CENTER FOR HEALTH
INFORMATION AND ANALYSIS

MANDATED BENEFIT REVIEW OF HOUSE BILL 3644 SUBMITTED TO THE 190TH GENERAL COURT: AN ACT RELATIVE TO CERTAIN GENETICALLY TARGETED DRUG COVERAGE FOR DUCHENNE MUSCULAR DYSTROPHY

MARCH 2018

CHIA

CHIA

TABLE OF CCONTENTS

CHIA

BENEFIT MANDATE OVERVIEW: H.B. 3644: AN ACT RELATIVE TO CERTAIN GENETICALLY TARGETED DRUG COVERAGE FOR DUCHENNE MUSCULAR DYSTROPHY

HISTORY OF THE BILL

The Joint Committee on Financial Services referred House Bill (H.B.) 3644, "An Act relative to certain genetically targeted drug coverage for Duchenne Muscular Dystrophy," [1] to the Center for Health Information and Analysis (CHIA) for review. Massachusetts General Laws (MGL), Chapter 3, Section 38C, requires CHIA to review and evaluate the potential fiscal impact of each mandated benefit bill referred to the agency by a legislative committee.

WHAT DOES THE BILL PROPOSE?

H.B. 3644, as submitted in the 190th General Court (General Court) of the Commonwealth of Massachusetts (Commonwealth), requires coverage of genetically targeted drugs[i] for Duchenne Muscular Dystrophy (DMD) when:

- The drug has been approved by the U.S. Food and Drug Administration (FDA) for the prescribed use, including pursuant to the accelerated approval provisions of section 506(c) of the U.S. Federal Food, Drug, and Cosmetic Act (FFDCA).[ii]
- The drug has been ordered or prescribed and determined to be medically necessary by a licensed physician who has thoroughly evaluated the patient and either possess expertise in DMD or has consulted with an expert in DMD, identified by the prescribing physician, who has determined the drug to be medically necessary for the patient.

Benefits under the bill shall not be subject to any greater deductible, coinsurance, co-payments, or out-of-pocket limits than any other benefit provided by the commission.[iii]

MEDICAL EFFICACY OF H.B. 3644

Muscular dystrophy is a genetic disease that leads to progressive weakness and loss of muscle mass. In DMD, genetic mutations prevent the production of the protein dystrophin, which keeps muscles intact by stabilizing and protecting muscle fibers. The onset of DMD is primarily between three and five years of age, and patients experience a delay in motor skill development. Most will begin to use a wheelchair between the ages 7 and 12. By the early teen years, the heart and respiratory muscles will be damaged, leading to cardiomyopathy, decreasing lung capacity, and developmental and learning difficulties. Patients with DMD are almost all males, and life expectancy currently averages into their 20s, with some patients surviving into their 30s.

There is no known cure for DMD, and standard treatment focuses on symptom control and improving a patient's quality of life. The completion of the human genome mapping, as well as other scientific advancements, has led to the development of genetically targeted drugs. The DMD gene is considered the longest in humans, and has made such targeted research complex, while the development of more accurate genetic diagnostic methods has resulted in the identification of specific mutations for individual patients. Currently, the most promising therapeutics focus on the most common DMD gene mutations, impacting relatively larger groups of patients with the disease.

---

i "Genetically targeted drug" shall mean a drug for which the approved use may result in the modulation, including suppression, up-regulation, or activation, of the function of a gene or its associated gene product and incorporates or utilizes non-replicating nucleic acid or analogous compounds to treat one or more patient subgroups, including subgroups of patients with different mutations of a gene.

ii Under the bill, insurance carriers shall not deny coverage by considering a genetically targeted drug experimental, investigational, or unproven when the drug has been approved pursuant to the accelerated approval of provisions of section 506(c) of the FFDCA.

iii This language has been interpreted to mean that the benefit cannot have cost-sharing in excess of the existing benefit with the greatest cost-sharing (i.e., a carrier cannot create a new cost-sharing structure for genetically targeted drugs to treat DMD—the drug must fit within the pre-existing cost-sharing formulary structure). This interpretation would not prevent a carrier from placing the drug in the highest (most expensive) tier, but it would prevent the carrier from creating a new and even higher tier.

One drug, Exondys 51, was approved in September 2016 by the FDA for DMD on a special approval pathway designed to give patients access to new treatments while clinical trials and verification of clinical benefit continues, as no other meaningful treatments currently exist to cure the disease or to slow its progression. As this approval was granted despite the recommendations of its external advisory committee and scientific staff, the FDA is requiring further clinical studies to prove the efficacy of the drug, and not just demonstrate increased dystrophin production, as the initial clinical trials had done.

In general, for genetically targeted drugs for DMD, problems with designing clinical trials, questions regarding appropriate outcomes and treatment efficacy, and high costs are being balanced against the lack of treatments to slow or stop a rapidly progressing fatal disease, as well as the significant scientific breakthroughs and advancements in recent years that show the possibility of effective therapy through genetically targeted drugs. Overall, it is unknown at this time whether the Commonwealth DMD population will benefit from use of these therapies, as their efficacy has not yet been proven through the results of clinical trials.

CURRENT COVERAGE

No Commonwealth state or federal law requires coverage of genetically targeted drugs for DMD.

In responses to a recent survey of insurance carriers in the Commonwealth, and based upon follow-up with the carriers, all but one small carrier reported that they cover Exondys 51, the only currently approved genetically targeted drug for DMD, provided the patient meets medical necessity criteria determined by the insurance carrier. At the time of the carrier surrey, one carrier had coverage under clinical review.

The Commonwealth's benchmark plan[2] does include coverage for prescription drugs but does not specifically include language to require coverage of genetically targeted therapies.

COST OF IMPLEMENTING THE BILL

Requiring coverage for this benefit by fully-insured health plans would result in an average annual increase, over five years, to the typical member's monthly health insurance premiums of between $0.06 and $0.64 PMPM,[iv] or between 0.012% and 0.125% of premium. The increase is driven primarily by shifting the determination of medical necessity from the insurance carrier to the physician and the expected growth of genetically targeted therapies.

The Commonwealth's Division of Insurance and the Commonwealth Health Insurance Connector Authority are responsible for determining any potential state liability associated with the proposed mandate under Section 1311 of the Affordable Care Act (ACA).

PLANS AFFECTED BY THE PROPOSED BENEFIT MANDATE

H.B. 3644 applies to commercial health insurance plans, hospital service corporations, medical service corporations, and health maintenance organizations (HMOs), as well as to both fully and self-insured plans operated by the Group Insurance Commission (GIC) for the benefit of public employees. It applies to plans grandfathered as exempt from the essential health benefit requirements of the ACA. The proposed mandate applies to Medicaid/MassHealth; however, CHIA's analysis does not estimate the potential effect of the proposed requirement on Medicaid expenditures.

PLANS NOT AFFECTED BY THE PROPOSED BENEFIT MANDATE

This analysis excludes members over 64 years of age with commercial, fully-insured plans. Self-insured plans (i.e., where the employer or policyholder retains the risk for medical expenses and uses a third-party administrator or insurer only to provide administrative functions), except for those provided by the GIC,[v] are not subject to state-level health insurance mandates. State mandates do not apply to Medicare and Medicare Advantage plans, the benefits for which are determined by or under rules set by the federal government. State mandates also do not apply to other federally funded plans, including TRICARE (covering military personnel and dependents), the Veterans Administration, and the Federal Employee's Health Benefit Plan.

iv PMPM refers to "per member per month."

v Although GIC plans are not included in the text of the bill as currently drafted, the sponsors indicate that GIC plans will be included in the final version.

MEDICAL EFFICACY ASSESSMENT

H.B. 3644, as submitted in the General Court, would require fully insured plans to cover genetically targeted,[vi] FDA-approved drugs for DMD when the drug has been determined by the patient's provider to be medically necessary, and the provider is either an expert in, or has consulted with an expert in, DMD.[3] Cost-sharing for these services must be similar to that for other services covered under the plan.

MGL Chapter 3 §38C charges the Commonwealth's CHIA with reviewing the medical efficacy of proposed mandated health insurance benefits. Medical efficacy reviews summarize current literature on the effectiveness and use of the mandated treatment or service, and describe the potential impact of a mandated benefit on the quality of patient care and the health status of the population.

DUCHENNE MUSCULAR DYSTROPHY

DMD occurs in approximately 1 in every 3,600 male births, and patients are almost exclusively males.[4] Researchers estimated the prevalence of DMD for males 5 – 24 years old between 1991 – 2010 to be approximately 1.02 per 10,000 males.[5]

Definite and Probable Cases of DMD Per 10,000 Male Individuals, By Age, 1991 – 2010[6]

Age	Cases/10,000 Males
5 – 9	1.04
10 – 14	1.29
15 – 19	1.08
20 – 24	0.67
All	1.02

DMD is one of nine types of muscular dystrophy, which is a genetic disorder that results in progressive muscle weakness and degeneration.[7] Patients with DMD have a genetic mutation that prevents the production of any of the functional protein dystrophin, which is located primarily in the skeletal and cardiac muscle, and works to keep muscle intact by stabilizing and protecting muscle fibers.[8,9] Comparatively, patients with inadequate or poor dystrophin are diagnosed with Becker Muscular Dystrophy (BMD), a condition that deteriorates much more slowly than DMD.[10] Together, these conditions are known as dystrophinopathies.[11]

Without dystrophin, the repeated contraction and relaxation of muscles damage the muscle cells themselves.[12] Eventually, the damaged muscle fibers weaken and die, leading to the heart and muscle weakness associated with DMD.[13] The onset of the disease is most often between three and five years of age and progresses rapidly.[14] DMD patients experience delayed motor skill development, resulting in trouble with sitting, standing, and walking.[15] Patients are often late walkers, as muscle weakness most often begins in the hips, pelvis, thighs, and shoulders, progressing to the voluntary skeletal muscles of the arms, legs, and trunk.[16] Patients often have enlarged calves, known as pseudohypertrophy, and most will begin to use a wheelchair between the ages of 7 and 12.[17]

vi Defined in H.B. 3644 as: "a drug for which the approved use may result in the modulation, including suppression, up-regulation, or activation, of the function of a gene or its associated gene product and incorporates or utilizes non-replicating nucleic acid or analogous compounds to treat one or more patient subgroups, including subgroups of patients with different mutations of a gene."

Clinical Abnormalities Associated With DMD[18]

Connective Tissue	Limbs	Cardiovascular System	Musculature
• Flexion contracture	• Calf muscle pseudohypertropy	• ECG[vii] abnormality • Heart failure • Primary dilated cardiomyopathy	• Calf muscle pseudohypertrophy • Flexion contracture • Gowers sign • Muscular dystrophy • Muscular hypotonia

Nervous System	Respiratory System	Skeletal System	Metabolism/Homeostasis
• Hyporeflexia • Intellectual disability (mild) • Waddling gait	• Hypoventilation • Respiratory failure	• Flexion contracture • Hyperlordosis • Scoliosis	• Creatine phosphokinase • Elevated serum

Damage eventually occurs to heart and respiratory muscles, usually by a patient's early teen years.[19] Patients may suffer from cardiomyopathy, as the heart muscle, or myocardium, weakens.[20] The heart muscle will later become enlarged and develop into dilated cardiomyopathy, a condition that deteriorates rapidly, and may include irregular heartbeat (arrhythmia), shortness of breath, swelling of the hands and feet, and extreme fatigue; most cases of dilated cardiomyopathy are life-threatening.[21]

Around age 10, the muscles around a patient's lungs begin to weaken, leading to decreased respiratory capacity. [22] This likewise makes coughing difficult, leading to an increase in the number of serious respiratory infections for DMD patients, including pneumonia.[23] These respiratory difficulties also lead to headaches, difficulty in staying awake or concentrating, nightmares, and mental dullness.[24] Approximately one-third of patients with DMD also have developmental and learning difficulties that impact their cognitive and emotional growth, most often associated with attention focusing, emotional interaction, and verbal learning and memory.[25] Life expectancy for patients with DMD has extended from the teen years and now averages into the 20s, with some patients surviving into the 30s, with advances in cardiac and respiratory therapies.[26,27]

To diagnose DMD, clinicians begin with a history and physical, including a diagnostic blood test to gauge the patient's creatine kinase (CK) level, measuring an enzyme that leaks from damaged muscle.[28] Abnormally high CK levels indicate muscle destruction, while very high levels suggest that the patient's weakness is caused by the muscles themselves, as opposed to the nerves controlling the muscles.[29] To further gauge the cause of a patient's weakness, a muscle biopsy is performed, which allows for a close examination of the presence or absence of dystrophin in the muscle tissue.[30] Additionally, patients undergo genetic testing to identify the type and location of the gene mutation that led to their disease.[31]

vii Electrocardiogram, also called ECG or EKG, is a test to measure electrical activity of the heartbeat.

TREATMENT FOR DMD

According to the Muscular Dystrophy Association, DMD patients were unlikely to survive out of the teen years until relatively recently.[32] There is no known cure for DMD, and standard treatment currently focuses on symptom control and quality of life improvement.[33] DMD patients require multidisciplinary care to address the range of physical and psychosocial issues that they may face. As the disease progresses, patients will need a variety of medical management interventions, including mobility aids such as walkers, braces, and wheelchairs, in addition to exercise and occupational and physical therapy.[34] Various clinicians manage cardiomyopathy and other cardiac complications, contractures, or fixation of the joints, as well as learning disabilities according to a patient's symptoms and needs.[35] Patients with gastroesophageal reflux may be treated with proton pump inhibitors.[viii,36] Respiratory care and therapy is also necessary to minimize infections and complications, as breathing muscles continue to weaken, and the body's ability to emit secretions diminishes.[37] Eventually, a patient may require assisted ventilation in order to breathe.[38]

Medications for DMD are also part of a normal course of treatment. Medications, including angiotensin converting enzyme inhibitors, diuretics, and beta blockers, may be used to improve heart function.[39] Clinicians often prescribe corticosteroids, including prednisone and deflazacort, to reduce inflammation and to try to slow the course of DMD progression by preserving muscle strength and function; prevent scoliosis; and enable patient mobility.[40] While these medications may increase strength, muscle, and pulmonary function, long-term use also may cause serious side effects, including weight gain, cataracts, and loss of bone mass; moreover, the rapid withdrawal of these drugs may lead to life-threatening complications.[41]

RESEARCH AND DEVELOPMENT FOR NEW DMD TREATMENTS

Research into new treatments for DMD has focused on a wide variety of areas, including replacement of the dystrophin protein, protection of muscles from additional damage, promotion of muscle repair and regrowth, care and treatment of associated conditions and syndromes, and improved methods for symptom management and control.[42]

The DMD gene itself has made research into genetic therapies exceptionally complex. The DMD gene is considered the longest in humans and includes 79 exons, or DNA regions that are translated into protein.[43,44,45] The gene's length makes it more susceptible to mutations, with some regions more likely than others to alter.[46] So far, researchers have identified over 7,000 mutations on the DMD gene.[47]

One approach to genetic therapy is gene transfer, in which genes are delivered as therapeutic agents to either replace mutated genes with healthy genes, or to deliver adjunct, or surrogate, genes to improve disease symptoms. For DMD, gene therapy research has thus far focused on delivering replacement genes to produce the missing dystrophin proteins; while the intent is for this treatment to provide longer-term benefits than other currently available therapies, this approach is not likely to reverse or completely cure the disease.[48] For a more detailed overview of the use of gene therapy in the treatment of DMD, please see the appendix.

