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Stem Cell Therapy for Type 2 Diabetes

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Executive Summary

Chronic conditions are becoming increasingly prevalent among the US population. Thus, the amount of healthcare spending is rapidly increasing nationwide. Treating many of these diseases is difficult, as many possible treatments are still in the research and development phase. However, many innovative cures are poised to make a big impact on the field of healthcare. The problem asks us to identify and quantify how one of these prospective cures will impact healthcare. We analyzed the potentially drastic impacts of stem cell therapy on diabetes treatment by studying how healthcare expenditures will change and predicting how many people will reap its benefits.

The specific technology that has shown the most potential to cure diabetes is mesenchymal stem cells, which originate from a variety of different tissues (most commonly bone marrow). They can differentiate into insulin-producing beta cells and replace the ineffective cells in diabetes patients, regenerate clusters of non-functioning beta cells, and stop functioning beta cells from inducing apoptosis (cell death). Their diverse applications have spawned a lot of interest from the scientific community.

We made several assumptions in our model. First, we only considered fee-for-service (FFS) Medicare beneficiaries diagnosed with diabetes. We also assumed that "diabetes" in the data referred to Type 2 diabetes. Furthermore, for specific costs and categories, we only looked at the standardized numbers adjusted for geographic variation. Finally, we assumed that healthcare spending doubles every 13 years.

The majority of our data on the diabetic population comes from the Centers for Medicare and Medicaid Services (CMS), a reliable and well-known source. Our remaining statistics come from peer-reviewed online or government sources. We found that stem cell therapy would eradicate Type 2 Diabetes in 70% of patients and developed models for diabetes-related spending per capita and the costs of the new therapy including anti-rejection medication. For comparison, we analyzed the total amount of spending on diabetes using existing treatments. These models allowed us to predict the changes in total spending if stem cell therapy replaces the existing treatments, and we forecasted the changes until 2100, the approximate end of Generation Z's lifespans. In the FFS population, we also examined the growth of the diabetic population, the mortality rate, and life expectancy to ascertain precise estimates of the annual savings through 2100 if stem-cell therapy is employed.

Our model indicates that if stem cell therapy is introduced in 2020, the government begins saving money in 2040 and reaches the point when the cumulative amount of money saved is commensurate to the startup costs in 2052. Hence, stem cell therapy will become a favorable treatment option for diabetes slightly before Generation Z becomes eligible for Medicare. If implemented in 2020, therapy could positively benefit 62.76 million people by 2100 and would cumulatively save Medicare $30.1 trillion. Our cost model is most sensitive to changes in the efficacy rate of therapy and least sensitive to changes in the percent of diabetes cases that are Type 2. This treatment will have a large impact on those who diabetes patients, insulin-producing companies, and the government among other groups. We recommend that patients adopt this treatment, that insulin producers lower prices to remain competitive, and that the government passes legislation to encourage stem cell research while staying in line with ethical concerns.

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1 Introduction: Technology Overview

Millions of people around the world suffer from diabetes each year. Among them, the vast majority suffer from Type 2 diabetes, which commonly develops during adulthood and centers around the body's inability to produce insulin. Not only does the body lack cells that can produce insulin, but cells also develop insulin resistance, rendering the body unable to use insulin even if adequate amounts of it are present (Barclay, 2015). Over 90% of diabetes cases are Type 2 (Barclay, 2015).

Despite the seemingly ominous projections of growth in diabetes prevalence, many promising treatments are on the horizon, one of which is stem cell therapy. When used in conjunction with other treatments, stem cell therapy has shown a lot of potential as a viable treatment option for Type 2 diabetes.

Stem cell therapy, in which cells can be used to divide and form cells that can differentiate into other cell types ("Stem cells: Frequently," 2018), is a new potential cure for diabetes. Therapy is most commonly used for transplants; stem cells can replace old, damaged cells and repair destroyed tissue ("Stem cells: Frequently," 2018). This is a form of regenerative medicine, which is when new tissues or organs are generated to replace non-functional ones ("Stem cells: Frequently," 2018).

In the last few years, there has been extensive animal testing on the use of stem cells to cure diabetes. In a study published in 2015, researchers fattened up mice to get them to develop diabetes (Bruin, Braun, Saber, 2015). The mice's cells then became insulin-resistant, as human cells do. The researchers then injected human embryonic stem cells — cells from embryos that are just a few days old — into the mice (Bruin, Braun, Saber, 2015). Over a few months, these stem cells, when exposed to different chemical/cellular signals associated with insulin deficiency, differentiated into cells capable of handling and producing insulin (Bruin, Braun, Saber, 2015). By six months, the severity of the mice's diabetes began to reduce (Bruin, Braun, Saber, 2015). Although the therapy did not completely get rid of their diabetes without subsequent anti-diabetic drug administration (Bruin, Braun, Saber, 2015) because the embryonic stem cells were not able to completely make up for the lack of functional beta cells, the improvement was still promising.

