California Health Benefits Review Program

Analysis of California Assembly Bill 114 Medi-Cal Benefits: Rapid Whole Genome Sequencing

A Report to the 2021–2022 California State Legislature

March 27, 2021

CALIFORNIA
HEALTH BENEFITS REVIEW PROGRAM

Key Findings

Analysis of California Assembly Bill 114
Medi-Cal Benefits: Rapid Whole Genome Sequencing

Summary to the 2021–2022 California State Legislature, March 27, 2021

CALIFORNIA HEALTH BENEFITS REVIEW PROGRAM

SUMMARY

The version of California Assembly Bill (AB) 114 analyzed by CHBRP would expand the Medi-Cal schedule of benefits to include rapid whole genome sequencing (rWGS), including individual sequencing, trio sequencing for a parent or parents and their baby, and ultra-rapid sequencing, for any Medi-Cal beneficiary who is 1 year of age or younger receiving inpatient hospital services in an intensive care unit (ICU). AB 114 would be relevant to the benefit coverage of the subset of Medi-Cal beneficiaries who are 1 year of age or younger receiving care in an ICU.

Benefit Coverage: The Department of Health Care Services (DHCS) considers genetic testing a lab test that is already a covered benefit for Medi-Cal beneficiaries. Rapid whole genome sequencing used to diagnose children 1 year of age or younger in an ICU is already included in the existing all-inclusive inpatient diagnosis related group (DRG) or per diem payment hospitals receive from Medi-Cal Managed Care plans, Medi-Cal fee-for-service (FFS), or California Children's Services (CCS). AB 114 would not result in new benefit coverage that exceeds the definition of essential health benefits (EHBs) in California.

Medical Effectiveness: A preponderance of evidence shows that rWGS is effective at providing diagnoses for ill infants with diseases of unknown cause, resulting in a higher diagnostic rate than other standard genetic tests and a faster turnaround time to diagnosis. There is limited evidence showing that rWGS improved clinical utility in the treatment of ill infants in an ICU who received a diagnosis, including more precise care management and reduced hospitalization.

Cost and Health Impacts[1]: At baseline, 100% of beneficiaries with Medi-Cal coverage that would be subject to AB 114 have coverage for rWGS delivered in an ICU setting. CHBRP's analysis found no claims or encounters paid during 2019 for rWGS or other genetic tests delivered to Medi-Cal beneficiaries in an ICU, suggesting that DHCS is not paying separately for rWGS, whole exome sequencing, other gene sequencing, or other genetic tests.

AB 114 would have no impact on Medi-Cal expenditures because it is already a covered benefit under current law for 100% of Medi-Cal beneficiaries 1 year of age or younger who would be in an ICU bed.

CHBRP estimates AB 114 would produce no measurable public health impact due to no projected change in coverage. CHBRP did not find evidence to suggest that AB 114 would impact utilization of rWGS differentially by race/ethnicity, gender, income, or geography and so projects no impact on these disparities related to genetic disorders and clinical outcomes.

It is expected that AB 114 would result in no long-term utilization impacts, cost impacts, or public health impacts.

CONTEXT

The Budget Act of 2018 (SB 840) appropriated $2,000,000 for the Whole Genome Sequencing Pilot Project. It required DHCS to provide a grant to a state nonprofit organization for a one-time pilot project to investigate the potential clinical and programmatic value of utilizing rapid whole genome sequencing (rWGS) in the Medi-Cal program. Whole genome sequencing is a method used to evaluate a person's entire genome to identify mutations that may be responsible for a health condition. *Rapid* refers to the length of time to receive test results.[2] This pilot was known as Project Baby Bear and ended in June 2020. It provided rWGS to babies aged less than 1 year of age enrolled in Medi-Cal who were receiving intensive care at one of five pilot sites. The results of this pilot program are available in the Project Baby Bear Final Report provided to the State.

[1] Similar cost and health impacts could be expected for the following year, though possible changes in medical science and other aspects of health make stability of impacts less certain as time goes by.

[2] Refer to CHBRP's full report for full citations and references.

BILL SUMMARY

AB 114 would expand the Medi-Cal schedule of benefits to include rapid whole genome sequencing, including individual sequencing, trio sequencing for a parent or parents and their baby, and ultra-rapid sequencing, for any Medi-Cal beneficiary who is 1 year of age or younger and is receiving inpatient hospital services in an intensive care unit (ICU).

AB 114 would be relevant to the benefit coverage of the subset of Medi-Cal beneficiaries age 1 year or younger receiving care in an ICU. These beneficiaries can be enrolled in health plans regulated by the Department of Managed Health Care (DMHC), in County Organized Health Systems (COHS), or be primarily associated with Medi-Cal's fee-for-service (FFS) program.

IMPACTS

Benefit Coverage, Utilization, and Cost

Benefit Coverage

At baseline, 100% of beneficiaries with Medi-Cal coverage that would be subject to AB 114 have coverage for rWGS or an equivalent service delivered in an ICU setting.

According to DHCS payment policy for inpatient services delivered through Medi-Cal Managed Care plans, Medi-Cal FFS, or the California Children's Services (CCS) program, rWGS is already covered through the diagnosis related group (DRG) or per diem payment for those inpatient stays.

Utilization

CHBRP used data from Medi-Cal encounters and claims data from Milliman to assess baseline utilization and estimate postmandate utilization. There were no claims or encounters paid during 2019 for rWGS or other genetic tests delivered to Medi-Cal or CCS beneficiaries in an ICU. This analysis provides evidence to suggest that DHCS is not paying separately for rWGS, whole exome sequencing, other gene sequencing, or other genetic tests. As stated above, the DRG and per diem payments used to reimburse different hospitals by Medi-Cal and CCS are all-inclusive, meaning that lab services such as rWGS would not result in an additional payment or claim.

Although individual genetic tests provided during a hospital stay in an ICU are not identifiable through claims analyses, it is possible for physicians to order the tests to facilitate diagnosis and treatment of their patients. In the case of rWGS, physicians may be required to request approval from hospital administrators to order the test. However, if hospitals are concerned about the relative cost of the test due to the level of DRG or per diem reimbursement available for an ICU patient covered by Medi-Cal or CCS, they might not approve providers' requests to order rWGS. The hospitals' current DRG or per diem rate in Medi-Cal or CCS for that inpatient stay would not change based on the number or type of tests ordered since these rates are intended to cover necessary tests. Due to the all-inclusive nature of the inpatient DRG or per diem rate, laboratory and genetic tests delivered in an inpatient setting are not reimbursed separately by Medi-Cal Managed Care plans, Medi-Cal FFS, or CCS.

Expenditures

AB 114 would not change total net annual expenditures for beneficiaries 1 year of age or younger with Medi-Cal Managed Care, CCS, or other Medi-Cal FFS coverage. AB 114 would have no impact on Medi-Cal expenditures because it is already a covered benefit under current law for 100% of Medi-Cal and CCS beneficiaries 1 year of age or younger who would be in an ICU bed.

Although CHBRP estimates that Medi-Cal expenditures for rWGS would not change, it is possible that hospitals paying for rWGS to facilitate early diagnoses of genetic disorders would spend less on the provision of clinical care during the ICU stay. Depending on circumstances and severity of illness, hospitals receiving an all-inclusive DRG or per diem rate may have an incentive to authorize use of rWGS to speed up the diagnostic process or increase efficiency.

CHBRP estimates that administrative costs would not change for Medi-Cal Managed Care plans, Medi-Cal FFS, or CCS due to AB 114.

Medical Effectiveness

CHBRP found a preponderance[3] of evidence from eight studies that rWGS is effective at providing diagnoses for ill infants with diseases of unknown cause. These studies provided substantial evidence that rWGS resulted in a higher diagnostic rate than other standard

[3] *Preponderance of evidence* indicates that the majority of the studies reviewed are consistent in their findings that treatment is either effective or not effective.

genetic tests and provided a faster turnaround time to diagnosis.

CHBRP found limited[4] evidence that rWGS is effective at improving clinical utility in the treatment of ill infants receiving care in an ICU. Results from six studies provided limited evidence that rWGS improved clinical utility in the treatment of those who received a diagnosis, including more precise care management and reduced hospitalization. There were several limitations that contributed to the gradings provided, most notably the inherent barriers to conducting strong comparative research designs within a population of critically ill infants, resulting in a literature base that is not as rigorous and thereby limiting the certainty of conclusions drawn from the evidence.

Public Health

There is a preponderance of evidence that rWGS is effective at providing diagnoses and limited evidence that it is effective at improving clinical utility, indicating that for critically ill infants and their families, rWGS could lead to improvements to or affirmation of the care plan. However, because there is no projected change in coverage, CHBRP estimates AB 114 would produce no measurable public health impact at the population level.

Disparities in the prevalence and detection of genetic disorders exist; however, CHBRP did not find evidence to suggest that AB 114 would impact utilization of rWGS differentially by race/ethnicity, gender, income, or geography. CHBRP projects no impact on these disparities related to genetic disorders and clinical outcomes.

Long-Term Impacts

No long-term utilization or cost impacts are expected due to current coverage for rWGS in the existing inpatient DRG or per diem payment made by Medi-Cal Managed Care plans, Medi-Cal FFS, or CCS. Because CHBRP estimates no change in utilization, it is not anticipated that AB 114 would result in any long-term public health impacts.

Essential Health Benefits and the Affordable Care Act

Benefit coverage of Medi-Cal beneficiaries is not subject to the same set of essential health benefits (EHBs) as the benefit coverage of enrollees in nongrandfathered small-group and individual market plans and policies. AB 114 would not result in new benefit coverage that exceeds the definition of EHBs in California.

[4] *Limited evidence* indicates that the studies have limited generalizability to the population of interest and/or the studies have a fatal flaw in research design or implementation.

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

An analytic staff based at the University of California, Berkeley, supports a task force of faculty and research staff from multiple University of California campuses to complete each CHBRP analysis. A strict conflict-of-interest policy ensures that the analyses are undertaken without bias. A certified, independent actuary helps to estimate the financial impact. Content experts with comprehensive subject-matter expertise are consulted to provide essential background and input on the analytic approach for each report.

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.

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POLICY CONTEXT

The California Assembly Committee on Health has requested that the California Health Benefits Review Program (CHBRP)[5] conduct an evidence-based assessment of the medical, financial, and public health impacts of AB 114, Medi-Cal Benefits: Rapid Whole Genome Sequencing. Whole genome sequencing is a method used by health care professionals to evaluate a person's entire genome to identify mutations that may be responsible for a health condition. *Rapid* refers to the length of time to receive test results.

Bill-Specific Analysis of AB 114, Medi-Cal Benefits: Rapid Whole Genome Sequencing

Bill Language

AB 114 would expand the Medi-Cal schedule of benefits to include rapid whole genome sequencing (rWGS), including individual sequencing, trio sequencing for a parent or parents and their baby, and ultra-rapid sequencing, for any Medi-Cal beneficiary who is 1 year of age or younger and is receiving inpatient hospital services in an intensive care unit (ICU). Each of these types of sequencing is described in more detail below. The full text of AB 114 can be found in Appendix A.

Relevant Populations

If enacted, AB 114 would apply to a subset of Medi-Cal beneficiaries,[6] specifically those age 1 year or younger receiving care in an ICU. If enacted, the law would affect the coverage of Medi-Cal beneficiaries in Department of Managed Health Care (DMHC)–regulated Medi-Cal Managed Care plans, County Organized Health Systems (COHS), and the fee-for-service (FFS) program.

Analytic Approach and Key Assumptions

Although rWGS may be used as a diagnostic tool for individuals of any age, AB 114 would apply to only Medi-Cal beneficiaries 1 year of age or younger receiving inpatient care in an ICU. AB 114 specifies the types of sequencing to be covered: individual sequencing, which is for the infant only; trio sequencing, which is for a parent or parents and their infant; and ultra-rapid sequencing, where results can be obtained in as few as 3 days.

DHCS administers the Medi-Cal program and the California Children's Services (CCS) program. Medi-Cal covers primarily low-income individuals and families, and CCS covers children and persons under age 21 years with conditions such as cystic fibrosis, hemophilia, cerebral palsy, heart disease, cancer, and traumatic injuries. DHCS considers rWGS to be a laboratory test and, as such, covers genetic testing when medically necessary as part of the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) benefit for Medi-Cal beneficiaries under age 21 years. The CCS program covers diagnostic, treatment, case management, and physical and occupational therapy services for children with a CCS-eligible condition. About 70% of children eligible for CCS are also eligible for Medi-Cal. CCS covers genetic testing, of which rWGS is one type, if it is medically necessary.

