California Health Benefits Review Program

Analysis of California Senate Bill 221
HIV Associated Lipodystrophy

A Report to the 2017–2018 California State Legislature April 3, 2017

CALIFORNIA
HEALTH BENEFITS REVIEW PROGRAM

Key Findings:

Analysis of California Senate Bill 221 HIV Associated Lipodystrophy

Summary to the 2017–2018 California State Legislature, April 3, 2017

CALIFORNIA HEALTH BENEFITS REVIEW PROGRAM

AT A GLANCE

The version of California Senate Bill 221 analyzed by CHBRP would require coverage for treatments related to HIV associated lipodystrophy. In 2018, 24 million enrollees in plans or policies regulated by DMHC or CDI will have health insurance that would be subject to SB 221

1. **Benefit coverage.** Postmandate, 5% of these enrollees would gain mandate-compliant benefit coverage.
2. **Utilization.** Postmandate, the number of enrollees using one or more treatments is expected to rise from 385 to 400.
3. **Expenditures.** Premiums and enrollee expenses for covered benefits (cost-sharing, deductibles, etc.) would be increase by $115,000 (0.0001%).
4. **Medical effectiveness.** A number of treatments provide short-term relief. However, their long-term effectiveness varies across treatments
5. **Public health.** New users may experience some short-term improvements in health and quality of life, but it is unclear whether these improvements will last or fade.
6. **Long-term impacts.** As the prevalence of HIV associated lipodystrophy is likely to continue to decline, the utilization, expenditure, and health outcome impacts projected for the first year after implementation are also expected to decrease.
7. **Medi-Cal** – in addition to impacting the health insurance of the 7.8 million Med-Cal beneficiaries enrolled in a DMHC-regulated plans (impacts included in the bullets above), SB 221 may similarly affect the health insurance of the additional 3.0 million Californians associated with either the Medi-Cal FFS program or COHS managed care.

BACKGROUND

Lipodystrophy associated with human immunodeficiency virus (HIV)[1] describes abnormal changes in body fat. It may involve either or both:

- Lipoatrophy — abnormal fat loss in the face, limbs, and buttocks. Facial lipoatrophy is the most common presentation. Lipoatrophy is distinct from HIV-related wasting, which is a general loss of fat and lean muscle tissue.

- Lipohypertrophy — abnormal fat deposition in the abdomen, breasts (in both men and women), upper back and shoulders (“buffalo hump”), and around the neck (“horse collar”).

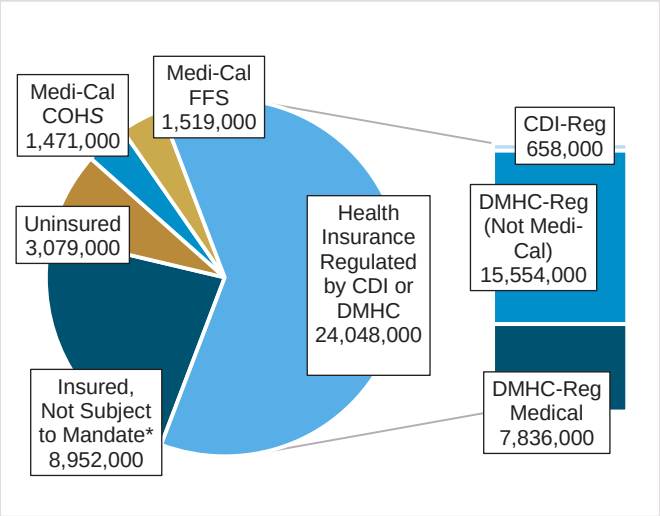
Some early antiretroviral therapy (ART) drugs — which have not been recommended or commonly used in California since 2003 — are strongly correlated with HIV associated lipodystrophy. The condition has declined along with use of those early ART drugs. CHBRP estimates current prevalence of HIV associated lipodystrophy among the HIV+ enrollees to be less than 1%.

BILL SUMMARY

SB 221 would require plans and policies regulated by either the California Department of Managed Health Care (DMHC) or the California Department of Insurance (CDI) to cover treatments (medical and drug) to correct, repair, or ameliorate effects of HIV associated lipodystrophy. In 2018, approximately 24 million Californians will be enrolled in or policies or plans regulated by CDI or DMHC (including 7.8 million Medi-Cal beneficiaries).

[1] Refer to CHBRP’s full report for full citations and references.

Figure 1. Health Insurance in CA and SB 221



Source: CHBRP 2017
Notes: *Medicare beneficiaries, enrollees in self-insured products, etc.

Although the bill language is unclear, CHBRP has assumed for this analysis that SB 221 would not prohibit generally applicable utilization management techniques, including application of medical necessity criteria, requiring prior authorization, or exclusion from coverage of treatments deemed to be experimental or investigational.

IMPACTS

Medical Effectiveness

SB 221 would require coverage for drug and medical/surgical treatments.

CHBRP's medical effectiveness analysis included several medical/surgical l treatments. CHBRP found:

- A *preponderance* of evidence that fillers increase facial fat (i.e., reduce the visible effects of facial lipoatrophy) and limited evidence that their effects persist for 2 to 5 years;
- *Limited* evidence that autologous fat transplantation increases facial fat, but *insufficient* evidence to determine how long the effect persists; and
- *Insufficient* evidence to determine whether fillers improve outcomes for persons with HIV associated buttock lipoatrophy.
- *Insufficient* evidence to determine whether liposuction affects outcomes for persons with breast hypertrophy or gynecomastia.
- *Insufficient* evidence to determine whether lipectomy or deoxycholic acid injections improve outcomes for persons with the form of lipohypertrophy referred to as "buffalo hump."

CHBRP's medical effectiveness analysis included several drug treatments. CHBRP found:

- A *preponderance* of evidence that switching ART to exclude stavudine or zidovudine, two drugs that are no longer routinely prescribed in California, increases facial and limb fat.
- A *preponderance* of evidence that metformin reduces body mass index and waist-to-hip ratio, but may increase the likelihood of lipoatrophy;
- A *preponderance* of evidence that tesamorelin (Egrifta) reduces abdominal visceral fat, preserves abdominal subcutaneous fat, and increases lean body mass but insufficient evidence of benefits and risks associated with long-term treatment.
- A *preponderance* of evidence that growth hormone reduces visceral fat. However, there is *conflicting* evidence as to whether effects persist after treatment ends. Using growth hormone is associated with increased risk of developing diabetes.

Benefit Coverage, Utilization, and Cost

The analysis considers SB 221's aggregate impacts on the medical/surgical and drug treatments most likely to be impacted by changes in benefit coverage.

Benefit Coverage

Postmandate, the percentage of enrollees with benefit coverage fully compliant with SB 221 would rise from 95% to 100%.

Utilization

Postmandate, among the 24 million enrollees in DMHC-regulated plans and CDI-regulated policies, CHBRP estimates that an additional 15 (and so a total of 400)

enrollees would use of treatments for HIV associated lipodystrophy.

Expenditures

Postmandate, as a result of the changed benefit coverage among the 24 million enrollees in DMHC-regulated plans and CDI-regulated policies, premium expenditures would increase by $115,000 (0.0001%).

As would be expected, some enrollees using newly compliant benefit coverage would incur some cost sharing, Although enrollees with newly compliant benefit coverage may have paid for some treatments during the baseline period, CHBRP cannot estimate the frequency with which such situations may have occurred and so cannot estimate the total expense for such situations. Postmandate, such expenses would be gone, though enrollees with newly compliant benefit coverage might, postmandate, pay for some treatments for which coverage is denied (e.g., through utilization management review). Some enrollees who always had compliant benefit coverage might also pay for some treatments. Again, CHBRP cannot estimate the frequency of such situations.

Medi-Cal

To the extent permitted by federal law, SB 221 would require the same benefit coverage for all Medi-Cal beneficiaries, including those with health insurance through County Organized Health System (COHS) managed care and those associated with the fee-for-service (FFS) program. Therefore, in addition to the Medi-Cal beneficiaries enrolled in DMHC-regulated plans, SB 221 could affect benefit coverage for another 3 million Med-Cal beneficiaries who are either enrolled in County Organized Health System (COHS) managed care or engaged in Medi-Cal's fee-for-service (FFS) system. In addition to the expected increase of $104,000 in premiums CHBRP is estimating for the 7.8 million Medi-Cal beneficiaries enrolled in DMHC-regulated plans (a figure which represents a 0.0004% increase in premiums), it seems reasonable to assume that a population proportional increase of $19,455 would occur for the 1.5 million beneficiaries enrolled in COHS managed care. It seems likely that a similar impact would occur for the 1.5 million beneficiaries with health insurance through the FFS program (though the exact amount is unknown).

CalPERS

CHBRP estimates no measurable change in premium impacts for CalPERS.

Number of Uninsured in California

CHBRP would expect no measurable impact of SB 221 on the number of uninsured persons.

Public Health

In the first year, postmandate, CHBRP would expect some increase in use of treatments by about 15 enrollees in DMHC-regulated plans and CDI-regulated policies. For those persons, there may be some improvements in health and quality of life.

Long-Term Impacts

Because the prevalence of HIV associated lipodystrophy appears to have declined along with use of early antiretroviral drugs there may be a shrinking number of persons for whom the treatments are medically necessary. This suggests that the utilization and expenditure impacts projected in this analysis for the first year after implementation of SB 221 would decline over time.

Furthermore, although treatments may, to varying degrees, provide short-term relief from the burden of symptoms, there is little or no evidence of long-term effectiveness. The lack of long-term effectiveness may both decrease utilization over time and may suggest that initial improvements in health outcomes may fade.

Essential Health Benefits and the Affordable Care Act

Because medically necessary treatments for HIV associated lipodystrophy are generally covered by health insurance in California, including the state's benchmark plan, it seems that SB 221 would not exceed the definition of essential health benefits (EHBs) in California. **However, the possibility that the language of the bill would prohibit generally applicable utilization management techniques, including application of medical necessity criteria, or exclusion from coverage of treatments deemed to be experimental or investigational makes it unclear whether the bill would exceed EHBs.**

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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 bills. The state funds CHBRP through an annual assessment on health plans and insurers in California.

An analytic staff in the University of California's Office of the President supports a task force of faculty and research staff from several campuses of the University of California 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, and content experts with comprehensive subject-matter expertise are consulted to provide essential background and input on the analytic approach for each report.

More detailed information on CHBRP's analysis methodology, authorizing statute, as well as all CHBRP reports and other publications are available at www.chbrp.org.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

Table 1. SB 221 Impacts on Benefit Coverage, Utilization, and Cost Among Persons With Health Insurance Regulated by DMHC or CDI, 2018

	Baseline	Postmandate	Increase/ Decrease	Percentage Change
Benefit coverage				
Total enrollees in DMHC/CDI-regulated plans/policies (a)	24,048,000	24,048,000	0	0%
Percentage of enrollees in DMHC/CDI-regulated plans/policies with health insurance subject to SB 221	100%	100%	0%	0%
Percentage of enrollees in DMHC/CDI plans/policies with fully SB 221 compliant health insurance	95%	100%	5%	5%
Utilization and unit cost				
Utilization of HIV associated lipodystrophy treatments per 1,000 enrollees				
Medical/surgical (e)	0.0284	0.0298	0.0014	5.0%
Drug (f)	0.0158	0.0162	0.0004	2.7%
Average annual unit cost/user of HIV associated lipodystrophy treatments				
Medical/surgical (e)	$789	$829	$39	5.0%
Drug (f)	$1,096	$1,125	$30	2.7%
Expenditures				
Premium expenditures by payer				
Private employers for group insurance (j)	$64,820,615,000	$64,820,615,000	$0	0.0000%
CalPERS HMO employer expenditures for DMHC-regulated plans (c)(j)	$4,884,262,000	$4,884,262,000	$0	0.0000%
Medi-Cal Managed Care Plan expenditures for DMHC-regulated plans (h)	$27,983,856,000	$27,983,960,000	$104,000	0.0004%
Enrollees for individually purchased insurance	$14,608,214,000	$14,608,223,000	$9,000	0.0001%
Individually purchased – outside exchange (j)	$6,304,061,000	$6,304,061,000	$0	0.0000%
Individually purchased – Covered California	$8,304,153,000	$8,304,162,000	$9,000	0.0001%
Enrollees with group insurance, CalPERS HMOs, Covered California, and Medi-Cal Managed Care (b)	$20,387,090,000	$20,387,091,000	$1,000	0.0000%
Enrollee expenses				
For covered benefits (deductibles, copayments, etc.)	$13,565,623,000	$13,565,624,000	$1,000	0.0000%
For noncovered benefits (d)(i)	—	—	—	—
Total expenditures	$146,249,665,000	$146,249,775,000	$115,000	0.0001%

Source: California Health Benefits Review Program, 2017.

Notes: (a) This population includes persons with privately funded (including Covered California) and publicly funded (e.g., CalPERS HMOs, Medi-Cal Managed Care Plans) health insurance products regulated by DMHC or CDI.

Population includes enrollees aged 0 to 64 years and enrollees 65 years or older covered by employer-sponsored health insurance.

(b) Premium expenditures by enrollees include employee contributions to employer-sponsored health insurance and enrollee contributions for publicly purchased insurance.

(c) Of the increase in CalPERS employer expenditures, about 56.7% would be state expenditures for CalPERS members who are state employees or their dependents. It should be noted, however, that should CalPERS choose to make similar adjustments for consistency to the benefit coverage of enrollees associated with CalPERS' self-insured products, the fiscal impact on CalPERS could be greater.

(d) Due to relevant income restrictions, CHBRP assumes no measurable expense for Medi-Cal beneficiaries enrolled in DMHC-regulated plans.

(e) Includes only those expenses that are paid directly by enrollees to providers for services related to the mandated benefit that are not currently covered by insurance. In addition this only includes those expenses that will be newly covered, post-mandate. Other components of expenditures in this table include all health care services covered by insurance.

(f) Medical treatments considered include liposuction / lipectomy, gynecomastia surgery, injections / fillers, and autologous fat transplantation.

(g) Drug treatments considered include tesamorelin.

(h) In addition to the possible increase of $104,000 increase in premiums CHBRP is estimating for the 7.8 million Medi-Cal beneficiaries enrolled in DMHC-regulated plans, CHBRP assumes that a proportional increase of $19,455 would occur for the 1.5 million beneficiaries enrolled in COHS managed care. It seems likely that there would also be an additional increase for the 1.5 million beneficiaries with health insurance through the FFS program (though the exact amount is unknown).

(i) Although enrollees with newly compliant benefit coverage may have paid for some treatments before SB 221, CHBRP cannot estimate the frequency with which such situations may have occurred or and so cannot estimate the total expense such situations might have incurred. Postmandate, such expenses would be gone, though enrollees with newly compliant benefit coverage might, postmandate, pay for some treatments for which coverage is denied (through utilization management review), as some enrollees who always had compliant benefit coverage may have done and may continue to do, postmandate. Again, CHBRP cannot estimate the frequency with which such situations might occur, and or the total expense such situations might incur.

(j) No measurable impact is projected.