GENETICALLY TARGETED DRUGS

Another approach to DMD treatment is the development of genetically targeted drugs that will alter or correct mutations that cause problems in how cells read genetic instructions, thus leading to DMD.

viii Medications used to reduce the amount of stomach acid produced.

The development of genetically targeted drugs has relied on decades of research that analyzed the types of mutations within this large gene, and the specific locations of each type. Additional studies have focused on predicting which types of mutations might be most amenable to which types of treatment, as well as on the development of diagnostic tools that allow better understanding of the proportion of patients who have each type of mutation, and which are most likely to benefit from mutation-specific therapies.[57] Human genome mapping, along with the availability of more accurate genetic diagnostic methods, have created the foundation upon which recent advancements and developments have relied. Currently, the most promising therapeutics focus on the most common mutations found in the DMD gene (see the appendix for more details):[50]

- Exon-skipping drugs introduce antisense oligonucleotide molecules (AONs) into a gene, and are designed to force muscle fibers to skip a gene's faulty section to allow partially functional dystrophin to develop. Scientists have estimated that about 60% of DMD cases are related to deletions of one of its 79 exons,[51] and 6% from their duplication.[52] These deletions and duplications, along with some other small mutations, amount to approximately 83% of all DMD mutations.[53] One study concluded that, of these mutations, 55% of the total would "potentially benefit" from exon-skipping therapy.[54] This approach will not cure the disease, but is intended to lessen its effects and symptoms.

  While this type of therapy may benefit a large proportion of DMD patients, the specific treatment is dependent of the specific location of the mutation. Therefore, research into these treatments is focused on those locations of this mutation that are most common, and the development of AONs to target those specific locations. These treatments include clinical trials targeting exon 51, which applies to approximately 13% of patients, the largest group of patients with a single-exon skipping mutation; exon 45, applicable to about 8% of patients; and exon 53, also applicable to about 8% of patients.[55,56] Researchers are also exploring drug development to target exons 44, 50, 52, and 55, as well as mutations at multiple exons.

- "Stop codon read through drugs" are designed to target so-called premature stop codons or nonsense mutations that result in dystrophin production ceasing before assembly is complete. These therapies are intended to push cells to ignore these nonsense signals, read through a premature stop, and continue dystrophin production. Approximately 10% of DMD patients have this type of mutation, and may therefore benefit from this approach to treatment.[57]

A search of the clinical studies database at the National Library of Medicine for active DMD studies yielded 84 current clinical trials at various phases of the research process.[58,59] At least 10 studies are focused on exon skipping therapies, and another 5 on a stop codon read through drug known as Ataluren.[60]

The only drug among these drug types approved to date by the FDA for treatment of DMD is the exon-skipping drug Exondys 51, which was approved in September 2016 on a special approval pathway designed to give patients access to new treatments while clinical trials and verification of clinical benefit continues, as no other meaningful treatments currently exist to cure the disease, or to slow its progression. The injectable drug, also known by its generic name eteplirsen, is specifically approved to treat a type of DMD that affects approximately 13% of DMD patients with a "confirmed mutation of the dystrophin gene amenable to exon 51 skipping."[61] The FDA pathway used is specifically available for treatments for serious and life-threatening conditions that "generally provide a meaningful advantage over existing treatments."[62] Different from the traditional approval process, the accelerated pathway allows for the submission of studies that show an effect on a "surrogate endpoint that is reasonably likely to predict clinical benefit to patients."[63] With accelerated approval, patients can gain access to new treatments while clinical trials and verification of clinical benefit continues.[64] As the approval of Exondys 51 was granted despite the contrary recommendations of its external advisory committee and scientific staff, the FDA is requiring further clinical studies to prove the efficacy of the drug, and not just demonstrate increased dystrophin production, as the initial clinical trials had done.[65]

This means that, for Exondys 51, some treated patients increased their skeletal muscle, which the FDA concluded "demonstrated an increase in dystrophin production that is reasonably likely to predict clinical benefit in some patients," but no clinical benefit from treatment has yet been established.[66] In a small double-blind, placebo-controlled study of 12 boys with DMD ages 7 to 13 whose genetic mutations were amenable to exon 51 skipping, treated patients' muscle fibers were found to be increasingly dystrophin positive with longer Exondys 51 injections, and patients were able to walk longer distances in a six-minute walk test (6MWT) with treatment.[67] Researchers reported no adverse events in this study.[68] However, some results in the clinical trials have contradicted one another, and the loss of patient ambulation was only delayed, and not stopped or reversed. These, and other findings, have led to a disagreement over the potential clinical benefit possible with eteplirsen.[69] While previously released clinical trial studies focused on dystrophin production and its potential impact on patient ambulation, clinical experts contacted for this analysis emphasized the use of the drug in the absence of other treatments, as it may slow DMD progression for patients at all disease stages, especially for those who are losing respiratory and cardiac function. The clinical intent is to increase dystrophin production in order to preserve skeletal, muscle, and respiratory strength and function, upper limb strength, and quality of life; the clinicians emphasized the use of the treatment as more life-prolonging and functionally-preserving than ambulation-improving.[70]

Because approval relied on demonstration of a surrogate endpoint versus proven clinical benefit, the FDA is requiring that the pharmaceutical company that submitted the drug for approval—Sarepta Therapeutics in Cambridge, Massachusetts—continue clinical trials to prove the drug's presumed clinical benefit of improved motor function.[71] In making its decision, the FDA evaluated the potential risks of the drug, the lack of available treatments, and the life-threatening and debilitating nature of DMD.[72] If the clinical trials fail to prove the clinical benefit, the FDA may conduct proceedings to withdraw its approval.[73] Currently, there are at least five clinical trials actively studying eteplirsen to evaluate not only its clinical benefit, but also its use in patients at various stages of DMD progression.[74]

In addition to its approval through the accelerated pathway, Exondys 51 was granted several other designations by the FDA, including:[75]

1. Fast-track designation: "[T]o facilitate the development and expedite the review of drugs that are intended to treat serious conditions and that demonstrate the potential to address an unmet medical need."
2. Priority review: "[G]ranted to applications for drugs that, if approved, would be a significant improvement in safety or effectiveness in the treatment of a serious condition."
3. Orphan drug designation: "[P]rovides incentives such as clinical trial tax credits, user fee waiver, and eligibility for orphan drug exclusivity to assist and encourage the development of drugs for rare diseases."
4. Pediatric disease priority review voucher: "[E]ncourage[s] development of new drugs and biologics for the prevention and treatment of rare pediatric diseases." Exondys 51 is only the seventh drug to be given such a voucher.

While exon-skipping therapy may be considered as a singular treatment strategy, AON exon skipping drugs are evaluated individually, depending on the genetic sequence targeted or the specific chemistry applied. Lengthy and expensive preclinical and clinical trials are required to evaluate the safety and efficacy of each individual drug. Researchers have pointed out that high research and development costs, long regulatory timelines, and small patient populations for each of these therapies may discourage drug manufacturers from developing additional versions, and will limit treatment access to the majority of DMD patients.[76]

Moreover, clinical trial design challenges have hampered researcher's ability to prove the clinical benefits of eteplirsen and other DMD genetically targeted drugs. Questions around appropriate control patients with whom to compare study patients; the heterogeneity of patients; patients' individual symptoms; disease progression and treatment goals; small sample sizes; and the definition and measurement standards for outcomes have challenged researchers as they attempt to analyze the safety and efficacy of these drugs.[77]

CONCLUSION

In order to develop targeted gene therapy for DMD, researchers and clinicians must first identify the type of mutation and location(s) along the largest and longest human gene sequence. And while the same general approach to correcting or ameliorating any type of mutation may be applied to different locations, each therapy must be specifically developed and studied for safety and efficacy, leading to the potential for a very large number of variations of these genetic treatments. Within this number, certain types and/or locations of mutations may be more amenable to treatment, and the number of patients with certain mutation/location combinations may be very small. (This thought sequence may be summarized as Mutation > Location > Population.)

While the scientific discovery that led to the development of Exondys 51 was made over 20 years ago, the FDA has approved only two drugs of this type to date, and only one for DMD. The completion of mapping of the human genome, and the development of better diagnostic genetic methods, has helped to accelerate research into DMD treatments. Likewise, scientists are designing new, more stable chemical modifications and better delivery systems that are predicted to improve both "the potency and efficacy of these drugs in RNA-targeting therapeutic applications,"[78] leading to a "resurgence" in the field of these types of treatments.[79] Other new technologies and scientific advancements "have triggered a major expansion of the RNA-therapeutics field," signaling that the approval of Exondys 51 may be the first of many such treatments for DMD and other genetic diseases and conditions in the near future.[80,81]

However, the approval of Exondys 51 itself was controversial, in that clinical benefit of the drug has not yet been proven.[82] In general for genetically targeted drugs for DMD, problems with designing clinical trials, questions regarding appropriate outcomes and treatment efficacy, and high costs are being balanced against the lack of treatments to slow or stop a rapidly progressing fatal disease, as well as the significant scientific breakthroughs and advancements in recent years which show the possibility of effective therapy through genetically targeted drugs. In the absence of other treatments, and while clinical trials are still in progress, clinicians are prescribing Exondys 51 to increase dystrophin production in order to preserve skeletal, muscle, and respiratory strength and function, upper limb strength, and quality of life, emphasizing its use as life-prolonging treatment for patients rather than ambulation-improving therapy. Overall, it is unknown at this time whether the Commonwealth's DMD population will benefit from use of these therapies, as their efficacy has not yet been proven through the results of clinical trials.

CENTER FOR HEALTH
INFORMATION AND ANALYSIS

APPENDIX

APPENDIX: EXCERPTED FROM THE MUSCULAR DYSTROPHY ASSOCIATION, DUCHENNE MUSCULAR DYSTROPHY RESEARCH SUMMARY[83]

INSERTING NEW DYSTROPHIN GENES

Gene therapy, or ***gene transfer***, refers to the delivery of genes as therapeutic agents. It is being developed in a wide range of disease areas because it has the potential to deliver healthy replacement genes to anyone with a gene mutation, or to deliver adjunct genes (sometimes called "surrogate" gene therapy) that can alleviate disease symptoms.

For gene therapy in DMD, a primary goal is to deliver a replacement copy of the dystrophin gene. Scientists hope that by introducing a functional dystrophin gene, gene therapy may offer a more permanent benefit than other therapies, but they are quick to caution that gene therapy for DMD is unlikely to completely halt or reverse the disease.

To accomplish gene transfer in DMD, some researchers aim to utilize the action of viruses. A virus works by inserting its own genetic material into a host, which causes the host's cells to manufacture viral proteins and create more virus (and in doing so, elicits an immune response that makes the host "sick"). But researchers believe it may be possible to swap out the viral genes for a dystrophin gene, which will trick the virus into delivering the dystrophin gene to people with DMD where the person's muscle cells will use it to manufacture dystrophin protein. To accomplish this without making the patient sick, scientists are utilizing viruses that do not cause illness in humans.

Research into the development of gene therapy for DMD is robust, but some challenges remain. The key difficulties researchers are working to overcome include dealing with the large size of the dystrophin gene, delivering a sufficient quantity of the new genes to muscle (while avoiding other tissues), and avoiding an unwanted immune response to the proteins made from the new genes.

The large size of the dystrophin gene poses a challenge because gene therapy relies on engineered viruses, and there is a limit to the size of the load that these viruses can carry. To address this, MDA-supported scientists have created smaller, but still functional, versions of dystrophin to use in gene therapy. Mini-dystrophin (rAAV2.5-CMV-minidystrophin) is a miniaturized, working dystrophin gene that has been tested in boys with DMD. At the end of clinical testing, scientists determined that the treatment was safe, but unfortunately some of the boys experienced an **unwanted immune response to the dystrophin protein.** This immune response prevented the newly synthesized mini-dystrophin protein from being used properly by muscle cells, and thereby limited the effectiveness of this approach.

Several research groups are now working toward the development of an even smaller version of dystrophin, called micro-dystrophin. Micro-dystrophin contains the minimum amount of information from the dystrophin gene needed to produce a functional protein. The most advanced of these therapies, rAAVrh74.MCK.Micro-Dystrophin, is being developed by a team at Nationwide Children's Hospital and currently is undergoing phase 1 clinical testing in boys with DMD.

To address delivery of genes specifically to muscles (while avoiding other tissues), researchers have introduced a muscle specific promotor that functions like a control switch for the new dystrophin gene. Muscle specific promoters selectively promote activation of the gene in the muscle, but in other tissues the gene remains dormant so it cannot create unwanted side effects. Researchers…are developing gene therapies that are activated by the muscle-specific promotor muscle creatine kinase (MCK). Potential therapies that utilize muscle specific promoters are currently in phase 1 clinical testing for DMD (rAAVrh74.MCK.micro-Dystrophin) and also phase 1-2 testing for LGMD (scAAVrh74.tMCK.hSGCA).

CONTROLLING HOW CELLS READ GENETIC INSTRUCTIONS

Exon skipping

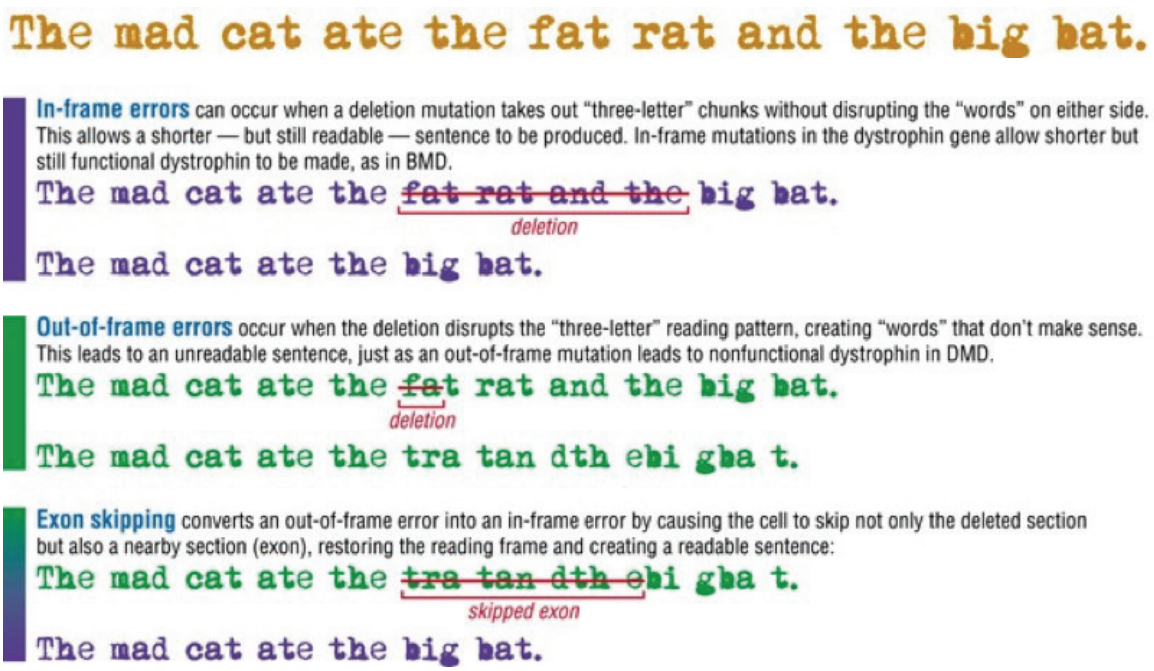
Exon skipping is a strategy currently being developed for DMD (although it may have application to other genetic diseases down the line) in which sections of genetic code (exons) are "skipped," allowing the creation of partially functional dystrophin, the muscle protein missing in DMD. Exon skipping is not a cure for DMD, but potentially could lessen the severe muscle weakness and atrophy that is the hallmark of this disease, making it more like Becker muscular dystrophy (BMD).