In addition to animal testing, many trials have also been conducted on humans. Many of these studies tackle the primary challenge of determining how to grow cells that are able to replace dysfunctional beta cells. Some studies tried using iPS (induced pluripotent) or embryonic stem cells to create beta cells ("Diabetes," n.d.). iPS cells are stem cells that originate from reprogramming cells in a lab environment (Chin, Mason, Xie, Volinia, Singer, Peterson, … Lowry, 2009), while embryonic stem cells are naturally formed as embryos develop (Chin, Mason, Xie, Volinia, Singer, Peterson, … Lowry, 2009). Both can be grown and converted to specific cell types (ie. beta cells) for usage by the body ("Diabetes," n.d.). Most studies have run into the roadblock of delivery, as it is difficult to get these beta cells to a specific place in a person's body ("Diabetes," n.d.). Additionally, they must prevent the immune system from attacking these foreign cells ("Diabetes," n.d.).

Another recent promising development is mesenchymal stem cells, which most commonly come from bone marrow (Zang, Hao, Liu, Li, Han, Mu, 2017) but can also come from the liver, lungs, and bloodstream ("Mesenchymal Stem Cells," n.d.). Aside from being able

to differentiate into insulin-producing cells, these cells can also regenerate the islet beta cells (clusters of cells in the pancreas that produce insulin) (Zang, Hao, Liu, Li, Han, Mu, 2017). Furthermore, they can prevent these islet beta cells from going into apoptosis (cell suicide) (Zang, Hao, Liu, Li, Han, Mu, 2017).

One of the main applications of mesenchymal stem cells is differentiating into new beta cells. In certain studies, mesenchymal stem cells that originate from bone marrow have been rather effective in differentiating into insulin-producing cells (Zang, Hao, Liu, Li, Han, Mu, 2017). However, research is also being done on other types of mesenchymal cells, such as ones deriving from the umbilical cord. In some cases, mesenchymal stem cells from the umbilical cord have been equally or more effective than bone marrow mesenchymal stem cells in differentiating into new insulin-producing cells (Zang, Hao, Liu, Li, Han, Mu, 2017). Regardless, both of these types of mesenchymal cells are promising cures, making them prime subjects for further research.

However, one problem with mesenchymal stem cells is that once they have transformed into other cell types, they typically can only survive for a very brief period (Zang, Hao, Liu, Li, Han, Mu, 2017). As they are differentiated, certain stimulating agents indirectly hinder their ability to perform work for an extended duration of time (Zang, Hao, Liu, Li, Han, Mu, 2017). In researching this survival issue, scientists have found a now-common solution involving the usage of direct mesenchymal transplants (Zang, Hao, Liu, Li, Han, Mu, 2017). Direct mesenchymal transplants refer to the process of removing bone marrow from a patient, filtering out extraneous tissue and blood, processing the cells, freezing them if they are not to be used immediately, and later injecting them into a patient's veins when they are needed ("Understanding," 2016).

Due to the promising research conducted in the last few years, scientists are particularly hopeful about the future of mesenchymal stem cells.

2 Data Methodology

2.1 Assumptions

1. We only consider fee-for-service (FFS) Medicare beneficiaries. CMS only contains complete data on FFS enrollees.
2. We only consider diagnosed diabetes. Many cases go undiagnosed; they therefore go untreated and do not incur any directly measurable medical costs.
3. "Diabetes" in all the data refers to type 2 diabetes. There is no distinction made between type 1 and type 2 in the data, but type 2 usually accounts for well over 90% of the cases of diagnosed diabetes in the general populace (Berry, 2018). Within the Medicare-eligible population, this number is likely even higher, as most enrollees are over 65, and age increases the likelihood of type 2 diabetes. As we are unable to determine an exact percentage of FFS enrollees who have type 2 versus type 1, we assume all cases refer to type 2 for the purposes of our model.
4. The development of stem cell therapy will not affect the trajectory of the prevalence of diagnosed diabetes. Since therapy will likely be a cure, not a preventative tool, we assume that it will not have an impact on the number of diagnoses.
5. All variables refer to national averages or aggregates. Since we are looking at the nationwide changes, we will only consider the standardized figures, as opposed to creating variables for specific groups.
6. US healthcare spending doubles every 13 years. An article by the MIT Technology Review reported this general trend in American healthcare spending (Regalado, 2013). This corresponds to an annual growth rate of $2^{1/13} = 1.055$, or 5.5%, reasonably outpacing inflation given current trends ("United States Inflation Rate," n.d.).
7. The technology is first brought to market in 2019. Though commercialization this year remains unlikely, clinical trials have been underway since at least 2010 ("Stem Cell Therapy for Type 2 Diabetes Mellitus", 2010). Since the date of commercialization is entirely unpredictable, we select a single year to showcase a hypothetical scenario. The model itself is entirely robust to changes in this value. We further assume that Medicare begins covering stem cell therapy for diabetes treatment in 2020.