[5] CHBRP's authorizing statute is available at www.chbrp.org/about_chbrp/faqs/index.php.
[6] CHBRP, *Estimates of Sources of Health Insurance in California for 2022*, February 4, 2021. www.chbrp.org/2021%20Projecting%202022%20Estimates%20of%20Sources%20FINAL%20020421.pdf.

For this analysis, CHBRP concluded that AB 114 would not change coverage for either Medi-Cal beneficiaries or those with a CCS-eligible condition who are 1 year of age or younger receiving care in an ICU because DHCS considers genetic testing to be a laboratory test that, when provided during an ICU stay, is included in the existing DRG or per diem payment structure for the hospital (for the CCS program, information is included in *NL 03-0518 Authorization of Genetic Testing – Revised*).

Interaction With Existing State and Federal Requirements

Health benefit mandates may interact and align with the following state and federal mandates or provisions.

California Policy Landscape

California law and regulations

The Budget Act of 2018 (SB 840) appropriated $2,000,000 for the Whole Genome Sequencing Pilot Project. It required DHCS to provide a grant to a state nonprofit organization for a one-time pilot project to investigate the potential clinical and programmatic value of utilizing rWGS in the Medi-Cal program. This pilot was known as Project Baby Bear and ended in June 2020. A more detailed description of Project Baby Bear is included in the *Medical Effectiveness* section of this report.

Related requirements in other states

Two other states — Florida and Michigan — have programs that were developed after Project Baby Bear was implemented in California, but neither appears to be mandated by the state.

A 2019 law in Utah (HB 435) requires the state Medicaid program and Public Employees' Benefit and Insurance Program to cover exome sequence testing,[7] and requires the Medicaid program to reimburse for exome sequence testing subject to a set of criteria (beneficiary under age 21 years, who remains undiagnosed after exhausting all other appropriate diagnostic-related tests; performed by a nationally recognized provider with significant experience in exome sequence testing; that is medically necessary; and at a rate set by the Medicaid program). Differences between the Utah law and AB 114 include: 1) The Utah law covers exome sequencing rather than whole genome sequencing; 2) the Utah law requires the Medicaid program to reimburse for the test when certain criteria are met, whereas AB 114 does not have this reimbursement requirement; 3) the Utah law does not specify the location of persons for whom such testing must be covered (e.g., outpatient, inpatient), whereas AB 114 specifies the patient location as the ICU; and 4) the Utah law applies to beneficiaries under age 21 years, whereas AB 114 applies to beneficiaries 1 year of age or younger.

Federal Policy Landscape

Affordable Care Act

A number of Affordable Care Act (ACA) provisions have the potential to or do interact with state benefit mandates. Below is an analysis of how AB 114 may interact with requirements of the ACA as presently exist in federal law, including the requirement for certain health insurance to cover essential health benefits (EHBs).[8,9]

[7] Whole exome sequencing is the identification and analysis of the protein-coding nuclear genes in the genome, which make up approximately 1% to 2% of the human genome, whereas whole genome sequencing examines all of the coding and noncoding nuclear DNA in the human genome (Wallace and Bean, 2020).
[8] The ACA requires nongrandfathered small-group and individual market health insurance — including, but not limited to qualified health plans sold in Covered California — to cover 10 specified categories of EHBs. Policy and issue

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 and regulations.

Essential Health Benefits

Benefit coverage of Medi-Cal beneficiaries is not subject to the same set of essential health benefits (EHBs) as the benefit coverage of enrollees in nongrandfathered small-group and individual market plans and policies. AB 114 would not result in new benefit coverage that exceeds the definition of EHBs in California.

briefs on EHBs and other ACA impacts are available on the CHBRP website: www.chbrp.org/other_publications/index.php.

[9] Although many provisions of the ACA have been codified in California law, the ACA was established by the federal government, and therefore, CHBRP generally discusses the ACA as a federal law.

BACKGROUND ON RAPID WHOLE GENOME SEQUENCING

This *Background* section provides context for understanding the scope and impact of rWGS to detect genetic disorders in critically ill infants 1 year of age or younger. Whole genome sequencing is a method used by health care professionals to evaluate a person's entire genome to identify mutations that may be responsible for a health condition. *Rapid* refers to the length of time to receive test results. The human genome is made up of all of an individual's genes, which contain deoxyribonucleic acid (DNA). A person's DNA contains the genetic coding to produce proteins, which are the building blocks of tissues and which carry out a multitude of functions.[10,11] A genetic disorder occurs when a there is a mutation in a gene that results in improper functioning. Gene mutations do not always have severe health implications; it depends on where they occur and what essential proteins are impacted.[12] In this section, we discuss genetic sequencing for diagnosis of critically ill infants, the focus of AB 114, rather than screening of all newborns.

For the purposes of this analysis, it is important to distinguish whole genome sequencing from whole exome sequencing. Whole exome sequencing is the identification and analysis of the protein-coding nuclear genes in the genome, which are approximately 1% to 2% of the human genome, whereas whole genome sequencing examines all of the coding and noncoding nuclear DNA in the human genome (Wallace and Bean, 2020). Both whole genome sequencing and whole exome sequencing are used increasingly in health care to identify a genetic basis for disease, but this *Background* section addresses whole genome sequencing specifically, because that is the focus of AB 114.

Genetic Disorders Diagnosed in Infants Less Than 1 Year Old

Genetic disorders can be diagnosed at any age depending on when the features are identified. However, disease can progress rapidly in infants, and the presentations of many genetic disorders overlap with symptoms observed in critically ill infants, such as seizures, respiratory failure, and cardiovascular failure (Kingsmore et al., 2019). Over 13,000 genetic disorders are currently known (Clark et al., 2019). According to the National Institutes of Health (NIH) U.S. National Library of Medicine, there are three broad categories of genetic disorders: monogenic, polygenic, and chromosomal.

Monogenic

Monogenic disorders are characterized by a single gene mutation[13] (Wallace and Bean, 2020). There are more than 6,250 known single gene disorders, with more discovered each year (Sanford et al., 2019). Examples of monogenic disorders are sickle cell disease, cystic fibrosis, neonatal diabetes mellitus, autosomal recessive polycystic kidney disease, and spinal muscular atrophy. Monogenic disorders can often be linked directly to an inherited gene from one or both of the parents, or may represent a new mutation in the patient (Glascock et al., 2018; Jackson et al., 2018; NIDDK, 2017a, 2017b).

Polygenic

Polygenic (also referred to as multifactorial or complex) disorders are caused by mutations in multiple genes, in combination with lifestyle and environmental factors. Examples of polygenic disorders are anencephaly and spina bifida (CDC, 2020a, 2020b; Children's Hospital of Philadelphia, 2021).

Chromosomal

Chromosomal disorders are characterized by missing or changed chromosomes or parts of chromosomes.[13] There are two classifications for chromosomal disorders: numerical disorders, in

[10] https://medlineplus.gov/genetics/understanding/basics/dna/.
[11] Personal communication with content expert Arthur D'Harlingue, MD, Director/Chief, Neonatology, UCSD Benioff Children's Hospital Oakland, March 22, 2021.
[12] https://medlineplus.gov/genetics/understanding/mutationsanddisorders/mutationscausedisease/.
[13] https://medlineplus.gov/geneticdisorders.html.

which there are too many or too few chromosomes (e.g., Down's syndrome, also known as trisomy 21); and structural disorders, which are more complex re-arrangements such as translocations or inversions (Jackson et al., 2018). Other than Down's syndrome, the most commonly known chromosomal abnormalities seen in live births are Turner syndrome; Klinefelter syndrome; and Edward's syndrome, also known as trisomy 18 (Genetic and Rare Disease Information Center, 2017).

Genetic Testing in Clinical Practice

Clinical presentation of genetic conditions in a critically ill neonate can vary widely and be complex and challenging due to the size of the child and rapid changes in health status. Symptoms of known genetic conditions could change quickly or not be evident at birth. In addition to known genetic conditions, there are instances of rare, unknown, or unexplained perinatal disorders (Hays and Wapner, 2021; van Diemen et al., 2017). If a genetic basis for disease is suspected, a clinician may order a genetic test accessible in the setting and according to the suspected disease etiology, if one is present. If not, a clinician may opt for whole genome sequencing to search the entire genome. Neonatal or infant genetic testing is performed on a sample of blood, umbilical cord, or buccal swab (Hays and Wapner, 2021). Depending on the severity of the child's condition, time to result of the genetic test may be a factor in testing approach. Although the paths leading to genetic testing may vary, CHBRP found literature recommending genetic testing pathways for patients with clinical presentation suggestive of a genetic condition (Hays and Wapner, 2021; Xue et al., 2015). Table 1 summarizes the types of sequencing that may be utilized in clinical practice for patients in a neonatal ICU (NICU) or pediatric ICU (PICU).

Table 1. Tests Used in Clinical Practice in NICU and PICU Patients for Suspected Genetic Disorders

Test	Description
Genome sequencing (a)	A laboratory test designed to identify and analyze the sequence of all coding and noncoding nuclear DNA.
Exome sequencing (a)	A laboratory test designed to identify and analyze the sequence of all protein-coding nuclear genes in the genome. Approximately 95% of the exome can be sequenced with currently available techniques.
Chromosomal microarray (CMA) (a) (b)	A molecular genetic test used to detect copy number variants (CNVs); CNVs are deletions (loss) or duplications (gain) of chromosome material that range in size from approximately one kilobase (kb) to multiple megabases (Mb), with the largest CNVs resulting in a loss or gain of an entire chromosome.
Karyotyping (a) (c)	A photographic representation of the chromosomes of a single cell, cut and arranged in pairs based on their size and banding pattern according to a standard classification. Involves direct microscopic examination of chromosomes from cultured cells.
Single-gene testing (a) (d)	Complete testing of one gene that might account for the phenotype observed. Single-gene testing may be used when the clinical features and other testing results for a patient are typical for a particular disorder and the association between the disorder and a specific gene is established.
Multigene panels (c)	Multigene panels allow simultaneous testing of two to more than 150 genes. The methods used in multigene panels may include sequence analysis, deletion/ duplication analysis, and/or other non–sequencing-based tests. There are two types of multigene panels: • Off the shelf: designed by a laboratory to include genes commonly associated with a broad phenotype (e.g., cardiomyopathy, ataxia, intellectual disability) or a recognizable syndrome with genetic heterogeneity (e.g., Noonan syndrome). • Custom designed: includes genes selected by a clinician for analysis by clinical sequencing. Results for each gene on the custom multigene panel are reported to the ordering clinician, whereas the results from the remaining genes sequenced (but not requested by the clinician) are not analyzed or included in the final

	laboratory report.
Trio sequencing (e) (f)	Sequencing of either exomes or whole genomes on both patients and parents. Results are improved by the availability of trio testing that includes both parents in addition to the patient.
Rapid whole genome sequencing (rWGS) (g)	Whole genome sequencing with an average turnaround time of 11 days. rWGS examines all exons and introns, approximately 90% of the genome.
Rapid whole exome sequencing (rWES) (g)	Whole exome sequencing with an average turnaround time of 11 days. rWES examines ~2% of the genome, representing almost all known exons and immediately flanking intronic regions typically within 10 to 20 base pairs of the exons.
Ultra-rapid whole genome sequencing (urWGS) (g)	Whole genome sequencing with an average turnaround time of 5.5 days.

Source: California Health Benefits Review Program, 2021.

Notes: (a) Wallace and Bean, 2020.

(b) Berg et al., 2017.

(c) Hays and Wapner, 2021.

(d) Xue et al., 2015.

(e) van Diemen et al., 2017.

(f) Personal communication with content expert Arthur D'Harlingue, MD, Director/Chief, Neonatology, UCSD Benioff Children's Hospital Oakland, March 2, 2021.

(g) Kingsmore et al., 2019.

Key: NICU = neonatal intensive care unit; PICU = pediatric intensive care unit.