Laboratory development of exon skipping began in the 1990s and has received significant funding from MDA since then.

Exon skipping uses molecules called ***antisense oligonucleotides*** (AONs) to coax muscle fibers to ignore certain parts of the genetic instructions for dystrophin, thereby restoring the genetic «reading frame.»

To understand this better, think of the genetic code for a protein as a sentence. Cells have to read the genetic "sentence" in units of three "letters" each.

For example:



Exon skipping is being tested in clinical trials in boys with DMD in the United States and in other countries.

On Sept. 19, 2016, the FDA granted accelerated approval to eteplirsen (brand name Exondys 51) as the first disease-modifying drug for DMD. Exondys 51 specifically targets a section of genetic code called exon 51 in the dystrophin gene. It's estimated that 13 percent of boys with DMD could benefit from skipping exon 51.

Additional exon skipping drugs that could impact other forms of DMD are moving through the drug development pipeline. At this time, researchers currently are working on development of exon skipping drugs to target exons 44, 45, 50, 52, 53 and 55, as well as strategies to target multiple exons.

Stop codon read-through

In stop codon read-through, drugs target mutations known as ***premature stop codons*** (also called ***nonsense mutations***), which tell the cell to stop making a protein — such as dystrophin — before it has been completely assembled. The drugs coax cells to ignore, or "read through," a premature stop codon in a gene. Between 5-10 percent of people with DMD have premature stop codon/nonsense mutations and may therefore someday benefit from read-through therapies.

A company called PTC Therapeutics, in conjunction with Genzyme Corp., and with funding from MDA, developed an experimental stop codon read-through drug called ataluren to treat DMD or Becker muscular dystrophy due to a premature stop codon. In October 2010, PTC announced that a lower dose of ataluren appeared to work better than a higher dose. In a clinical trial, those on the lower dose walked an average of 29.7 meters (about 97 feet) more in six minutes than those in the high-dose or placebo groups (although all groups' walking distance declined over the course of the trial). Ataluren (Translarna), now owned wholly by PTC, will soon be evaluated by the FDA for approval in the US. It is currently available to DMD patients in the EU.

Researchers at a company called Nobelpharma have developed another stop codon read-through therapy called NPC14. This potential therapy may function similarly to Ataluren and is currently undergoing clinical testing in Japan.

DRIVING MUSCLE GROWTH: MYOSTATIN INHIBITORS

A prominent symptom of DMD is loss of muscle, so researchers aim to develop therapies that promote regrowth of muscle and, in turn, increase muscle strength.

One strategy that has received considerable MDA support involves inhibiting the actions of a naturally occurring protein called myostatin that limits muscle growth. In healthy muscle, myostatin performs an important role: it pushes back against growth signals to maintain muscle at a reasonable size. But in DMD, where muscle loss contributes to a decline in function, myostatin exacerbates the problem. Thus, researchers hope that blocking myostatin may allow DMD muscles to grow larger and stronger.

Inhibitors of myostatin have received much attention from the neuromuscular disease research community since it was found years ago that people and animals with a genetic deficiency of myostatin appear to have large muscles and good strength without apparent ill effects.

[One] unique strategy to block the action of myostatin uses gene therapy to introduce follistatin, a naturally occurring inhibitor of myostatin. Mice with a DMD-like disease that received genes for the follistatin protein showed an overall increase in body mass and weight of individual muscles. Furthermore, monkeys that received follistatin gene transfer had stronger, larger muscles. A gene therapy for delivering follistatin to people with DMD called rAAV1.CMV.huFollistatin344 is currently being developed by Milo Biotechnology. This potential therapy is now being tested in an early-stage (phase 1) clinical trial.

ENDNOTES

1 The 190th General Court of the Commonwealth of Massachusetts, House Bill 3644, "An Act relative to certain genetically targeted drug coverage for Duchenne Muscular Dystrophy." Accessed 29 January 2018: https://malegislature.gov/Bills/190/H3644.

2 Essential Health Benefit Benchmark Plan – 2017. Accessed 19 January 2018. Accessed 19 January 2018: http://www.mass.gov/ocabr/insurance/providers-and-producers/doi-regulatory-info/essential-health-benefit-benchmark-plan-2017.html

3 The 190th General Court of the Commonwealth of Massachusetts, House Bill 3644, "An Act relative to certain genetically targeted drug coverage for Duchenne Muscular Dystrophy." Accessed 10 July 2017: https://malegislature.gov/Bills/190/H3644.

4 NIH, National Library of Medicine (NIH-NLM). Duchenne muscular dystrophy. Reviewed 15 January 2016; accessed 13 September 2017: https://medlineplus.gov/ency/article/000705.htm.

5 Romitti PA, Zhu Y, Puzhankara S, et. al. Prevalence of Duchenne and Becker muscular dystrophies in the United States. Pediatrics. 2015;135(3):513–21. Accessed 8 January 2018: http://pediatrics.aappublications.org/content/135/3/513.

6 *Op. cit.* Romitti PA, Zhu Y, Puzhankara S, et. al.

7 Muscular Dystrophy Association (MDA). Duchenne Muscular Dystrophy (DMD): About Duchenne Muscular Dystrophy. Accessed 22 July 2017: https://www.mda.org/disease/duchenne-muscular-dystrophy.

8 *Op. cit.* MDA. DMD: About Duchenne Muscular Dystrophy.

9 National Institutes of Health, National Library of Medicine, Genetics Home Reference (NLM-GHR). Duchenne and Becker muscular dystrophy. Published 5 September 2017; accessed 6 September 2017: https://ghr.nlm.nih.gov/condition/duchenne-and-becker-muscular-dystrophy.

10 MDA. Becker Muscular Dystrophy (BMD). Accessed 5 August 2017: https://www.mda.org/disease/becker-muscular-dystrophy.

11 *Op. cit.* NLM-GHR: Duchenne and Becker muscular dystrophy.

12 *Op. cit.* NLM-GHR: Duchenne and Becker muscular dystrophy.

13 *Op. cit.* NLM-GHR: Duchenne and Becker muscular dystrophy.

14 *Op. cit.* NLM-GHR: Duchenne and Becker muscular dystrophy.

15 *Op. cit.* NLM-GHR: Duchenne and Becker muscular dystrophy.

16 MDA. DMD: Signs and Symptoms. Accessed 22 July 2017: https://www.mda.org/disease/duchenne-muscular-dystrophy/signs-and-symptoms.

17 *Op. cit.* MDA. DMD: Signs and Symptoms.

18 Darras BT, Miller DT, Urion DK. Duchenne muscular dystrophy. NIH, National Center for Biotechnology Information, Genetic Testing Registry (NCBI-GTR). Accessed 13 September 2017: https://www.ncbi.nlm.nih.gov/gtr/conditions/C0013264/.

19 *Op. cit.* MDA. DMD: Signs and Symptoms.

20 *Op. cit.* NLM-GHR: Duchenne and Becker muscular dystrophy.

21 *Op. cit.* NLM-GHR: Duchenne and Becker muscular dystrophy.

22 *Op. cit.* MDA. DMD: Signs and Symptoms.

23 *Op. cit.* MDA. DMD: Signs and Symptoms.

24 *Op. cit.* MDA. DMD: Signs and Symptoms.

25 *Op. cit.* MDA. DMD: Signs and Symptoms.

26 *Op. cit.* NLM-GHR: Duchenne and Becker muscular dystrophy.

27 *Op. cit.* MDA. DMD: About Duchenne Muscular Dystrophy.

28 MDA. DMD: Diagnosis. Accessed 8 August 2017: https://www.mda.org/disease/duchenne-muscular-dystrophy/diagnosis.

29 *Op. cit.* MDA. DMD: Diagnosis.

30 *Op. cit.* MDA. DMD: Diagnosis.

31 *Op. cit.* MDA. DMD: Diagnosis.

32 *Op. cit.* MDA. DMD: About Duchenne Muscular Dystrophy.

33 *Op. cit.* NIH-NLM. Duchenne muscular dystrophy.

34 MDA. DMD: Medical Management. Accessed 22 July 2017: https://www.mda.org/disease/duchenne-muscular-dystrophy/medical-management.

35 *Op. cit.*. MDA. DMD: Medical Management.

36 *Op. cit.* NIH-NLM. Duchenne muscular dystrophy.

37 *Op. cit.* MDA. DMD: Medical Management.

38 *Op. cit.* MDA. DMD: Medical Management.

37 *Op. cit.* NIH-NLM. Duchenne muscular dystrophy.

40 *Op. cit.* MDA. DMD: Medical Management.

41 *Op. cit.* MDA. DMD: Medical Management.

42 MDA. DMD: Research. Accessed 13 September 2017: https://www.mda.org/disease/duchenne-muscular-dystrophy/research.

43 Roberts RG, Coffey AJ, Bobrow M, et. al. Exon structure of the human dystrophin gene. Genomics. 1993 May; 16(2):536-8. Accessed 10 January 2018: https://www.ncbi.nlm.nih.gov/pubmed/8314593.

44 Koenig M, Hoffman EP, Bertelson CJ, et. al. Complete cloning of the Duchenne muscular dystrophy (DMD) cDNA and preliminary genomic organization of the DMD gene in normal and affected individuals. Cell. 1987 Jul 31;50(3):509-17. Accessed 10 January 2018: https://www.ncbi.nlm.nih.gov/pubmed/3607877.

45 National Center for Biotechnology Information (NCBI). Genetics Review, MLA CE Course Manual: Molecular Biology Information Resources. Accessed 10 January 2018: https://www.ncbi.nlm.nih.gov/Class/MLACourse/Original8Hour/Genetics/gene.html.

46 Buzin CH, Feng J, Yan J, et. al. Mutation rates in the dystrophin gene: a hotspot of mutation at a CpG dinucleotide. Hum Mutat. 2005 Feb;25(2):177-88. Accessed 10 January 2018: https://www.ncbi.nlm.nih.gov/pubmed/15643612.

47 Bladen CL, Salgado D, Monges S, et. al. The TREAT-NMD DMD Global Database: analysis of more than 7,000 Duchenne muscular dystrophy mutations. Hum Mutat. 2015 Apr;36(4):395-402. Accessed 23 January 2018: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4405042/.

48 *Op. cit.* MDA. DMD: Research.

49 Bello L, Pegoraro E. Genetic diagnosis as a tool for personalized treatment of Duchenne muscular dystrophy. Acta Myol. 2016 Dec;35(3):122-127. Accessed 8 January 2018: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5416739/.

50 Lim KR, Maruyama R, Yokota T. Eteplirsen in the treatment of Duchenne muscular dystrophy. Drug Des Devel Ther. 2017 Feb 28;11:533-545. Accessed 11 January 2018: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5338848.

51 van Deutekom JC, van Ommen GJ. Advances in Duchenne muscular dystrophy gene therapy. Nat Rev Genet. 2003;4(10):774–783. Accessed 11 January 2018: https://www.ncbi.nlm.nih.gov/pubmed/14526374.

52 White S, Kalf M, Liu Q, et al. Comprehensive detection of genomic duplications and deletions in the DMD gene, by use of multiplex amplifiable probe hybridization. Am J Hum Genet. 2002;71(2):365–374. Accessed 11 January 2018: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC379168/.

53 Aartsma-Rus A, Fokkema I, Verschuuren J, et. al. Theoretic applicability of antisense-mediated exon skipping for Duchenne muscular dystrophy mutations. Hum Mutat. 2009 Mar;30(3):293-9. Accessed 23 January 2018: https://www.ncbi.nlm.nih.gov/pubmed/19156838.

54 *Op. cit.* Bladen CL, Salgado D, Monges S, et. al.

55 Aartsma-Rus A, Straub V, Hemmings R, et. al. Development of Exon Skipping Therapies for Duchenne Muscular Dystrophy: A Critical Review and a Perspective on the Outstanding Issues. Nucleic Acid Ther. 2017 Oct;27(5):251-259. doi: 10.1089/nat.2017.0682. Accessed 24 January 2018: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5649120/.

56 *Op. cit.* Lim KR, Maruyama R, Yokota T.

57 *Op. cit.* Bladen CL, Salgado D, Monges S, et. al.

58 U.S. National Library of Medicine, ClinicalTrials.gov. Accessed 25 January 2018: https://www.clinicaltrials.gov/ct2/results?recrs=abdf&cond=Duchenne+Muscular+Dystrophy+AND+%22Duchenne+Muscular+Dystrophy%22.

59 Pires VB, Simões R, Mamchaoui K, et. al. Short (16-mer) locked nucleic acid splice-switching oligonucleotides restore dystrophin production in Duchenne Muscular Dystrophy myotubes. PLoS One. 2017 Jul 24;12(7):e0181065. doi: 10.1371/journal.pone.0181065. eCollection 2017. Accessed 8 January 2018: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5524367/.

60 *Op. cit.* ClinicalTrials.gov.

61 U.S. Food and Drug Administration (FDA). FDA News Release: FDA grants accelerated approval to first drug for Duchenne muscular dystrophy. Released 19 September 2016; accessed 22 July 2017: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm521263.htm.

62 *Op. cit.*. FDA News Release: FDA grants accelerated approval to first drug for Duchenne muscular dystrophy.

63 *Op. cit.* FDA News Release: FDA grants accelerated approval to first drug for Duchenne muscular dystrophy.

64 *Op. cit.* FDA News Release: FDA grants accelerated approval to first drug for Duchenne muscular dystrophy.

65 Kesselheim AS, Avorn J. Approving a Problematic Muscular Dystrophy Drug: Implications for FDA Policy. JAMA. 2016 Dec 13;316(22):2357-2358. Accessed 21 September 2017: http://jamanetwork.com/journals/jama/article-abstract/2572614.

66 *Op. cit.* FDA News Release: FDA grants accelerated approval to first drug for Duchenne muscular dystrophy.

67 Mendell JR, Rodino-Klapac LR, Sahenk Z, et. al.; Eteplirsen Study Group. Eteplirsen for the treatment of Duchenne muscular dystrophy. Ann Neurol. 2013 Nov;74(5):637-47. doi: 10.1002/ana.23982. Accessed 21 September 2017: https://www.ncbi.nlm.nih.gov/pubmed/23907995.

68 National Institutes of Health, Clinical Trials. Efficacy Study of AVI-4658 to Induce Dystrophin Expression in Selected Duchenne Muscular Dystrophy Patients. Clinical Trials Identifier: NCT01396239. Sponsor: Sarepta Therapeutics. Accessed 21 September 2017: https://clinicaltrials.gov/ct2/show/study/NCT01396239.

69 *Op. cit.* Lim KR, Maruyama R, Yokota T.

70 Phone conversation, 30 January 2018. Laura Hagerty, PhD. Scientific Program Officer, Muscular Dystrophy Association.

Phone conversation, 1 February 2018. Kathryn R. Wagner, MD, PhD. Director, Center for Genetic Muscle Disorders, Kennedy Krieger Institute; Professor of Neurology and Neuroscience, Johns Hopkins School of Medicine.

Phone conversation, 1 February 2018. Claudia Senesac, PT, PhD, PCS. Clinical Associate Professor, University of Florida Department of Physical Therapy.