2.2 Definitions and Formulas for Data Generation

D.1 Standardized spending: spending adjusted for geographic variation ("CMS," 2013).
D.2 DME: Durable Medical Equipment as defined by CMS ("Referring," 2018).
D.3 Per capita: per person with diagnosed diabetes enrolled in Medicare fee-for-service (FFS).
D.4 Therapy: mesenchymal stem cell therapy as described in Zang, Hao, Liu, Li, Han, Mu, 2017.

Table 1. Symbols and definitions used throughout the paper.

Symbol	Definition	Unit
$s_c(y)$	Reducible direct medical costs per capita of diabetes in year y	$
$M(y)$	Number of Medicare enrollees in year y	People

$b(y)$	Number of FFS enrollees with diabetes in year y	People
$P(y)$	US population in year y	People
$p(y)$	Percentage of US population on FFS and diagnosed with diabetes	%
$D(y)$	Percentage of US population diagnosed with diabetes	%
$F(y)$	Percentage of US population enrolled in FFS	%
$m(y)$	Mortality rate of the FFS population in year y	$
$S_c(y)$	Total cost per capita of therapy in year y, using the appropriate model	$
$S_{c1}(y)$	Total cost per capita of therapy in year y, using the phase one model	$
$S_{c2}(y)$	Total cost per capita of therapy in year y, using the phase two model	$
$T(y)$	Total standardized spending on diabetes in year y if therapy is used	$
$B(y)$	Net savings on total expenditure if therapy is used	$
$C(y)$	Cumulative savings on total expenditure if therapy is used	$
$l(y)$	Remaining life expectancy of a 65-year-old US resident.	years
$L(y)$	Remaining life expectancy after a diabetes diagnosis	years
$a_1(y)$	The cost of anti-rejection medication unique to the first year after therapy	$
$a(y)$	The cost of anti-rejection medication each year	$
$n(y)$	The number of beneficiaries receiving therapy this year	People
$N(y)$	The number of living beneficiaries for which therapy was successful	People

To obtain population, $P(y)$, we extracted Statista's US resident population data from 1980-2018 ("Resident population," n.d.) and US Census projections from 2020 to 2060 ("Population projections," n.d.). Statista, being an academic database, was a trustworthy source that we were able to use to extract accurate data on the US population by year. We also obtained data on the number of diabetic FFS enrollees, $b(y)$, from Table B.2.a of CMS' Medicare Tables and Reports ("Medicare Tables," n.d.). We used CMS because it contains the most complete and accurate numbers on diabetic FFS enrollees.

To obtain data on the current costs of type 2 diabetes, we used a comprehensive survey conducted in 2009 by Dall et al (Dall, Mann, Zhang, Quick, Seifert, Martin, … Zhang, 2009) that includes specific breakdowns of national spending on all costs associated with diabetes. The source data used to create their cost-breakdown was not readily available, and given that this was a credible study, we opted to use their results. As a note, we also tried manually filtering and combining CMS data, but this yielded incomplete cost data. The yielded annualized per-capita spending on diabetes ($300) was too low to be reasonable. Also, costs such as the various kinds of outpatient care were neglected or difficult to enumerate and find.

Our model also requires knowledge of mortality rates and life expectancies. FFS population annual mortality rates from 1999 to 2013 were obtained from an analysis of CMS data (Krumholz, Nuti, Downing, Normand, Wang, 2015). US Population life expectancy data was obtained from Table 15 of the 2017 CDC Health Statistics ("Data Finder," n.d.).