Barriers to Genetic Testing

Much of the literature CHBRP found cites barriers to genetic testing outside of the critically ill infant population. These barriers can include lack of insurance coverage, lack of results clarity or ability to interpret results, or inconsistent referral to services (National Academies of Sciences, Engineering, and Medicine, 2018). For the population that AB 114 affects, some of these barriers may not be as relevant because they generally imply that the patient has decision-making power related to this health care tool. In the critically ill infant population, the most common barriers to receiving genetic testing are ability of the health care setting to interpret the clinically relevant results among the other variants observed, the availability and efficacy of medical interventions for results found, and cost associated with genomic sequencing (Friedman et al., 2019). Although academic medical centers, level IV NICUs, or other pediatric specialty facilities may have the capacity to interpret results, there is uncertainty whether other hospitals, especially those in more rural locations, have this capacity given the specialized nature of the test. Clark and colleagues cite a lack of trained experts in the field with the ability to analyze and interpret genomic test results, particularly rare results, making adoption of genetic testing a challenge in intensive care settings (Clark et al., 2019).

Prevalence of Genetic Disorders in Infants in California

Genetic disorders individually are rare, but together are a leading cause of infant mortality in the United States (Clark et al., 2019) and have remained in the top five leading causes of infant death in the United States since 2010. These conditions accounted for approximately 119 per 100,000 live births in 2018 (Ely et al., 2020). According to DHCS, there are 209,885 children enrolled in Medi-Cal under age 1 year; [14] therefore, approximately 250 of these children would be born with a genetic condition, of which a subset would potentially have rWGS utilized in their care. In California, approximately 1 in every 33 babies is born with a birth defect (March of Dimes, 2021). These conditions can have serious impacts on an infant's

[14] E-mail communication from DHCS, March 11, 2021.

health and the family. The state maintains the California Birth Defects Monitoring Program[15] surveillance system to gather data on a representative sample of approximately 30% of the births in California to follow trends in this health measure. Prevalence rates of birth defects are reported by individual condition and not in aggregate. Table 2 reports cases and prevalence rates for select genetic conditions. While these systems exist to help estimate prevalence of genetic disorders, CHBRP found literature indicating that genetic disorders may be under-diagnosed (Ceyhan-Birsoy et al., 2019; Kingsmore et al., 2019), and therefore may be underestimated in prevalence rates.

Table 2. Prevalence of Selected Genetic Disorders in Infants in California, 2012–2016

Genetic Condition	Cases	Prevalence Rate (Cases per 10,000 Live Births)	95% Confidence Interval
Anophthalmia/microphthalmia	56	1.8	1.3 – 2.3
Anotia/microtia	128	4.0	3.4 – 4.8
Neural tube defects (NTDs)	224	7.0	6.2 – 8.0
Trisomy 13	46	2.1	1.1 – 1.9
Trisomy 18	98	3.1	2.5 – 3.8
Trisomy 21	505	15.9	14.5 – 17.3

Source: California Health Benefits Review Program, 2021 (from California Birth Defects Monitoring Program Report of Birth Defects 2012–2016, available from: www.cdph.ca.gov/Programs/CFH/DGDS/CDPH%20Document%20Library/CBDMP%20Documents/Summary%20Birth%20Defect%20Prevalence%20Table.pdf. Accessed March 5, 2021).

Disparities[16] and Social Determinants of Health[17] in Genetic Disorders

Per statute, CHBRP includes discussion of disparities and social determinants of health (SDoH) as it relates to rWGS for genetic disorders. Disparities are noticeable and preventable differences between groups of people. CHBRP found literature identifying disparities by race/ethnicity and SDoH differences related to socioeconomic status and geographic location. Additionally, poor health contributes to reduced income, creating a negative feedback loop (Khullar and Chokshi, 2018).

Disparities

Race or ethnicity

According to the Centers for Disease Control and Prevention (CDC), there is evidence that some racial and ethnic groups have a significantly higher or lower occurrence of certain genetic disorders as compared to non-Hispanic Whites.[18] Specifically, trisomy 18 (extra 18th chromosome that affects development) has a much higher occurrence in those of non-Hispanic American Indian/Alaskan Native descent and in non-Hispanic Blacks, whereas anotia/microtia (birth defects of a baby's ear) has a higher occurrence in those of non-Hispanic American Indian/Alaskan Native descent and Hispanics.

[15] www.cdph.ca.gov/Programs/CFH/DGDS/Pages/cbdmp/default.aspx.
[16] Several competing definitions of "health disparities" exist. CHBRP relies on the following definition: Health disparity is defined as the differences, whether unjust or not, in health status or outcomes within a population. (Wyatt et al., 2016).
[17] CHBRP defines social determinants of health as conditions in which people are born, grow, live, work, learn, and age. These social determinants of health (economic factors, social factors, education, physical environment) are shaped by the distribution of money, power, and resources and impacted by policy (adapted from: CDC, 2014; Healthy People 2020, 2019). See CHBRP's SDoH white paper for further information: http://chbrp.com/analysis_methodology/public_health_impact_analysis.php.
[18] www.cdc.gov/ncbddd/birthdefects/features/racialethnicdifferences.html, accessed March 6, 2021.

Despite these findings, it is important to note that identifying the prevalence of genetic disorders among newborns for specific race/ethnic groups has limitations. It is widely stated that studies of genetic variation and diversity have focused on those of European descent and that not enough is known about genetic variation in other populations.[19] Additionally, there is a lack of diversity across state screening programs (Feuchtbaum et al., 2012). The existing research on primarily non-Hispanic Whites cannot be applied universally, which speaks to the inaccessibility of genetic diagnoses for underrepresented groups and need for race/ethnic-specific genetic research (Smith et al., 2016). There may also be a bias on the part of clinicians against recognition of certain genetic disorders that are contingent upon facial features described for certain disorders in racial and ethnic populations not of European descent (Fraiman and Wojcik, 2020). Further, it has been reported that underrepresented racial/ethnic groups may still have inconclusive results even if genetic services are provided due to reduced ability to interpret pathogenicity of variants found in populations categorized by ancestry, contributing further to disparities in diagnostic rates (Fraiman and Wojcik, 2020).

Sex or gender[20]

Sex or gender disparities related to genetic disorders in infants or use of rWGS are not widespread, but CHBRP found literature that identified some differences: for example, polygenic disorders usually affect one gender more than the other (Children's Hospital of Philadelphia, 2021). Additionally, gender differences among mixed-gender twins showed no significant difference in fetal mortality, but males had higher rates of neonatal mortality and overall infant mortality due to congenital abnormalities (Zhao et al., 2017).

Social Determinants of Health

Social determinants of health (SDoH) include factors outside of the traditional medical care system that influence health status and health outcomes (e.g., income, education, geography). CHBRP found literature citing differences in genetic disorders and use of rWGS by income and geography.

Income

Income may play a role in diagnosis of genetic conditions for several reasons. First, it is possible that for children in low-income communities, there may be bias on the part of clinicians to attribute developmental concerns to adverse childhood events, and this may delay suspicion of genetic disorders contributing to these concerns (Fraiman and Wojcik, 2020). Another way that income may impact these diagnoses is fewer referrals to genetic services in low-income communities. In one study of genetic diagnosis of Down's syndrome in an underserved community, Sobering and colleagues (2018) cited some barriers to accessing a genetic diagnosis as difficulty obtaining a referral to a geneticist and challenges with ultimately receiving a diagnostic confirmation from results of genetic tests. Critically ill infants of lower income families may also be more likely to be in a hospital that is unable to bear the cost of genomic testing. Conversely, families of a higher socioeconomic status may be able to pay out of pocket for genetic testing if necessary, making it more accessible for a rapid diagnosis.

Geography

Genetic testing offers the opportunity for individualized treatment plans, but the barriers to accessing such technology can be impacted by pediatric geneticists being located close to academic institutions and the lack of referrals for underserved populations (Fraiman and Wojcik, 2020; Hawkins and Hayden, 2011).

[19] Personal communication with content expert Arthur D'Harlingue, MD, Director/Chief, Neonatology, UCSD Benioff Children's Hospital Oakland, March 2, 2021.
[20] CHBRP uses the NIH distinction between "sex" and "gender": "'Sex' refers to biological differences between females and males, including chromosomes, sex organs, and endogenous hormonal profiles. 'Gender' refers to socially constructed and enacted roles and behaviors which occur in a historical and cultural context and vary across societies and over time." (NIH, 2019).

Genetic services remain sparse in rural settings, with experts in the field and health care settings capable of such testing centering increasingly in more urban areas and with funding from academic and industry endeavors (Strauss et al., 2018). If an infant in an ICU setting has been transferred from a more rural setting, the financial burden and time associated with travel, time off of work, and accommodations may be a major barrier for parents (Hawkins and Hayden, 2011). These barriers may result in poorer health outcomes for rural populations.

Societal Impact of Genetic Disorders in the United States

The presence of genetic disorders in the United States has direct and indirect economic and societal costs. In 2019, Gonzaludo and colleagues published the largest all-payer database review of pediatric discharges in the United States and found that patients with suspected genetic disorders had total costs between $12,000 and $77,000 higher per discharge compared to patients without a genetic disorder-linked International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code (Gonzaludo et al., 2019).

MEDICAL EFFECTIVENESS

As discussed in the *Policy Context* section, AB 114 would expand the Medi-Cal schedule of benefits to include rapid whole genome sequencing (rWGS), including individual sequencing, trio sequencing for parents and their babies, and ultra-rapid sequencing for patients 1 year of age or younger in an ICU. Additional information on rWGS is included in the *Background* section. The medical effectiveness review summarizes findings from evidence[21] on using rWGS to diagnose and treat critically ill infants and the effects on clinical outcomes.

Research Approach and Methods

Studies of rWGS as a diagnostic tool and use of rWGS in the treatment of critically ill infants were identified through searches of Medline Complete, the Cochrane Library, Web of Science, Scopus, the Cumulative Index of Nursing and Allied Health Literature, 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 Rady Children's Institute for Genomic Medicine website and available resources were also searched as pertinent to this bill and reviewed.

The search was limited to abstracts of studies published in English. The search was limited to studies published from 2011 to present. Of the 278 articles found in the literature review, 53 were reviewed for potential inclusion in this report on AB 114, and a total of eight studies were included in the medical effectiveness review for this report. The other articles were eliminated because they did not focus on the specific population of interest, 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.

The conclusions below are based on the best available evidence from peer-reviewed and grey literature.[22] Unpublished studies not yet accepted to peer-reviewed journals are not reviewed because the results of such studies, if they exist, do not meet the inclusion criteria for the medical effectiveness literature review and a published paper cannot be obtained within the 60-day timeframe for CHBRP reports.

Key Questions

1. What is the effectiveness of rWGS on diagnostic performance in ill infants with diseases of unknown cause?

2. Is treatment informed by rWGS effective in improving clinical utility in treatment of ill infants (1 year of age or younger) in an ICU?

[21] Much of the discussion in this section is focused on reviews of available literature. However, as noted in the section on Implementing the Hierarchy of Evidence on page 11 of the *Medical Effectiveness Analysis and Research Approach* document (posted at http://chbrp.com/analysis_methodology/medical_effectiveness_analysis.php), in the absence of fully applicable to the analysis peer-reviewed literature on well-designed randomized controlled trials (RCTs), CHBRP's hierarchy of evidence allows for the inclusion of other evidence.

[22] Grey literature consists of material that is not published commercially or indexed systematically in bibliographic databases. For more information on CHBRP's use of grey literature, visit http://chbrp.com/analysis_methodology/medical_effectiveness_analysis.php.

Methodological Considerations

The literature regarding use of rWGS for diagnosis and treatment of ill infants is limited, as there are several ethical barriers to conducting randomized controlled trials (RCTs) in this population. As a clinical tool, rWGS is also relatively new; therefore, the research on its clinical utility is limited. These factors result in a literature base that is not as rigorous, thereby limiting the certainty of conclusions drawn from the evidence.

Outcomes Assessed

The primary outcomes of interest for use of rWGS in critically ill infants are the diagnostic performance of the test and the resulting clinical utility for those diagnosed.

Diagnostic performance captures several indicators of the utility of the test, including sensitivity, specificity, accuracy, and time to diagnosis.

Clinical utility is measured here by specific changes in medical or surgical treatment — including changes to medications, treatments/therapies, and reduced hospitalization (including transitions to palliative care and/or decisions to end supportive care).