Phone conversation, 2 February 2018. Elizabeth M McNally, MD, PhD. Director, Center for Genetic Medicine, Elizabeth J. Ward Professor of Genetic Medicine, Professor of Medicine (Cardiology) and Biochemistry and Molecular Genetics, Feinberg School of Medicine, Northwestern University.

71 Op. cit. FDA News Release: FDA grants accelerated approval to first drug for Duchenne muscular dystrophy.

72 *Op. cit.*. FDA News Release: FDA grants accelerated approval to first drug for Duchenne muscular dystrophy.

73 *Op. cit.* FDA News Release: FDA grants accelerated approval to first drug for Duchenne muscular dystrophy.

74 *Op. cit.* ClinicalTrials.gov.

75 *Op. cit.*FDA News Release: FDA grants accelerated approval to first drug for Duchenne muscular dystrophy.

76 *Op. cit.* Lim KR, Maruyama R, Yokota T.

77 *Op. cit.* Lim KR, Maruyama R, Yokota T.

78 Pires VB, Simões R, Mamchaoui K, et. al. Short (16-mer) locked nucleic acid splice-switching oligonucleotides restore dystrophin production in Duchenne Muscular Dystrophy myotubes. PLoS One. 2017 Jul 24;12(7):e0181065. Accessed 23 January 2018: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5524367/.

79 McClorey G, Wood MJ. An overview of the clinical application of antisense oligonucleotides for RNA-targeting therapies. Curr Opin Pharmacol. 2015 Oct;24:52-8. Accessed 23 January 2018: https://www.ncbi.nlm.nih.gov/pubmed/26277332/.

80 Kaczmarek JC, Kowalski PS, Anderson DG. Advances in the delivery of RNA therapeutics: from concept to clinical reality. Genome Med. 2017 Jun 27;9(1):60. Accessed 23 January 2018: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5485616/.

81 Kaczmarek JC, Kowalski PS, Anderson DG. Advances in the delivery of RNA therapeutics: from concept to clinical reality. Genome Med. 2017 Jun 27;9(1):60. Accessed 8 January 2018: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5485616/.

82 Dalakas MC. Gene therapy for Duchenne muscular dystrophy: balancing good science, marginal efficacy, high emotions and excessive cost. Ther Adv Neurol Disord. 2017 Aug;10(8):293-296. Accessed 8 January 2018: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5518962/.

83 *Op. cit*. MDA. DMD: Research.

center
for health
information
and analysis

For more information, please contact:

CENTER FOR HEALTH INFORMATION AND ANALYSIS
501 Boylston Street
Boston, MA 02116
617.701.8100

www.chiamass.gov
Publication Number 18-67-CHIA-01

BerryDunn

Actuarial Assessment of House Bill 3644 Submitted to the 190th General Court of the Commonwealth of Massachusetts: "An Act Relative to Certain Genetically Targeted Drug Coverage for Duchenne Muscular Dystrophy"

Prepared for:
Commonwealth of Massachusetts
Center for Health Information and Analysis

Prepared by:
March 2018

Table of Contents

This report was prepared by Larry Hart; Amy Raslevich, MBA, MPP; Valerie Hamilton, RN, MHA, JD; Andrea Clark, MS; Jennifer Elwood, FSA, MAAA; James Highland, PhD.

1.0 Executive Summary

Massachusetts House Bill (H.B.) 3644, as submitted in the 190th General Court (General Court) of the Commonwealth of Massachusetts (Commonwealth), would require fully-insured plans to cover genetically targeted U.S. Food and Drug Administration (FDA)-approved drugs for Duchenne Muscular Dystrophy (DMD) when the drug has been determined by the patient's provider to be medically necessary, and the provider is either expert in, or has consulted with an expert in, DMD.[1] Cost-sharing for these services must be similar to those for other services covered under the plan.

Massachusetts General Laws (MGL) Chapter 3, Section 38C, charges the Massachusetts Center for Health Information and Analysis (CHIA) with, among other duties, reviewing the potential impact of proposed mandated healthcare insurance benefits on the premiums paid by businesses and consumers. CHIA has engaged BerryDunn[i] to provide an actuarial estimate of the effect enactment of the bill would have on the cost of health insurance in the Commonwealth.

1.1 Background

DMD is one of nine types of muscular dystrophy, a genetic disease that leads to progressive weakness and loss of muscle mass, and almost exclusively affects males.[2,3] Researchers estimated the prevalence of DMD for males 5 – 24 years old between 1991 – 2010 to be approximately 1.02 per 10,000 males.[4] Patients with DMD have a genetic mutation that prevents the production of any of the functional protein dystrophin, which is located primarily in the skeletal and cardiac muscle, and works to keep muscle intact by stabilizing and protecting muscle fibers.[5,6] Without dystrophin, the repeated contraction and relaxation of muscles damage the muscle cells, which eventually weaken and die, leading to the heart and muscle weakness associated with DMD.[7] The onset of the disease is most often between 3 and 5 years of age and progresses rapidly, with patients beginning to use a wheelchair between the ages of 7 and 12, and suffering from heart and respiratory muscle damage by the early teens.[8,9] With advances in cardiac and respiratory therapies, life expectancy for patients with DMD has extended from the teen years and now averages into the 20s, with some patients surviving into their 30s.[10,11]

There is no known cure for DMD, and standard treatment currently focuses on symptom control and quality of life improvement through multidisciplinary care.[12,13]

Research into new treatments for DMD has focused on a wide variety of areas, including the development of genetically targeted drugs that will alter or correct mutations that cause problems in how cells read genetic instructions, thus leading to DMD.[14] Currently, the most promising therapeutics focus on the most common mutation types found in the DMD gene, including exon-skipping drugs and stop codon read-through drugs.[15] While these treatment

[i] Formerly Compass Health Analytics, Inc.

approaches are applicable to relatively large proportions of patients with DMD, each drug developed must be specific to not only the mutation type, but also to the exact location on the mutated gene for that specific patient.[16,17]

The only drug approved for the treatment of DMD to date is Exondys 51 (generic name: eteplirsen), an exon-skipping drug targeting DMD gene location exon 51, which impacts approximately 13% of DMD patients. Approved in September 2016, the drug is not intended to cure DMD or to improve a patient's condition, but to stop the progression of the disease and prevent further muscle damage.[18] The injectable drug, which requires weekly patient infusions, was approved on an accelerated pathway by the FDA designed to give patients access to new treatments while clinical trials and verification of clinical benefit continue, as no other meaningful treatments currently exist to cure the disease or to slow its progression.[19] As the approval of Exondys 51 was granted despite the contrary recommendations of its external advisory committee and scientific staff, the FDA is requiring further clinical studies to prove the drug's efficacy, and not just demonstrate increased dystrophin production, as the initial clinical trials had done.[20] If the clinical trials fail to prove the clinical benefit, the FDA may conduct proceedings to withdraw its approval.[21] In addition to further clinical trials for Exondys 51, two other exon-skipping drugs are currently in clinical trials, targeting exon locations 45 and 53, each of which impact 8% of DMD patients; clinical experts estimate that one of these drugs may enter the market within one year, with the other to follow in the subsequent year.[22] A stop codon read-through drug, known as Ataluren, is also currently in clinical trials, and may enter the market within five years to treat another type of DMD gene mutation that impacts approximately 10% of patients.[23,24,25]

H.B. 3644 requires fully-insured plans to cover genetically targeted drugs for DMD, including Exondys 51 as well as other pipeline DMD drugs that could potentially receive FDA approval in the report's five-year time horizon. The cost estimates provided in this report include a separate cost estimate range for the current drug, Exondys 51, as well as costs potentially stemming from the pipeline drugs for fullyinsured commercial Commonwealth carriers projected over the five-year period from 2019 – 2023.

1.2 Current Insurance Coverage

BerryDunn surveyed insurance carriers in the Commonwealth, and the majority indicated they are currently covering Exondys 51 for DMD patients. At the time of the carrier surrey, one small carrier had coverage under clinical review. Each carrier that provides coverage applies its own proprietary medical necessity criteria, which are, however, similar across carriers. In most cases, insurers will only approve Exondys 51 for six months at a time if the following conditions are met:

- The patient must have DMD with a confirmed mutation of the DMD gene that is amenable to exon 51 skipping (approximately 13% of DMD cases)[26].
- The prescription is written by a board certified/board eligible neurologist.

- There is documentation of ambulation without assistance or devices (often use a six-minute walk test).
- There is documentation of dystrophin levels.
- One carrier requires concurrent use of glucocorticoids, unless clinically contraindicated.
- Another carrier requires that prior to approval of Exondys 51, the patient must have tried and failed corticosteroids for at least 6 months, or be intolerant to corticosteroids.

Additionally, in order to continue Exondys 51 after the initial six months, most carriers require the patient to demonstrate that, in addition to continuing medical need and patient tolerance of the therapy, the treatment has been effective by showing improvement in dystrophin levels or the six-minute walk distance. Given that Exondys 51 is not intended to improve patient function or ambulation, but rather to slow disease progression, requiring improvement in the six-minute walk test for extending authorization past the first six months may not be feasibly met, and would be irrelevant for patients who have already lost ambulation and are prescribed the drug to preserve respiratory and cardiac function, according to clinical experts interviewed for this report.[27] These clinicians emphasized the use of the treatment as more life prolonging and functionally preserving than ambulation improving.

Some carriers also have specific requirements about the use of corticosteroids by patients, including prednisone and deflazacort, which are often prescribed to reduce inflammation and to try to slow the course of DMD progression by preserving muscle strength and function, preventing scoliosis, and enabling patient mobility.[28] While these medications may increase strength, muscle, and pulmonary function, long-term use also may cause serious side effects, including weight gain, cataracts, and loss of bone mass; moreover, the rapid withdrawal of these drugs may lead to life-threatening complications.[29]

1.3 Analysis

BerryDunn estimated the impact of H.B. 3644 by estimating the potential contribution of each of two components.

- Incremental cost due to shifting the medical necessity determination for the 13% of DMD patients amenable to exon 51 skipping from carriers, which have limited approval of the drug, to treating physicians.
- Cost of genetically targeted DMD pipeline drugs. The current pipeline includes drugs for other exon skipping genes, including exon 45 and exon 53, each of which is indicated for approximately 8% of patients, as well as the stop codon read-through drug Ataluren, indicated for approximately 10% of DMD patients.

BerryDunn then aggregated these components and projected them forward over the next five years (2019 – 2023) for the fully-insured Commonwealth population, and added insurer retention (administrative cost and profit) to arrive at an estimate of the bill's effect on premiums. Note the estimates assume carriers would fully comply with the provisions of the bill if it becomes law.

1.4 Summary Results

Table ES-1, on the following page, summarizes the estimated effect of H.B. 3644 on premiums for fully-insured plans over five years. This analysis estimates that the bill, if enacted as drafted for the General Court, would increase fully-insured premiums by as much as 0.125% on average over the next five years; a more likely increase is in the range of 0.053%, equivalent to an average annual expenditure of $6.9 million over the period 2019 – 2023.

The impact on premiums is driven by the potential impact the requirements will have on medical necessity criteria, as well as the entry of new drugs into the market in the given timeframe.

The impact of the bill on any one individual, employer group, or carrier may vary from the overall results, depending on the current level of benefits each receives or provides, and on how those benefits would change under the proposed language of the bill.

Table ES-1: Summary Results

	2019	2020	2021	2022	2023	Weighted Average	Five-Year Total
Members (000s)	2,154	2,150	2,146	2,142	2,138		
Medical Expense Low ($000s)	$1,507	$2,243	$952	$1,010	$1,072	$1,440	$6,783
Medical Expense Mid ($000s)	$3,165	$6,055	$4,283	$9,089	$6,430	$6,159	$29,022
Medical Expense High ($000s)	$6,631	$13,456	$11,422	$20,199	$17,147	$14,613	$68,854
Premium Low ($000s)	$1,698	$2,527	$1,072	$1,138	$1,207	$1,622	$7,643
Premium Mid ($000s)	$3,566	$6,822	$4,826	$10,241	$7,245	$6,940	$32,700
Premium High ($000s)	$7,471	$15,161	$12,869	$22,758	$19,319	$16,464	$77,579
PMPM Low	$0.09	$0.10	$0.04	$0.04	$0.05	$0.06	$0.06
PMPM Mid	$0.19	$0.26	$0.19	$0.40	$0.28	$0.27	$0.27
PMPM High	$0.41	$0.59	$0.50	$0.89	$0.75	$0.64	$0.64
Estimated Monthly Premium	$493	$502	$512	$523	$533	$513	$513
Premium % Rise Low	0.019%	0.019%	0.008%	0.008%	0.009%	0.012%	0.012%
Premium % Rise Mid	0.039%	0.053%	0.037%	0.076%	0.053%	0.053%	0.053%
Premium % Rise High	0.082%	0.117%	0.098%	0.169%	0.141%	0.125%	0.125%

1.5 Executive Summary Endnotes

[1] The 190th General Court of the Commonwealth of Massachusetts, House Bill 3644 (MA-HB3644), "An Act relative to certain genetically targeted drug coverage for Duchenne Muscular Dystrophy." Accessed 2 February 2018: https://malegislature.gov/Bills/190/H3644.

Genetically targeted drug defined as:

> "a drug for which the approved use may result in the modulation, including suppression, up-regulation, or activation, of the function of a gene or its associated gene product and incorporates or utilizes non-replicating nucleic acid or analogous compounds to treat one or more patient subgroups, including subgroups of patients with different mutations of a gene."

[2] Muscular Dystrophy Association (MDA). Duchenne Muscular Dystrophy (DMD): About Duchenne Muscular Dystrophy. Accessed 22 July 2017: https://www.mda.org/disease/duchenne-muscular-dystrophy.

[3] NIH, National Library of Medicine (NIH-NLM). Duchenne muscular dystrophy. Reviewed 15 January 2016; accessed 13 September 2017: https://medlineplus.gov/ency/article/000705.htm.

[4] Romitti PA, Zhu Y, Puzhankara S, et. al. Prevalence of Duchenne and Becker muscular dystrophies in the United States. Pediatrics. 2015;135(3):513–21. Accessed 8 January 2018: http://pediatrics.aappublications.org/content/135/3/513.

[5] *Op. cit.* MDA. DMD: About Duchenne Muscular Dystrophy.

[6] National Institutes of Health, National Library of Medicine, Genetics Home Reference (NLM-GHR). Duchenne and Becker muscular dystrophy. Published 5 September 2017; accessed 6 September 2017: https://ghr.nlm.nih.gov/condition/duchenne-and-becker-muscular-dystrophy.

[7] *Op. cit.* NLM-GHR: Duchenne and Becker muscular dystrophy.

[8] *Op. cit.* NLM-GHR: Duchenne and Becker muscular dystrophy.

[9] *Op. cit.* MDA. DMD: Signs and Symptoms.

[10] *Op. cit.* NLM-GHR: Duchenne and Becker muscular dystrophy.

[11] *Op. cit.* MDA. DMD: About Duchenne Muscular Dystrophy.

[12] *Op. cit.* NIH-NLM. Duchenne muscular dystrophy.

[13] MDA. DMD: Medical Management. Accessed 22 July 2017: https://www.mda.org/disease/duchenne-muscular-dystrophy/medical-management.

[14] MDA. DMD: Research. Accessed 13 September 2017: https://www.mda.org/disease/duchenne-muscular-dystrophy/research.

[15] Lim KR, Maruyama R, Yokota T. Eteplirsen in the treatment of Duchenne muscular dystrophy. Drug Des Devel Ther. 2017 Feb 28;11:533-545. Accessed 11 January 2018: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5338848.