Key: COHS = County Organized Health Systems; CalPERS HMOs = California Public Employees' Retirement System Health Maintenance Organizations; CDI = California Department of Insurance; DMHC = Department of Managed Health Care; FFS = fee-for-service.

POLICY CONTEXT

The California Senate Committee on Health has requested that the California Health Benefits Review Program (CHBRP)[2] conduct an evidence-based assessment of the medical, financial, and public health impacts of SB 221 (Wiener) Lipodystrophy.

If enacted, SB 221 could affect the health insurance of approximately 24.1 million Californians who will have health insurance regulated by the California Department of Managed Health Care (DMHC) or the California Department of Insurance (CDI) in 2018. This figure includes 7.8 million Medi-Cal beneficiaries enrolled in DMHC-regulated plans. In addition, SB 221 would be relevant to the benefit coverage of 1.5 million beneficiaries enrolled in County Organized Health System (COHS) managed care and another 1.5 million beneficiaries engaged in Medi-Cal's fee-for-service (FFS) program. The full 27.1 million represent 69% of Californians.

Bill-Specific Analysis of SB 221 Lipodystrophy

SB 221 would, when a provider has indicated the treatment is necessary due to HIV associated lipodystrophy, require DMHC-regulated plans and CDI-regulated policies to cover treatments (medical and drug) to correct, repair, or ameliorate effects of HIV associated lipodystrophy. Lipodystrophy includes both abnormal fat accumulation (lipohypertrophy) and/or abnormal fat loss (lipoatrophy)."Treatments would be inclusive of (but not limited to):

- Reconstructive surgery, such as suction-assisted lipectomy;
- Dermal injections or fillers for reversal of facial lipoatrophy; and
- Other restorative procedures.

To the extent permitted by federal law, SB 221 would require the same benefit coverage for all Medi-Cal beneficiaries.

The full text of SB 221 can be found in Appendix A .

Explanations of the relevant treatments are included in in the *Medical Effectiveness* section of this report and additional information about the condition, HIV associated lipodystrophy, is present in the *Background* section.

Analytic Approach and Key Assumptions

The bill indicates that coverage shall be subject to a statement from a treating provider indicating medical necessity. For this analysis, CHBRP has assumed that the bill would not prohibit generally applicable utilization management techniques, including application of medical necessity criteria, requiring prior authorization, or exclusion from coverage of treatments deemed to be experimental or investigational. **However, the language of the bill is unclear as to whether such utilization management techniques would be allowed.**

[2] CHBRP's authorizing statute is available at http://chbrp.org/faqs.php.

The bill includes alterations to the Welfare & Institutions (W&I) Code that, if permitted by federal law, would ensure that all Medi-Cal beneficiaries have similar coverage for treatment of HIV associated lipodystrophy. For this analysis, CHBRP has assumed that alteration of the W&I Code would impact benefit coverage of Medi-Cal Beneficiaries enrolled in County Organized Health System (COHS) managed care and Medi-Cal beneficiaries whose general health insurance is through the fee-for-service (FFS) program. **However, prior to a federal decision (which is not available at this time), the effect the bill would have through alteration of the W&I Code is unknown.**

General Caveat for All CHBRP Analyses

It is important to note that CHBRP's analysis of proposed legislation address the incremental effects — how the proposed legislation would impact benefit coverage, utilization, costs, and public health. CHBRP's estimates of these incremental effects are presented in this report.

Interaction With Existing Requirements

Health benefit mandates may interact with state and/or federal mandates. SB 221 would appear to overlap with one of each and is similar to a benefit mandate present in one other state.

State Requirements

California law and regulations

CHBRP is aware of a California benefit mandate that requires all DMHC-regulated plans and CDI-regulated policies to cover reconstructive surgery to correct or repair abnormal structures of the body caused by congenital defects, developmental abnormalities, trauma, infection, tumors, or disease to improve function or to create a normal appearance, to the extent possible.[3] This law appears relevant to treatment of HIV associated lipodystrophy. Although reasonably referred to as "medical," since they are covered by health insurance under a "medical benefit," lipectomy, autologous fat transplantation, and gynecomastia surgery could, in the presence of HIV associated lipodystrophy, be considered medically necessary reconstructive surgery.

Similar requirements in other states

For treatment of HIV associated lipodystrophy, CHBRP is aware of one state with a similar benefit mandate (BCBSA, 2016). In 2016, Massachusetts passed into law S.2137,[4] which requires coverage for treatment of HIV associated lipodystrophy. The Massachusetts law language is very similar to the language in SB 221.

[3] Health & Safety Code 1367.63 and Insurance Code 10123.88.
[4] The MA language is available at https://malegislature.gov/Bills/189/S2137.

Federal Requirements

Medicare

For treatment of HIV associated lipodystrophy, CHBRP is aware that Medicare covers facial injections/fillers when depression is a comorbidity,[5] covers lipectomy in California,[6] and covers gynecomastia in other states.[7]

Affordable Care Act

A number of Affordable Care Act (ACA) provisions described below have the potential to or do interact with state benefit mandates. Below is an analysis of how SB 221 may interact with requirements of the ACA as presently exists in federal law, including the requirement for certain health insurance to cover essential health benefits (EHBs).[8]

Any changes at the federal level may impact the analysis or implementation of this bill, were it to pass into law. However, CHBRP analyzes bills in the current environment, given current law.

Essential health benefits

State health insurance marketplaces, such as Covered California, are responsible for certifying and selling qualified health plans (QHPs) in the small-group and individual markets. QHPs are required to meet a minimum standard of benefits as defined by the ACA as EHBs. In California, EHBs are related to the benefit coverage available in the Kaiser Foundation Health Plan Small Group Health Maintenance Organization (HMO) 30 plan, the state's benchmark plan for EHBs.[9,10]

States may require QHPs to offer benefits that exceed EHBs.[11] However, a state that chooses to do so must make payments to defray the cost of those additionally mandated benefits, either by paying the purchaser directly or by paying the QHP.[12,13] State rules related to provider types, cost-sharing, or

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[5] See 2010 bulletin / change request.
[6] See Local Coverage Determination L35163. Considered reconstructive surgery when performed to alleviate specific conditions.
[7] See Local Coverage Determination L35090, Considered a second line treatment (drug discontinuance should first be considered).
[8] The ACA requires nongrandfathered small-group and individual market health insurance — including but not limited to QHPs sold in Covered California — to cover 10 specified categories of EHBs. Resources on EHBs and other ACA impacts are available on the CHBRP website: http://www.chbrp.org/other_publications/index.php.
[9] The U.S. Department of Health and Human Services (HHS) has allowed each state to define its own EHBs for 2014 and 2015 by selecting one of a set of specified benchmark plan options. CCIIO, Essential Health Benefits Bulletin. Available at: cciio.cms.gov/resources/files/Files2/12162011/essential_health_benefits_bulletin.pdf.
[10] H&SC Section 1367.005; IC Section 10112.27.
[11] ACA Section 1311(d)(3).
[12] State benefit mandates enacted on or before December 31, 2011, may be included in a state's EHBs, according to the U.S. Department of Health and Human Services (HHS). Patient Protection and Affordable Care Act: Standards Related to Essential Health Benefits, Actuarial Value, and Accreditation. Final Rule. Federal Register, Vol. 78, No. 37. February 25, 2013. Available at: www.gpo.gov\fdsys\pkg\FR-2013-02-25\pdf\2013-04084.pdf.
[13] However, as laid out in the Final Rule on EHBs HHS released in February 2013, state benefit mandates enacted on or before December 31, 2011, would be included in the state's EHBs, and there would be no requirement that the state defray the costs of those state-mandated benefits. For state benefit mandates enacted after December 31, 2011, that are identified as exceeding EHBs, the state would be required to defray the cost.

reimbursement methods would *not meet* the definition of state benefit mandates that could exceed EHBs.[14]

Because medically necessary treatments for HIV associated lipodystrophy are generally covered by health insurance in California, including the state's benchmark plan, it seems that SB 221 would not exceed the definition of EHBs in California. **However, the possibility that the language of the bill would prohibit generally applicable utilization management techniques, including application of medical necessity criteria, or exclusion from coverage of treatments deemed to be experimental or investigational makes it unclear whether the bill would exceed EHBs.**

[14] Essential Health Benefits. Final Rule. A state's health insurance marketplace would be responsible for determining when a state benefit mandate exceeds EHBs, and QHP issuers would be responsible for calculating the cost that must be defrayed.

BACKGROUND ON HIV ASSOCIATED LIPODYSTROPHY

Lipodystrophy, clinically recognized as a specific set of symptoms in body fat distribution and appearance observed among HIV-infected patients, was first recognized in 1998, and has had a decline in prevalence since shortly after its recognition, following the introduction of antiretroviral therapies with less lipodystrophy-related side effects in the early 2000's (Carr et al., 1998; Carter et al., 2001; Nguyen et al., 2006). Lipodystrophy may occur in men, women, and children, and typically progresses unless therapeutically managed (Baril et al., 2005). For the purposes of this review, the term *lipodystrophy* will be applied broadly to describe abnormal changes in body fat distribution and metabolism related to HIV and HIV treatment.

Lipodystrophy presents as two clinically distinct conditions, or a mixture of both:

- **Lipoatrophy:** fat loss in the face, limbs, and buttocks, of which facial lipoatrophy is the most common presentation (Bacchetti et al., 2005; Guaraldi et al., 2013). Lipoatrophy is distinct from HIV-related wasting, which is a general loss of fat and lean muscle tissue (Lichtenstein, 2005).
- **Lipohypertrophy:** fat deposition in the abdomen, breasts (in both men and women), upper back and shoulders ("buffalo hump"), and around the neck ("horse collar") (Guaraldi et al., 2013). Lipohypertrophy is sometimes referred to as lipodeposition or lipoaccumulation. This fat can be subcutaneous ("pinchable") or visceral, which wraps around internal organs.

Lipodystrophy is a chronic condition, and there is currently no cure for the underlying metabolic dysfunction that causes lipodystrophy; rather, treatments for lipodystrophy comprise a set of preventive strategies and medical or surgical interventions to ameliorate lipodystrophy-associated body changes. For a detailed discussion of treatments for lipodystrophy, see the *Medical Effectiveness* section.

Risk Factors

The literature suggests that risk for lipodystrophy is multifactorial. Numerous epidemiologic studies have documented risks associated with intrinsic biological traits and processes such as gender and aging (Bacchetti et al., 2005; FRAM, 2006; Guaraldi et al., 2014; Jacobson et al., 2005), and with the severity and duration of HIV infection (Guaraldi et al., 2013; Jacobson et al., 2005; Lichtenstein, 2005; McDermott et al., 2005). However, lipodystrophy has been most strongly correlated with use of antiretroviral therapies (medications that prevent HIV from progressing to AIDS). In particular, certain combinations of nucleoside reverse transcriptase inhibitors and protease inhibitors — drug classes used in antiretroviral therapy (ART) regimens — have been linked to both clinical presentations of lipodystrophy (most strongly with lipoatrophy and less so with lipohypertrophy) (Jacobson et al., 2005; McDermott et al., 2005; Miller et al., 2003; Moyle et al., 2010), and may interact synergistically when used in combination therapy (Guaraldi et al., 2013; Shlay et al., 2009). Since 2003, however, the primary drugs implicated in presentation of lipodystrophy have not been prescribed in contemporary antiretroviral regimens, and subsequently, the number of new cases of lipodystrophy have decreased (Nguyen et al., 2008).

Although many patients present with a mixed syndrome, the causes of lipodystrophy differ by subgroup presentation:

Lipoatrophy

The primary risk factor for lipoatrophy (fat loss) is exposure to certain antiretroviral medications, in particular the drugs *stavudine* or *zidovudine,* which are thought to interrupt mitochondrial function (Guaraldi et al., 2013; Lichtenstein, 2005), and are not currently recommended for use in HIV. In a 2005 review of large epidemiologic studies, stavudine use was significantly associated with lipoatrophy in six of nine studies (Lichtenstein, 2005). Risk of lipoatrophy with zidovudine is less established, but has been documented in longitudinal cohorts and clinical trial settings (McDermott et al., 2005; Shlay et al., 2009). Lipoatrophy is also closely linked to higher HIV viral load, lower body fat at baseline, and duration of antiretroviral medication use (Jacobson et al., 2005; Lichtenstein, 2005; McDermott et al., 2005; Shlay et al., 2009).

Lipohypertrophy

Compared with lipoatrophy, lipohypertrophy is not as strongly associated with antiretroviral therapies. Although fat accumulation with protease inhibitor use has been documented, lipohypertrophy has not been linked to specific medications and can occur, to varying degrees, with any treatment regimen (Guaraldi et al., 2013; Lichtenstein, 2005; Shlay et al., 2009). Rather, epidemiologic studies suggest that lipohypertrophy risk may be more directly mediated by biological and lifestyle factors. Among an HIV-positive cohort of subjects participating in the U.S.-based National Health and Nutrition Examination Survey, risk for lipohypertrophy was higher among women, subjects with a greater proportion of body fat at baseline, and high triglyceride levels (Jacobson et al., 2005). Among a large Italian cohort, incidence of lipohypertrophy increased progressively with each year of observation, suggesting that lipohypertrophy risk is associated with the aging process itself (Guaraldi et al., 2014).

Effects of Untreated Lipodystrophy

Although lipodystrophy is not considered to be a life-threatening condition, lipoatrophy and lipohypertrophy are both associated with metabolic abnormalities that may increase a patient's risk for cardiovascular disease (Lake et al., 2011). Furthermore, the physical presentation of lipodystrophy is associated with quality-of-life deficits and social isolation (Collins et al., 2000; Guaraldi et al., 2008; Leclercq et al., 2013; Power et al., 2003). Patients experiencing fat accumulation in the breasts, back, and chin areas have reported restricted range of movement, back pain, and breathing difficulties (Cofrancesco et al., 2009), whereas patients with lipoatrophy reported discomfort when sitting or lying down (Power et al., 2003). Furthermore, appearance changes resulting from lipodystrophy, particularly facial lipoatrophy, are linked to depression, decreased self-esteem, sexual dysfunction, and social isolation; which may be due in part to concern that the effects of lipodystrophy are a recognizable indicator of HIV status (Collins et al., 2000; Guaraldi et al., 2007; Leclercq et al., 2013). Although awareness may be low among the general public, lipodystrophy has been recognized as "the new Kaposi's sarcoma" — which led to highly recognizable facial lesions — among communities disproportionately affected by HIV (Power et al., 2003).

Prior to the discontinuation of the primary medications known to cause lipoatrophy, fear of lipodystrophy-associated morbidities may have caused patients to switch to less effective regimens or discontinue use overall (Power et al., 2003). The literature linking lipodystrophy with HIV treatment adherence is mixed (Guaraldi et al., 2008); however, a French study evaluating antiretroviral use among HIV-infected patient found that up to 30% of participants discontinued treatment after experiencing one lipodystrophy-associated symptom.