Study Findings

This following section summarizes CHBRP's findings regarding the strength of evidence for the effectiveness of using rWGS to diagnose and treat critically ill infants. Each section is accompanied by a corresponding figure. The title of the figure indicates the test, treatment, or service for which evidence is summarized. The statement in the box above the figure presents CHBRP's conclusion regarding the strength of evidence about the effect of a particular test, treatment, or service based on a specific relevant outcome and the number of studies on which CHBRP's conclusion is based. Definitions of CHBRP's grading scale terms are included in the box below, and more information is included in Appendix B.

The following terms are used to characterize the body of evidence regarding an outcome:

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.

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

Limited evidence indicates that the studies have limited generalizability to the population of interest and/or the studies have a fatal flaw in research design or implementation.

Inconclusive 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.

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.

More information is available in Appendix B.

Project Baby Bear Clinical Outcomes

As mentioned in the *Policy Context* section, a pilot program implemented across the State of California from 2018 to 2020, called Project Baby Bear, provided rWGS to babies enrolled in Medi-Cal who were receiving intensive care at one of five pilot sites to investigate the potential clinical value of utilizing rWGS in this population. The results of this pilot program are available in the Project Baby Bear Final Report provided to the State but are not yet published in a peer-reviewed format (Rady Children's Hospital, 2020). Though it does not meet CHBRP's requirements for inclusion in the medical effectiveness grading, the results from the pilot program are described here for context, given their relevance to AB 114.

The Project Baby Bear pilot program enrolled 178 infants (aged less than 1 year) who were hospitalized and in ICUs with unexplained critical illnesses. All 178 infants received rWGS and of those, 76 (43%) resulted in a diagnosis. The median time to receive provisional results was reported to be 3 days, with 31.5% of the cases analyzed using ultra-rapid whole genome sequencing (urWGS). The diagnoses led to a change in care for 55 infants (31% of overall sample; 72% of those with a diagnosis), including changes to medication, treatments, and procedures, as well as discontinuing futile care. To model reductions in health care utilization, a retrospective analysis was performed on a sample of 29 infants from this program for whom rWGS resulted in significant clinical benefit. This analysis estimated that use of rWGS in this sample of 29 infants resulted in 16 fewer invasive diagnostic tests, 11 fewer major surgeries, and 454 to 573 fewer hospitalization days in total.

Effectiveness of rWGS on Diagnostic Performance in Intensive Care for Infants

CHBRP identified eight studies that examined the effectiveness of rWGS on diagnostic performance in ill children with diseases of unknown cause.

The newborn sequencing in genomic medicine and public health RCT (NSIGHT1) by Petrikin et al. (2018) examined whether rWGS increased the proportion of infants in a neonatal ICU (NICU) or pediatric ICU (PICU) receiving a genetic diagnosis within 28 days. The participants were families with infants aged <4 months in a regional NICU and PICU, with illnesses of unknown etiology. The study randomized participants to receive rWGS plus standard genetic testing (n = 32) or standard genetic testing alone (n = 33). However, the authors cited a loss of clinical equipoise during the study, which refers to genuine uncertainty over whether a treatment will be beneficial and provides an ethical basis to randomly assign patients to different treatment arms. This meant that preliminary results provided enough evidence for rWGS to be a superior treatment arm to standard genetic testing, such that they could no longer ethically continue to randomly assign participants to the different treatment arms. As a result, the study was terminated early and intention-to-treat analyses were performed. Intention-to-treat analyses showed the rate of genetic diagnosis within 28 days of study enrollment to be higher in the rWGS group (31%, 10 of 32) than with standard genetic tests alone (3%, 1 of 33; $p = 0.003$). Additionally, among infants enrolled in the first 25 days of life, the rate of neonatal diagnosis was higher in the rWGS group (32%, 7 of 22) than with standard genetic tests alone (0%, 0 of 23; $p = 0.004$). The time to diagnosis was also found to be significantly faster through rWGS than with standard genetic testing (median = 13 and 107 days, respectively; $p = 0.04$).

NSIGHT2, a second RCT by Kingsmore et al. (2019), examined the effectiveness of rWGS or rapid whole exome sequencing (rWES) in ill infants with diseases of unknown etiology. Due to the limitations discussed in the first RCT presented above, rWES is used in this trial as a more equitable comparison group. As mentioned in the *Background* section, rWES and rWGS are both used as diagnostic tools to identify genetic causes of disease, with rWES targeting specified regions and covering approximately 2% of the genome and rWGS covering approximately 90% of the genome (Wallace and Bean, 2020). The trial included 213 infants (<4 months of age) who were enrolled in the study within 96 hours of hospital admission or development of a new presentation suggestive of underlying genetic cause. Of the 213 infants, 95 were randomized to rWES and 94 to rWGS; 24 (11%) were not randomized because they were critically ill and received urWGS. The analytic performance of rWGS, which refers to the test's sensitivity to identify variants, was found to be significantly greater than for rWES ($p < 0.0001$). However,

the diagnostic rate of the tests was not found to be significantly different, with rWGS resulting in 18 diagnoses in 94 infants (19%) and rWES resulting in 19 diagnoses in 95 infants (20%). The authors note that one of the diagnoses obtained through rWGS would have been missed had the infant received rWES, because rWES would not have analyzed the region of the genome where the gene abnormality was found. The median time to achieve the diagnostic result was also found to be similar between rWGS (11 days) and rWES (11.2 days). For those critically ill infants that received urWGS, diagnostic performance was higher than in rWGS or rWES, with 11 diagnoses in 24 infants (46%; $p = 0.004$), and the time to achieve the result was also found to be significantly less (median = 4.6 days; $p < 0.0001$).

A retrospective comparison study by Farnaes et al. (2018) examined the diagnostic and clinical utility of rWGS and the related health outcomes in acutely ill inpatient infants. The study included 42 infants (<1 year of age) from a regional children's hospital who had received rWGS, as well as standard genetic tests, and compared outcomes on diagnostic performance, clinical utility, health outcomes, and health care utilization. The diagnostic performance of rWGS was found to be significantly greater than that of standard genetic tests, with 18 (43%) genetic disease diagnoses by rWGS versus 4 (10%) by standard genetic testing ($p = 0.005$).

A retrospective comparison study by Willig et al. (2015) compared rWGS and standard genetic testing to assess the diagnostic utility and the effect of diagnoses that are likely to change medical management in critically ill infants. The study included 35 infants (<4 months of age) admitted to the NICU or PICU with an acute illness of suspected genetic cause. Trio sequencing, including both parents and their affected infant, was performed on all 35 patients. Standard genetic testing was also done per clinical recommendations on 32 of the 35 infants. The rate of diagnosis from rWGS was found to be significantly higher than from standard genetic testing, with 20 (57%) of 35 infants diagnosed through rWGS compared to 3 (9%) of 32 infants diagnosed through standard genetic testing ($p = 0.0002$).

A retrospective cohort study by Sanford et al. (2019) evaluated use of rWGS in pediatric critical care, including diagnostic and clinical utility. The study included 38 children (4 months to 17 years of age; median age = 3 years) in the PICU at a single-site children's hospital. Trio sequencing, including the patient and their parents, was preferred in all cases where parental samples were available (63% trio sequencing, 11% parent–child duos, and 26% single sequencing). Of the 38 children who received rWGS, 17 (45%) received a genetic diagnosis.

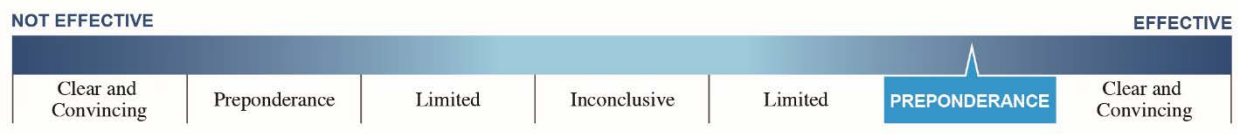
French et al. (2019) performed whole genome sequencing on a prospective cohort of families (n = 195) with children (1 day to 16 years of age) admitted to the NICU or PICU at a single site in the United Kingdom. Trio sequencing was the preferred method and was performed in 90% of cases (9% parent–child duos, 1% singleton), with an average time to diagnosis of 2 to 3 weeks. A diagnosis for an underlying genetic condition was determined in 40 (21%) of 195 cases.

A prospective cohort study by Mestek-Boukhibar et al. (2018) sought to demonstrate diagnostic and clinical utility of rWGS for critically ill children in a U.K. National Health Service setting. Trio rWGS was performed on a sample of 24 children in a PICU (median age = 2.5 months; range: 7 days to 13 years of age). A primary genetic diagnosis was determined through rWGS in 10 (42%) of the 24 cases, with a median time to diagnosis of 8 days.

Wang et al. (2020) conducted a prospective cohort study in a large children's hospital in China to examine the use of trio rWGS as a first-tier genetic diagnostic test in critically ill infants. The study enrolled 130 infants (<1 year of age) admitted to the NICU or PICU and suspected of having an underlying genetic disorder. A genetic diagnosis was determined in 62 of 130 infants, resulting in a diagnostic rate of 47.7%, with an average time to diagnosis of 4 days (range of 3 to 5 days).

Summary of findings regarding the diagnostic performance of rWGS in intensive care for infants: There is a *preponderance of evidence* that rWGS is effective at providing diagnoses for ill infants with diseases of unknown cause based on two RCTs, two retrospective comparison studies, three prospective cohort studies, and one retrospective cohort study.

Figure 1. Effectiveness of rWGS on Diagnostic Performance



Effectiveness of rWGS on Clinical Utility in Intensive Care for Infants

CHBRP identified six studies that examined the effectiveness of rWGS on clinical utility in the treatment of ill children in an ICU.

The retrospective comparison study by Farnaes et al. (2018) reported that clinical utility, defined here by specific changes in medical or surgical treatment, occurred in 13 of the 42 patients (31%; 13 of 18 diagnosed [72%]) and was significantly greater than with standard genetic testing (1 of 42; $p = 0.0015$). As a result of these changes in care, 11 patients (26%) were predicted to have avoided further morbidity, 1 patient was predicted to have a 43% reduction in likelihood of mortality, and 1 patient started palliative care. Additionally, the authors modeled health care utilization changes based on six of these patients for whom they had a historical matched control and estimated that the changes in care for these six patients reduced the length of hospital stays by a total of 124 days (ranging from a minimum of 1 to a maximum of 42 fewer hospitalization days).

In the retrospective comparison study by Willig et al. (2015), clinical utility was reported in 65% of infants (13 of 20) with a diagnosis through rWGS, meaning that the diagnosis informed the treatment team to make changes to their current care plan. These included medication changes, treatment/therapy changes, change in genetic counseling, and transition to palliative care. In four of these cases, the authors modeled that the clinical utility of the diagnosis resulted in substantial change to possible mortality, further morbidity, and length of stay in the ICU as compared to standard clinical care had these conditions gone undiagnosed.

In the retrospective cohort study by Sanford et al. (2019), for 14 of the 17 diagnosed children (82%; 37% of total sample), the diagnosis resulted in changes to clinical management outside of the ICU, including avoidance of unnecessary procedures and changes to the types of treatments or therapies used for disease management. Additionally, 4 of the 17 diagnoses resulted in a specific change to ICU management, including medication changes and transition to palliative care.

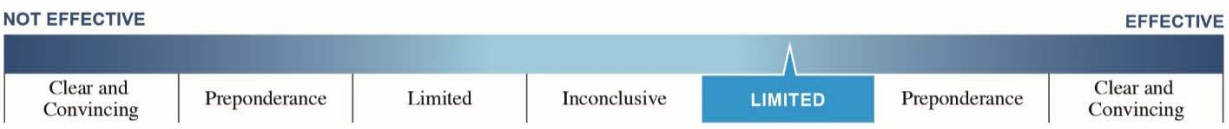
The French et al. (2019) prospective cohort study found that of those who received a genetic diagnosis, change to clinical management was reported in 68% of cases (27 of 40), including modification of treatment, initiating new disease-specific care, or transition to palliative care. In the neonate group specifically (0 to 4 weeks old), change to clinical management was reported in 83% (10 of 12) of cases.