[16] Aartsma-Rus A, Straub V, Hemmings R, et. al. Development of Exon Skipping Therapies for Duchenne Muscular Dystrophy: A Critical Review and a Perspective on the Outstanding Issues. Nucleic Acid Ther. 2017 Oct;27(5):251-259. doi: 10.1089/nat.2017.0682. Accessed 24 January 2018: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5649120/.

[17] *Op. cit.* Lim KR, Maruyama R, Yokota T.

[18] Bladen CL, Salgado D, Monges S, et. al. The TREAT-NMD DMD Global Database: analysis of more than 7,000 Duchenne muscular dystrophy mutations. Hum Mutat. 2015 Apr;36(4):395-402. Accessed 23 January 2018: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4405042/.

[19] U.S. Food and Drug Administration (FDA). FDA News Release: FDA grants accelerated approval to first drug for Duchenne muscular dystrophy. Released 19 September 2016; accessed 22 July 2017: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm521263.htm.

[20] Kesselheim AS, Avorn J. Approving a Problematic Muscular Dystrophy Drug: Implications for FDA Policy. JAMA. 2016 Dec 13;316(22):2357-2358. Accessed 21 September 2017: http://jamanetwork.com/journals/jama/article-abstract/2572614.

[21] *Op. cit.* FDA News Release: FDA grants accelerated approval to first drug for Duchenne muscular dystrophy.

[22] Phone conversation, 30 January 2018. Laura Hagerty, PhD. Scientific Program Officer, Muscular Dystrophy Association.

Phone conversation, 1 February 2018. Kathryn R. Wagner, MD, PhD. Director, Center for Genetic Muscle Disorders, Kennedy Krieger Institute; Professor of Neurology and Neuroscience, Johns Hopkins School of Medicine.

Phone conversation, 1 February 2018. Claudia Senesac, PT, PhD, PCS. Clinical Associate Professor, University of Florida Department of Physical Therapy.

Phone conversation, 2 February 2018. Elizabeth M McNally, MD, PhD. Director, Center for Genetic Medicine, Elizabeth J. Ward Professor of Genetic Medicine, Professor of Medicine (Cardiology) and Biochemistry and Molecular Genetics, Feinberg School of Medicine, Northwestern University.

[23]U.S. National Library of Medicine, ClinicalTrials.gov. Accessed 25 January 2018: https://www.clinicaltrials.gov/ct2/results?recrs=abdf&cond=Duchenne+Muscular+Dystrophy+AND+%22Duchenne+Muscular+Dystrophy%22.

[24] *Op. cit.* Phone conversations, Hagerty, Wagner, Senesac, McNally.

[25] *Op. cit.* Romitti PA, Zhu Y, Puzhankara S, et. al.

[26] Romitti PA, Zhu Y, Puzhankara S, et. al. Prevalence of Duchenne and Becker muscular dystrophies in the United States. Pediatrics. 2015;135(3):513–21. Accessed 8 January 2018: http://pediatrics.aappublications.org/content/135/3/513.

[27] *Op. cit.* Phone conversations, Hagerty, Wagner, Senesac, McNally.

[28] *Op. cit.* MDA. DMD: Medical Management.

[29] *Op. cit.* MDA. DMD: Medical Management.

2.0 Introduction

H.B. 3644, as submitted in the General Court, would require fully-insured plans to cover genetically targeted, FDA-approved drugs for DMD when the drug has been determined by the patient's provider to be medically necessary, and the provider is either expert in, or has consulted with an expert in, DMD.[1] Cost-sharing for these services must be similar to that for other services covered under the plan.

MGL, Chapter 3, Section 38C, charges CHIA with, among other duties, reviewing the potential impact of proposed mandated healthcare insurance benefits on the premiums paid by businesses and consumers. CHIA has engaged BerryDunn to provide an actuarial estimate of the effect that enactment of the bill would have on the cost of health insurance in the Commonwealth.

Assessing the impact of the proposed mandate on premiums entails analyzing its incremental effect on spending by insurance plans. This, in turn, requires comparing spending under the provisions of the bill to spending under current statutes and current benefit plans for the relevant services.

Section 3.0 of this analysis outlines the provisions and interpretations of the bill. Section 4.0 summarizes the methodology used for the estimate. Section 5.0 discusses important considerations in translating the bill's language into estimates of its incremental impact on healthcare costs and steps through the calculations. Section 6.0 summarizes the results.

2.1 Background

DMD occurs in approximately one in every 3,600 male births, and patients are almost exclusively males.[2] Researchers estimated the prevalence of DMD for males 5 – 24 years old between 1991 – 2010 to be approximately 1.02 per 10,000 males.[3]

DMD is one of nine types of muscular dystrophy, a genetic disease that results in progressive muscle weakness and degeneration.[4] Patients with DMD have a genetic mutation that prevents the production of any of the functional protein dystrophin, which is located primarily in the skeletal and cardiac muscles, and works to keep muscle intact by stabilizing and protecting muscle fibers.[5,6]

Without dystrophin, the repeated contraction and relaxation of muscles damage the muscle cells themselves.[7] Eventually, the damaged muscle fibers weaken and die, leading to the heart and muscle weakness associated with DMD.[8] The onset of the disease is most often between 3 and 5 years of age and progresses rapidly[9]; most DMD patients will begin to use a wheelchair between the ages of 7 and 12.[10] Damage eventually occurs to heart and respiratory muscles, usually by a patient's early teen years.[11] Patients may suffer from cardiomyopathy, as well as severely decreased respiratory capacity, both of which are life-threatening.[12,13] Approximately one-third of patients with DMD also have developmental and learning difficulties that impact

their cognitive and emotional growth.[14] With advances in cardiac and respiratory therapies, life expectancy for patients with DMD has extended from the teen years and now averages into the 20s, with some patients surviving into their 30s.[15,16]

There is no known cure for DMD, and standard treatment currently focuses on symptom control and quality of life improvement.[17] DMD patients require multidisciplinary care to address the range of physical and psychosocial issues that they may face, including cardiac and respiratory care and assisted ventilation; durable medical equipment; physical and occupational therapy; and medications to treat the symptoms of the disease.[18,19]

Research into new treatments for DMD has focused on a wide variety of areas, including replacement of the dystrophin protein; protection of muscles from additional damage; promotion of muscle repair and regrowth; care and treatment of associated conditions and syndromes; and improved methods for symptom management and control.[20] Scientists are exploring gene transfer, where genes are delivered to either replace mutated genes with healthy genes or deliver surrogate genes to improve disease symptoms, though this approach is not likely to reverse or completely cure the disease.[21]

Another approach to DMD treatment is the development of genetically targeted drugs that will alter or correct mutations that cause problems in how cells read genetic instructions, thus leading to DMD. Currently, the most promising therapeutics focus on the most common mutation types found in the DMD gene, including exon-skipping drugs and stop codon read-through drugs.[22] While these treatment approaches are applicable to relatively large proportions of patients with DMD, each drug developed must be specific to not only the mutation type, but to the exact location on the mutated gene for that specific patient.[23,24]

Currently, the only drug approved for the treatment of DMD is Exondys 51 (generic name: eteplirsen), an exon-skipping drug targeting DMD gene location exon 51. Approved in September 2016, the drug is not intended to cure DMD or to improve a patient's condition, but to stop the progress of the disease and prevent further muscle damage.[25] The injectable drug, which requires weekly patient infusions, was approved on a accelerated pathway by the FDA designed to give patients access to new treatments while clinical trials and verification of clinical benefit continues, as no other meaningful treatments currently exist to cure the disease or to slow its progression.[26] Because the approval of Exondys 51 was granted despite the contrary recommendations of its external advisory committee and scientific staff, the FDA is requiring further clinical studies to prove the the drug's efficacy, and not just demonstrate increased dystrophin production as the initial clinical trials had done.[27] If the clinical trials fail to prove the clinical benefit, the FDA may conduct proceedings to withdraw its approval.[28] In addition to further clinical trials for Exondys 51, two other exon-skipping drugs are currently in clinical trials, targeting exon locations 45 and 53, each of which impact approximately 8% of DMD patients; clinical experts estimate that one of these drugs may enter the market within one year, with the other to follow in the subsequent year.[29,30] A stop codon read-through drug, known as Ataluren,

is also currently in clinical trials, and may enter the market within five years to treat other types of DMD gene mutations impacting approximately 10% of DMD patients.[31,32,33]

3.0 Interpretation of H.B. 3644

Current Commonwealth law does not require coverage nor defines medical necessity criteria for genetically targeted drugs for the treatment of DMD. H.B. 3644 would require commercial carriers to cover these drugs when approved by the FDA, including the currently available Exondys 51 and other pipeline drugs that may gain FDA approval in the future, and would require that a patient's provider determine the medical necessity of their use, rather than such coverage being subject to a carrier's medical necessity determination.

3.1 Plans Affected By the Proposed Mandate

The bill as drafted amends statutes that regulate healthcare carriers in the Commonwealth. The bill includes six sections, each of which addresses statutes dealing with a particular type of health insurance policy:

- Section 1: Chapter 32A – Plans Operated By the Group Insurance Commission (GIC) for the Benefit of Public Employees
- Section 2: Chapter 118E – MassHealth (Medicaid) Plans
- Section 3: Chapter 175 – Commercial Health Insurance Company Plans
- Section 4: Chapter 176A – Hospital Service Corporation Plans
- Section 5: Chapter 176B – Medical Service Corporation Plans
- Section 6: Chapter 176G – Health Maintenance Organization (HMO) Plans

Self-insured plans, except for those managed by the GIC, are not subject to state-level health insurance benefit mandates. State mandates do not apply to Medicare or Medicare Advantage plans, the benefits of which are qualified by Medicare; this analysis excludes members of fully-insured commercial plans over 64 years of age and does not address any potential effect on Medicare supplement plans, even to the extent they are regulated by state law. This analysis does not apply to Medicaid/MassHealth.

3.2 Covered Services

3.2.1 Exondys 51

BerryDunn surveyed insurance carriers in the Commonwealth, and all but one small carrier reports currently covering Exondys 51 for DMD patients. At the time of the carrier surrey, one carrier had coverage under clinical review. Each carrier that provides coverage applies its own proprietary medical necessity criteria, which are, however, similar across carriers. In most cases, insurers will only approve Exondys 51 for six months at a time if the following conditions are met:

- The patient must have DMD with a confirmed mutation of the DMD gene that is amenable to exon 51 skipping (approximately 13% of DMD cases[34]).
- The prescription is written by a board certified/board eligible neurologist.
- There is documentation of ambulation without assistance or devices (often use a six-minute walk test).
- There is documentation of dystrophin levels.
- One carrier requires concurrent use of glucocorticoids, unless clinically contraindicated.
- Another carrier requires that prior to approval of Exondys 51, the member must have tried and failed corticosteroids for at least six months, or be intolerant to corticosteroids.

Additionally, in order to continue Exondys 51 after the initial six months, most carriers require that the patient demonstrate that, in addition to continuing medical need and patient tolerance of the therapy, the treatment has been effective by showing improvement in dystrophin levels or the six-minute walk distance. Given that Exondys 51 is not intended to improve patient function or ambulation, but rather to slow disease progression, the latter requirement may not be feasibly met, and would be irrelevant for patients who have already lost ambulation and are prescribed the drug to preserve respiratory and cardiac function, according to clinical experts interviewed for this report.[35] These clinicians emphasized the use of the treatment as more life prolonging and functionally preserving than ambulation improving.

Some carriers also have specific requirements around the use of corticosteroids by patients, including prednisone and deflazacort, which are often prescribed to reduce inflammation and to try to slow the course of DMD progression by preserving muscle strength and function, preventing scoliosis, and enabling patient mobility.[36] While these medications may increase strength, muscle, and pulmonary function, long-term use also may cause serious side effects, including weight gain, cataracts, and loss of bone mass; moreover, the rapid withdrawal of these drugs may lead to life-threatening complications.[37]

3.3 Existing Laws Affecting the Cost of H.B. 3644

The proposed mandate is not redundant to or in conflict with any existing state or federal mandates. The federal Affordable Care Act (ACA) mandates that there are no annual or lifetime caps on covered benefits, including for expensive treatments such as Exondys 51.[38]

Exondys 51 was granted approval on an accelerated pathway first defined in the 2012 Food and Drug Administration Safety Innovations Act (FDASIA), which allows the FDA to approve drugs for "serious conditions that fill an unmet medical need on whether the drug has an effect on a surrogate or an intermediate clinical endpoint."[39] Because the approval relied on demonstration of a surrogate endpoint (increased levels of dystrophin) versus proven clinical benefit, the FDA is requiring that the pharmaceutical company that submitted the drug for approval—Sarepta

Therapeutics in Cambridge, Massachusetts—continue clinical trials to prove the drug's presumed clinical benefits.[40] In making its decision, the FDA evaluated the potential risks of the drug, the lack of available treatments, and the life-threatening and debilitating nature of DMD.[41] If the clinical trials fail to prove the clinical benefit, the FDA may conduct proceedings to withdraw its approval.[42]

4.0 Methodology

4.1 Overview

Estimating the impact of H.B. 3644 on premiums requires assessing the incremental impacts of two components:

- Incremental cost due to shifting the medical necessity determination for the 13% of DMD patients who are amenable to Exon 51 skipping from carriers, which currently have limited approval of the drug, to treating physicians.
- Cost of genetically targeted DMD pipeline drugs. The current pipeline includes drugs for other exon-skipping genes, including exon 45 and exon 53, each of which is indicated for approximately 8% of patients, as well as the stop codon read-through drug Ataluren, indicated for approximately 10% of DMD patients.

Incremental cost of genetically targeted DMD drugs, which are reasonably estimated to receive FDA approval in the next five years. The incremental costs for these provisions are estimated using projected prevalence of the condition and the projected drug cost for treating the condition. Combining these components, and accounting for carrier retention, results in a baseline estimate of the proposed mandate's incremental effect on premiums, which is then projected over the five years following the assumed January 1, 2019, implementation date of the law.

4.2 Data Sources

The primary data sources used in the analysis are:

- Information about the intended effect of the bill, gathered from sponsors
- Information, including descriptions of current coverage, from responses to a survey of commercial health insurance carriers in the Commonwealth
- Academic literature, published reports, and population data, cited as appropriate
- Discussion with various clinical experts and providers

4.3 Steps in the Analysis

To implement the analysis, BerryDunn performed the steps summarized in this section.

1. *Estimated marginal costs to insurers due to shifting determination of medical necessity to patient provider rather than carrier criteria.*

In order to estimate the impact of the change in the control of medical necessity for currently covered drugs, BerryDunn:

A. Conducted and reviewed responses to a survey of Commonwealth insurance carriers and concluded that all but one of the carriers cover the cost of Exondys 51.

B. Calculated the number of male fully-insured residents in the Commonwealth aged 5 – 24.

C. Used publicly available literature to estimate the prevalence rate of DMD among males aged 5 – 24.

D. Adjusted this prevalence rate based on input from carrier surveys and clinical experts to better align with actual experience.

E. Multiplied the adjusted prevalence rate by the number of males aged 5 – 24 with fully-insured coverage to determine the number of people with DMD in the study population.

F. Used publicly available literature and estimated the portion of patients with DMD who can be treated with Exondys 51.

G. Multiplied the number of people with DMD by the portion of patients who could be treated with Exondys 51 to determine the number treated for the cost analysis.