Prevalence of HIV and Lipodystrophy in California

According to the California Department of Public Health Office of HIV/AIDS, an estimated 126,000 people were living with an HIV/AIDS diagnosis in California as of December 2014 (Office of AIDS, 2016a). Between 2010 and 2014, the yearly number and rate of new HIV/AIDS diagnoses decreased; however, the number of people living with an HIV/AIDS diagnosis in California increased over that same period of time (Office of AIDS, 2016b). This trend is attributed to prolonged life expectancy among individuals living with HIV due to antiretroviral therapies and improved access to medical care (Eckert, 2012).

Although there are many people living with HIV in California, for the following reasons, the prevalence of lipodystrophy in the population subject to the changes proposed in SB 221 is uncertain:

- Due to the lack of an objective case definition for lipodystrophy, estimates of lipodystrophy prevalence among the HIV-infected population vary widely, ranging from 11% to 83%, and estimates may not be comparable across time and setting (Carr et al., 2003; Carter et al., 2001; Guaraldi et al., 2013). For example, among a single cohort of HIV-positive Australian men, Carter et al. (2001) showed that lipodystrophy prevalence estimates ranged from 19% to 65%, depending on which definition and measurements were utilized.
- The majority of available prevalence estimates were generated from cohorts exposed to the principle antiretroviral medications associated with lipodystrophy. In the early 2000's, stavudine and zidovudine were replaced on lists of recommended HIV treatments with newer medications, leading to a decrease in incidence of lipodystrophy, particularly lipoatrophy, among patients using antiretroviral medications (Nguyen et al., 2008). However, the most recent studies assessing the prevalence of lipodystrophy among U.S. patients were conducted in cohorts recruited in the late 1990s (Bacchetti et al., 2005; FRAM, 2006; Jacobson et al., 2005; Lichtenstein et al., 2001; Palella et al., 2004). Contemporary cohort studies, (i.e., conducted in populations recruited post-2003) were subject to selection bias (Guaraldi et al., 2014) or were conducted in resource-limited countries where stavudine and zidovudine are still prescribed due to their low price relative to other drugs (Mercier et al., 2009; Signorini et al., 2010; van Griensven et al., 2007).
- It is difficult to disaggregate the symptoms of obesity-related metabolic dysfunction (i.e., diabetes) and lifestyle and age-related accumulation of body fat from HIV associated lipohypertrophy. HIV-positive patients experiencing prolonged life expectancy through use of antiretroviral medications are now thought to be susceptible to chronic conditions and weight gain attributed to aging and poor diet, rather than the HIV infection itself (Guaraldi and Baraboutis, 2009).
- CHBRP's estimates of current prevalence in California, less than 1% of the HIV+ population, are much lower than literature estimates. This could reflect a continued reduction in lipodystrophy prevalence, limited billing for lipodystrophy medical care, or both.

Following removal of the early ARTs from recommended treatment, new diagnoses of HIV associated lipodystrophy have become much less common (Nguyen et al., 2008). This decrease, along with deaths of some of the HIV+ persons who were diagnosed with HIV associated lipodystrophy, has resulted in a much reduced number of Californians living with the condition.[15]

[15] Personal communication, E. Murphy, March 8, 2017.

Health Disparities[16] in Lipodystrophy

"'Health disparity' denotes differences, whether unjust or not. 'Health inequity' on the other hand, denotes differences in health [status or] outcomes that are systematic, avoidable, and unjust." (Wyatt et al., 2016). Despite the lack of a reasonable prevalence estimate and the presumably decreasing incidence of lipodystrophy, there are known differences in the incidence of HIV associated lipodystrophy syndrome by age, gender, race/ethnicity. Consistent with the majority of literature on lipodystrophy, these differences are typically described by clinical presentation group: lipoatrophy, lipohypertrophy, or mixed syndrome. CHBRP found no literature identifying inequities in the overall burden of lipodystrophy.

Race/Ethnicity

Differences in prevalence of lipodystrophy exist by racial/ethnic group. Although it is unclear to what extent the broad presentation of lipodystrophy differs by race or ethnicity, several studies have found white race to be significantly associated with lipoatrophy (Lichtenstein, 2005). White participants in the multisite, US-based HIV Outpatient Study (HOPS) were almost five times more likely to develop lipoatrophy during a year of observation compared with nonwhites (Lichtenstein et al., 2003); moreover whites enrolled in the Ontario Cohort Study (OCS) – a cohort of HIV-infected Canadian adults taking ART – reported more severe lipoatrophy symptoms than their nonwhite comparators (Andany et al., 2011). In contrast, no studies have described statistically significant racial/ethnic differences in the prevalence of lipohypertrophy. However almost 40% of black participants in the OCS reported fat accumulation compared with 30% of whites and 26% of other races (Andany et al., 2011).

CHBRP found no literature addressing lipodystrophy-related disparities in quality of life by race or ethnicity.

Gender

Gender differences in lipodystrophy prevalence have been well-documented. There is some disagreement as to whether gender differences exist in the overall presentation of lipodystrophy (Andany et al., 2011; Galli et al., 2003; Miller et al., 2003); however, men are significantly more likely to experience lipoatrophy than women, who are more likely to develop lipohypertrophy. Men and women are equally likely to present with a mixed syndrome (Andany et al., 2011; Bacchetti et al., 2005; FRAM, 2006; Galli et al., 2003; Jacobson et al., 2005; Leclercq et al., 2013; Miller et al., 2003; Verolet et al., 2015). Compared with women, men in the previously discussed Ontario Cohort Survey (OCS) were almost twice as likely to experience some form of lipoatrophy and present with more severe symptoms (Andany et al., 2011). Additionally, the literature suggests that facial lipoatrophy (the most common form of lipoatrophy) may be more prevalent in men (Andany et al., 2011; Miller et al., 2003), with one French study reporting that HIV-treated men were 2.6 times more likely than women to have facial lipoatrophy (Leclercq et al., 2013). By contrast, women in the Ontario Cohort Study were 2.3 times more likely than their male counterparts to experience lipohypertrophy, particularly in the abdomen and breasts, and reported more severe symptoms associated with fat accumulation (Andany et al., 2011).

[16] Several competing definitions of "health disparities" exist. CHBRP relies on the following definition: "Health disparity is defined as the difference in health outcomes between groups within a population. While the terms may seem interchangeable, 'health disparity' is different from 'health inequity.' 'Health disparity' denotes differences, whether unjust or not. 'Health inequity,' on the other hand, denotes differences in health [status or] outcomes that are systematic, avoidable, and unjust." Wyatt et al., 2016.

A more limited body of literature suggests that the impact of lipodystrophy on quality of life is unevenly distributed between men and women. Women in both French and Swiss cross-sectional cohort studies reported overall lower quality of life associated with lipodystrophy compared with men; moreover, Swiss women were more likely to present with anxiety and depression (Leclercq et al., 2013; Verolet et al., 2015).

Age

CHBRP identified few studies addressing differences in lipodystrophy prevalence and risk by age. One cross-sectional study of an HIV-positive cohort in Australia documented a three-fold increase in risk for lipodystrophy at age 50 years and older compared with patients aged younger than 35 years (Miller et al., 2003). Additionally, persons aged 50 years and older in the previously discussed HOPS study were almost three times as likely to have lipoatrophy, and two times as likely to experience lipohypertrophy compared with participants aged 30 to 39 years (Lichtenstein et al., 2001). However, given that lipodystrophy is strongly associated with exposure to early antiretroviral regimens, these observed age trends may be proxies for exposure to what are now out-of-date regimens and overall duration of treatment.

Age was not independently associated with differential lipodystrophy-related quality-of-life impacts, although anecdotal evidence from qualitative studies suggests that younger people may experience a greater psychological impact due to the body shape changes and appearance of early aging caused by lipodystrophy (Power et al., 2003).

MEDICAL EFFECTIVENESS

As discussed in the *Introduction*, SB 221 would mandate coverage of treatments for HIV associated lipodystrophy syndrome, which encompasses lipoatrophy and lipohypertrophy. The medical effectiveness review summarizes findings from the literature from 2002 to present on the effectiveness of treatments for HIV associated lipoatrophy and lipohypertrophy.

The medical effectiveness review discusses evidence of the effectiveness of the treatments listed in SB 221, which include, but are not limited to, "reconstructive surgery, such as suction assisted lipectomy, other restorative procedures and dermal injections or fillers for reversal of facial lipoatrophy syndrome," as well as other treatments for HIV associated lipoatrophy and lipohypertrophy that are discussed in guidelines issued by the Health Resources and Services Administration (HRSA, 2014) or were identified by CHBRP's content expert.[17]

Table 2. Treatments for HIV Associated Lipodystrophy Syndrome

Lipoatrophy	Lipohypertrophy
Preventive strategies	
• Switching to an antiretroviral therapy (ART) drug regimen that avoids ARTs associated with lipoatrophy	• Diet • Exercise
Medical/surgical interventions	
• Injectable synthetic fillers for facial or buttock lipoatrophy (temporary or permanent) • Autologous fat transplantation	• Surgical fat removal (e.g., lipectomy or liposuction of buffalo hump or breast reduction mammoplasty) • Deoxycholic acid injections (Kybella)
Prescription drugs	
	• Metformin • Tesamorelin (Egrifta) • Growth hormone

Source: CHBRP, 2017 (adapted from HRSA, 2014)

Research Approach and Methods

Studies of treatments for HIV associated lipodystrophy were identified through searches of PubMed, the Cochrane Library, Web of Science, EconLit, Business Source Complete, the Cumulative Index of Nursing and Allied Health Literature (CINAHL), and PsycINFO. Websites maintained by the following organizations that produce and/or index meta-analyses and systematic reviews were also searched: the Agency for Healthcare Research and Quality (AHRQ), the International Network of Agencies for Health Technology Assessment (INAHTA), the National Health Service (NHS) Centre for Reviews and

[17] Personal communication, E. Murphy, March 2017.

Dissemination, the National Institute for Health and Clinical Excellence (NICE), and the Scottish Intercollegiate Guideline Network.

The search was limited to abstracts of studies published in English. The search was limited to studies published from 2002 to present. CHBRP relied on a systematic review published in 2011 for findings from studies on growth hormone and a synthetic analog of growth hormone (tesamorelin) published prior to 2011. CHBRP relied on a systematic review published in 2015 for findings from studies on fillers and autologous fat transplantation published prior to 2015. CHBRP relied on two systematic reviews published in 2013 for findings from studies on antiretroviral therapy (ART) drugs published prior to 2013. CHBRP relied on a systematic review published in 2010 for findings from studies on insulin sensitizing drugs published prior to 2010. Of the 338 articles found in the literature review, 50 were reviewed for potential inclusion in this report on SB 221, and a total of 20 studies were included in the medical effectiveness review for this report. The other articles were eliminated because they did not focus on HIV associated lipodystrophy, were of poor quality, or did not report findings from clinical research studies. A more thorough description of the methods used to conduct the medical effectiveness review and the process used to grade the evidence for each outcome measure is presented in Appendix B: Literature Review Methods.

Methodological Considerations

The term *HIV associated lipodystrophy* typically refers to changes in fat distribution that are often associated with increased risk for cardiovascular disease and metabolic abnormalities, including dyslipidemia (elevated cholesterol and/or fat in the blood) and insulin resistance (diabetes and pre-diabetes). Insulin resistance refers to a person's resistance to the hormone insulin, resulting in increasing blood sugar. This can eventually lead to type 2 diabetes. Lipodystrophy includes both lipoatrophy (fat loss) and lipohypertrophy (fat gain) which appear to be separate processes that should be addressed independently in a given patient, if they coexist. Patients with lipoatrophy have loss of subcutaneous (pinchable) fat (most noticeably in the limbs, face, and/or buttocks areas). Patients with lipohypertrophy have a gain of visceral fat in the abdomen and may have dorsocervical fat pad enlargement (buffalo hump) and breast enlargement. In contrast to subcutaneous fat, visceral fat in the abdomen is usually not treated by surgical or ultrasonic procedure because it is wrapped around important internal organs, such as the liver, intestines, and pancreas. Procedures to extract fat wrapped around these organs are not recommended due to the risk of injury to these organs. This report discusses treatments and outcomes for lipoatrophy and lipohypertrophy separately.

Outcomes Assessed

Studies of HIV associated lipodystrophy have examined the effects of treatments on the following objective measures of outcomes: cheek thickness, mean cheek volume, facial fat thickness, reduction in visceral fat, reduction in subcutaneous fat, lean body mass, and body mass index.

Subjective outcome measures include: patient's self-perception of improvement, body image perception, depression as assessed by a visual analogue scale score (VAS), the Facial Lipoatrophy Grading Scale, the Assessment of Body Change and Distress questionnaire (ABCD), and the Beck Depression Inventory (BDI) questionnaire.

The HRSA guidelines for diagnosis and treatment of HIV associated lipodystrophy indicate that some persons with HIV may consider discontinuing or interrupting ART due to lipodystrophy (HRSA, 2014). However, CHBRP did not identify any studies on the impact of treating HIV associated lipodystrophy on adherence to ART.

Study Findings

As discussed in the Background section the ART drugs associated with lipodystrophy have not been recommended or routinely prescribed in the United States since 2003.

Preventive Strategies

Lipoatrophy

There are more than 25 ART drugs in six classes that are usually used in combination to treat HIV infection.[18] ART drugs are broadly classified by the phase of the retrovirus lifecycle that the drug inhibits. These six classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), a fusion inhibitor (FI), a CCR5 antagonist, and integrase strand transfer inhibitors (INSTIs). Typical combinations include two NRTIs as a "backbone" along with one NNRTI, PI, or INSTI as a "base."

Multiple open-label randomized controlled trials (RCTs)[19] have assessed the impact of differences in ART treatment regimens on lipoatrophy.

A systematic review of open-label RCTs found that exposure to NRTIs that are thymidine analogues (in particular stavudine and zidovudine) is a major factor associated with peripheral lipoatrophy (defined as >20% loss of limb fat). Patients on NRTI-sparing regimens showed a significantly lower incidence of peripheral lipoatrophy than patients on NRTI-containing regimens (de Waal et al., 2013).

Modifying the antiretroviral regimen so that stavudine or zidovudine is replaced with a different NRTI, specifically tenofovir or abacavir (ABC), is another medical approach to lipoatrophy that increases facial and limb fat. A systematic review of open-label RCTs by de Waal et al. (2013), found that participants who were switched away from thymidine analogue-containing NRTI regimens gained limb fat over time compared with participants who continued NRTI or thymidine analogue-containing regimens, who generally lost limb fat. Another systematic review of RCTs (Cruciani et al., 2013) also reported that two of three RCTs included in the systematic review that assessed ABC-containing regimens found that persons on ABC-containing regimens had lower incidence of lipoatrophy.

Studies have not found evidence that switching a PI to a different third drug reduces lipoatrophy (de Waal et al., 2013; Fisac et al., 2005).

Lipohypertrophy

Eating a healthier diet and exercising regularly are standard recommendations for preventing fat accumulation and achieving weight loss. The HRSA guidelines recommend that clinicians encourage all persons with HIV to engage in moderate aerobic exercise, and state that studies have found that exercise can reduce visceral fat without producing lipoatrophy (HRSA, 2014). The guidelines indicate that no studies have been conducted on the impact of a healthier diet on lipohypertrophy, but it stands to reason that eating more healthfully would improve the overall health of persons with lipohypertrophy.