In their prospective cohort study, Mestek-Boukhibar et al. (2018) reported that the diagnoses led to immediate clinical utility in 3 of the 10 diagnosed individuals (30%), including changes to care pathways and informed treatments and procedures. The authors also noted that in all families that received a genetic diagnosis, the diagnosis enabled proper education and counseling about the child's condition, avoided unnecessary tests, and informed families on the risk of recurrence.

The Wang et al. (2020) prospective cohort study demonstrated clinical utility in 30 of the 62 diagnosed patients (48%; 23% of overall sample), with immediate changes to clinical management such as informing procedures and treatments and starting or changing medication. The authors compared positive clinical outcomes between those who received a diagnosis (n = 62) and those who remained undiagnosed (n = 68) and found the outcomes to be significantly improved in those with a diagnosis ($p < 0.001$).

Summary of findings regarding the clinical utility of rWGS in intensive care for infants: There is *limited evidence* that rWGS is effective at improving clinical utility in the treatment of ill infants receiving care in an ICU based on two retrospective comparison studies, three prospective cohort studies, and one retrospective cohort study. Some of the limiting factors that contributed to this evidence grading are the quality of the research designs, absence of control or contemporaneous comparison groups, and the nonuniform assessment of clinical utility outcomes across studies.

Figure 2. Effectiveness of rWGS on Clinical Utility



Summary of Findings

CHBRP found a *preponderance of evidence* from eight studies, including two RCTs, three retrospective comparison and cohort studies, and three prospective cohort studies, that rWGS is effective at providing diagnoses for ill infants with diseases of unknown cause. These studies provided substantial evidence that rWGS resulted in a higher diagnostic rate than other standard genetic tests and provided a faster turnaround time to diagnosis. CHBRP found *limited evidence* from three retrospective comparison and cohort studies and three prospective cohort studies that rWGS is effective at improving clinical utility in the treatment of ill infants receiving care in an ICU. These studies provided limited evidence that rWGS improved clinical utility in the treatment of those who received a diagnosis, including more precise care management and reduced hospitalization. There were several limitations that contributed to the gradings provided in this review, most notably the inherent barriers to conducting strong comparative research designs within a population of critically ill infants, resulting in a literature base that is not as rigorous and thereby limiting the certainty of conclusions drawn from the evidence.

BENEFIT COVERAGE, UTILIZATION, AND COST IMPACTS

As discussed in the *Policy Context* section, AB 114 would expand the Medi-Cal schedule of benefits to include rWGS, including individual sequencing, trio sequencing for a parent or parents and their baby, and ultra-rapid sequencing, for any Medi-Cal beneficiary who is 1 year of age or younger and is receiving inpatient hospital services in an ICU. The full text of AB 114 can be found in Appendix A.

This section reports the potential incremental impacts of AB 114 on estimated baseline benefit coverage, utilization, and overall cost.

Assumptions on utilization and cost:

- CHBRP assumes that many of the conditions that could be diagnosed through rWGS will trigger eligibility for the California Children's Services (CCS) program. Claims for CCS cases are typically handled through the Medi-Cal FFS program rather than managed care plans, except in the few specific counties with County Organized Health Systems (COHS), where CCS benefits are carved-in to the COHS plan.
- CHBRP assumes that AB 114 would cause dual coverage for rWGS, such that the Medi-Cal Managed Care plan or Medi-Cal FFS and the CCS program would cover the benefit. However, due to the context in which children 1 year of age or younger in an ICU bed are likely to obtain care, most of the actual use of rWGS would be administered through CCS.
- CHBRP assumes utilization of health care services in 2022 will be roughly equivalent to utilization in 2018,[23] with adjustments made to account for changes in enrollment and population. CHBRP does not make additional assumptions to adjust for changes in utilization due to COVID-19 because recent 2020 claims data indicates utilization in aggregate has mostly returned to pre-pandemic levels. However, CHBRP acknowledges utilization has not rebounded for some services and for some groups of enrollees (i.e., visits for younger children had not returned to pre-pandemic baseline as of October 2020) (Mehrotra et al., 2020). There are additional unknown factors that may impact utilization as a result of COVID-19, such as the potential impacts of deferred care and long-term impacts from COVID-19 infections. For this analysis of AB 114, it is unlikely that COVID-19 would alter the care needed or received by the infants covered by the bill due to the seriousness of illnesses that would benefit from rWGS.

Additional considerations used to develop estimates of utilization and cost:

- CHBRP estimates that the turnaround time for results from rWGS will be faster than other methods of genetic testing, reducing the diagnosis time for undiagnosed or difficult to diagnose conditions.
- CHBRP used existing policy and *NL 03-0518 Authorization of Genetic Testing – Revised* to conclude that whole genome sequencing and other genetic tests delivered in an ICU setting are considered a lab test and are currently part of the diagnosis related group (DRG) or per diem payments made by Medi-Cal Managed Care plans, Medi-Cal FFS, or the CCS program to private and public hospitals providing care to Medi-Cal beneficiaries. AB 114 would only cover rWGS when delivered to an ICU patient 1 year of age or younger; therefore, DHCS would not make an additional, separate reimbursement for a genetic test outside of the existing inpatient DRG or per diem payment received by hospitals from the CCS program or Medi-Cal.

For further details on the underlying data sources and methods used in this analysis, please see Appendix C.

[23] CHBRP uses Milliman's 2018 Consolidated Health Cost Guidelines Sources Database (CHSD) and 2018 MarketScan Commercial Claims and Encounters Database (MarketScan) to estimate utilization in 2022.

Baseline and Postmandate Benefit Coverage

At baseline, 100% of Medi-Cal beneficiaries with coverage that would be subject to AB 114 have coverage for rWGS or an equivalent service delivered in an ICU setting. According to DHCS payment policy for inpatient services delivered through Medi-Cal Managed Care, Medi-Cal FFS, or CCS, rWGS is already covered through the DRG or per diem payment for those inpatient stays. The inpatient DRG payment model has been used since 2013 in private hospitals and since 2014 in nondesignated public hospitals, and it is an all-inclusive rate for the entire stay.[24] For designated public hospitals in California, ICU hospitalizations for Medi-Cal or CCS beneficiaries are reimbursed using a per diem rate for each day a patient is hospitalized.[25] Per diem payments also represent an all-inclusive rate and are paid for each day.

The Project Baby Bear pilot, which provided rWGS to 178 infants and parents, is not equivalent to the benefit coverage proposed in AB 114. DHCS provided a grant to Rady Children's Hospital to fund Project Baby Bear and support the ordering, processing, and interpretation of rWGS. However, the grant did not provide for reimbursement of the test even though Rady Children's Hospital was compensated for their time and effort through the grant to provide the rWGS tests ordered by five children's hospital sites in California.

Baseline and Postmandate Utilization

CHBRP used data from Medi-Cal encounters and claims data from Milliman to assess baseline utilization and estimate postmandate utilization. There were no claims or encounters paid during 2019 for rWGS or other genetic tests delivered to Medi-Cal or CCS beneficiaries in an ICU. This analysis provides evidence to suggest that DHCS is not paying separately for rWGS, whole exome sequencing, other gene sequencing, or other genetic tests. As stated above, the DRG and per diem payments used to reimburse different hospitals by Medi-Cal and CCS are all-inclusive, meaning that lab services like rWGS would not result in an additional payment or claim.

Although individual genetic tests provided during a hospital stay in an ICU are not identifiable through claims analyses, it is possible for physicians to order the tests to facilitate diagnosis and treatment of their patients. In the case of rWGS, physicians may be required to request approval from hospital administrators to order the test. However, if hospitals are concerned about the relative cost of the test due to the level of DRG or per diem reimbursement available for an ICU patient covered by Medi-Cal or CCS, they might not approve providers' requests to order rWGS. Under current law or AB 114, hospitals that decided to order an rWGS test for a current ICU patient would need to pay Rady Children's Hospital or an equivalent lab provider for rWGS. The hospitals' current DRG or per diem rate in Medi-Cal or CCS for that inpatient stay would not change based on the number or type of tests ordered since these rates are intended to cover necessary tests. Due to the all-inclusive nature of the inpatient DRG or per diem rate, laboratory and genetic tests delivered in an inpatient setting are not reimbursed separately by Medi-Cal Managed Care plans, Medi-Cal FFS, or CCS.

Baseline and Postmandate Per-Unit Cost

As stated in the *Policy Context* section, the Budget Act of 2018 (SB 840) appropriated $2,000,000 for a Whole Genome Sequencing Pilot Project. The pilot, Project Baby Bear, awarded a grant to Rady Children's Hospital to facilitate rWGS for children aged less than 1 year in the NICU or PICU at five children's hospitals in the state. The cost for each rWGS test in the pilot was $8,500, which was funded

[24] For details about the use of diagnosis related group (DRG) payments to hospitals for inpatient services, please visit www.dhcs.ca.gov/provgovpart/Pages/DRG.aspx.
[25] Information on CCS and payment for inpatient stays to private hospitals, nondesignated public hospitals, and designated public hospitals is available here: www.dhcs.ca.gov/services/ccs/Documents/ccsnl040715.pdf.

by the grant award and not through a separate Medi-Cal reimbursement. Because rWGS is already a covered Medi-Cal benefit for children 1 year of age or younger in the ICU, there are no separate claims for the services in Medi-Cal claims to calculate the per unit cost. There were also no separate commercial insurance claims for rWGS through CHBRP's analysis of 2019 insurance claims in California. This lack of claims is expected given that rWGS was not a covered benefit for any commercial plan in California until March 2020.

Baseline and Postmandate Expenditures

AB 114 would not change total net annual expenditures for beneficiaries 1 year of age or younger with Medi-Cal Managed Care, CCS, or other Medi-Cal FFS coverage. AB 114 would have no impact on Medi-Cal expenditures because it is already a covered benefit under current law for 100% of Medi-Cal and CCS beneficiaries 1 year of age or younger who would be in an ICU bed.

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

Evidence suggests that use of rWGS would reduce the average length of stay for specific ICU cases (i.e., those with a likely genetic disorder) by 16 to 21 days (Farnaes, et al. 2018; Rady Children's Hospital, 2020) and facilitate changes in clinical management of the newly diagnosed condition (French et al., 2019; Mestek-Boukhibar et al., 2018; Sanford et al., 2019; Willig et al., 2015). Although CHBRP estimates that Medi-Cal expenditures for rWGS would not change, it is possible that hospitals paying for rWGS to facilitate early diagnoses of genetic disorders would spend less on the provision of clinical care during the ICU stay. Depending on circumstances and severity of illness, hospitals receiving an all-inclusive DRG or per diem rate may have an incentive to authorize use of rWGS to speed up the diagnostic process or increase efficiency. However, because there is already 100% coverage for the services covered by AB 114, this incentive already exists, assuming hospitals know that Rady Children's Hospital or other laboratories can provide effective rWGS.

Postmandate Administrative Expenses and Other Expenses

CHBRP estimates that administrative costs would not change for Medi-Cal Managed Care plans, Medi-Cal FFS, or CCS due to AB 114.

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.

Potential Cost of Exceeding Essential Health Benefits

Benefit coverage of Medi-Cal beneficiaries is not subject to the same set of essential health benefits (EHBs) as the benefit coverage of enrollees in nongrandfathered small-group and individual market plans and policies. AB 114 would not result in new benefit coverage that exceeds the definition of EHBs in California.

Changes in Public Program Enrollment

CHBRP estimates that the mandate would produce no impact on enrollment in publicly funded insurance programs due to the enactment of AB 114.

PUBLIC HEALTH IMPACTS

As discussed in the *Policy Context* section, AB 114 would expand the Medi-Cal schedule of benefits to include rapid whole genome sequencing (rWGS), including individual sequencing, trio sequencing for a parent or parents and their baby, and ultra-rapid sequencing, for any Medi-Cal beneficiary who is 1 year of age or younger and is receiving inpatient hospital services in an ICU. 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[26] of AB 114 on diagnostic performance (sensitivity, specificity, accuracy, and time to diagnosis) and clinical utility (changes to medications, treatments/therapies, and reduced hospitalization). See *Long-Term Impacts* for discussion of social determinants of health.

Estimated Public Health Outcomes

As presented in the *Medical Effectiveness* section, there is a preponderance of evidence that rWGS is effective at providing diagnoses (sensitivity, specificity, accuracy, and time to diagnosis), and limited evidence that it is effective at improving clinical utility (e.g., changes to medications, treatments/therapies, reduced hospitalization).