H. Used publicly available sources and cost information provided by the insurance carriers to estimate the average annual per patient cost of Exondys 51.

I. Multiplied the average annual per patient cost of Exondys 51 (from Step H) by the number of new users attributable to the changed requirement (from Step G) to determine the incremental cost.

J. Divided the incremental cost calculated in Step I by the total of 2017 fully-insured member months for members under 65 to determine the incremental cost paid per member per month (PMPM).

K. Projected this baseline paid PMPM cost forward over the five-year analysis period, 2019 – 2023.

2. *Estimated incremental costs to insurers for new genetically targeted DMD drugs in the pipeline reasonably estimated to receive FDA approval in the next five years.*

In order to estimate the impact of the new DMD drugs in the pipeline, BerryDunn:

A. Began analysis starting with the number of people with DMD calculated in Steps A – E previously.

B. Used publicly available literature and obtained the portion of patients with DMD who can be treated with the three pipeline drugs under development and likely to be approved by the FDA during the projection period.

C. For each pipeline drug, multiplied the number of people with DMD by the portion of patients who can be treated with each therapy to determine the number of people who are treatable with each pipeline drug.

D. Used the portion of members approved by the carriers for treatment using Exondys 51 to approximate the number of users who would be approved for treatment for each pipeline drug in the absence of the requirement.

E. Determined a baseline cost for each pipeline drug based on the projections made for Exondys 51, given clinical input that these new drugs are expected to be similar in cost. Adjusted the baseline cost for trend throughout the 2019 – 2023 projection period. Multiplied the number of users by the average annual per patient cost and accounted for a likely six-month delay before the insurers cover each new drug absent the proposed mandate. This baseline represents the costs of the pipeline drugs absent the mandate.

F. For each pipeline drug, determined the number of new covered users who would not have been covered by insurers, absent the proposed mandate, due to application of the carriers' medical necessity criteria.

G. Summed the total number of approved users under the proposed mandate.

H. Multiplied the average annual per patient cost of the pipeline drugs by the total expected approved users.

I. Subtracted the cost of the baseline from the cost of the pipeline drugs under the proposed mandate to determine the incremental cost.

J. Divided the incremental cost calculated in the previous step by total 2017 fully-insured member months for members under 65 to determine the incremental cost PMPM.

K. Projected the incremental cost forward over the five-year analysis period, 2019 – 2023.

3. Calculated the impact of the combined projected claim costs on insurance premiums.

To add the other components of health insurance premiums to the estimated claims costs, BerryDunn:

A. Summed the estimated incremental paid PMPM costs associated with changes to the application of medical necessity criteria for currently covered drugs and the incremental costs for adding coverage for pipeline drugs.

B. Estimated the fully-insured Commonwealth population under age 65, projected for the next five years (2019 – 2023).

C. Multiplied the estimated aggregate incremental paid PMPM cost of the mandate by the projected population estimate to calculate the total estimated marginal claims cost of H.B. 3644.

D. Estimated insurer retention (administrative costs and profit) and applied the estimate to the final incremental claims cost calculated in Step C.

4.4 Limitations

The only drug currently approved by the FDA, Exondys 51, received accelerated approval based on a surrogate endpoint (increased levels of dystrophin), with clinical trials to determine efficacy still ongoing. At this time, most carriers require that the drug show efficacy to continue treatment. Because the drug is still very new, drug outcomes and efficacy levels still have a wide range of potential outcomes that could affect coverage. The FDA is requiring Sarepta to conduct follow-up studies to demonstrate clinical benefit for full approval. If the FDA reverses its approval decision, that would likely have an impact on the costs and carriers' decisions, if applicable, on covering the drug therapy, and would likewise impact future approval of other similar treatments in the pipeline, including those for exon 45 and exon 51.

The number of patients estimated in this analysis is based in part on a widely cited study of DMD prevalence in the male patient population ages 5 – 24; no Commonwealth-specific published prevalence rates are available. The initial calculation of the expected population based on the published prevalence rate was half of that found in the carrier survey, and the prevalence rate used in this study was therefore adjusted to reflect carrier experience. Although the population of DMD patients amenable to these specific treatments will be small, the impact of varying this prevalence even slightly may be significant, given the high per patient cost of the drug.

Dosage levels, and therefore the cost of Exondys 51, per patient are based on patient weight, which can vary significantly; there is no published literature on average weight per DMD patient by age. As so few patients are currently receiving this treatment, and the average weight of this population is unknown, the cost of treatment was estimated using publically availability sources and limited carrier claim information.

Estimated annual costs of Exondys 51 are widely variable in published articles. While Sarepta estimated annual costs of $300,000 based on significant discounts, other analysts estimated annual costs of $425,000, $654,000, and $750,000, while a drug plan manager representative cited an estimated range of $750,000 to $1.5 million a year.[43,44] There are currently no claims for Exondys 51 in the Massachusetts All Payer Claim Database (MA APCD), as the drug's approval was granted in September 2016. Of carriers that were able to respond with specific cost information, annualized per patient costs for Exondys 51 were between $1.2 and $2.4 million, though patient weight was not available to enable calculation of per unit cost of the drug.

The projected release of new genetically targeted pipeline drugs for DMD is based on information regarding clinical trial stages for each drug, as well as on estimates provided by several clinical experts who were interviewed for this analysis. Estimated release dates are highly speculative, and may change based on the results of the clinical trials, as well as a variety of other factors. This analysis assumes a reasonably conservative timeline for release of these drugs into the market for patients. Similarly, there is no information available regarding the anticipated costs of any of these drugs when they are released. However, given that the drugs for exon 45 and exon 53 are very similar to those for exon 51, it is reasonable to assume that the costs per patient will be the same or very similar as well. Using these estimates for Ataluren is less certain, but is a reasonable and conservative best guess based on currently available information.

5.0 Analysis

This section describes the calculations outlined in the previous section in more detail. The analysis includes development of a best estimate middle-cost scenario, as well as a low-cost scenario using assumptions that produced a lower estimate and a high-cost scenario using more conservative assumptions that produced a higher estimated cost impact.

Section 5.1 describes the steps used to calculate the PMPM expenses associated with expanded usage of Exondys 51 due to changes in carriers' application of medical necessity criteria to drugs of this type. Section 5.2 describes the PMPM expenses for other pipeline drugs. Section 5.3 aggregates the marginal PMPM costs. Section 5.4 projects the fully-insured population age 0 – 64 in the Commonwealth over the 2019 – 2023 analysis period. Section 5.5 calculates the total estimated marginal cost of H.B. 3644, and Section 5.6 adjusts these projections for carrier retention to arrive at an estimate of the bill's effect on premiums for fully-insured plans.

5.1 Exondys 51 Cost

Estimated marginal costs to insurers due to shifting determination of medical necessity to patient provider rather than carrier criteria.

One of the two components contributing to H.B. 3644's effect on premiums is the requirement that medical necessity be determined by treating physicians rather than by insurance carriers. To measure the impact of this change in medical necessity determination, BerryDunn first estimated how many people in the Commonwealth have DMD. Using the MA APCD and population estimates, BerryDunn determined that there are 316,139 aged 5 – 24 commercially fully-insured males in the Commonwealth. Based on published literature, the national prevalence rate of DMD is estimated to be 1.02 per 10,000 males between 5 – 24 years old. BerryDunn multiplied the population by this prevalence rate of DMD and determined that, based on this rate, there are approximately 32 males with DMD in the Commonwealth.

Researchers have estimated that approximately 13% of the DMD population has a genetic mutation at exon 51, which is amenable to treatment with Exondys 51.[45,46] BerryDunn multiplied this percent by the number of people with DMD in the Commonwealth to estimate approximately 4 expected users of Exondys 51 in the commercial fully-insured market. However, responses from the insurance carriers indicate that there are six people who applied for treatment in the previous year, indicating that the published national prevalence rate may be understated for the Commonwealth population. Moreover, clinical experts have indicated that not all patients who may be eligible for treatment with Exondys 51 will necessarily apply for it, in part because of the inconvenience of weekly clinic-based infusion treatments, as well as low expectations of probable outcomes for individual patients. In order to account for the discrepancy between the published national prevalence rate, carrier experience, and the input of clinical experts, BerryDunn assumed that a prevalence rate of two patients per 10,000 males aged 5 – 24 in the

commercial fully-insured population. This results in 63 DMD patients, with 8 amenable to treatment with Exondys 51.

All Commonwealth fully-insured carriers, with the exception of one small carrier, responded via survey that they cover Exondys 51 for treatment of DMD. Each applies its own proprietary medical necessity criteria before paying for treatment, with some requiring ambulation and/or corticosteroid use prior to first approval, and improved patient symptoms for continuing approval. Given these criteria, carriers indicated current coverage for five patients with DMD, with an additional patient who had applied and been denied for coverage. Additionally, clinical experts suggested that more patients who would have been eligible for treatment may not have applied for coverage given carrier requirements for ambulation, and/or based on patient decisions to forego treatment with Exondys 51.

The proposed mandate, if passed, would shift determination of medical necessity away from carrier criteria to the patient's treating physician. This change was estimated by BerryDunn in the low- and mid-scenarios to add one new patient to those currently covered, based on carrier denials to date. In the high scenario, Berry Dunn estimated two new patients, assuming at least one who had not previously applied for coverage, or who may not yet have been diagnosed as eligible for treatment with Exondys 51.

The annual cost per patient for Exondys 51 is based upon individual patient weight, as the current recommended dose is 30 milligrams per kilogram of patient weight.[47] No published reports are available regarding the average weight of patients or patient weight by age for those amenable to treatment with Exondys 51, or of the overall DMD population. However, clinical experts and published reports indicate that the population is generally overweight or obese at younger ages due to lack of ambulation, inactivity, and use of corticosteroids, while older patients are often underweight.[48] Published information from Sarepta, the manufacturer of Exondys 51, estimated the average annual cost of the drug per patient as $300,000 based on an average patient weight of 25 kilograms (55.1 pounds), as well as the application of deep discounts to manufacturer prices. BerryDunn used published information from the manufacturer and other financial analysts, as well as cost data provided by two insurance carriers, to estimate the average cost annual cost per user as $750,000 in the low scenario, $1,125,000 in the middle scenario, and $1,500,000 in the high scenario. In addition to the cost of the drugs themselves, the above amounts include an estimated $10,500 per patient annual cost for weekly infusion therapy conducted in a clinic. The number of new cases estimated based on the change to the determination of medical necessity were then multiplied by these annual costs to obtain an annual incremental cost. Results are displayed on the following page in Table 1.

Table 1: Baseline Cost for DMD Patients with Exon 51 Mutation

	New DMD Cases	Average Per Patient Annual Unit Cost	Annual Cost
Low Scenario	1	$750,000	$750,000
Mid Scenario	1	$1,125,000	$1,125,000
High Scenario	2	$1,500,000	$3,000,000

Projecting this expense over the analysis period requires applying an estimated cost growth trend for Exondys 51. The trend applies the long-term average national projection for cost increases to pharmaceuticals over the study period.[49]

The 2017 baseline marginal Exondys 51 cost is divided by the corresponding medical member months of 25.9 million, and increased by the trend factor to project the PMPM impact of shifting the determination of medical necessity from the carriers to patients' physicians for treatment. Table 2 displays the results.

Table 2: Estimated Marginal PMPM Cost of Exondys 51

	Baseline	2019	2020	2021	2022	2023
Low Scenario	$0.02	$0.03	$0.03	$0.03	$0.03	$0.04
Mid Scenario	$0.02	$0.03	$0.03	$0.03	$0.03	$0.04
High Scenario	$0.05	$0.06	$0.06	$0.06	$0.07	$0.07

5.2 Pipeline Costs

Estimated incremental costs to insurers for the cost of covering new genetically targeted DMD drugs in the pipeline without use of any medical necessity review, as reasonably estimated to receive FDA approval in the next five years.

As discussed above, the Commonwealth commercial fully-insured patient population with DMD was estimated to be 63. Of these, researchers have estimated that 8% have a genetic mutation at exon 45, and another 8% at exon 53; treatments for both of these mutations are in late stage of clinical trials.[50,51] Ataluren, a treatment for another type of mutation known as "stop codon read-through therapy," is also in development, and will impact approximately 10% of overall DMD patients.[52]

Using these DMD population percentages for each of the pipeline products, BerryDunn calculated the number of patients with these specific mutations and the number of new patients to be covered under current carrier rules, based on the assumption that carriers would cover the new drugs similarly to current coverage for Exondys 51. To project the impact of the new requirement, BerryDunn estimated the number of additional patients who would receive

coverage as a result of the proposed language impacting carrier's application of medical necessity criteria to these drugs. In the low scenario, it is assumed that no new patients would receive additional additional drugs due to the new requirements. In the mid scenario, BerryDunn assumed that one new case would be approved for each pipeline drug. In the high scenario, Berry Dunn estimated that all patients with the specific mutation would be approved, adding two additional patients per each drug as a result of the new requirement.

Table 3: Estimated New Patients to Be Treated With Pipeline Drugs

	Exon 45	Exon 53	Stop Codon
Total patients	5	5	6
Patients covered under current carrier rules	3	3	4
Additional Patients to Be Covered Due to Mandate			
Low Scenario	0	0	0
Mid Scenario	1	1	1
High Scenario	2	2	2

Based on input from clinical experts, as well as a review of the relevant clinical trials,[53] BerryDunn assumed that one of the Exon drugs will be available in the market for patients in 2019 (assumed for this analysis to be Exon 45), with the other to follow in 2020 (assumed for this analysis to be Exon 53). The projected availability of the stop codon read-through therapy (assumed to be Ataluren) is less predictable, but its release is conservatively assumed to be in 2022.

There is no available data on the anticipated annual costs for these pipeline drugs. Given, however, that the drugs for Exon 45 and Exon 53 treatment will be similar to that of Exon 51, BerryDunn assumed the cost for the new drugs to be identical to its estimate for Exondys 51, as outlined previously and summarized in Table 1. With no other available information, this estimate was likewise used to estimate the annual cost per patient for the stop codon read-through therapy.

Absent the proposed requirement, BerryDunn has assumed that the carriers would cover the pipeline drugs after they had an opportunity to clinically review them, as had been done for Exondys 51. BerryDunn calculated a baseline cost using the low estimate of annual per patient costs for each drug, as well as the assumption that carriers would start to cover the new drugs on average six months after FDA approval. This is based on responses from the carrier survey, and the fact that some carries did not cover Exondys 51 immediately after its release. For each year in the projection period, the number of months that the drug would be covered by the carriers was multiplied by the monthly per patient cost and by the number of users. The calculations are show on the following page in Table 4.

Table 4: Baseline Cost of Exon 45

	2019	2020	2021	2022	2023
# of Months Covered	6	12	12	12	12
Cost Per Month Low	$70,623	$75,072	$79,802	$84,829	$90,174
Cost Per Month Mid	$105,935	$112,608	$119,703	$127,244	$135,260
Cost Per Month High	$141,246	$150,145	$159,604	$169,659	$180,347
New Cases	3	3	3	3	3
Baseline Cost Low	$1,271,215	$2,702,603	$2,872,867	$3,053,858	$3,246,251
Baseline Cost Mid	$1,906,823	$4,053,905	$4,309,301	$4,580,787	$4,869,377
Baseline Cost High	$2,542,430	$5,405,207	$5,745,735	$6,107,716	$6,492,502

To calculate the incremental cost after implementation of the proposed language of the bill, the same calculations are done using the total new cases covered as a result of the proposed mandate. The number of months covered in 2019 is also assumed to increase from 6 to 12, as carriers will not be permitted under the proposed language to delay coverage for the drug, as had been done for Exondys 51.