[18] ARTs are sometimes referred to as antiretroviral therapy (ARV), combination antiretroviral therapy (cARV), or highly active antiretroviral therapy (HAART).

[19] Open-label RCTs are RCTs in which researchers and participants know which treatment participants are receiving. This is a weaker study design than a blinded RCT because knowledge of the treatment a participant receives may influence perception of the effectiveness of the treatment.

Switching from a NRTI-containing or thymidine analogue-containing ART regimen does not reduce trunk and/or visceral fat. de Waal and colleagues' systematic review of open-label RCTs (2013) found that there were no significant changes in trunk and/or visceral fat over time for those who were switched away from NRTI-containing regimes compared to those who continued NRTI-containing regimes or thymidine analogue-containing regimens (de Waal et al., 2013).

CHBRP did not identify any studies that address the impact of diet and exercise on lipohypertrophy. However, it stands to reason that eating more healthfully would improve the overall health of persons with lipohypertrophy.

There is a preponderance of evidence that switching to an antiretroviral regimen that does not include stavudine or zidovudine increases facial and limb fat based on two systematic reviews of RCTs, but there is insufficient evidence regarding the impact of modifying ART regimen on lipohypertrophy, specifically trunk and/or visceral fat based on one systematic review.

Medical and Surgical Treatments

Lipoatrophy

Facial fillers

Facial contouring is used to restore the faces of persons with lipoatrophy to a more typical appearance. Approaches to facial contouring that have been studied include autologous fat transfer, as well as minimally invasive procedures, such as the use of the injectable filler devices. Fillers include poly-L-lactic acid (PLLA), calcium hydroxylapatite (CaHA), hyaluronic acid (HA), polyacrylamide gel (PAAG), polyalkylimide gel (PAIG), polymethylmethacrylate (PMMA), and silicone oil. Studies suggest there are benefits, including high patient satisfaction and significantly improved quality of life, as evidenced by improvement in scores for quality of life on visual analog scales and increased tissue depth measured by computed tomography imaging, with few serious adverse events (Jagdeo et al., 2015).

Studies that examine both facial fillers and fat transplantation

A large systematic review of 76 studies that compared multiple fillers and autologous fat transplantation found that the studies demonstrated sustained improvement in facial lipoatrophy severity for 12 to 18 months with PLLA, CaHA, HA, and silicone oil injections, and up to 4 to 5 years with autologous fat transplantation, PAAG, PAIG, and PMMA injections. The degree and duration of improvement for each treatment option is closely related to the severity of lipoatrophy prior to treatment and the biophysical and longevity profile of each filler agent. Some patients experienced adverse events, such as pain, discomfort, ecchymosis (skin discoloration), edema (swelling), and erythema (reddening of skin due to injury or irritation) that usually resolved within 1 month (Jagdeo et al., 2015).

Most of the studies included in the Jagdeo et al. systematic review were observational studies without comparison groups. None of the studies compared persons treated with fillers to a comparison group that was not treated, and PLLA and PAIG are the only fillers for which persons treated immediately were compared with persons whose treatment was delayed. It is also important to note that interstudy

comparison among studies was difficult because different scales were used to measure objective and subjective outcomes. Additionally, the authors of the Jagdeo systematic review point out the lack of RCTs with direct head-to-head comparisons to evaluate the efficacy and safety of different fillers (Jagdeo et al., 2015).

One of the few studies to make a head-to-head comparison is an observational study that compared persons who received autologous fat transplantation with persons who received a filler (PLLA or PAAG) (Guaraldi et al., 2005). At 24 weeks post-treatment, the two groups had similar increases in dermal and subcutaneous thickness, and satisfaction with appearance improved in both groups.

Studies included in the systematic review suggest that the effects of some fillers persist for at least 2 years. Four case reports demonstrated PLLA treatment reduced severity of lipoatrophy for up to 2 years, and eight studies reported that persons treated with PAAG had improvement in cheek thickness at 2 to 5 years after treatment. One study of PMMA found that patients reported better quality of life 2 years after treatment (Jagdeo et al., 2015). However, the research designs of these studies are weak because they do not include comparison groups.

Studies of autologous fat transplantation

One uncontrolled observational study examined 15 subjects with facial lipoatrophy who were treated with fat transplantation using Coleman's technique of harvesting abdominal fat and injecting it into the face. The treatment resulted in increases in facial fat thickness lasting for up to 24 weeks, with a majority of patients (13 of 15) being happy with the result (Levan et al., 2002).

One uncontrolled observational study, comparing 26 patients pre- and postoperatively, treated with fat transplantation using Coleman's technique to evaluate the long-term viability of fat grafting found a statistically significant improvement in mean cheek volume ($P < 0.001$) that was maintained for 12 months following treatment (Fontdevila et al., 2008).

Based on evidence from a large systematic review that included both RCTs and observational studies without comparison groups, there is a preponderance of evidence that fillers decrease the visible effects of HIV associated facial lipoatrophy and are associated with high patient satisfaction. There is limited evidence from one systematic review that the effects of fillers persist for 2 to 5 years following treatment. There is limited evidence from one observational study with a comparison group and two uncontrolled observational studies that autologous fat transplantation increases facial fat for up to 12 months post treatment.

Studies of fillers for buttock lipoatrophy

Lipoatrophy of the buttocks may cause both functional (e.g., pain when sitting) and esthetic problems. One 18-month prospective, open-label, pre-post of 10 HIV-infected subjects with buttock lipoatrophy who were unable to sit for more than 30 minutes because of pain (Claude et al., 2015) found mean pain score reduction, an increase in mean time that subjects could remain seated, and increased mental health scores after treatment with hyaluronic acid gel fillers. At 6 months after treatment, 9 subjects (90%) experienced decreased pain after 15 minutes of sitting. The mean time that subjects could remain seated was 37 minutes longer compared with baseline for up to 12 months for all subjects for whom data were recorded ($n = 5$). The mean mental health score on the Medical Outcomes Study-HIV questionnaire increased significantly from baseline to 9 months. Scores were not significantly different from baseline at

other time points. Patients experienced only mild adverse events, such as redness or swelling at the injection site. This study had limited long-term data because of subjects being lost to follow-up.

One observational study of 156 patients who received PMMA fillers for lipoatrophy of the buttocks found that most of the patients (93%) were satisfied with the treatment and reported more comfort when seated and that they had been able to be seated for longer periods of time (Serra et al., 2015).

There is insufficient evidence that fillers decrease the effects of HIV associated lipoatrophy in the buttocks based on two pre-post studies without comparison groups, although stands to reason that use of fillers could make sitting more comfortable because the fillers replace fat tissue in the buttocks.

Lipohypertrophy

Liposuction and lipectomy

Liposuction includes both suction-assisted lipectomy (SAL) and ultrasonic-assisted liposuction (UAL), and are options for various manifestations of lipohypertrophy, including breast lipohypertrophy in women or gynecomastia in men, and fat deposition in the neck and jaw. Liposuction is not used to treat lipohypertrophy in the abdomen because that is due to an increase in visceral fat within the peritoneal cavity rather than subcutaneous fat. Liposuction can be used to remove visceral fat in the peritoneal cavity but is not recommended due to the risk of damage to internal organs.[20]

CHBRP did not identify any studies of the use of liposuction to treat breast hypertrophy in women or gynecomastia in men.

Cervicodorsal lipodystrophy, or "buffalo hump" deformity, is a common form of lipohypertrophy. Evidence from several small uncontrolled studies suggests that the use of excisional lipectomy to correct cervicodorsal lipodystrophy can decrease neck strain and improve range of motion and satisfaction with appearance (Connolly et al., 2004; Gold and Annino, 2005; Hultman et al., 2007; Ion and Raveendran, 2011; Roostaeian et al., 2008; Warren and Borud, 2008). One study reported that 3 of 10 patients had partial recurrence between 12 to 30 months following lipectomy (Hultman et al., 2007). An important weakness of these studies is that they did not include comparison groups.

CHBRP did not identify any studies of the use of liposuction to treat breast lipohypertrophy in women or gynecomastia in men. However, it stands to reason that liposuction would remove excess fat from the breast area and, thus reduce breast size.

Based on six uncontrolled studies with small sample sizes, there is insufficient evidence that lipectomy decreases the visible effects of HIV associated lipohypertrophy. However, it stands to reason that lipectomy removes excess fat in patients with HIV associated “buffalo hump” deformity, which is likely to alleviate symptoms, such as difficulty sleeping, neck pain, limited range of motion in upper extremities, and disfigurement, and, thus, improve quality of life. However, it is important to note that the duration of impact these treatments have is unknown because only one study tracked patients for more than 1 year.

[20] Personal communication, E. Murphy, March 2017.

Studies of deoxycholic acid injections (Kybella)

The Food and Drug Administration has recently approved deoxycholoic acid injections (Kybella) as a treatment for severe convexity or fullness associated with submental fat (i.e., double chin). Some physicians are also using it to treat HIV associated lipohypertrophy.[21] CHBRP found no studies that assessed the effects of deoxycholic acid injections on HIV associated lipohypertrophy.

CHBRP found no studies of the impact of deoxycholic acid injections on HIV associated lipohypertrophy.

Prescription Drugs

Lipoatrophy

No prescription drugs are recommended for treatment of lipoatrophy aside from the preventive strategy of switching to an ART regimen that avoids drugs that place patients at higher risk for experiencing lipoatrophy. CHBRP also found no studies that assessed the effects of other prescription drugs on lipoatrophy.

CHBRP found no studies of the impact of prescription drugs on lipoatrophy, aside from the preventive strategy of switching to an ART regimen that avoids drugs that place patients a high risk for lipoatrophy, a strategy that has been followed in the United States since 2003.

Lipohypertrophy

Insulin-sensitizing agents (metformin) on lipohypertrophy

One meta-analysis of RCTs of multiple insulin-sensitizing drugs found that metformin, compared with rosiglitazone or pioglitazone, was the only insulin sensitizer to demonstrate beneficial effects on HIV associated lipohypertrophy. Six unique trials compared metformin to placebo or no treatment in 287 subjects with one or more symptoms of lipohypertrophy, regardless of insulin status, over a mean duration of 27 months. Use of metformin was associated with statistically significant reductions in body mass index and waist-to-hip ratio. Three trials directly compared metformin to rosiglitazone and effects on measures of fat redistribution all favored metformin (Sheth and Larson, 2010).

According to the HRSA guidelines, metformin has been modestly effective in treating visceral fat in patients with insulin resistance, but may exacerbate lipoatrophy. Additionally, metformin should be used with caution in patients with chronic liver or renal disease (HRSA, 2014).

[21] Personal communication, E. Murphy, March 2017.

Based on evidence from a systematic review of nine RCTs, there is a preponderance of evidence that metformin reduces body mass index and waist-to-hip ratio relative to a placebo and to rosiglitazone.

Tesamorelin

Studies have assessed the effects of several forms of growth hormone on HIV associated lipohypertrophy. Evidence suggests that tesamorelin, an injectable synthetic analogue of human growth hormone-releasing factor (GHRH), significantly reduces visceral fat, preserves abdominal subcutaneous fat, increases lean body mass, and improves body mass index. Findings about reduction in visceral fat are especially important because visceral fat is more strongly related to diabetes and other poor health outcomes than other types of fat.

A systematic review of double-blinded placebo-controlled RCTs examined the effects of growth hormone treatments on visceral fat, subcutaneous fat, and lean body mass (Sivakumar et al., 2011). Four RCTs included in the systematic review evaluated tesamorelin. The duration of treatment was either 12 or 26 weeks. The authors pooled findings from the four RCTs of tesamorelin and found that tesamorelin reduced visceral fat and increased lean body mass, but did not change subcutaneous fat.

One study published after the studies included in the systematic review pooled data from two RCTs of tesamorelin (Mangili et al., 2015). The study of 806 persons found that subjects treated with tesamorelin had 3.9 times the odds of a reduction in visceral fat to <140 cm^2 after 6 months of treatment with tesamorelin than subjects randomized to receive a placebo in analyses that adjusted for gender, body mass index, and amount of visceral fat prior to treatment.[22]

None of the six RCTS reported whether the effects of treatment with tesamorelin persist after treatment ends. The HRSA guidelines state that patients quickly regain visceral fat after tesamorelin is discontinued (HRSA 2014). If tesamorelin treatment must continue indefinitely to maintain reduction in visceral fat, some persons with HIV associated lipohypertrophy may not choose to pursue it or may discontinue treatment because they find it burdensome.

Based on evidence from a systematic review of RCTs and an RCT published after the studies included in the systematic review, there is a preponderance of evidence that tesamorelin reduces abdominal visceral fat, preserves abdominal subcutaneous fat, and increases lean body mass. There is insufficient evidence about risks, or benefits, such as improved quality of life, with long-term treatment or whether benefits persist after treatment is discontinued.

Growth Hormone

Studies have assessed the effects of several forms of growth hormone on HIV associated lipohypertrophy, including recombinant growth hormone (rhGH) and growth hormone releasing hormone

[22] In this study, persons with baseline MetS-NCEP (metabolic syndrome), elevated triglyceride levels, or white race were most likely to experience reductions in visceral fat after 6 months of tesamorelin treatment.

(GHRH). Evidence suggests that recombinant growth hormone (rhGH) significantly reduce visceral fat, preserves abdominal subcutaneous fat, increases lean body mass, and improves body mass index.

A large systematic review of double-blinded placebo-controlled RCTs identified six RCTs that compared growth hormone treatments to a placebo and assessed effects on visceral fat, subcutaneous fat, and lean body mass (Sivakumar et al., 2011). Pooled findings from the six RCTs indicate that rhGH reduces visceral fat and subcutaneous fat and may also increase lean body mass. Patients who received rhGH had higher rates of arthralgias (joint pain) and peripheral edema (swelling in peripheral vascular tissue, usually in the lower limbs) than patients who received the placebo.

One open-label RCT not included in the systematic review (Bickel et al., 2006) compared visceral fat at baseline to visceral fat following 12 weeks and 24 weeks for 26 persons who were randomly assigned to one of two rhGH treatment regimens. One group was given 4 mg of rhGH per day for 12 weeks followed by 2 mg per day for 12 more weeks, and the other group was given 4 mg of rhGH three times per week for 12 weeks followed by 2 mg per day for 12 weeks. The two rhGH treatment regimens resulted in similar reductions in visceral fat relative to baseline. The ratio of visceral fat to total fat also decreased in both groups. There were no differences in facial fat or limb fat, suggesting that treatment did not increase the risk of lipohypertrophy in those parts of the body. Adverse effects were more common among persons in the group that received the larger dose of rhGH during the first 12 weeks and included dyspepsia (stomach pain), peripheral edema, transient hyperglycemia (high blood sugar), and pain in the extremities. A follow-up nonrandomized observational study of 16 persons enrolled in the RCT found that overall visceral fat remained 18% below baseline at a median of 9 months following the end of treatment (Bickel et al., 2008).