As discussed in the *Benefit Coverage, Utilization, and Cost Impacts* section, 100% of beneficiaries affected by AB 114 currently have coverage for rWGS or an equivalent service delivered in an ICU setting. For these beneficiaries, the passage of AB 114 would not result in a change in benefit coverage. Although some cost savings are estimated due to reduced length of hospital admission for some patients, it is not anticipated that AB 114 would result in a change in utilization sufficient to result in public health improvements at the population level. For this reason, CHBRP concludes that AB 114 would have no measurable impact on public health outcomes in the first year postmandate.

As reported in *Medical Effectiveness*, there is a preponderance of evidence that rWGS is effective at providing diagnoses and limited evidence that it is effective at improving clinical utility, indicating that for critically ill infants and their families, rWGS could lead to improvements to or affirmation of the care plan. However, because there is no projected change in coverage, CHBRP estimates AB 114 would produce no measurable public health impact at the population level.

Impact on Disparities[27]

Insurance benefit mandates that bring more state-regulated plans and policies to parity may change an existing disparity. As described in the *Background* section, some disparities in genetic conditions or use of rWGS exist by race/ethnicity, gender, income, and geography. AB 114 would require compliance for the coverage of all Medi-Cal beneficiaries but would not be applicable to the health insurance of other enrollees in DMHC-regulated plans or to any enrollees in CDI-regulated policies. CHBRP estimates AB 114 would not change the identified disparities in the first 12 months postmandate due to no change in existing coverage or utilization. If a change in coverage, access, or utilization were to occur, rWGS could potentially become more accessible to those currently impacted by health disparities.

[26] CHBRP defines short-term impacts as changes occurring within 12 months of bill implementation.
[27] For details about CHBRP's methodological approach to analyzing disparities, see the *Benefit Mandate Structure and Unequal Racial/Ethnic Health Impacts* document here: http://chbrp.com/analysis_methodology/public_health_impact_analysis.php.

Disparities in the prevalence and detection of genetic disorders exist; however, CHBRP did not find evidence to suggest that AB 114 would impact utilization of rWGS differentially by race/ethnicity, gender, income, or geography due to no projected change in coverage for Medi-Cal beneficiaries. Therefore, CHBRP projects no impact on these disparities related to genetic disorders and clinical outcomes.

LONG-TERM IMPACTS

In this section, CHBRP estimates the long-term impact of AB 114, 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.

Long-Term Utilization and Cost Impacts

Utilization Impacts

No long-term utilization impacts are expected due to current coverage for rWGS in the existing inpatient DRG or per diem payment made by Medi-Cal Managed Care plans, Medi-Cal FFS, or CCS.

Cost Impacts

No long-term cost impacts are expected due to current coverage for rWGS in the existing inpatient DRG or per diem payment made by Medi-Cal Managed Care plans, Medi-Cal FFS, or CCS.

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, including impacts on social determinants of health. In the case of AB 114, CHBRP estimates no change in utilization; therefore, it is not anticipated that AB 114 would result in any long-term public health impacts.

APPENDIX A TEXT OF BILL ANALYZED

On January 27, 2021, the California Assembly Committee on Health requested that CHBRP analyze AB 114.

ASSEMBLY BILL **NO. 114**

Introduced by Assembly Member Maienschein

December 17, 2020

An act to amend Section 14132 of the Welfare and Institutions Code, relating to Medi-Cal.

LEGISLATIVE COUNSEL'S DIGEST

AB 114, as amended, Maienschein. Medi-Cal benefits: rapid Whole Genome Sequencing.

Existing law provides for the Medi-Cal program, which is administered by the State Department of Health Care Services, under which qualified low-income individuals receive health care services pursuant to a schedule of benefits. The Medi-Cal program is, in part, governed and funded by federal Medicaid program provisions. The Budget Act of 2018 appropriates $2,000,000 for the Whole Genome Sequencing Pilot Project, and requires the department to provide a grant to a state nonprofit organization for the execution of a one-time pilot project to investigate the potential clinical and programmatic value of utilizing clinical Whole Genome Sequencing in the Medi-Cal program.

This bill would expand the Medi-Cal schedule of benefits to include rapid Whole Genome ~~Sequencing, including individual sequencing, trio sequencing, and ultra rapid sequencing.~~ *Sequencing, as specified, for any Medi-Cal beneficiary who is one year of age or younger and is receiving inpatient hospital services in an intensive care unit.* The bill would authorize the department to implement this provision by various means without taking regulatory action.

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

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

SECTION 1. Section 14132 of the Welfare and Institutions Code is amended to read:

14132. The following is the schedule of benefits under this chapter:

(a) Outpatient services are covered as follows:

Physician, hospital or clinic outpatient, surgical center, respiratory care, optometric, chiropractic, psychology, podiatric, occupational therapy, physical therapy, speech therapy, audiology, acupuncture to the extent federal matching funds are provided for acupuncture, and services of persons rendering treatment by prayer or healing by spiritual means in the practice of any church or religious denomination insofar as these can be encompassed by federal participation under an approved plan, subject to utilization controls.

(b) (1) Inpatient hospital services, including, but not limited to, physician and podiatric services, physical ~~therapy~~ *therapy*, and occupational therapy, are covered subject to utilization controls.

(2) For *a* Medi-Cal fee-for-service ~~beneficiaries,~~ *beneficiary*, emergency services and care that are necessary for the treatment of an emergency medical condition and medical care directly related to the emergency medical condition. This paragraph ~~shall not be construed to~~ *does not* change the obligation of Medi-Cal managed care plans to provide emergency services and care. For the purposes of this paragraph, "emergency services and care" and "emergency medical condition" ~~shall~~ have the same meanings as those terms are defined in Section 1317.1 of the Health and Safety Code.

(c) Nursing facility services, subacute care services, and services provided by any category of intermediate care facility for the developmentally disabled, including podiatry, physician, nurse practitioner services, and prescribed drugs, as described in subdivision (d), are covered subject to utilization controls. Respiratory care, physical therapy, occupational therapy, speech therapy, and audiology services for patients in nursing facilities and any category of intermediate care facility for the developmentally disabled are covered subject to utilization controls.

(d) (1) Purchase of prescribed drugs is covered subject to the Medi-Cal List of Contract Drugs and utilization controls.

(2) Purchase of drugs used to treat erectile dysfunction or any off-label uses of those drugs are covered only to the extent that federal financial participation is available.

(3) (A) To the extent required by federal law, the purchase of outpatient prescribed drugs, for which the prescription is executed by a prescriber in written, nonelectronic form on or after April 1, 2008, is covered only when executed on a tamper resistant prescription form. The implementation of this paragraph shall conform to the guidance issued by the federal Centers for Medicare and Medicaid Services but shall not conflict with state statutes on the characteristics of tamper resistant prescriptions for controlled substances, including Section 11162.1 of the Health and Safety Code. The department shall provide providers and beneficiaries with as much flexibility in implementing these rules as allowed by the federal government. The department shall notify and consult with appropriate stakeholders in implementing, interpreting, or making specific this paragraph.

(B) Notwithstanding Chapter 3.5 (commencing with Section 11340) of Part 1 of Division 3 of Title 2 of the Government Code, the department may take the actions specified in subparagraph (A) by means of a provider bulletin or notice, policy letter, or other similar instructions without taking regulatory action.

(4) (A) (i) For the purposes of this paragraph, nonlegend has the same meaning as defined in subdivision (a) of Section 14105.45.

(ii) Nonlegend acetaminophen-containing products, with the exception of children's acetaminophen-containing products, selected by the department are not covered benefits.

(iii) Nonlegend cough and cold products selected by the department are not covered benefits. This clause shall be implemented on the first day of the first calendar month following 90 days after the effective date of the act that added this clause, or on the first day of the first calendar month following 60 days after the date the department secures all necessary federal approvals to implement this section, whichever is later.

(iv) ~~Beneficiaries~~ *A beneficiary* under the Early and Periodic Screening, ~~Diagnosis,~~ *Diagnostic*, and Treatment Program shall be exempt from clauses (ii) and (iii).

(B) Notwithstanding Chapter 3.5 (commencing with Section 11340) of Part 1 of Division 3 of Title 2 of the Government Code, the department may take the actions specified in subparagraph (A) by means of a provider bulletin or notice, policy letter, or other similar instruction without taking regulatory action.

(e) Outpatient dialysis services and home hemodialysis services, including physician services, medical supplies, drugs, and equipment required for dialysis, are covered, subject to utilization controls.

(f) Anesthesiologist services when provided as part of an outpatient medical procedure, nurse anesthetist services when rendered in an inpatient or outpatient setting under conditions set forth by the director, outpatient laboratory services, and ~~X-ray~~ *x-ray* services are covered, subject to utilization controls. ~~Nothing in this subdivision shall be construed to~~ *This subdivision does not* require prior authorization for anesthesiologist services provided as part of an outpatient medical procedure or for portable ~~X-ray~~ *x-ray* services in a nursing facility or any category of intermediate care facility for the developmentally disabled.

(g) Blood and blood derivatives are covered.

(h) (1) Emergency and essential diagnostic and restorative dental services, except for orthodontic, fixed bridgework, and partial dentures that are not necessary for balance of a complete artificial denture, are covered, subject to utilization controls. The utilization controls shall allow emergency and essential diagnostic and restorative dental services and prostheses that are necessary to prevent a significant disability or to replace previously furnished prostheses that are lost or destroyed due to circumstances beyond the beneficiary's control. Notwithstanding the foregoing, the director may by regulation provide for certain fixed artificial dentures necessary

for obtaining employment or for medical conditions that preclude the use of removable dental prostheses, and for orthodontic services in cleft palate deformities administered by the department's California Children Services Program.

(2) For persons 21 years of age or older, the services specified in paragraph (1) shall be provided subject to the following conditions:

(A) Periodontal treatment is not a benefit.

(B) Endodontic therapy is not a benefit except for vital pulpotomy.

(C) Laboratory processed crowns are not a benefit.

(D) Removable prosthetics shall be a benefit only for patients as a requirement for employment.

(E) The director may, by regulation, provide for the provision of fixed artificial dentures that are necessary for medical conditions that preclude the use of removable dental prostheses.

(F) Notwithstanding the conditions specified in subparagraphs (A) to (E), inclusive, the department may approve services for persons with special medical disorders subject to utilization review.

(3) Paragraph (2) shall become inoperative July 1, 1995.

(i) Medical transportation is covered, subject to utilization controls.

(j) Home health care services are covered, subject to utilization controls.

(k) Prosthetic and orthotic devices and eyeglasses are covered, subject to utilization controls. Utilization controls shall allow replacement of prosthetic and orthotic devices and eyeglasses necessary because of loss or destruction due to circumstances beyond the beneficiary's control. Frame styles for eyeglasses replaced pursuant to this subdivision shall not change more than once every two years, unless the department so directs.

Orthopedic and conventional shoes are covered when provided by a prosthetic and orthotic supplier on the prescription of a physician and when at least one of the shoes will be attached to a prosthesis or brace, subject to utilization controls. Modification of stock conventional or orthopedic shoes when medically ~~indicated, is covered~~ *indicated is covered,* subject to utilization controls. ~~When~~ *If* there is a clearly established medical need that cannot be satisfied by the modification of stock conventional or orthopedic shoes, custom-made orthopedic shoes are covered, subject to utilization controls.

Therapeutic shoes and inserts are covered when provided to ~~beneficiaries~~ *a beneficiary* with a diagnosis of diabetes, subject to utilization controls, to the extent that federal financial participation is available.

(l) Hearing aids are covered, subject to utilization controls. Utilization controls shall allow replacement of hearing aids necessary because of loss or destruction due to circumstances beyond the beneficiary's control.

(m) Durable medical equipment and medical supplies are covered, subject to utilization controls. The utilization controls shall allow the replacement of durable medical equipment and medical supplies when necessary because of loss or destruction due to circumstances beyond the beneficiary's control. The utilization controls shall allow authorization of durable medical equipment needed to assist a disabled beneficiary in caring for a child for whom the disabled beneficiary is a parent, stepparent, foster parent, or legal guardian, subject to the availability of federal financial participation. The department shall adopt emergency regulations to define and establish criteria for assistive durable medical equipment in accordance with the rulemaking provisions of the Administrative Procedure Act (Chapter 3.5 (commencing with Section 11340) of Part 1 of Division 3 of Title 2 of the Government Code).