The incremental cost is the difference between the total cost and the baseline cost calculated in Table 4. Results for the mid scenario, which uses the mid-estimate of per unit annual patient cost, is shown in Table 5 (below), and results for the high scenario, which uses the high-estimate of per unit annual patient cost, is shown in Table 6 (on the following page). Because the change in determination of medical necessity will not impact the low scenario as no additional patients are assumed to be added to coverage, the only incremental cost is in the first year, where there would be a full 12 months of coverage under the proposed language of the bill, rather than the 6 months of coverage assumed in the baseline. The incremental cost in 2019 in the low scenario is estimated to be $1,271,215.

Table 5: Estimated Marginal Cost of Exon 45 Mid Scenario

	2019	2020	2021	2022	2023
# of Months	12	12	12	12	12
Cost Per Month	$105,935	$112,608	$119,703	$127,244	$135,260
New Cases	4	4	4	4	4
Total Cost	$5,084,861	$5,405,207	$5,745,735	$6,107,716	$6,492,502
Incremental Cost	**$3,178,038**	**$1,351,302**	**$1,436,434**	**$1,526,929**	**$1,623,126**

Table 6: Estimated Marginal Cost of Exon 45 High Scenario

	2019	2020	2021	2022	2023
# of Months	12	12	12	12	12
Cost Per Month	$141,246	$150,145	$159,604	$169,659	$180,347
New Cases	5	5	5	5	5
Total Cost	$8,474,768	$9,008,678	$9,576,225	$10,179,527	$10,820,837
Incremental Cost	**$5,932,337**	**$3,603,471**	**$3,830,490**	**$4,071,811**	**$4,328,335**

The same set of calculations was performed for Exon 53. In this case, FDA approval is assumed to occur in 2020. Results are shown in Tables 7, 8, and 9. The baseline costs absent the mandate are shown below in Table 7.

Table 7: Estimated Baseline Cost of Exon 53

	2019	2020	2021	2022	2023
# of Months	0	6	12	12	12
Cost Per Month Low	$0	$75,072	$79,802	$84,829	$90,174
Cost Per Month Mid	$0	$112,608	$119,703	$127,244	$135,260
Cost Per Month High	$0	$150,145	$159,604	$169,659	$180,347
New Cases	0	3	3	3	3
Baseline Cost Low	$0	$1,351,302	$2,872,867	$3,053,858	$3,246,251
Baseline Cost Mid	$0	$2,026,953	$4,309,301	$4,580,787	$4,869,377
Baseline Cost High	$0	$2,702,603	$5,745,735	$6,107,716	$6,492,502

The incremental cost is the difference between the total cost and the baseline cost calculated in Table 7. In the low scenario, the incremental cost in the first year (2020) is estimated at $1,351,302, attributable to a full year under the new requirement, versus only six months of costs in its absence. Results for the middle scenario and the high scenario are shown on the following page in Tables 8 and 9, again varying the number of new cases to be receive the drug attributable to the new requirement, as well as the variable estimates of annual per patient costs in each scenario.

Table 8: Estimated Marginal Cost of Exon 53 Mid Scenario

	2019	2020	2021	2022	2023
# of Months	0	12	12	12	12
Cost Per Month	$0	$112,608	$119,703	$127,244	$135,260
New Cases	0	4	4	4	4
Total Cost	$0	$5,405,207	$5,745,735	$6,107,716	$6,492,502
Incremental Cost	**$0**	**$3,378,254**	**$1,436,434**	**$1,526,929**	**$1,623,126**

Table 9: Estimated Marginal Cost of Exon 53 High Scenario

	2019	2020	2021	2022	2023
# of Months	0	12	12	12	12
Cost Per Month	$0	$150,145	$159,604	$169,659	$180,347
New Cases	0	5	5	5	5
Total Cost	$0	$9,008,678	$9,576,225	$10,179,527	$10,820,837
Incremental Cost	**$0**	**$6,306,074**	**$3,830,490**	**$4,071,811**	**$4,328,335**

The same set of calculations were performed for introduction of a stop codon read-through treatment (Ataluren), which is conservatively projected to gain FDA approval in 2022. Results are shown in Tables 10, 11, and 12. The costs absent the proposed requirement are shown below in Table 10.

Table 10: Estimated Baseline Cost of Ataluren

	2019	2020	2021	2022	2023
# of Months	0	0	0	6	12
Cost Per Month Low	$0	$0	$0	$84,829	$90,174
Cost Per Month Mid	$0	$0	$0	$127,244	$135,260
Cost Per Month High	$0	$0	$0	$169,659	$180,347
New Cases	0	0	0	4.0	4.0
Baseline Cost Low	**$0**	**$0**	**$0**	**$2,035,905**	**$4,328,335**
Baseline Cost Mid	**$0**	**$0**	**$0**	**$3,053,858**	**$6,492,502**
Baseline Cost High	**$0**	**$0**	**$0**	**$4,071,811**	**$8,656,670**

The incremental cost is the difference between the total cost and the baseline cost calculated in Table 10. In the low scenario, the incremental cost is assumed to be zero, given that the approval path of this drug is less certain than for new exon-skipping drugs, which are similar to the approved Exondys 51. Results for the middle scenario are in Table 11, and results for the high scenario are in Table 12, below.

Table 11: Estimated Marginal Cost of Ataluren Mid Scenario

	2019	2020	2021	2022	2023
# of Months	0	0	0	12	12
Cost Per Month	$0	$0	$0	$127,244	$135,260
New Cases	0	0	0	5	5
Total Cost	$0	$0	$0	$7,634,645	$8,115,628
Incremental Cost	**$0**	**$0**	**$0**	**$4,580,787**	**$1,623,126**

Table 12: Estimated Marginal Cost of Ataluren High Scenario

	2019	2020	2021	2022	2023
# of Months	0	0	0	12	12
Cost Per Month	$0	$0	$0	$169,659	$180,347
New Cases	0	0	0	6	6
Total Cost	$0	$0	$0	$12,215,432	$12,985,004
Incremental Cost	**$0**	**$0**	**$0**	**$8,143,621**	**$4,328,335**

Finally, the marginal costs for the three pipeline drugs were added together, and the totals were divided by 25.9 million commercially insured member months to get the marginal PMPM associated with the pipeline drugs; results are show below in Table 13.

Table 13: Estimated Marginal PMPM Cost Associated With Pipeline Cost for New Drugs

	2019	2020	2021	2022	2023
Low Scenario	$0.05	$0.05	$0.00	$0.00	$0.00
Mid Scenario	$0.12	$0.18	$0.11	$0.29	$0.19
High Scenario	$0.23	$0.38	$0.30	$0.63	$0.50

5.3 Marginal Cost Per Member Per Month

Adding together the estimated PMPM costs associated with the two relevant provisions (from Tables 2 and 13) yields the total PMPM incremental cost, shown on the following page in Table 14.

Table 14: Estimated Marginal PMPM Cost of DMD Mandate

2019	2020	2021	2022	2023	2019
Low Scenario	$0.08	$0.09	$0.04	$0.04	$0.04
Mid Scenario	$0.17	$0.23	$0.17	$0.35	$0.25
High Scenario	$0.36	$0.52	$0.44	$0.79	$0.67

5.4 Projected Fully-insured Population in the Commonwealth

Table 15 shows the fully-insured population in the Commonwealth ages 0 to 64 projected for the next five years. Appendix A describes the sources of these values.

Table 15: Projected Fully-insured Population in the Commonwealth, Ages 0 – 64

Year	Total (0 – 64)
2019	2,153,622
2020	2,149,554
2021	2,145,579
2022	2,141,700
2023	2,137,917

5.5 Total Marginal Medical Expense

Multiplying the total estimated PMPM cost by the projected fully-insured membership over the analysis period results in the total cost (medical expense) associated with the proposed requirement, shown on the following page in Table 16. This analysis assumes the bill, if enacted, would be effective January 1, 2019.[ii]

[ii] The analysis assumes the mandate would be effective for policies issued and renewed on or after January 1, 2019. Based on an assumed renewal distribution by month, by market segment, and by the Commonwealth market segment composition, 71.3% of the member months exposed in 2019 will have the proposed mandate coverage in effect during calendar year 2017. The annual dollar impact of the mandate in 2017 was estimated using the estimated PMPM and applying it to 71.3% of the member months exposed.

Table 16: Estimated Marginal Cost of DMD

	2019	2020	2021	2022	2023
Low Scenario	$1,507,065	$2,242,615	$951,797	$1,009,931	$1,071,660
Mid Scenario	$3,164,837	$6,055,062	$4,283,085	$9,089,376	$6,429,959
High Scenario	$6,631,087	$13,455,693	$11,421,560	$20,198,614	$17,146,558

5.6 Carrier Retention and Increase in Premium

Assuming an average retention rate of 11.2% based on CHIA's analysis of administrative costs and profit in the Commonwealth,[54] the increase in medical expense was adjusted upward to approximate the total impact on premiums. Table 17 shows the result.

Table 17: Estimate of Increase in Carrier Premium Expense

	2019	2020	2021	2022	2023
Low Scenario	$1,698,049	$2,526,812	$1,072,413	$1,137,915	$1,207,466
Mid Scenario	$3,565,902	$6,822,392	$4,825,861	$10,241,231	$7,244,799
High Scenario	$7,471,414	$15,160,870	$12,868,962	$22,758,291	$19,319,463

6.0 Results

The estimated impact of the proposed requirement on medical expense and premiums appears below. The analysis includes development of a best estimate "mid-level" scenario, as well as a low-level scenario using assumptions that produced a lower estimate and a high-level scenario using more conservative assumptions that produced a higher estimated impact.

The impact on premiums is driven by the provisions of H.B. 3644 that modifies a carrier's acceptance of genetically targeted drugs for DMD by moving the determination for medical necessity from carriers to patient physicians, and by providing for immediate coverage for all such FDA-approved medications without a lag period. Variation between scenarios is attributable to the number of patients who are assumed to gain coverage given the proposed requirement, as well as the various annual per patient cost estimates used for the projections.

Starting in 2021, the federal ACA will impose an excise tax, commonly known as the "Cadillac Tax," on expenditures on health insurance premiums and other relevant items (e.g., health savings account contributions) that exceed specified thresholds. To the extent that relevant expenditures exceed those thresholds (in 2021), H.B. 3644, by increasing premiums, has the

potential of creating liability for additional amounts under the tax. Estimating the amount of potential tax liability requires information on the extent to which premiums, notwithstanding the effect of H.B. 3644, will exceed or approach the thresholds, and is beyond the scope of this analysis.

6.1 Five-Year Estimated Impact

For each year in the five-year analysis period, Table 18 (on the following page) displays the projected net impact of the proposed language on medical expense and premiums using a projection of Commonwealth fully-insured membership. Note that the relevant provisions of H.B. 3644 are assumed effective January 1, 2019.[55]

The low scenario impact is $1.6 million per year on average, and is due to the lowest estimate of per patient annual costs of the treatment; to new patients being added to coverage for Exondys 51 due to the proposed langage; and to the removal of any lag period for coverage provision of new pipeline drugs that will enter the market during the study period. The high scenario includes the same assumption regarding removal of a lag period, but uses higher estimates of annual per patient costs of treatment, and of the number of patients who will gain access to pipeline drugs as a result of the proposed language. The middle scenario uses assumptions between these two, and has average annual costs of $6.9 million, or an average of 0.053% of premium.

Finally, the impact of the proposed law on any one individual, employer group, or carrier may vary from the overall results, depending on the current level of benefits each receives or provides, and on how the benefits will change under the proposed language.

Table 18: Summary Results

	2019	2020	2021	2022	2023	Weighted Average	Five-Year Total
Members (000s)	2,154	2,150	2,146	2,142	2,138		
Medical Expense Low ($000s)	$1,507	$2,243	$952	$1,010	$1,072	$1,440	$6,783
Medical Expense Mid ($000s)	$3,165	$6,055	$4,283	$9,089	$6,430	$6,159	$29,022
Medical Expense High ($000s)	$6,631	$13,456	$11,422	$20,199	$17,147	$14,613	$68,854
Premium Low ($000s)	$1,698	$2,527	$1,072	$1,138	$1,207	$1,622	$7,643
Premium Mid ($000s)	$3,566	$6,822	$4,826	$10,241	$7,245	$6,940	$32,700
Premium High ($000s)	$7,471	$15,161	$12,869	$22,758	$19,319	$16,464	$77,579
PMPM Low	$0.09	$0.10	$0.04	$0.04	$0.05	$0.06	$0.06
PMPM Mid	$0.19	$0.26	$0.19	$0.40	$0.28	$0.27	$0.27
PMPM High	$0.41	$0.59	$0.50	$0.89	$0.75	$0.64	$0.64
Estimated Monthly Premium	$493	$502	$512	$523	$533	$513	$513
Premium % Rise Low	0.019%	0.019%	0.008%	0.008%	0.009%	0.012%	0.012%
Premium % Rise Mid	0.039%	0.053%	0.037%	0.076%	0.053%	0.053%	0.053%
Premium % Rise High	0.082%	0.117%	0.098%	0.169%	0.141%	0.125%	0.125%

6.2 Impact on the GIC

The proposed legislative change is assumed to apply to both fully-insured and self-insured plans operated for state and local employees by the GIC, with an effective date for all GIC policies on July 1, 2019.

Because the benefit offerings of GIC plans are similar to those of most other commercial plans in the Commonwealth, and based on our carrier surveys that did not indicate GIC had different coverage, the estimated PMPM effect of the proposed legislative language on GIC medical expense is assumed not to differ from that calculated for the other fully-insured plans in the Commonwealth.

To estimate the medical expense separately for the GIC, the PMPM medical expense for the general fully-insured population was applied to the GIC membership starting in July 2019.

Table 19 breaks out the GIC-only fully-insured membership and the GIC self-insured membership, as well as the corresponding incremental medical expense and premium. Note

that the total medical expense and premium values for the general fully-insured membership displayed in Table 18 also include the GIC fully-insured membership. Finally, the proposed legislative requirement is assumed to require the GIC to implement the provisions on July 1, 2019; therefore, the results in 2019 are approximately one-half of an annual value.

Table 19: GIC Summary Results

	2019	2020	2021	2022	2023	Weighted Average	Five-Year Total
GIC Fully-insured							
Members (000s)	54	54	54	54	55		
Medical Expense Low ($000s)	$26	$56	$24	$26	$27	$35	$159
Medical Expense Mid ($000s)	$55	$151	$107	$230	$164	$157	$708
Medical Expense High ($000s)	$116	$336	$285	$510	$438	$375	$1,686
Premium Low ($000s)	$30	$63	$27	$29	$31	$40	$179
Premium Mid ($000s)	$62	$170	$121	$259	$185	$177	$797
Premium High ($000s)	$131	$379	$321	$575	$494	$422	$1,900
GIC Self-Insured							
Members (000s)	269	269	268	271	273		
Medical Expense Low ($000s)	$132	$280	$119	$128	$137	$177	$796
Medical Expense Mid ($000s)	$277	$756	$535	$1,148	$822	$786	$3,539
Medical Expense High ($000s)	$581	$1,681	$1,426	$2,552	$2,192	$1,873	$8,432

Appendix: Membership Affected By the Proposed Language

Membership potentially affected by a proposed mandated change to the use of medical necessity criteria may include Commonwealth residents with fully-insured employer-sponsored health insurance issued by a Commonwealth-licensed company (including through the GIC); non-residents with fully-insured employer-sponsored insurance issued in the Commonwealth; Commonwealth residents with individual (direct) health insurance coverage; and lives covered by GIC self-insured coverage. BerryDunn's 2019 – 2023 membership projections for these populations are derived from the following sources.