One important adverse effect of growth hormone is that it increases the risk of developing diabetes. An open-label RCT (Macallan et al., 2008) compared persons who received rhGH alone with persons who received rhGH plus rosiglitazone, a drug used to treat diabetes. Receiving rosiglitazone in addition to rhGH prevented patients from experiencing an increase in fasting insulin but did not change the effect on visceral fat. However, as Macallan notes, rosiglitazone is associated with adverse cardiac events.

An important limitation of most of the studies of growth hormone treatments is limited follow-up after patients are treated. Aside from Bickel (2008) and Macallan et al. (2008), they provide little information about whether the effects of growth hormone treatment persist after patients stop receiving treatment. Macallan et al.'s (2008) findings suggest that patients regain visceral fat after treatment with rhGH ends, whereas Bickel et al (2008) found that reduction in visceral fat persisted a median of 9 months following treatment. The authors of the systematic review also noted that they did not identify any studies that examined the risks and benefits of use of growth hormone for an extended period of time (Sivakumar et al., 2011).

The systematic review of double-blinded placebo-controlled RCTs also examined the effects of growth hormone releasing hormone (GHRH) on visceral fat, subcutaneous fat, and lean body mass (Sivakumar et al., 2011). The one RCT in the systematic review that evaluated GHRH found increases in lean body mass, but no difference in visceral or subcutaneous fat (Koutkia et al., 2004).

Based on evidence from a systematic review of RCTs, there is a preponderance of evidence from RCTs that rhGH reduces visceral fat. There is conflicting evidence about whether the effects of growth hormone treatments persist after patients stop taking them. One important adverse effect of growth hormone is that it increases the risk of developing diabetes. There is insufficient evidence regarding other risks and benefits associated with long-term treatment.

Summary of Findings

The charts in this section summarize CHBRP's findings regarding the strength of the evidence for the effects of specific medications, treatments, and services relevant to SB 221. Separate charts are presented for each medication, treatment, or service for which the bill would mandate coverage and for each outcome for which evidence of the effectiveness of a treatment is available. The title of the chart indicates the medication, treatment or service for which evidence is summarized. The statement under the heading "Conclusion" presents CHBRP's conclusion regarding the strength of evidence about the effect of a particular medication, treatment, or service on a specific relevant outcome and the number of studies on which CHBRP's conclusion is based. For medications, treatments, and services for which CHBRP concludes that there is clear and convincing, preponderance, limited, or conflicting evidence, the placement of the vertical bar indicates the strength of the evidence. If CHBRP concludes that evidence is insufficient, a graph that states "Insufficient Evidence" will be presented.

Figure 2. Antiretroviral Drugs

Conclusion

CHBRP finds preponderance of evidence that switching to an antiretroviral regimen that does not include stavudine or zidovudine is effective in increasing facial and limb fat based on two systematic reviews of RCTs.

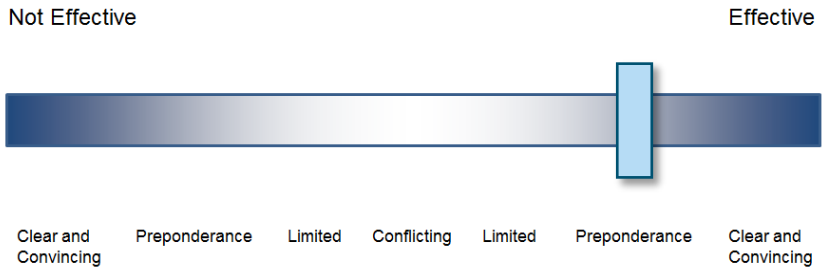


Figure 3. Fillers for Facial Lipoatrophy

Conclusion

Preponderance of evidence that fillers increase facial fat (i.e., reduce the visible effects of facial lipoatrophy) based on a systematic review of 76 studies with multiple types of research designs. There is insufficient evidence to determine how long the effects of fillers persist following treatment.

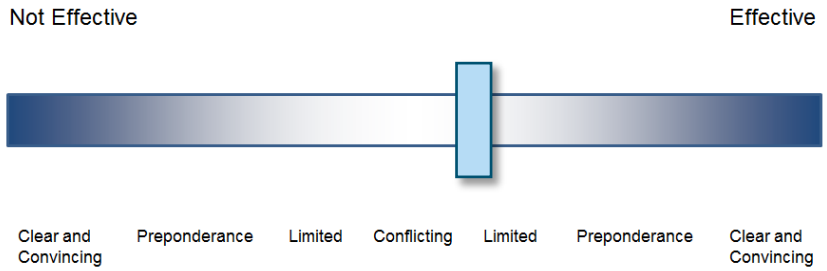


Figure 4. Autologous Fat Transplantation

Conclusion

Limited evidence that autologous fat transplantation increases facial fat (i.e., reduces the visible effects of facial lipoatrophy) based on two studies. There is insufficient evidence to determine how long the effects of autologous fat transplantation persist following treatment.

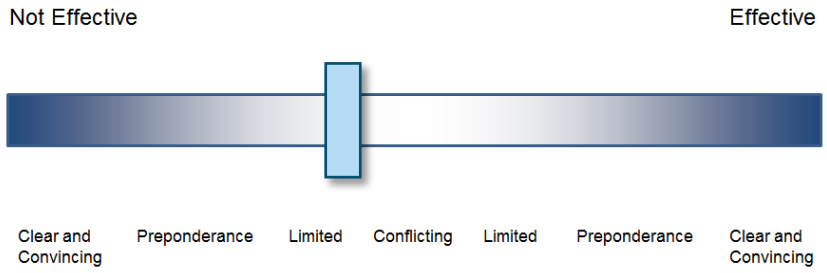


Figure 5. Fillers for Buttock Lipoatrophy

Conclusion

Insufficient evidence to determine whether fillers for buttock lipoatrophy improve outcomes for persons with HIV associated buttock lipoatrophy and how long the effects last based on two studies.

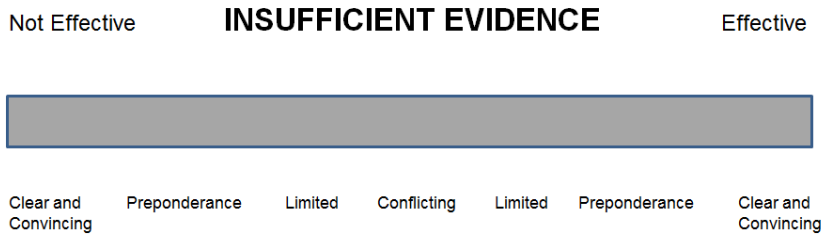


Figure 6. Lipectomy

Conclusion

Insufficient evidence to determine whether lipectomy improves outcomes for persons with “buffalo hump” deformity based on six uncontrolled studies.

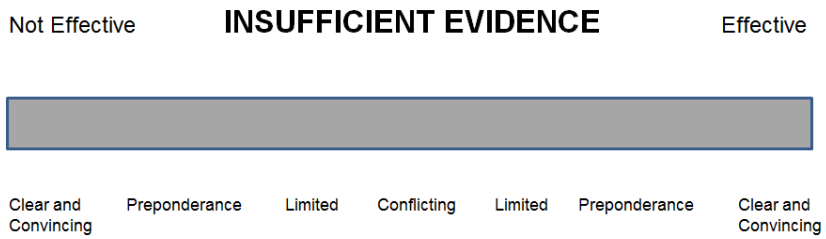


Figure 7. Deoxycholic Acid Injections

Conclusion

Insufficient evidence to determine whether deoxycholic acid injections improve outcomes for persons with HIV associated lipohypertrophy because there are no studies.

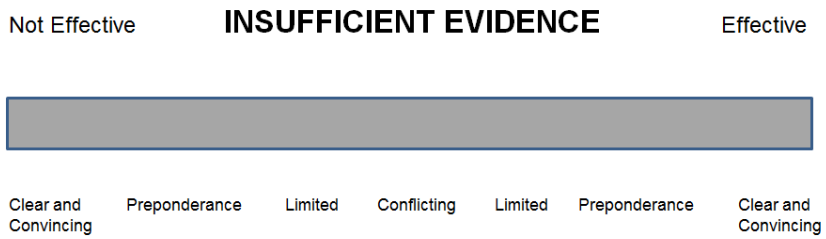


Figure 8. Metformin

Conclusion

Clear and convincing evidence that metformin reduces body mass index and waist-to-hip ratio among persons with HIV associated lipohypertrophy based on one meta-analysis of six RCTs.

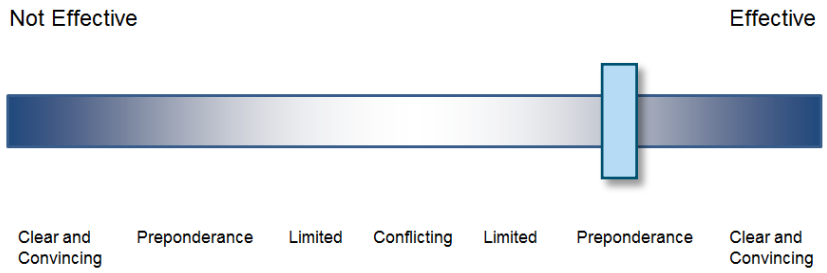


Figure 9. Tesamorelin

Conclusion

Based on evidence from a systematic review of RCTs and an RCT published after the studies included in the systematic review, there is a preponderance of evidence that tesamorelin reduces abdominal visceral fat, preserves abdominal subcutaneous fat, and increases lean body mass. There is insufficient evidence about risks, or benefits, such as improved quality of life, with long-term treatment, or whether the benefits of tesamorelin persist after treatment is discontinued.

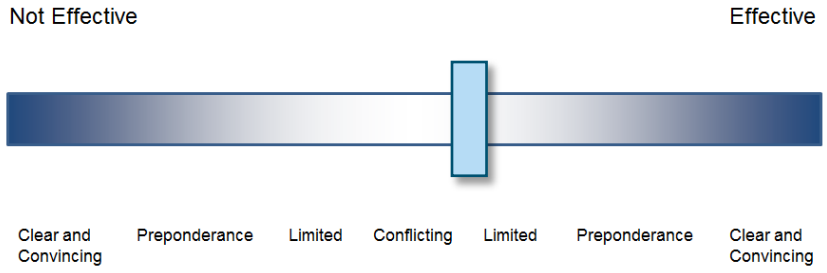
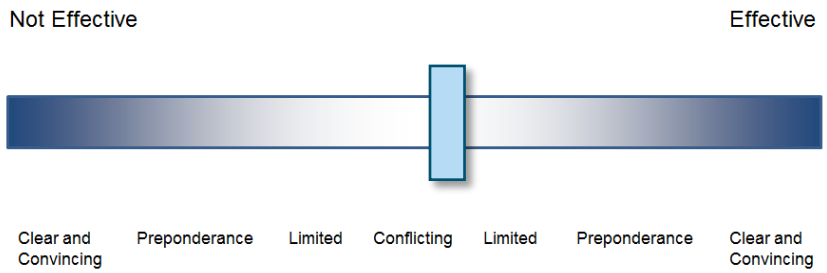


Figure 10. Growth Hormone

Conclusion

Preponderance of evidence based on one meta-analysis of RCTs and four additional RCTs that growth hormone reduces visceral fat but treatment is associated with increased risk of diabetes. There is also conflicting evidence about whether reduction in visceral fat persists after treatment ends.



BENEFIT COVERAGE, UTILIZATION, AND COST IMPACTS

This section reports on benefit coverage, utilization, and overall cost related to the potential incremental impacts of SB 221. SB 221 would require DMHC-regulated plans and CDI-regulated policies to cover medical or drug treatments to correct or repair disturbances of body composition caused by human immunodeficiency virus (HIV) associated lipodystrophy syndrome, including, but not limited to,

- Reconstructive surgery, such as suction assisted lipectomy;
- Other restorative procedures; and
- Dermal injections or fillers for reversal of facial lipoatrophy syndrome.

To the extent permitted by federal law, SB 221 would require the same benefit coverage for all Medi-Cal beneficiaries. Therefore, in addition to impacting the benefit coverage of the 7.8 million Medical beneficiaries enrolled in DMHC-regulated plans, SB 221 could also apply to the benefit coverage of the 1.5 million Medi-Cal beneficiaries enrolled in County Organized Health System (COHS) managed care and the additional 1.5 million beneficiaries engaged in Medi-Cal's fee-for-service (FFS) program.

Analytic Approach

Although SB 221 is an exception (because it would alter the Welfare & Institutions Code as well), the benefit coverage of the 3 million Medi-Cal beneficiaries associated with COHS and FFS are not commonly subject to the proposed legislation CHBRP considers (because neither is subject to the California Health & Safety Code or the California Insurance Code, which regulate DMHC-regulated plans and CDI-regulated policies). The analysis which follows, unless otherwise specified, is relevant to the 24 million Californians enrolled in a plan or policy regulated by DMHC or CDI (a figure which does includes 7.8 million Medi-Cal beneficiaries enrolled in DMHC-regulated plans).

At baseline, (without implementation of SB 221), the percentage of enrollees with health insurance fully compliant with SB 221 is 95%. For those with fully compliant health insurance, we assume that their health insurance postmandate will not change (and service use will remain the same postmandate). For the 5% at baseline with health insurance not fully compliant with SB 221, we assume postmandate insurance will be compliant with SB 221 (and the service use will match the pattern of the other 95%).

The benefit coverage, cost, and utilization impact analysis does include some of the treatments discussed in the *Medical Effectiveness* section. Preventive treatment (switching to newer ARTs) is not included because CHBRP believes coverage for such changes to have been present for all HIV+ enrollees and that all California enrollees switched soon after the 2003 recommendations supports doing so (see *Background* section). CHBRP also assumes no postmandate change in the use of metformin, as metformin is a relatively inexpensive and relatively common drug that is also used in treatment of diabetes. Assuming most people with HIV associated lipodystrophy had premandate benefit coverage for metformin, metformin has not been included in the impact analysis. In term of growth hormone, CHBRP identified no measurable evidence of use among persons with compliant coverage at baseline, and so assumes there will be no measurable postmandate use in the year following implementation of SB 221, so growth hormone has not been included in the impact analysis. Like the drug treatments already discussed, a new medical/surgical treatment, deoxycholic acid injections (Kybella) has not been included in the impact analysis. Although there is anecdotal discussion of off-label use as a treatment for a particular form of lipohypertrophy (buffalo hump), CHBRP cannot estimate what would presumably be limited (by prevalence of the specific subcondition) potential utilization and has not included deoxycholic acid injections in the impact analysis. In summary, not included in the impact analysis are metformin,

growth hormone or deoxycholic acid injections. Respective average annual unit costs for these treatments are $6, $750 and $340.