(n) Family planning services are covered, subject to utilization controls. However, for Medi-Cal managed care plans, ~~any~~ utilization controls shall be subject to Section 1367.25 of the Health and Safety Code.

(o) Inpatient intensive rehabilitation hospital services, including respiratory rehabilitation services, in a general acute care hospital are covered, subject to utilization controls, when either of the following criteria are met:

(1) A patient with a permanent disability or severe impairment requires an inpatient intensive rehabilitation hospital program as described in Section 14064 to develop function beyond the limited amount that would occur in the normal course of recovery.

(2) A patient with a chronic or progressive disease requires an inpatient intensive rehabilitation hospital program as described in Section 14064 to maintain the patient's present functional level as long as possible.

(p) (1) Adult day health care is covered in accordance with Chapter 8.7 (commencing with Section 14520).

(2) Commencing 30 days after the effective date of the act that added this paragraph, and notwithstanding the number of days previously approved through a treatment authorization request, adult day health care is covered for a maximum of three days per week.

(3) As provided in accordance with paragraph (4), adult day health care is covered for a maximum of five days per week.

(4) As of the date that the director makes the declaration described in subdivision (g) of Section 14525.1, paragraph (2) shall become inoperative and paragraph (3) shall become operative.

(q) (1) Application of fluoride, or other appropriate fluoride treatment as defined by the department, and other prophylaxis treatment for children 17 years of age and under are covered.

(2) All dental hygiene services provided by a registered dental hygienist, registered dental hygienist in extended functions, and registered dental hygienist in alternative practice licensed pursuant to Sections 1753, 1917, 1918, and 1922 of the Business and Professions Code may be covered as long as they are within the scope of Denti-Cal benefits and they are necessary services provided by a registered dental hygienist, registered dental hygienist in extended functions, or registered dental hygienist in alternative practice.

(r) (1) Paramedic services performed by a city, county, or special district, or pursuant to a contract with a city, county, or special district, and pursuant to a program established under former Article 3 (commencing with Section 1480) of Chapter 2.5 of Division 2 of the Health and Safety Code by a paramedic certified pursuant to that article, and consisting of defibrillation and those services specified in subdivision (3) of former Section 1482 of the article.

(2) ~~All providers~~ *A provider* enrolled under this subdivision shall satisfy all applicable statutory and regulatory requirements for becoming a Medi-Cal provider.

(3) This subdivision shall be implemented only to the extent funding is available under Section 14106.6.

(s) *(1)* In-home medical care services are covered when medically appropriate and subject to utilization controls, for ~~beneficiaries~~ *a beneficiary* who would otherwise require care for an extended period of time in an acute care hospital at a cost higher than in-home medical care services. The director shall have the authority under this section to contract with organizations qualified to provide in-home medical care services to those persons. These services may be provided to ~~patients placed in~~ *a patient placed in a* shared or congregate living ~~arrangements,~~ *arrangement,* if a home setting is not medically appropriate or available to the beneficiary. ~~As~~

(2) As used in this section, "in-home medical care service" includes utility bills directly attributable to continuous, 24-hour operation of life-sustaining medical equipment, to the extent that federal financial participation is available.

~~As~~

(3) As used in this subdivision, in-home medical care services include, but are not limited to:

~~(1)~~

(A) Level-of-care and cost-of-care evaluations.

~~(2)~~

(B) Expenses, directly attributable to home care activities, for materials.

~~(3)~~

(C) Physician fees for home visits.

~~(4)~~

(D) Expenses directly attributable to home care activities for shelter and modification to shelter.

~~(5)~~

(E) Expenses directly attributable to additional costs of special diets, including tube feeding.

~~(6)~~

(F) Medically related personal services.

~~(7)~~

(G) Home nursing education.

~~(8)~~

(H) Emergency maintenance repair.

~~(9)~~

(I) Home health agency personnel benefits that permit coverage of care during periods when regular personnel are on vacation or using sick leave.

~~(10)~~

(J) All services needed to maintain antiseptic conditions at stoma or shunt sites on the body.

~~(11)~~

(K) Emergency and nonemergency medical transportation.

~~(12)~~

(L) Medical supplies.

~~(13)~~

(M) Medical equipment, including, but not limited to, scales, gurneys, and equipment racks suitable for paralyzed patients.

~~(14)~~

(N) Utility use directly attributable to the requirements of home care activities that are in addition to normal utility use.

~~(15)~~

(O) Special drugs and medications.

~~(16)~~

(P) Home health agency supervision of visiting staff that is medically necessary, but not included in the home health agency rate.

~~(17)~~

(Q) Therapy services.

~~(18)~~

(R) Household appliances and household utensil costs directly attributable to home care activities.

~~(19)~~

(S) Modification of medical equipment for home use.

~~(20)~~

(T) Training and orientation for use of life-support systems, including, but not limited to, support of respiratory functions.

~~(21)~~

(U) Respiratory care practitioner services as defined in Sections 3702 and 3703 of the Business and Professions Code, subject to prescription by a physician and surgeon.

~~Beneficiaries~~

(4) A beneficiary receiving in-home medical care services ~~are~~ *is* entitled to the full range of services within the Medi-Cal scope of benefits as defined by this section, subject to medical necessity and applicable utilization control. Services provided pursuant to this subdivision, which are not otherwise included in the Medi-Cal schedule of benefits, shall be available only to the extent that federal financial participation for these services is available in accordance with a home- and community-based services waiver.

(t) Home- and community-based services approved by the United States Department of Health and Human Services are covered to the extent that federal financial participation is available for

those services under the state plan or waivers granted in accordance with Section 1315 or 1396n of Title 42 of the United States Code. The director may seek waivers for any or all home- and community-based services approvable under Section 1315 or 1396n of Title 42 of the United States Code. Coverage for those services shall be limited by the terms, conditions, and duration of the federal waivers.

(u) Comprehensive perinatal services, as provided through an agreement with a health care provider designated in Section 14134.5 and meeting the standards developed by the department pursuant to Section 14134.5, subject to utilization controls.

The department shall seek any federal waivers necessary to implement the provisions of this subdivision. The provisions for which appropriate federal waivers cannot be obtained shall not be implemented. Provisions for which waivers are obtained or for which waivers are not required shall be implemented notwithstanding any inability to obtain federal waivers for the other provisions. No provision of this subdivision shall be implemented unless matching funds from Subchapter XIX (commencing with Section 1396) of Chapter 7 of Title 42 of the United States Code are available.

(v) Early and periodic screening, diagnosis, and treatment for any individual under 21 years of age is covered, consistent with the requirements of Subchapter XIX (commencing with Section 1396) of Chapter 7 of Title 42 of the United States Code.

(w) Hospice service ~~which~~ *that* is Medicare-certified hospice service is covered, subject to utilization controls. Coverage shall be available only to the extent that no additional net program costs are incurred.

(x) When a claim for treatment provided to a beneficiary includes both services that are authorized and reimbursable under this chapter, and services that are not reimbursable under this ~~chapter~~ *chapter*, that portion of the claim for the treatment and services authorized and reimbursable under this chapter shall be payable.

(y) Home- and community-based services approved by the United States Department of Health and Human Services for ~~beneficiaries~~ *a beneficiary* with a diagnosis of ~~AIDS or ARC, who require~~ *acquired immunodeficiency syndrome (AIDS) or AIDS-related complex who requires* intermediate care or a higher level of care.

Services provided pursuant to a waiver obtained from the Secretary of the United States Department of Health and Human Services pursuant to this subdivision, and ~~which~~ *that* are not otherwise included in the Medi-Cal schedule of benefits, shall be available only to the extent that federal financial participation for these services is available in accordance with the waiver, and subject to the terms, conditions, and duration of the waiver. These services shall be provided to ~~individual beneficiaries~~ *a beneficiary* in accordance with the client's needs as identified in the plan of care, and subject to medical necessity and applicable utilization control.

The director may under this section contract with organizations qualified to provide, directly or by subcontract, services provided for in this subdivision to ~~eligible beneficiaries.~~ *an eligible*

beneficiary. Contracts or agreements entered into pursuant to this division shall not be subject to the Public Contract Code.

(z) Respiratory care when provided in organized health care systems as defined in Section 3701 of the Business and Professions Code, and as an in-home medical service as outlined in subdivision (s).

(aa) (1) There is hereby established in the ~~department,~~ *department* a program to provide comprehensive clinical family planning services to any person who has a family income at or below 200 percent of the federal poverty level, as revised annually, and who is eligible to receive these services pursuant to the waiver identified in paragraph (2). This program shall be known as the Family Planning, Access, Care, and Treatment (Family PACT) Program.

(2) The department shall seek a waiver in accordance with Section 1315 of Title 42 of the United States Code, or a state plan amendment adopted in accordance with Section 1396a(a)(10)(A)(ii)(XXI) of Title 42 of the United States Code, which was added to Section 1396a of Title 42 of the United States Code by Section 2303(a)(2) of the federal Patient Protection and Affordable Care Act (PPACA) (Public Law 111-148), for a program to provide comprehensive clinical family planning services as described in paragraph (8). Under the waiver, the program shall be operated only in accordance with the waiver and the statutes and regulations in paragraph (4) and subject to the terms, conditions, and duration of the waiver. Under the state plan amendment, which shall replace the waiver and shall be known as the Family PACT successor state plan amendment, the program shall be operated only in accordance with this subdivision and the statutes and regulations in paragraph (4). The state shall use the standards and processes imposed by the state on January 1, 2007, including the application of an eligibility discount factor to the extent required by the federal Centers for Medicare and Medicaid Services, for purposes of determining eligibility as permitted under Section 1396a(a)(10)(A)(ii)(XXI) of Title 42 of the United States Code. To the extent that federal financial participation is available, the program shall continue to conduct education, outreach, enrollment, service delivery, and evaluation services as specified under the waiver. The services shall be provided under the program only if the waiver and, when applicable, the successor state plan amendment are approved by the federal Centers for Medicare and Medicaid Services and only to the extent that federal financial participation is available for the services. ~~Nothing in this section shall~~ *This section does not* prohibit the department from seeking the Family PACT successor state plan amendment during the operation of the waiver.

(3) Solely for the purposes of the waiver or Family PACT successor state plan amendment and notwithstanding any other law, the collection and use of an individual's social security number shall be necessary only to the extent required by federal law.

(4) Sections 14105.3 to 14105.39, inclusive, 14107.11, 24005, and 24013, and any regulations adopted under these statutes shall apply to the program provided for under this subdivision. No other ~~provision of~~ law under the Medi-Cal program or the State-Only Family Planning Program shall apply to the program provided for under this subdivision.

(5) 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, without taking regulatory action, the provisions of the waiver after its approval by the federal Centers for Medicare and Medicaid Services and the provisions of this section by means of an all-county letter or similar instruction to providers. Thereafter, the department shall adopt regulations to implement this section and the approved waiver in accordance with the requirements of Chapter 3.5 (commencing with Section 11340) of Part 1 of Division 3 of Title 2 of the Government Code. Beginning six months after the effective date of the act adding this subdivision, the department shall provide a status report to the Legislature on a semiannual basis until regulations have been adopted.

(6) ~~In the event that~~ *If* the Department of Finance determines that the program operated under the authority of the waiver described in paragraph (2) or the Family PACT successor state plan amendment is no longer cost effective, this subdivision shall become inoperative on the first day of the first month following the issuance of a 30-day notification of that determination in writing by the Department of Finance to the chairperson in each house that considers appropriations, the chairpersons of the committees, and the appropriate subcommittees in each house that considers the State Budget, and the Chairperson of the Joint Legislative Budget Committee.

(7) If this subdivision ceases to be operative, all persons who have received or are eligible to receive comprehensive clinical family planning services pursuant to the waiver described in paragraph (2) shall receive family planning services under the Medi-Cal program pursuant to subdivision (n) if they are otherwise eligible for Medi-Cal with no share of cost, or shall receive comprehensive clinical family planning services under the program established in Division 24 (commencing with Section 24000) either if they are eligible for Medi-Cal with a share of cost or if they are otherwise eligible under Section 24003.