The 2014 MA APCD formed the base for the projections. The MA APCD provided fully-insured and self-insured membership by insurance carrier. The MA APCD was also used to estimate the number of non-residents covered by a Commonwealth policy. These are typically cases in which a non-resident works for a Commonwealth employer that offers employer-sponsored coverage. Adjustments were made to the data for membership not in the MA APCD, based on published membership reports available from CHIA and the Massachusetts Department of Insurance (DOI).

CHIA publishes a quarterly enrollment trends report and supporting databook (enrollment-trends-july-2016-databook[56]), which provides enrollment data for Commonwealth residents by insurance carrier for most carriers (some small carriers are excluded). CHIA uses supplemental information beyond the data in the MA APCD to develop its enrollment trends report and provided BerryDunn with details regarding the use of supplemental carrier information for its December 2014 reported enrollment. The supplemental data was used to adjust the resident totals from the MA APCD.

The DOI publishes reports titled Quarterly Report of Health Maintenance Organization Membership in Closed Network Health Plans as of December 31, 2014[57] and Massachusetts Division of Insurance Annual Report Membership in MEDICAL Insured Preferred Provider Plans by County as of December 31, 2014.[58] These reports provide fully-insured covered members for licensed Commonwealth insurers where the member's primary residence is in Commonwealth. The DOI reporting includes all insurance carriers and was used to supplement the MA APCD membership for small carriers not in the MA APCD.

The distribution of members by age and gender was estimated using MA APCD population distribution ratios and was checked for reasonableness and validated against U.S. Census Bureau data.[59] Membership was projected forward from the 2014 base year to 2015 using the American Community Survey,[60] and then from 2015 through 2021 using Census Bureau population growth rate estimates by age and gender.[61]

Projections for the GIC self-insured lives were developed using the GIC base data for 2014[62] and 2015,[63] as well as the same projected growth rates from the Census Bureau that were used for the Commonwealth population. Breakdowns of the GIC self-insured lives by gender and age were based on the Census Bureau distributions.

Endnotes

[1] The 190th General Court of the Commonwealth of Massachusetts, House Bill 3644 (MA-HB3644), "An Act relative to certain genetically targeted drug coverage for Duchenne Muscular Dystrophy." Accessed 2 February 2018: https://malegislature.gov/Bills/190/H3644.

Genetically targeted drug defined as:

> "a drug for which the approved use may result in the modulation, including suppression, up-regulation, or activation, of the function of a gene or its associated gene product and incorporates or utilizes non-replicating nucleic acid or analogous compounds to treat one or more patient subgroups, including subgroups of patients with different mutations of a gene."

[2] NIH, National Library of Medicine (NIH-NLM). Duchenne muscular dystrophy. Reviewed 15 January 2016; accessed 13 September 2017: https://medlineplus.gov/ency/article/000705.htm.

[3] Romitti PA, Zhu Y, Puzhankara S, et. al. Prevalence of Duchenne and Becker muscular dystrophies in the United States. Pediatrics. 2015;135(3):513–21. Accessed 8 January 2018: http://pediatrics.aappublications.org/content/135/3/513.

[4] Muscular Dystrophy Association (MDA). Duchenne Muscular Dystrophy (DMD): About Duchenne Muscular Dystrophy. Accessed 22 July 2017: https://www.mda.org/disease/duchenne-muscular-dystrophy.

[5] *Op. cit.* MDA. DMD: About Duchenne Muscular Dystrophy.

[6] National Institutes of Health, National Library of Medicine, Genetics Home Reference (NLM-GHR). Duchenne and Becker muscular dystrophy. Published 5 September 2017; accessed 6 September 2017: https://ghr.nlm.nih.gov/condition/duchenne-and-becker-muscular-dystrophy.

[7] *Op. cit.* NLM-GHR: Duchenne and Becker muscular dystrophy.

[8] *Op. cit.* NLM-GHR: Duchenne and Becker muscular dystrophy.

[9] *Op. cit.* NLM-GHR: Duchenne and Becker muscular dystrophy.

[10] *Op. cit.* MDA. DMD: Signs and Symptoms.

[11] *Op. cit.* MDA. DMD: Signs and Symptoms.

[12] *Op. cit.* NLM-GHR: Duchenne and Becker muscular dystrophy.

[13] *Op. cit.* MDA. DMD: Signs and Symptoms.

[14] *Op. cit.* MDA. DMD: Signs and Symptoms.

[15] *Op. cit.* NLM-GHR: Duchenne and Becker muscular dystrophy.

[16] *Op. cit.* MDA. DMD: About Duchenne Muscular Dystrophy.

[17] *Op. cit.* NIH-NLM. Duchenne muscular dystrophy.

[18] MDA. DMD: Medical Management. Accessed 22 July 2017: https://www.mda.org/disease/duchenne-muscular-dystrophy/medical-management.

[19] *Op. cit.* NIH-NLM. Duchenne muscular dystrophy.

[20] MDA. DMD: Research. Accessed 13 September 2017: https://www.mda.org/disease/duchenne-muscular-dystrophy/research.

[21] *Op. cit.* MDA. DMD: Research.

[22] Lim KR, Maruyama R, Yokota T. Eteplirsen in the treatment of Duchenne muscular dystrophy. Drug Des Devel Ther. 2017 Feb 28;11:533-545. Accessed 11 January 2018: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5338848/#b17-dddt-11-533.

[23] Aartsma-Rus A, Straub V, Hemmings R, et. al. Development of Exon Skipping Therapies for Duchenne Muscular Dystrophy: A Critical Review and a Perspective on the Outstanding Issues. Nucleic Acid Ther. 2017 Oct;27(5):251-259. doi: 10.1089/nat.2017.0682. Accessed 24 January 2018: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5649120/.

[24] Lim KR, Maruyama R, Yokota T. Eteplirsen in the treatment of Duchenne muscular dystrophy. Drug Des Devel Ther. 2017 Feb 28;11:533-545. Accessed 8 January 2018: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5338848/.

[25] Bladen CL, Salgado D, Monges S, et. al. The TREAT-NMD DMD Global Database: analysis of more than 7,000 Duchenne muscular dystrophy mutations. Hum Mutat. 2015 Apr;36(4):395-402. Accessed 23 January 2018: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4405042/.

[26] U.S. Food and Drug Administration (FDA). FDA News Release: FDA grants accelerated approval to first drug for Duchenne muscular dystrophy. Released 19 September 2016; accessed 22 July 2017: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm521263.htm.

[27] Kesselheim AS, Avorn J. Approving a Problematic Muscular Dystrophy Drug: Implications for FDA Policy. JAMA. 2016 Dec 13;316(22):2357-2358. Accessed 21 September 2017: http://jamanetwork.com/journals/jama/article-abstract/2572614.

[28] *Op. cit.* FDA News Release: FDA grants accelerated approval to first drug for Duchenne muscular dystrophy.

[29] Phone conversation, 30 January 2018. Laura Hagerty, PhD. Scientific Program Officer, Muscular Dystrophy Association.

Phone conversation, 1 February 2018. Kathryn R. Wagner, MD, PhD. Director, Center for Genetic Muscle Disorders, Kennedy Krieger Institute; Professor of Neurology and Neuroscience, Johns Hopkins School of Medicine.

Phone conversation, 1 February 2018. Claudia Senesac, PT, PhD, PCS. Clinical Associate Professor, University of Florida Department of Physical Therapy.

Phone conversation, 2 February 2018. Elizabeth M McNally, MD, PhD. Director, Center for Genetic Medicine, Elizabeth J. Ward Professor of Genetic Medicine, Professor of Medicine (Cardiology) and Biochemistry and Molecular Genetics, Feinberg School of Medicine, Northwestern University.

[30] Romitti PA, Zhu Y, Puzhankara S, et. al. Prevalence of Duchenne and Becker muscular dystrophies in the United States. Pediatrics. 2015;135(3):513–21. Accessed 8 January 2018: http://pediatrics.aappublications.org/content/135/3/513.

[31]U.S. National Library of Medicine, ClinicalTrials.gov. Accessed 25 January 2018: https://www.clinicaltrials.gov/ct2/results?recrs=abdf&cond=Duchenne+Muscular+Dystrophy+AND+%22Duchenne+Muscular+Dystrophy%22.

[32] *Op. cit.* Phone conversations, Hagerty, Wagner, Senesac, McNally.

[33] Romitti PA, Zhu Y, Puzhankara S, et. al.

[34] Romitti PA, Zhu Y, Puzhankara S, et. al. Prevalence of Duchenne and Becker muscular dystrophies in the United States. Pediatrics. 2015;135(3):513–21. Accessed 8 January 2018: http://pediatrics.aappublications.org/content/135/3/513.

[35] *Op. cit.* Phone conversations, Hagerty, Wagner, Senesac, McNally.

[36] *Op. cit.* MDA. DMD: Medical Management.

[37] *Op. cit.* MDA. DMD: Medical Management.

[38] U.S. Department of Health and Human Services (HHS). About the ACA: Lifetime & Annual Limits. Updated 31 January 2017; accessed 2 February 2018: https://www.hhs.gov/healthcare/about-the-aca/benefit-limits/index.html.

[39] FDA: Accelerated Approval. Updated 4 January 2018; accessed 2 February 2018: https://www.fda.gov/ForPatients/Approvals/Fast/ucm405447.htm.

[40] *Op. cit.* FDA News Release: FDA grants accelerated approval to first drug for Duchenne muscular dystrophy.

[41] *Op. cit.* FDA News Release: FDA grants accelerated approval to first drug for Duchenne muscular dystrophy.

[42] *Op. cit.* FDA News Release: FDA grants accelerated approval to first drug for Duchenne muscular dystrophy.

[43] Court E. “At $300,000 a year, Sarepta’s new drug is considered a steal.” MarketWatch. Published 21 September 2016; accessed 2 February 2018: https://www.marketwatch.com/story/at-300000-a-year-sareptas-new-drug-is-considered-a-steal-2016-09-20.

[44] Thomas K. “Insurers Battle Families Over Costly Drug for Fatal Disease.” New York Times. Published 22 June 2017; accessed 2 February 2018: https://www.nytimes.com/2017/06/22/health/duchenne-muscular-dystrophy-drug-exondys-51.html.

[45] Aartsma-Rus A, Straub V, Hemmings R, et. al. Development of Exon Skipping Therapies for Duchenne Muscular Dystrophy: A Critical Review and a Perspective on the Outstanding Issues. Nucleic Acid Ther. 2017 Oct;27(5):251-259. doi: 10.1089/nat.2017.0682. Accessed 24 January 2018: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5649120/.

[46] Lim KR, Maruyama R, Yokota T. Eteplirsen in the treatment of Duchenne muscular dystrophy. Drug Des Devel Ther. 2017 Feb 28;11:533-545. Accessed 11 January 2018: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5338848.

[47] Exondys 51 (eteplirsen) injection label, highlights of prescribing information. Initial U.S. Approval: 2016; accessed 4 February 2018: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/206488lbl.pdf.

[48] Martigne L, Salleron J, Mayer M, et. al. Natural evolution of weight status in Duchenne muscular dystrophy: a retrospective audit. Br J Nutr. 2011 May;105(10):1486-91. Accessed 4 February 2018: https://www.cambridge.org/core/journals/british-journal-of-nutrition/article/natural-evolution-of-weight-status-in-duchenne-muscular-dystrophy-a-retrospective-audit/F0D4289A0417E89AF7C77BD89E3FD552.

[49] U.S. Centers for Medicare and Medicaid Services (CMS), Office of the Actuary. National Health Expenditure Projections. Table 11, Prescription Drug Expenditures; Aggregate and per Capita Amounts, Percent Distribution and Annual Percent Change by Source of Funds: Calendar Years 2008-2024; Private Insurance. Accessed 29 January 2016: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/NationalHealthAccountsProjected.html.

[50] Aartsma-Rus A, Straub V, Hemmings R, et. al. Development of Exon Skipping Therapies for Duchenne Muscular Dystrophy: A Critical Review and a Perspective on the Outstanding Issues. Nucleic Acid Ther. 2017 Oct;27(5):251-259. doi: 10.1089/nat.2017.0682. Accessed 24 January 2018: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5649120/.

[51] Lim KR, Maruyama R, Yokota T. Eteplirsen in the treatment of Duchenne muscular dystrophy. Drug Des Devel Ther. 2017 Feb 28;11:533-545. Accessed 11 January 2018: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5338848.

[52] Bladen CL, Salgado D, Monges S, et. al. The TREAT-NMD DMD Global Database: analysis of more than 7,000 Duchenne muscular dystrophy mutations. Hum Mutat. 2015 Apr;36(4):395-402. Accessed 23 January 2018: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4405042/.

[53] U.S. National Library of Medicine, ClinicalTrials.gov. Accessed 25 January 2018: https://www.clinicaltrials.gov/ct2/results?recrs=abdf&cond=Duchenne+Muscular+Dystrophy+AND+%22Duchenne+Muscular+Dystrophy%22.

[54] Massachusetts Center for Health Information and Analysis. Annual Report on the Massachusetts Health Care System, September 2017. Accessed 27 December 2017: http://www.chiamass.gov/annual-report.

[55] With an assumed start date of January 1, 2016, dollars were estimated at 70.7% of the annual cost, based upon an assumed renewal distribution by month (Jan through Dec) by market segment and the Massachusetts market segment composition.

[56] Center for Health Information and Analysis. Estimates of fully-insured and self insured membership by insurance carrier. Accessed 22 September 2016. www.chiamass.gov/enrollment-in-health-insurance/.

[57] Massachusetts Department of Insurance. HMO Group Membership and HMO Individual Membership http://www.mass.gov/ocabr/docs/doi/managed-care/hmo/4q14dist-group.pdf, http://www.mass.gov/ocabr/docs/doi/managed-care/hmo/4q14dist-individual.pdf.

[58] Massachusetts Department of Insurance. Membership 2014. Accessed 22 September 2016 http://www.mass.gov/ocabr/docs/doi/managed-care/prefprov/2014-prefprov2.pdf.

[59] U.S. Census Bureau. Annual Estimates of the Population for the United States, Regions, States, and Puerto Rico: April 1, 2010 to July 1, 2015. Accessed 28 April 2016: http://www.census.gov/popest/data/state/totals/2015/index.html.

[60] American Factfinder U.S. Census Bureau, Annual estimate of populations. Accessed 22 September 2016 http://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid=PEP_2015_PEPANNRES&src=pt

Methodology described http://www.census.gov/popest/methodology/2015-natstcopr-meth.pdf.

[61] U.S. Census Bureau. Annual Estimates of the Population for the United States, Regions, States, and Puerto Rico: April 1, 2010 to July 1, 2015. Accessed 28 April 2016: http://www.census.gov/popest/data/state/totals/2015/index.html.

[62] Group Insurance Commission. GIC Health Plan Membership by Insured Status FY2014. Accessed 28 March 2016: http://www.mass.gov/anf/docs/gic/annual-report/fy2014annual-report.pdf.

[63] Group Insurance Commission, Group Insurance Commission Fiscal Year 2015 Annual Report. Accessed 25 January 2016: http://www.mass.gov/anf/docs/gic/annual-report/gic-annual-reportfy15.pdf.