CHBRP includes the following treatments for HIV associated lipodystrophy in the benefit coverage, cost and utilization analysis: 1) lipectomy; 2) gynecomastia surgery; 3) injection/fillers; 4) autologous fat transplantation; and 5) tesamorelin (Egrifta). The first four are considered "medical/surgical" treatments, covered under an enrollee's medical benefit, and tesamorelin is considered a "drug" treatment, covered under an enrollee's OPD benefit. Additionally, a simple two-category treatment categorization allows the consideration of three types of potential benefits to patients from this mandate: 1) gaining coverage for "medical/surgical" treatments; 2) gaining coverage for tesamorelin (drug) treatment; or 3) gaining both types of coverage. The aggregation into two main treatment categories "medical/surgical" and "drug" allows the analysis to address some complexity without becoming too unwieldy.

As noted in the *Policy Context* section, CHBRP has assumed that SB 221 would require benefit coverage, but would not affect utilization management (prior authorization requirements and medical review for medical treatments, and use of formularies). Further discussion of bill-specific caveats and assumptions are detailed in Appendix C where further details on the underlying data sources and methods also appear.

Baseline and Postmandate Benefit Coverage

As noted in Table 1, currently, 95% of enrollees with health insurance regulated by DMHC or CDI have benefit coverage that is fully compliant with SB 221. Postmandate analyses consider when this is increased to 100%.

Current coverage of the HIV associated lipodystrophy treatments was determined by a survey of the largest (by enrollment) providers of health insurance in California. Responses to this survey represent 85% of enrollees with private market health insurance that can be subject to state mandates. Queries were also sent to CalPERS, to California Department of Health Care Services (related to Medi-Cal benefits), and to several of the larger (by enrollment) Medi-Cal Managed Care Plans to understand impacts on other affected market segments. Results were used to estimate the percentage of enrollees who had HIV associated lipodystrophy treatment coverage at baseline.

Where **Table 1** presents baseline and postmandate aggregates, **Table 3**, below, presents the baseline specifics for treatments included in the benefit coverage, cost, and utilization impact analysis.

Table 3. Treatment-Specific Baseline Estimates

Treatment Category	Enrollees With SB 221–Compliant Benefit Coverage	Annual Units Used	Average Annual Unit Cost Per User
Medical/surgical treatments			
Lipectomy	95%	51	$3,027
Gynecomastia surgery	95%	35	$14,208
Injection/fillers	95%	502	$409
Autologous fat transplantation	95%	95	$1,515
Drug treatments			
Tesamorelin (Egrifta)	97%	380	$3,314

Source: CHBRP, 2017.

Baseline and Postmandate Utilization

To prepare the reader for the findings in this section, it is important to remember the SB 221 mandate affects enrollees with benefit coverage that is already almost entirely fully compliant (e.g., SB 221 increases compliance from 95% to 100%). In addition, the quantity of potential users of treatments affected by the mandate will be quite small. CHBRP estimates less than 1% of the HIV+ population has lipodystrophy. Given the considerably higher figures estimated in the early literature, it seems that there has been a drastic reduction in the prevalence HIV associated lipodystrophy. The context for SB 221 is that of mandate that would affect health insurance that is almost already fully compliant and that the number of potential users with changed benefit coverage (CHBRP estimates that the number as approximately 15) is limited. For these reasons, Estimates of the utilization and expenditure (premium and enrollee cost sharing) impacts are smaller than one might initially expect in a state the size of California. Specifically, among the 24 million enrollees in DMHC-regulated plans and CDI-regulated policies, postmandate, CHBRP estimates a total of 400 enrollees would use of treatments for HIV associated lipodystrophy (an additional 15 more than at baseline), and as a result of this changed benefit coverage, premium expenditures would increase by $114,000 (0.0001%).

As noted in **Table 1**, baseline use of “medical/surgical” treatments per 1,000 enrollees among enrollees in DMHC-regulated plans and CDI-regulated policies is estimated to be 0.0284. For the drug treatment tesamorelin, the baseline estimated use is 0.0158 per 1,000 enrollees. These rates are expected to increase to 0.0298 and 0.0162, postmandate. This corresponds to increases of 0.0014 and 0.0004, respectively or in percentage terms, 5.0% and 2.7%.

The magnitude of the change can also be appreciated through the number of users at baseline and postmandate. At baseline, there are 385 users of treatment. **Table 3** presents the distribution of the treatments being used. This can be found in the column labeled Annual Units Used. Postmandate, CHBRP estimates that there will be 400 users. This is a gain of 15 more users (about 4%) related to increasing from 95% to 100% the percentage of enrollees with health insurance fully compliant with SB 221.

Baseline and Postmandate Per-Unit Cost

Given the limited changes in benefit coverage and utilization, CHBRP anticipates no impact on unit costs. Aggregate unit costs are presented in **Table 1**, and treatment-specific unit costs are presented in **Table 3**.

Baseline and Postmandate Expenditures

Table 4 and **Table 5** present baseline and postmandate expenditures by market segment for enrollees in DMHC-regulated plans and CDI-regulated policies. The tables present per member per month (PMPM) premiums, enrollee expenses for both covered and noncovered benefits, and total expenditures (premiums as well as enrollee expenses).

Table 5 indicates that SB 221 would increase total net annual expenditures by $110,000 or 0.0001% for enrollees with DMHC-regulated plans and CDI-regulated policies, postmandate. This is mainly due to the administrative costs associated with providing coverage for the benefit to persons who do not currently have it.

Premiums

Table 5 shows a $114,000 (0.0001%) increase in total premiums (composed of an average portion of premium paid by employers of $104,000 and an average portion of premium paid by employee of $10,000). As noted in **Table 1**, the distribution of the impact on premiums varies. CHBRP estimates nearly no change in total premiums for private employers purchasing group health insurance and CalPERS HMOs. CHBRP estimates no measurable change in total premiums for purchasers of group insurance and an increase of $9,000 (0.0001%) in premiums in the individual market. CHBRP estimates that state expenditures for Medi-Cal Managed Care Plans would increase by $104,000 (0.0004%).

The overall percent change in insured premiums is 0.0001% (**Table 5**), but changes in premiums appear to vary by market segment. For the Small Group Markets (both CDI and DMHC-regulated) CHBRP estimates no change in premiums. There is some variability in the impacts on Publicly Funded plans with DMHC-regulated Medi-Cal Managed Care Plans expecting a 0.0004% increase in insured premiums for those <65 years, but a 0.0001% increase in insured premiums for those ≥65 years.

In addition to the expected $104,000 increase in premiums, CHBRP is estimating for the 7.8 million Medi-Cal beneficiaries enrolled in DMHC-regulated plans, it seems reasonable to assume that a proportional increase of $19,455 would occur for the 1.5 million beneficiaries enrolled in COHS managed care. CHBRP assumes the two populations to be relatively similar and to have relatively similar benefit coverage. In addition, it seems likely that there would also be some additional increase for the 1.5 million Medi-Cal beneficiaries with health insurance through the FFS program. However, the similarity of this population with the group enrolled in DMHC-regulated plans is unknown and their benefit coverage may differ, so the exact amount of such an increase is unknown.

Enrollee Expenses

SB 221–related changes in enrollee expenses for covered benefits and enrollee expenses for noncovered benefits vary by market segment. Such changes are related to the number of enrollees (see **Table 4** and **Table 5**), with health insurance that would be subject to SB 221 and expected to use the relevant treatments during the year after enactment. As would be expected, some enrollees using newly compliant benefit coverage would incur some cost sharing,

Although enrollees with newly compliant benefit coverage may have paid for some treatments without SB 221, CHBRP cannot estimate the frequency with which such situations may have occurred and so cannot estimate the total expense such situations might have incurred. Postmandate, such expenses would be gone, though enrollees with newly compliant benefit coverage might, postmandate, pay for some treatments for which coverage is denied (through utilization management review), as some enrollees who always had compliant benefit coverage may have done before SB 221 and may continue to do postmandate. Again, CHBRP cannot estimate the frequency with which such situations might occur, and or the total expense such situations might incur.

Potential Cost Offsets or Savings in the First 12 Months After Enactment

CHBRP anticipates no measurable cost offsets or savings during the first 12 months after implementation.

Postmandate Administrative Expenses and Other Expenses

CHBRP estimates that the increase in administrative costs of DMHC-regulated plans and/or CDI-regulated policies will remain proportional to the increase in premiums. All health plans and insurers

include a component for administration and profit in their premiums. CHBRP assumes that the administrative cost portion of premiums is unchanged.

Assuming that the impacts associated with SB 221 would be similar for COHS and the FFS program, CHBRP would similarly expect the changes to have no measurable impact on those programs' administrative costs.

Other Considerations for Policymakers

In addition to the impacts a bill may have on benefit coverage, utilization, and cost, related considerations for policymakers are discussed below.

Postmandate Changes in the number of uninsured persons[23]

Because the change in average premiums does not exceed 1% for any market segment (see **Table 5**), CHBRP would expect no measurable change in the number of uninsured persons due to the enactment of SB 221.

Changes in public program enrollment

CHBRP estimates that the mandate would produce no measurable impact on enrollment in publicly funded insurance programs due to the enactment of SB 221.

How Lack of Benefit Coverage Results in Cost Shifts to Other Payers

CHBRP assumes that a limited number of enrollees without benefit coverage paid for some or all of the relevant treatments themselves, but that others did without. Therefore, SB 221 would not shift costs from any other payers.

[23] See also CHBRP's *Criteria and Methods for Estimating the Impact of Mandates on the Number of Uninsured*, available at www.chbrp.org/analysis_methodology/cost_impact_analysis.php.

Table 4. Baseline Per Member Per Month Premiums and Total Expenditures by Market Segment, California, 2018

	DMHC-Regulated						CDI-Regulated			
	Privately Funded Plans (by Market) (a)			Publicly Funded Plans			Privately Funded Plans (by Market) (a)			
	Large Group	*Small Group*	*Individual*	*CalPERS HMOs (b)*	*MCMC (Under 65) (c)*	*MCMC (65+) (c)*	*Large Group*	*Small Group*	*Individual*	**Total**
Enrollee counts										
Total enrollees in plans/policies subject to state mandates (d)	9,128,000	3,163,000	2,379,000	884,000	7,192,000	644,000	276,000	145,000	237,000	24,048,000
Total enrollees in plans/policies subject to SB 221	9,128,000	3,163,000	2,379,000	884,000	7,192,000	644,000	276,000	145,000	237,000	24,048,000
Premiums										
Average portion of premium paid by employer	$456.42	$324.76	$0.00	$460.43	$257.00	$751.00	$527.06	$433.40	$0.00	$97,688,732,000
Average portion of premium paid by employee	$115.59	$149.62	$469.56	$115.11	$0.00	$0.00	$166.32	$157.88	$423.05	$34,995,304,000
Total premium	$572.01	$474.38	$469.56	$575.54	$257.00	$751.00	$693.38	$591.28	$423.05	$132,684,037,000
Enrollee expenses										
for covered benefits (deductibles, copays, etc.)	$44.11	$103.11	$126.07	$31.49	$0.00	$0.00	$115.39	$166.25	$75.74	$13,565,623,000
Enrollee expenses for noncovered benefits (e)(f)	—	—	—	—	—	—	—	—	—	—
Total expenditures	$616.12	$577.49	$595.64	$607.03	$257.00	$751.00	$808.77	$757.53	$498.79	$146,249,664,000

Source: California Health Benefits Review Program, 2017.

Notes: (a) Includes enrollees with grandfathered and nongrandfathered health insurance, both on Covered California and outside the exchange.

(b) As of September 2016, 57% of CalPERS HMO members were state retirees under age 65, state employees or their dependents. CHBRP assumes the same ratio for 2018.

(c) Medi-Cal Managed Care Plan expenditures for members over 65 include those who also have Medicare coverage. This population does not include enrollees in COHS.

(d) This population includes both persons who obtain health insurance using private funds (group and individual) and through public funds (e.g., CalPERS HMOs, Medi-Cal Managed Care Plans).Only those enrolled in health plans or policies regulated by the DMHC or CDI are included. Population includes all enrollees in state-regulated plans or policies aged 0 to 64 years, and enrollees 65 years or older covered by employer-sponsored health insurance.

(e) Includes only those expenses that are paid directly by enrollees or other sources to providers for services related to the mandated benefit that are not currently covered by insurance. This only includes those expenses that will be newly covered, postmandate. Other components of expenditures in this table include all health care services covered by insurance.

(f) Although enrollees with newly compliant benefit coverage may have paid for some treatments at baseline, CHBRP cannot estimate the frequency with which such situations may have occurred or and so cannot estimate the total expense such situations might have incurred. Postmandate, such expenses would be gone, though enrollees with newly compliant benefit coverage might, postmandate, pay for some treatments for which coverage is denied (through utilization management review), as some enrollees who always had compliant benefit coverage may have done before SB 221 and may continue to do, postmandate. Again, CHBRP cannot estimate the frequency with which such situations might occur, and or the total expense such situations might incur.

Key: CalPERS HMOs = California Public Employees' Retirement System Health Maintenance Organizations; CDI = California Department of Insurance; COHS = County Organized Health Systems; DMHC = Department of Managed Health Care; MCMC = Medi-Cal Managed Care.

Table 5. Postmandate Per Member Per Month Premiums and Total Expenditures by Market Segment, California, 2018

	DMHC-Regulated						CDI-Regulated			
	Privately Funded Plans (by Market) (a)			Publicly Funded Plans			Privately Funded Plans (by Market) (a)			
	Large Group	*Small Group*	*Individual*	*CalPERS HMOs (b)*	*MCMC (Under 65) (c)*	*MCMC (65+) (c)*	*Large Group*	*Small Group*	*Individual*	**Total**
Enrollee counts										
Total enrollees in plans/policies subject to state mandates (d)	9,128,000	3,163,000	2,379,000	884,000	7,192,000	644,000	276,000	145,000	237,000	24,048,000
Total enrollees in plans/policies subject to SB 221	9,128,000	3,163,000	2,379,000	884,000	7,192,000	644,000	276,000	145,000	237,000	24,048,000
Premiums										
Average portion of premium paid by employer	$0.0000	$0.0000	$0.0000	$0.0001	$0.0011	$0.0011	$0.0000	$0.0000	$0.0000	$104,000
Average portion of premium paid by employee	$0.0000	$0.0000	$0.0003	$0.0000	$0.0000	$0.0000	$0.0000	$0.0000	$0.0000	$10,000
Total premium	$0.0000	$0.0000	$0.0003	$0.0001	$0.0011	$0.0011	$0.0000	$0.0000	$0.0000	$114,000
Enrollee expenses										
for covered benefits (deductibles, copays, etc.)	$0.0000	$0.0000	$0.0000	$0.0000	$0.0000	$0.0000	$0.0000	$0.0000	$0.0000	$1,000
for noncovered benefits (e)(f)	—	—	----	—	—	—	—	—	—	—
Total expenditures	$0.0000	$0.0000	$0.0002	$0.0000	$0.0011	$0.0011	$0.0000	$0.0000	$0.0000	$115,000
Percent change										
Premiums	0.0000%	0.0000%	0.0001%	0.0000%	0.0004%	0.0001%	0.0000%	0.0000%	0.0000%	0.0001%
Total expenditures	0.0000%	0.0000%	0.0000%	0.0000%	0.0004%	0.0001%	0.0000%	0.0000%	0.0000%	0.0001%

Source: California Health Benefits Review Program, 2017.

