must make a prior authorization determination within 72 hours of a request.[5]

Impact of Prior Authorization

The sections below summarize the research CHBRP examined of the impact of prior authorization on processes of care and health outcomes.

Processes of Care (e.g. timeliness of testing and timeliness of receipt of treatment)

CHBRP did not identify any studies on the impact of prior authorization for genetic biomarker testing on processes of care, such as timeliness of testing and timeliness of receipt of cancer treatment. One study was identified that examined the impact of prior authorization for *breast cancer medications* on the process of care at a breast cancer oncology clinic (Agarwal et al., 2017). The researchers tracked prior authorization approval rates and time to approval for various specialty breast cancer medications. They found that the majority of prior authorizations (97.5%) were approved on the first prior authorization request after an average time of 0.82 days (range = 0 to 14 days). The most common medication type requiring prior authorization was targeted therapy, which made up 28.1% of the prior authorizations examined. However, the researchers found that differences in drug indication (i.e., reason for prescribing the drug) did not have a statistically significant impact on approval time. Additionally, the researchers noted that while their study took place at a clinic in an academic center with a more centralized prior authorization process, the prior authorization process is often more convoluted in most practices, which is likely to result in further delays. However, given that this study is about prior authorization requirements for medications, the results may not be generalizable to prior authorization for genetic biomarker testing.

CHBRP also did not identify any literature related to delayed cancer treatment as a result of prior authorization for genetic biomarker testing. Lack of evidence is not evidence of a lack of effect. Instead, it indicates that the effect of prior authorization on timeliness of cancer treatment is unknown. If prior authorization were to delay testing, it might lead to delays in obtaining test results which could delay treatment. Lim et al. (2015) found that delays in obtaining test results delayed treatment decisions and initiation for patients with advanced non-small cell lung cancer.

Summary of findings regarding the impact of prior authorization on process of care: There is insufficient evidence that prior authorization for genetic biomarker testing impacts the process of care for individuals with metastatic or advanced stage 3 or 4 cancer. No studies were identified that examined the impact of prior authorization for genetic biomarker testing on processes of care, such as delayed testing, probability of receipt of targeted therapy for those who would benefit from it, or timeliness of receipt of targeted therapy.

[4] California Insurance Code 2695.11.
[5] California Insurance Code 10123.135(h)(2).

Figure 1. Impact of Prior Authorization for Genetic Biomarker Testing on Processes of Care

Health Outcomes

CHBRP did not identify any studies of the impact of prior authorization for genetic biomarker testing on the health outcomes of people with advanced stage 3 or 4 cancer.

Summary of findings regarding the impact of prior authorization on health outcomes: There is insufficient evidence that prior authorization for genetic biomarker testing impacts cancer outcomes for individuals with metastatic or advanced stage 3 or 4 cancer. No studies were identified that examined the impact of prior authorization for genetic biomarker testing's impacts on remission rates, incidence of death, or survival rates.

Figure 2. Impact of Prior Authorization for Genetic Biomarker Testing on Health Outcomes

Conclusion

Genetic biomarker testing is an emerging tool to use in the treatment of advanced cancer. There is currently a lack of evidence about the impact of utilization management tools such as prior authorization on the timeliness of testing and treatment, as well as their impact on health outcomes. This lack of research presents a challenge to payers who offer health insurance coverage for such testing, and for policymakers who wish to impact the terms of health insurance coverage of genetic biomarker tests.

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ABOUT CHBRP

The California Health Benefits Review Program (CHBRP) was established in 2002. As per its authorizing statute, CHBRP provides the California Legislature with independent analysis of the medical, financial, and public health impacts of proposed health insurance benefit-related legislation. The state funds CHBRP through an annual assessment on health plans and insurers in California.

An analytic staff based at the University of California, Berkeley, supports a task force of faculty and research staff from multiple University of California campuses to complete each CHBRP analysis. A strict conflict-of-interest policy ensures that the analyses are undertaken without bias. A certified, independent actuary helps to estimate the financial impact. Content experts with comprehensive subject-matter expertise are consulted to provide essential background and input on the analytic approach for each report. Detailed information on CHBRP's analysis methodology, authorizing statute, as well as all CHBRP reports and other publications are available at http://www.chbrp.org/

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CHBRP assumes full responsibility for the report and the accuracy of its contents. All CHBRP bill analyses and other publications are available at www.chbrp.org.

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