(8) For purposes of this subdivision, "comprehensive clinical family planning services" means the process of establishing objectives for the number and spacing of children, and selecting the means by which those objectives may be achieved. These means include a broad range of acceptable and effective methods and services to limit or enhance fertility, including contraceptive methods, federal Food and Drug Administration approved contraceptive drugs, devices, and supplies, natural family planning, abstinence methods, and basic, limited fertility management. Comprehensive clinical family planning services include, but are not limited to, preconception counseling, maternal and fetal health counseling, general reproductive health care, including diagnosis and treatment of infections and conditions, including cancer, that threaten reproductive capability, medical family planning treatment and procedures, including supplies and followup, and informational, counseling, and educational services. Comprehensive clinical family planning services shall not include abortion, pregnancy testing solely for the purposes of referral for abortion or services ancillary to abortions, or pregnancy care that is not incident to the diagnosis of pregnancy. Comprehensive clinical family planning services shall be subject to utilization control and include all of the following:

(A) Family planning related services and male and female sterilization. Family planning services for men and women shall include emergency services and services for complications directly related to the contraceptive method, federal Food and Drug Administration approved

contraceptive drugs, devices, and supplies, and followup, consultation, and referral services, as indicated, which may require treatment authorization requests.

(B) All United States Department of Agriculture, federal Food and Drug Administration approved contraceptive drugs, devices, and supplies that are in keeping with current standards of practice and from which the individual may choose.

(C) Culturally and linguistically appropriate health education and counseling services, including informed consent, that include all of the following:

(i) Psychosocial and medical aspects of contraception.

(ii) Sexuality.

(iii) Fertility.

(iv) Pregnancy.

(v) Parenthood.

(vi) Infertility.

(vii) Reproductive health care.

(viii) Preconception and nutrition counseling.

(ix) Prevention and treatment of sexually transmitted infection.

(x) Use of contraceptive methods, federal Food and Drug Administration approved contraceptive drugs, devices, and supplies.

(xi) Possible contraceptive consequences and followup.

(xii) Interpersonal communication and negotiation of relationships to assist individuals and couples in effective contraceptive method use and planning families.

(D) A comprehensive health history, updated at the next periodic visit (between 11 and 24 months after initial examination) that includes a complete obstetrical history, gynecological history, contraceptive history, personal medical history, health risk factors, and family health history, including genetic or hereditary conditions.

(E) A complete physical examination on initial and subsequent periodic visits.

(F) Services, drugs, devices, and supplies deemed by the federal Centers for Medicare and Medicaid Services to be appropriate for inclusion in the program.

(9) In order to maximize the availability of federal financial participation under this subdivision, the director shall have the discretion to implement the Family PACT successor state plan amendment retroactively to July 1, 2010.

(ab) (1) Purchase of prescribed enteral nutrition products is covered, subject to the Medi-Cal list of enteral nutrition products and utilization controls.

(2) Purchase of enteral nutrition products is limited to those products to be administered through a feeding tube, including, but not limited to, a gastric, nasogastric, or jejunostomy tube. ~~Beneficiaries~~ *A beneficiary* under the Early and Periodic Screening, ~~Diagnosis,~~ *Diagnostic,* and Treatment Program shall be exempt from this paragraph.

(3) Notwithstanding paragraph (2), the department may deem an enteral nutrition product, not administered through a feeding tube, including, but not limited to, a gastric, nasogastric, or jejunostomy tube, a benefit for patients with diagnoses, including, but not limited to, malabsorption and inborn errors of metabolism, if the product has been shown to be neither investigational nor experimental when used as part of a therapeutic regimen to prevent serious disability or death.

(4) 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 amendments to this subdivision made by the act that added this paragraph by means of all-county letters, provider bulletins, or similar instructions, without taking regulatory action.

(5) The amendments made to this subdivision by the act that added this paragraph shall be implemented June 1, 2011, or on the first day of the first calendar month following 60 days after the date the department secures all necessary federal approvals to implement this section, whichever is later.

(ac) Diabetic testing supplies are covered when provided by a pharmacy, subject to utilization controls.

(ad) (1) Nonmedical transportation is covered, subject to utilization controls and permissible time and distance standards, for a beneficiary to obtain covered Medi-Cal services.

(2) (A) (i) Nonmedical transportation includes, at a minimum, round trip transportation for a beneficiary to obtain covered Medi-Cal services by passenger car, taxicab, or any other form of public or private conveyance, and mileage reimbursement when conveyance is in a private vehicle arranged by the beneficiary and not through a transportation broker, bus passes, taxi vouchers, or train tickets.

(ii) Nonmedical transportation does not include the transportation of *a* sick, injured, invalid, convalescent, infirm, or otherwise incapacitated ~~beneficiaries by ambulances, litter vans, or wheelchair vans~~ *beneficiary, by ambulance, litter van, or wheelchair van* licensed, operated, and equipped in accordance with state and local statutes, ordinances, or regulations.

(B) Nonmedical transportation shall be provided for a beneficiary who can attest in a manner to be specified by the department that other currently available resources have been reasonably exhausted. For ~~beneficiaries~~ *a beneficiary* enrolled in a managed care plan, nonmedical transportation shall be provided by the beneficiary's managed care plan. For *a* Medi-Cal fee-for-service ~~beneficiaries,~~ *beneficiary,* the department shall provide nonmedical transportation when those services are not available to the beneficiary under Sections 14132.44 and 14132.47.

(3) Nonmedical transportation shall be provided in a form and manner that is accessible, in terms of physical and geographic accessibility, for the beneficiary and consistent with applicable state and federal disability rights laws.

(4) It is the intent of the Legislature in enacting this subdivision to affirm the requirement under Section 431.53 of Title 42 of the Code of Federal Regulations, in which the department is required to provide necessary transportation, including nonmedical transportation, for recipients to and from covered services. This subdivision shall not be interpreted to add a new benefit to the Medi-Cal program.

(5) The department shall seek any federal approvals that may be required to implement this subdivision, including, but not limited to, approval of revisions to the existing state plan that the department determines are necessary to implement this subdivision.

(6) This subdivision shall be implemented only to the extent that federal financial participation is available and not otherwise ~~jeopardized,~~ *jeopardized* and any necessary federal approvals have been obtained.

(7) Prior to the effective date of any necessary federal approvals, nonmedical transportation was not a Medi-Cal managed care benefit with the exception of when provided as an Early and Periodic Screening, ~~Diagnosis, and Treatment (EPSDT)~~ *Diagnostic, and Treatment* service.

(8) Notwithstanding Chapter 3.5 (commencing with Section 11340) of Part 1 of Division 3 of Title 2 of the Government Code, the department, without taking any further regulatory action, shall implement, interpret, or make specific this subdivision by means of all-county letters, plan letters, plan or provider bulletins, or similar instructions until the time regulations are adopted. By July 1, 2018, the department shall adopt regulations in accordance with the requirements of Chapter 3.5 (commencing with Section 11340) of Part 1 of Division 3 of Title 2 of the Government Code. Commencing January 1, 2018, and notwithstanding Section 10231.5 of the Government Code, the department shall provide a status report to the Legislature on a semiannual basis, in compliance with Section 9795 of the Government Code, until regulations have been adopted.

(ae) (1) Rapid Whole Genome Sequencing, including individual sequencing, trio sequencing for ~~parents~~ *a parent or parents* and their baby, and ultra-rapid sequencing, is a covered ~~benefit.~~ *benefit for any Medi-Cal beneficiary who is one year of age or younger and is receiving inpatient hospital services in an intensive care unit.*

(2) Notwithstanding Chapter 3.5 (commencing with Section 11340) of Part 1 of Division 3 of Title 2 of the Government Code, the department, without taking any further regulatory action, shall implement, interpret, or make specific this subdivision by means of all-county letters, plan letters, plan or provider bulletins, or similar instructions until the time regulations are adopted.

APPENDIX B LITERATURE REVIEW METHODS

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

Studies of rWGS as a diagnostic tool and use of rWGS in the treatment of critically ill infants were identified through searches of Medline Complete, the Cochrane Library, Web of Science, Scopus, the Cumulative Index of Nursing and Allied Health Literature, 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 Rady Children's Institute for Genomic Medicine website and available resources were also searched as pertinent to this bill and reviewed. The search was limited to abstracts of studies published in English. The search was limited to studies published from 2011 to present.

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.

Medical Effectiveness Review

The medical effectiveness literature review returned abstracts for 278 articles, of which 53 were reviewed for inclusion in this report. A total of eight studies were included in the medical effectiveness review for AB 114.

Medical Effectiveness Evidence Grading System

In making a "call" for each outcome measure, the medical effectiveness lead considers 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;
- 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;*

[28] Available at: http://chbrp.com/analysis_methodology/medical_effectiveness_analysis.php.

- *Inconclusive 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 *inconclusive 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.

Search Terms

NOTE: The terms below represent major concepts used for the literature search. They were modified for each database and searched using Boolean and proximity operators, wildcards/truncation, subject headings, keywords, and keyword phrases as appropriate.

- Chromosomal Disorders/Abnormalities
- Costs and Cost Analysis
- Death/Fatality Rate
- Diagnostic Accuracy/Performance
- Diagnostic Errors
- Disease Management
- Disease-Free Survival
- Door-to-Treatment Time
- Early Detection/Diagnosis
- Economics
- Ethnic Groups
- Facilities and Services Utilization
- Fees and Charges
- Gender Equity
- Genetic Diseases/Disorders
- Genetic Predisposition to Disease
- Genomic Sequencing
- Health Care Outcome and Process Assessment
- Health Care Outcome Assessment
- Health Care Sector
- Health Services Accessibility
- Health Status Disparities
- Healthcare Disparities
- Healthcare/Treatment/Therapy Accessibility
- Health-Related Quality of Life
- Hospital Economics
- Hospitalization Duration/Length
- Inborn Genetic Diseases
- Individual Sequencing
- Length of Stay
- Minority Groups
- Minority Health
- Misdiagnosis
- Monogenic Diseases/Disorders
- Morbidity
- Mortality
- Patient Admission
- Patient Discharge
- Patient Readmission
- Polygenic/Multifactorial/Complex Disorders
- Prevalence
- Procedures/Therapy/Treatment/Surgery/Diagnosis
- Progression-Free Survival
- Quality of Life
- Race Factors
- Rapid Precision Medicine
- Rapid Whole Genome Sequencing
- Rare Genetic Diseases/Disorders

- Resource Allocation
- Sensitivity and Specificity
- Sex Factors
- Single-Gene Defects
- Singleton Genome Sequencing
- Therapeutic Index
- Time to Treatment
- Timeliness
- Treatment Delay
- Treatment Failure
- Treatment Outcomes
- Treatment/Therapy Accuracy/Efficacy
- Trio Rapid Whole Genome Sequencing
- Trio Sequencing
- Ultra-Rapid Whole Genome Sequencing
- Utilization
- Utilization Review
- Wasteful/Avoidable/Ineffective/ Unneeded/Unnecessary

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

The cost analysis presented in this report was prepared by the faculty and researchers connected to CHBRP's Task Force with expertise in health economics.[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 analysis-specific data sources, estimation methods, caveats, and assumptions used in preparing this cost impact analysis.

Second-Year Impacts on Benefit Coverage, Utilization, and Cost

There will be no second-year impact of AB 114 due to the existing coverage for rWGS.

[29] CHBRP's authorizing statute, available at https://chbrp.org/about_chbrp/index.php, requires that CHBRP use a certified actuary or "other person with relevant knowledge and expertise" to determine financial impact.
[30] See method documents posted at http://chbrp.com/analysis_methodology/cost_impact_analysis.php; in particular, see 2021 Cost Analyses: Data Sources, Caveats, and Assumptions.

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.

Valencia J. RE: Assembly Bill 114 (Maienschein) Medi-Cal benefits: rapid Whole Genome Sequencing [letter]. Valencia Government Relations, Inc., Illumina. February 10, 2021.

U.S. Patent and Trademark Office. Trademark application for “Rapid Whole Genome Sequencing” filed by Rady Children’s Hospital Research Center. Available at: https://tmsearch.uspto.gov/bin/showfield?f=doc&state=4803:g3aavt.2.1. Accessed March 2021.

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 researchers and analysts who are **Task Force 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, **Milliman**, 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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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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Please direct any questions concerning this document to: California Health Benefits Review Program; MC 3116; Berkeley, CA 94720-3116, info@chbrp.org, or www.chbrp.org.