Notes: (a) Includes enrollees with grandfathered and nongrandfathered health insurance, inside and outside the exchange.

(b) As of June 1, 2016, 58.82% of CalPERS members were state retirees, state employees, or their dependents. CHBRP assumes the same ratio for 2018.

(c) Medi-Cal Managed Care Plan expenditures for members over 65 include those who are also Medicare beneficiaries. This population does not include enrollees in COHS.

(d) This population includes both persons who obtain health insurance using private funds (group and individual) and through public funds (e.g., CalPERS HMOs, Medi-Cal Managed Care Plans). Only those enrolled in health plans or policies regulated by the DMHC or CDI are included. Population includes all enrollees in state-regulated plans or policies aged 0 to 64 years, and enrollees 65 years or older covered by employer-sponsored health insurance.

(e) Includes only those expenses that are paid directly by enrollees or other sources to providers for services related to the mandated benefit that are not currently covered by insurance. This only includes those expenses that will be newly covered, postmandate. Other components of expenditures in this table include all health care services covered by insurance.

(f) Although enrollees with newly compliant benefit coverage may have paid for some treatments at baseline, CHBRP cannot estimate the frequency with which such situations may have occurred or and so cannot estimate the total expense such situations might have incurred. Postmandate, such expenses would be gone, though enrollees with newly compliant benefit coverage might, postmandate, pay for some treatments for which coverage is denied (through utilization management review), as some enrollees who always had compliant benefit coverage may have done before SB 221 and may continue to do, postmandate. Again, CHBRP cannot estimate the frequency with which such situations might occur, and or the total expense such situations might incur.

Key: CalPERS HMOs = California Public Employees' Retirement System Health Maintenance Organizations; CDI = California Department of Insurance; COHS = County Organized Health Systems; DMHC = Department of Managed Health Care; MCMC = Medi-Cal Managed Care.

PUBLIC HEALTH IMPACTS

SB221 would mandate coverage of treatments to repair or ameliorate maldistributions of body fat caused by HIV associated lipodystrophy syndrome for enrollees in DMHC-regulated plans and CDI-regulated policies, including Medi-Cal beneficiaries, as well as for Medi-Cal beneficiaries with health insurance through a county organized health system (COHS) managed care program or Medi-Cal's fee-for-service (FFS) program.

Analytic Approach

As noted in the *Benefit Coverage, Cost, and Utilization* section, although SB 221 is an exception (because it would alter the Welfare & Institutions Code as well), the benefit coverage of the 3 million Medi-Cal beneficiaries associated with COHS and FFS are not commonly subject to the proposed legislation CHBRP considers (because neither is subject to the California Health & Safety Code or the California Insurance Code, which regulate DMHC-regulated plans and CDI-regulated policies). The analysis which follows, unless otherwise specified, is and relevant to the 24 million Californians enrolled in a plan or policy regulated by DMHC or CDI (a figure with does includes 7.8 million Medi-Cal beneficiaries enrolled in DMHC-regulated plans).

The public health impact analysis includes estimated impacts in the short term (within 12 months of implementation) and in the long term (beyond the first 12 months postmandate). This section estimates the short-term impact[24] of SB 221 on the burden of lipodystrophy-associated morbidity, quality of life, and financial burden among patients with lipodystrophy. See the *Long-Term Impacts* section for a discussion of economic loss, and quality of life improvements for enrollees being treated for HIV infection.

Estimated Public Health Outcomes

As described more fully in the *Background* section of this report, lipodystrophy is not considered to be a clinically life-threatening condition; however, it can be painful or restrictive and potentially result in quality-of-life deficits (Collins et al., 2000; Guaraldi et al., 2007, 2008; Power et al., 2003; Rajagopalan et al., 2008). Treatments for lipodystrophy are not curative, but may prevent, correct, or ameliorate the burden of physical changes caused by underlying metabolic dysfunction characteristic of lipodystrophy.

As presented in the *Medical Effectiveness* section, treatments for the effects of HIV associated lipoatrophy or lipohypertrophy include reconstructive surgery, prescription medications, and switching antiretroviral regimens. The benefits of switching antiretroviral regimens are being realized by Californians independent of whether SB 221 is enacted because the antiretroviral drugs that are most likely to cause lipoatrophy are no longer routinely prescribed. Evidence from several studies suggests that use of certain treatments (i.e., dermal fillers, autologous fat transplantation, liposuction, and tesamorelin) may result in short-term relief from symptoms as well as improvements in physical appearance and quality of life. Given that CHBRP estimates a postmandate increase in new users for the drug and medical surgical lipodystrophy treatments included in the analysis (as described in the *Benefit Coverage, Utilization, and Cost Impacts* section), it stands to reason that, if enacted, the amendments proposed in SB 221 would result in a reduction of the physical and psychological burden of lipodystrophy among the HIV-positive population in California, and produce short-term health and quality-of-life improvements such as improved

[24] CHBRP defines short-term impacts as changes occurring within 12 months of bill implementation.

range of motion or satisfaction with appearance, for the 15 enrollees with HIV associated lipodystrophy who would newly use these medically effective treatments.

In the first year postmandate, CHBRP estimates that there would be new use of medical/surgical and drug treatments for lipodystrophy, resulting in a reduction of outward lipodystrophy symptoms and associated health and quality of life improvements among those new users. However, CHBRP projects no measurable public health impact at the population level due to the small estimated increase in enrollees (15 individuals) who would use medical/surgical and drug treatments for lipodystrophy.

LONG-TERM IMPACTS

In this section, CHBRP estimates the long-term impact[25] of SB 221, which CHBRP defines as impacts occurring beyond the first 12 months after implementation. These estimates are qualitative and based on the existing evidence available in the literature. CHBRP does not provide quantitative estimates of long-term impacts because of unknown improvements in clinical care, changes in prices, implementation of other complementary or conflicting policies, and other unexpected factors.

As noted in the *Background* section and in the *Benefit Coverage, Cost, and Utilization* section, the prevalence of HIV associated lipodystrophy appears to have drastically declined, currently present in less than 1% of California's HIV+ enrollees in plans and policies regulated by DMHC or CDI. In the long term, CHBRP expects that the prevalence of HIV associated lipodystrophy will continue to decline. In part, this is due to discontinued use of antiretroviral therapies that produce lipoatrophy following the introduction of less lipotoxic antiretroviral medications in the early 2000s (Nguyen et al., 2008). Therefore, CHBRP assumes that the demand for lipoatrophy treatments, such as dermal fillers and autologous fat transplantation, is likely to continue to decrease over time, as will their relative impact on the overall burden of lipodystrophy symptoms among HIV-positive populations in California.

Long-Term Utilization and Cost Impacts

As the prevalence of HIV associated lipodystrophy appears to have declined along with use of early antiretroviral drugs (considerably fewer new diagnoses since the 1990s), there may be a shrinking number of persons for whom the treatments are medically necessary. This suggests that the utilization and cost impacts projected in this analysis for the first year after implementation of SB 221 would not be constant, rather, they would likely decline over time.

Long-Term Public Health Impacts

Some interventions in proposed mandates provide immediate measurable impacts (e.g., maternity service coverage or acute care treatments), whereas other interventions may take years to make a measurable impact (e.g., coverage for tobacco cessation or vaccinations). When possible, CHBRP estimates the long-term effects (beyond 12 months postmandate) to the public's health that would be attributable to the mandate.

For the population that remains affected by lipodystrophy, there is no treatment that cures the underlying metabolic dysfunction causing abnormal fat distribution; rather, as evidenced in the *Medical Effectiveness* section, treatments may, to varying degrees, provide short-term relief from the burden of lipoatrophy- or lipohypertrophy-related symptoms and result in potential improvements in quality of life.

However, to the extent that treatments for lipodystrophy symptoms may be used, there is little or insufficient evidence of long-term effectiveness for lipodystrophy treatments. In particular, one form of lipohypertrophy, "buffalo hump," has been found to recur within 1 year in 30% to 100%[26] of cases treated with liposuction (Hultman et al., 2007). Similarly, although there are no trials evaluating safety and use of tesamorelin in the long term, short-term research suggests that patients using tesamorelin to control

[25] See also CHBRP's *Criteria and Guidelines for the Analysis of Long-Term Impacts on Healthcare Costs and Public Health*, available at http://www.chbrp.org/analysis_methodology/cost_impact_analysis.php.
[26] Personal communication, E. Murphy, March 14, 2017.

lipodystrophy-associated abdominal fat gain typically regain fat after treatment ends (Moyle et al., 2010). Synthetic dermal fillers have been shown to correct facial lipoatrophy up through 2 years (Jagdeo et al., 2015); however, there is insufficient evidence of effectiveness in the long term.

In addition, there are several reasons why patients would discontinue use of treatments for lipodystrophy over time. In the case of tesamorelin, patients may not be willing to receive daily injections indefinitely to control a condition (lipohypertrophy) that is not life-threatening.[27] Surgical treatments are invasive, and even when covered by insurance, patients may be reluctant to have them if they are enrolled in health plans that require high cost sharing for surgery. Considering that some patients may need to repeat or utilize multiple treatments, the financial burden associated with out-of-pocket costs could be a deterrent to treatment over time (Hornberger et al., 2009). Finally, as patients age, the demand for treatments may decrease as the effects of both lipoatrophy and lipohypertrophy to some extent mimic common physiologic changes associated with aging (Guaraldi et al., 2014).

In the case of SB 221, CHBRP estimates that utilization of treatments for HIV associated lipodystrophy beyond 12 months will decrease due to the decline in incidence of lipodystrophy among the HIV positive population. Therefore, any impacts of treatment for lipodystrophy (i.e., reductions in lipodystrophy-associated morbidity or quality of life improvements) on the health of HIV positive persons in California may decrease over time concurrent with changing incidence.

Impacts on Economic Loss

Economic loss associated with disease is generally presented in the literature as an estimation of the value of the YPLL in dollar amounts (i.e., valuation of a population's lost years of work over a lifetime). In addition, morbidity associated with the disease or condition of interest can also result in lost productivity by causing a worker to miss days of work due to illness or acting as a caregiver for someone else who is ill.

Persons living with lipodystrophy report a range of quality-of-life deficits, including social isolation due to the outward appearance of illness. Anecdotal evidence from qualitative studies has linked the visible body alterations cause by lipodystrophy to job loss and decreased productivity, including missed or reduced opportunities for advancement (Collins et al., 2000; Power et al., 2003). Additionally, among a cohort of HIV positive persons living in the United Kingdom, Ibrahim et al. found that participants living with visible appearance alterations associated with their HIV status had twice the odds of being unemployed compared with participants who exhibited no outward signs of infection (Ibrahim et al., 2008).

To the extent that medically effective treatments for lipodystrophy may reduce recognizable, physical indicators of HIV infection, the long-term impacts of lipodystrophy on unemployment and work loss may be reduced for those newly receiving treatments due to the coverage extended in SB 221.

[27] Personal communication, E. Murphy, March 14, 2017.

APPENDIX A TEXT OF BILL ANALYZED

On February 3, 2017, the California Senate Committee on Health requested that CHBRP analyze SB 221.

CALIFORNIA LEGISLATURE— 2017–2018 REGULAR SESSION

SENATE BILL No. 221

Introduced by Senator Wiener
(Coauthors: Senators Atkins and Galgiani)

February 02, 2017

An act to add Section 1367.47 to the Health and Safety Code, to add Section 10123.92 to the Insurance Code, and to add Section 14132.04 to the Welfare and Institutions Code, relating to health care coverage.

LEGISLATIVE COUNSEL'S DIGEST

SB 221, as introduced, Wiener. Health care coverage: lipodystrophy syndrome.

Existing law, the Knox-Keene Health Care Service Plan Act of 1975, provides for the licensure and regulation of health care service plans by the Department of Managed Health Care and makes a willful violation of the act a crime. Existing law also provides for the regulation of health insurers by the Department of Insurance. Existing law requires health care service plan contracts and health insurance policies to provide coverage for specified benefits.

This bill would require health care service plan contracts and health insurance policies issued, amended, renewed, or delivered on or after January 1, 2018, to include coverage for medical or drug treatments to correct or repair disturbances of body composition caused by human immunodeficiency virus (HIV) associated lipodystrophy syndrome, including, but not limited to, reconstructive surgery, such as suction assisted lipectomy, other restorative procedures and dermal injections or fillers for reversal of facial lipoatrophy syndrome, as provided. Because a

willful violation of the bill's provisions by a health care service plan would be a crime, it would impose a state-mandated local program.

Existing law provides for the Medi-Cal program, which is administered by the State Department of Health Care Services and under which qualified low-income persons receive health care benefits. The Medi-Cal program is, in part, governed and funded by federal Medicaid provisions. Existing law provides for coverage of certain medical services, including, but not limited to, physician, hospital or clinic outpatient, surgical center, optometric, chiropractic, psychology, occupational therapy, physical therapy, speech therapy, and audiology under the Medi-Cal program.

This bill would require the Medi-Cal program to cover medical or drug treatments to correct or repair disturbances of body composition caused by HIV associated lipodystrophy syndrome, including, but not limited to, reconstructive surgery, such as suction assisted lipectomy, other restorative procedures and dermal injections or fillers for reversal of facial lipoatrophy syndrome, as provided.

The California Constitution requires the state to reimburse local agencies and school districts for certain costs mandated by the state. Statutory provisions establish procedures for making that reimbursement.

This bill would provide that no reimbursement is required by this act for a specified reason.

DIGEST KEY
Vote: majority Appropriation: no Fiscal Committee: yes Local Program: yes

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BILL TEXT

THE PEOPLE OF THE STATE OF CALIFORNIA DO ENACT AS FOLLOWS:

SECTION 1.
Section 1367.47 is added to the Health and Safety Code, to read:

1367.47.
(a) A health care service plan contract issued, amended, renewed, or delivered on or after January 1, 2018, shall include coverage for medical or drug treatments to correct or repair disturbances of body composition caused by human immunodeficiency virus (HIV) associated lipodystrophy syndrome, including, but not limited to, reconstructive surgery, such as suction assisted lipectomy, other restorative procedures and dermal injections or fillers for reversal of facial lipoatrophy syndrome. Coverage shall be subject to a statement from a treating provider that the treatment is necessary for correcting, repairing, or ameliorating the effects of HIV associated lipodystrophy syndrome.

(b) This section shall not apply to accident-only, specified disease, hospital indemnity, Medicare supplement, dental-only, or vision-only health care service plan contracts.

SEC. 2.
Section 10123.92 is added to the Insurance Code, to read:

10123.92.
(a) A health insurance policy issued, amended, renewed, or delivered on or after January 1, 2018, shall include coverage for medical or drug treatments to correct or repair disturbances of body composition caused by human immunodeficiency virus (HIV) associated lipodystrophy syndrome, including, but not limited to, reconstructive surgery, such as suction assisted lipectomy, other restorative procedures and dermal injections or fillers for reversal of facial lipoatrophy syndrome. Coverage shall be subject to a statement from a treating provider that the treatment is necessary for correcting, repairing, or ameliorating the effects of HIV associated lipodystrophy syndrome.
(b) This section shall not apply to accident-only, specified disease, hospital indemnity, CHAMPUS supplement, TRI-CARE supplement, Medicare supplement, dental-only, or vision-only health insurance policies.

SEC. 3.
Section 14132.04 is added to the Welfare and Institutions Code, to read:

14132.04.
(a) A covered Medi-Cal benefit shall include medical or drug treatments to correct or repair disturbances of body composition caused by human immunodeficiency virus (HIV) associated lipodystrophy syndrome, including, but not limited to, reconstructive surgery, such as suction assisted lipectomy, other restorative procedures and dermal injections or fillers for reversal of facial lipoatrophy syndrome. Coverage shall be subject to a statement from a treating provider that the treatment is necessary for correcting, repairing, or ameliorating the effects of HIV associated lipodystrophy syndrome.
(b) This section shall be implemented only to the extent permitted by federal law.
(c) Notwithstanding Chapter 3.5 (commencing with Section 11340) of Part 1 of Division 3 of Title 2 of the Government Code, the department may implement the provisions of this section by means of all-county letters, provider bulletins, or similar instructions, without taking further regulatory action.
(d) The department shall seek any necessary federal approval for federal financial participation and coverage of services in this section under the Medi-Cal program.

SEC. 4.
No reimbursement is required by this act pursuant to Section 6 of Article XIII B of the California Constitution because the only costs that may be incurred by a local agency or school district will be incurred because this act creates a new crime or infraction, eliminates a crime or infraction, or

changes the penalty for a crime or infraction, within the meaning of Section 17556 of the Government Code, or changes the definition of a crime within the meaning of Section 6 of Article XIII B of the California Constitution.

APPENDIX B LITERATURE REVIEW METHODS

Appendix B describes methods used in the medical effectiveness literature review conducted for this report. A discussion of CHBRP's system for grading evidence, as well as lists of MeSH Terms, publication types, and keywords, follows.

Studies of treatments for HIV associated lipodystrophy were identified through searches of PubMed, the Cochrane Library, Web of Science, EconLit, Business Source Complete, the Cumulative Index of Nursing and Allied Health Literature (CINAHL), and PsycINFO. Websites maintained by the following organizations that produce and/or index meta-analyses and systematic reviews were also searched: the Agency for Healthcare Research and Quality (AHRQ), the International Network of Agencies for Health Technology Assessment (INAHTA), the National Health Service (NHS) Centre for Reviews and Dissemination, the National Institute for Health and Clinical Excellence (NICE), and the Scottish Intercollegiate Guideline Network.

The search was limited to abstracts of studies published in English. The search was limited to studies published from 2002 to present. CHBRP relied on a systematic review published in 2011 for findings from studies on growth hormone and a synthetic analog of growth hormone (tesamorelin) published prior to 2011. CHBRP relied on a systematic review published in 2015 for findings from studies on fillers and autologous fat transplantation published prior to 2015. CHBRP relied on two systematic reviews published in 2013 for findings from studies on antiretroviral therapy (ART) drugs published prior to 2013. CHBRP relied on a systematic review published in 2010 for findings from studies on insulin sensitizing drugs published prior to 2010.

Reviewers screened the title and abstract of each citation retrieved by the literature search to determine eligibility for inclusion. The reviewers acquired the full text of articles that were deemed eligible for inclusion in the review and reapplied the initial eligibility criteria.

Of the 338 articles found in the literature review, 50 were reviewed for potential inclusion in this report on SB 221, and a total of 20 studies were included in the medical effectiveness review for this report. The other articles were eliminated because they did not focus on HIV associated lipodystrophy, were of poor quality, or did not report findings from clinical research studies.

Evidence Grading System

In making a "call" for each outcome measure, the medical effectiveness lead and the content expert consider the number of studies as well the strength of the evidence. Further information about the criteria CHBRP uses to evaluate evidence of medical effectiveness can be found in CHBRP's *Medical Effectiveness Analysis Research Approach.*[28] To grade the evidence for each outcome measured, the team uses a grading system that has the following categories:

- Research design;
- Statistical significance;
- Direction of effect;

[28] Available at: www.chbrp.org/analysis_methodology/docs/medeffect_methods_detail.pdf.

- Size of effect; and
- Generalizability of findings.

The grading system also contains an overall conclusion that encompasses findings in these five domains. The conclusion is a statement that captures the strength and consistency of the evidence of an intervention's effect on an outcome. The following terms are used to characterize the body of evidence regarding an outcome:

- Clear and convincing evidence;
- Preponderance of evidence;
- Limited evidence
- Conflicting evidence; and
- Insufficient evidence.

A grade of *clear and convincing evidence* indicates that there are multiple studies of a treatment and that the large majority of studies are of high quality and consistently find that the treatment is either effective or not effective.

A grade of *preponderance of evidence* indicates that the majority of the studies reviewed are consistent in their findings that treatment is either effective or not effective.

A grade of *limited evidence* indicates that the studies had limited generalizability to the population of interest and/or the studies had a fatal flaw in research design or implementation.

A grade of *conflicting evidence* indicates that although some studies included in the medical effectiveness review find that a treatment is effective, a similar number of studies of equal quality suggest the treatment is not effective.

A grade of *insufficient* evidence indicates that there is not enough evidence available to know whether or not a treatment is effective, either because there are too few studies of the treatment or because the available studies are not of high quality. It does not indicate that a treatment is not effective.

The search terms used to locate studies relevant to SB 221 were as follows:

Major MeSH terms used to search PubMed

HIV Associated Lipodystrophy Syndrome [Majr]

Subheadings used with above heading:

/surgery
/rehabilitation
/drug therapy
/therapy
/economics
/statistics and numerical data
/ethnology
/epidemiology
Age Factors
Costs and Cost Analysis [EXP]
Epidemiologic Factors [EXP[
Outcome Assessment [EXP]
Vital Statistics [EXP]

Keywords used to search Embase, Cochrane Library, Web of Science, and relevant websites:

"HIV Associated Lipodystrophy"
(HIV AND Lipodystrophy) in Title
Age Factors
Comorbidities
Cost or Costs
Demand
Drug Therapy
Economics
Epidemiologic Factors or Epidemiology
Ethnicity
Morbidity
Mortality
Outcome*
Prevalence
Quality of Life
Racial Disparities
Savings
Statistics
Supply
Surgery
Therapy
Utilization
Vital Statistics

* = Truncation

APPENDIX C COST IMPACT ANALYSIS: DATA SOURCES, CAVEATS, AND ASSUMPTIONS

The cost analysis in this report was prepared by the members of the cost team, which consists of CHBRP task force members and contributors from the University of California, Los Angeles, and the University of California, Davis, as well as the contracted actuarial firms, PricewaterhouseCoopers (PwC).[29]

Information on the generally used data sources and estimation methods, as well as caveats and assumptions generally applicable to CHBRP's cost impacts analyses are available at CHBRP's website.[30]

This appendix describes any analysis-specific data sources, estimation methods, caveats and assumptions used in preparing this cost impact analysis.

Analysis Specific Caveats and Assumptions

This subsection discusses the caveats and assumptions relevant to the analysis of SB 221.

The population with health insurance that would be subject to SB 221 includes enrollees by DMHC-regulated commercial insurance plans (including plans with enrollees associated with CalPERS and Medi-Cal and CDI-regulated policies and would further impact the benefit coverage of Medi-Cal beneficiaries whose health insurance is through the COHS and FFS programs). Health plans and insurers could comply with this mandate) as part of their basic benefit package.

CHBRP assumed that the mandate would not impact any forms of cost sharing, such as deductibles, copays, and coinsurance. It is also assumed that the bill would not affect plan/insurer methods of utilization management that may impact postmandate coverage of medical and drug treatments between, such as use of prior authorization requirements and medical review for medical treatments, and use of formularies, tiered copayments, or mandatory generic substitutions for drug treatments.

Additionally, the following is a description of methodology and assumptions used to develop the estimates of cost impacts:

- For medical treatment of HIV associated lipodystrophy, Healthcare Common Procedure Coding System (HCPCS) and Current Procedural Terminology (CPT) codes were identified with carrier coverage guidelines and reviewed by a content expert. Additionally, for drug treatment of HIV associated lipodystrophy, National Drug Codes (NDC) codes were identified using the Truven Health Analytics Red Book™ and reviewed by a content expert.
- The estimated unit cost per service of HIV associated lipodystrophy treatment services, both for baseline and postmandate, used 2014 and 2015 MarketScan® Commercial Claims and Encounters Database, which reflects the most recent periods that are available. Two years of data were used to increase data credibility.
- Because lipodystrophy treatments were similar between HIV and non-HIV members, unit cost per service were analyzed using claims from members identified with lipodystrophy regardless of HIV

[29] CHBRP's authorizing statute, available at www.chbrp.org/docs/authorizing_statute.pdf, requires that CHBRP use a certified actuary or "other person with relevant knowledge and expertise" to determine financial impact.
[30] See *2017 Cost Impact Analyses: Data Sources, Caveats, and Assumptions*, available at www.chbrp.org/analysis_methodology/cost_impact_analysis.php.

status. From the 2014 and 2015 MarketScan® Commercial Claims and Encounters Database, utilization and unit cost information was developed for each service category.

- Baseline unit costs were trended at 3.1% annual rate of increase from 2015 to 2017 based on 2016 medical CPI rate, for a total increase of 9.6% over the time period. Baseline drug cost was trended at 6.5% annual rate of increase from 2014 to 2017 based on 2016 CPI rate, for a total increase of 20.8%.
- The analysis assumed that the unit cost per service do not change postmandate.
- The analysis assumed that utilization rates per 1,000 enrollees change postmandate only due to increased coverage.
- Baseline utilization rates per 1,000 enrollees were developed based on MarketScan® data for members diagnosed with HIV associated lipodystrophy. These members were identified by isolating incurred claims containing lipodystrophy and HIV ICD-9 and ICD-10 diagnosis codes between 2014 and 2015. Despite different treatments for those with lipoatrophy and those with lipodeposition, ICD-9 and ICD-10 codes do not distinguish between these two conditions. Prevalence assumptions were made for the population 65 and older, due to absence of MarketScan® data for this segment. Kaiser Family Foundation estimates HIV prevalence for Medicare beneficiaries to be 0.5%. Using the 0.5% HIV prevalence rate, CHBRP applied lipodystrophy prevalence among HIV patients age 60 to 64 observed in Truven data to estimate number of HIV- associated lipodystrophy patients 65 and older.
- Carrier surveys were administered to estimate the percentage of enrollees who had HIV-associated lipodystrophy treatment coverage in the baseline period.
- In the baseline and postmandate period, all enrollees with HIV are assumed to have outpatient drug coverage.
- There are likely out-of-pocket cost savings to enrollees postmandate who were in plans not compliant with SB221 and were paying for treatments out of pocket because their coverage was denied. However, there are no data to suggest what the current prevalence is for HIV associated lipodystrophy patients who pay for treatment out of pocket when treatment is denied and how much they pay out of pocket. Thus, CHBRP is unable to determine out-of-pocket cost savings estimates for these users.
- Due to the elasticity of demand for lipodystrophy treatments, in the baseline period, the analysis assumed individuals without coverage for treatments is 50% as likely to pay for treatment as individuals with coverage for treatments unless they are enrolled in Medi-Cal. In the baseline period, Medi-Cal individuals without coverage for treatments will not pay for treatments.

Determining Public Demand for the Proposed Mandate

This subsection discusses public demand for the benefits SB 221 would mandate. Considering the criteria specified by CHBRP's authorizing statute, CHBRP reviews public demand for benefits relevant to a proposed mandate in two ways. CHBRP:

- Considers the bargaining history of organized labor; and
- Compares the benefits provided by self-insured health plans or policies (which are not regulated by the DMHC or CDI and therefore not subject to state-level mandates) with the benefits that are provided by plans or policies that would be subject to the mandate.

On the basis of conversations with the largest collective bargaining agents in California, CHBRP concluded that unions currently do not include cost-sharing arrangements for description treatment or service. In general, unions negotiate for broader contract provisions such as coverage for dependents, premiums, deductibles, and broad coinsurance levels.

Among publicly funded self-insured health insurance policies, the preferred provider organization (PPO) plans offered by CalPERS currently have the largest number of enrollees. The CalPERS PPOs currently provide benefit coverage similar to what is available through group health insurance plans and policies that would be subject to the mandate.

To further investigate public demand, CHBRP used the bill-specific coverage survey to ask carriers who act as third-party administrators for (non-CalPERS) self-insured group health insurance programs whether the relevant benefit coverage differed from what is offered in group market plans or policies that would be subject to the mandate. The responses indicated that there were no substantive differences.

APPENDIX D INFORMATION SUBMITTED BY OUTSIDE PARTIES

In accordance with the California Health Benefits Review Program (CHBRP) policy to analyze information submitted by outside parties during the first 2 weeks of the CHBRP review, the following parties chose to submit information.

The following information was submitted by Ann Fryman, Office of California State Senator Scott Wiener, in February, 2017.

Cranston K, and Fukuda HD, *Massachusetts Department of Public Health Letter to M. Sciortino, of the Massachusetts House of Representatives*. February 26, 2014

Office of California State Senator Scott Wiener, *SB 221 – HEAL (Help End Antiretroviral-related Lipodystrophy) Act Fact Sheet.* January, 2017.

Submitted information is available upon request. For information on the processes for submitting information to CHBRP for review and consideration please visit: www.chbrp.org/requests.html.

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CALIFORNIA HEALTH BENEFITS REVIEW PROGRAM COMMITTEES AND STAFF

A group of faculty, researchers, and staff complete the analysis that informs California Health Benefits Review Program (CHBRP) reports. The CHBRP **Faculty Task Force** comprises rotating senior faculty from University of California (UC) campuses. In addition to these representatives, there are other ongoing contributors to CHBRP from UC that conduct much of the analysis. The **CHBRP staff** coordinates the efforts of the Faculty Task Force, works with Task Force members in preparing parts of the analysis, and manages all external communications, including those with the California Legislature. As required by CHBRP's authorizing legislation, UC contracts with a certified actuary, PricewaterhouseCoopers, to assist in assessing the financial impact of each legislative proposal mandating or repealing a health insurance benefit.

The **National Advisory Council** provides expert reviews of draft analyses and offers general guidance on the program to CHBRP staff and the Faculty Task Force. CHBRP is grateful for the valuable assistance of its National Advisory Council. CHBRP assumes full responsibility for the report and the accuracy of its contents.

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**A small percentage of AJ Scheitler's time is available to serve as a backup CHBRP staff resource.*

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A group of faculty and staff undertakes most of the analysis that informs reports by the California Health Benefits Review Program (CHBRP). The CHBRP Faculty Task Force comprises rotating representatives from multiple University of California (UC) campuses. In addition to these representatives, there are other ongoing contributors to CHBRP from UC. This larger group provides advice to the CHBRP staff on the overall administration of the program and conducts much of the analysis.

CHBRP staff coordinates the efforts of the Faculty Task Force, works with Task Force members in preparing parts of the analysis, and coordinates all external communications, including those with the California Legislature.

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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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