For validation purposes, we also obtained percentages of the US population that were diagnosed with diabetes (D) from a report on long-term trends in diabetes from the Centers for Disease Control and Prevention ("Long-term Trends," 2017). The CDC, being focused on disease control, contains some of the most complete data on the historical trends of diabetes. In addition, we obtained percentages of the US population that were enrolled in FFS by dividing FFS enrollment numbers found in Table A.1.a of CMS' Medicare Tables and Reports ("Medicare Tables," n.d.) by US population data from Statista.

3 Mathematics Methodology

To predict the change in costs, we develop models for (1) total spending on diabetes with current treatments, (2) FFS population mortality rate, and (3) the immediate and long-term costs of therapy treatment, which in turn requires modeling (4) the mean years of life remaining after diagnosis with Type 2 Diabetes. Using these models, we then calculate the projected total spending on diabetes with therapy attempting to completely replace current treatments. Our models extend at minimum from 2020 to 2100 and are based on data from various time periods. We choose 2100 as our ending year because it represents the approximate length of our (Generation Z's) lifespans.

First, to model the frequency of the change and to make some per capita-total conversions, we need to project the number of FFS enrollees with diagnosed diabetes up until 2100. Using Statista's census data and US Census Bureau projections, we fit a regression to the US resident population by year. Of several regression models, the linear model obtains the best R^2 value. Using least-squares regression on US population data from 2007 to 2018, we thus obtain the equation

$$P(y) = 1,924,807.53y - 3,555,845,475.85 \quad (1)$$

for the population.

Next, we perform a linear regression on the percentage of diabetic FFS enrollees out of the whole population, which is represented by

$$p(y) = \frac{b(y)}{P(y)}. \quad (2)$$

Running the linear regression on p yields a correlation coefficient R of 0.665213794252 and a p-value of 0.0358130100243 against the null hypothesis that the slope of the line is zero, indicating that the linear growth is significant. Hence, we tentatively arrive at the equation

$$p(y) = (1.33 \times 10^{-4})y - 2.38 \times 10^{-1} \quad (3)$$

to model the percentage of the US population that is both diabetic and enrolled in FFS each year.

To further confirm that this linear regression on p makes sense, we observe the data on D and F. We obtain

$$D(y) = 0.108365363926y - 211.991147846 \quad (4)$$

with a correlation coefficient of 0.940326283508 and a p-value of 4.64905126236e-25 (nonzero growth is significant), and we then obtain

$$F(y) = -0.0264137970909y + 63.2835433344 \quad (5)$$

with a correlation coefficient of -0.680273172854 and a p-value of 0.0304078094304 (growth is also significant).

As D is significantly increasing while F is decreasing (less significantly), it makes sense that p would linearly increase at a rate less significant than F, as p reflects both $D(y)$ and $F(y)$. However, it makes more sense to model $p(y)$ directly to account for hidden trends or influential factors. Hence, we arrive at the equation

$$b(y) = p(y) \times P(y) \quad (6)$$

Now that we have a beneficiary model, we turn to predicting reducible spending.

First, to ascertain current per capita spending, we sum the total national Inpatient Care, Outpatient Care, and Outpatient Medication and Supplies costs for Type 2 Diabetes in 2007 from Dall et al. We then adjust for inflation by 15% to yield the dollar amount in 2014 (Cho, Miranda,

Wang, Wong, 2014). This procedure is well documented for Type 1 Diabetes in literature (Cho, Miranda, Wang, Wong, 2014); we repeat it using the data for Type 2 Diabetes instead. Using assumption (3), we can divide this by the number of diabetes cases in the US ("Long-term Trends," 2017) to yield in $5379.06 annual reducible direct medical costs per diabetes case in 2014. To predict total spending on diabetes with current treatments in the future, we use assumption (6) from section 2.1, which gives us the following model:

$$s_c(y) = s_c(y-1) \times 2^{\frac{1}{13}} = 5379.06 \times 2^{\frac{t-2014}{13}}. \quad (7)$$

We use a two stage model for therapy costs. The first stage models when therapy is first commercialized and is under patent. The second stage models the cost after a generic comes to market. In the first stage, pricing is most heavily based on two factors: (1) the cost savings to the beneficiary and insurance provider and (2) the potential increase in quality of life; however, the former dominates pricing (Cho, Miranda, Wang, Wong, 2014). As such, in the first stage we model the potential cost lifetime cost savings per beneficiary and price the drug at this cost minus Medicare FFS's likely 40% discount (Cho, Miranda, Wang, Wong, 2014). To do this, we must model the mean remaining years of a beneficiary's life after diagnosis with Type 2 Diabetes. A linear regression on life-expectancy at 65 from the CDC from 1950 to 2016 yields the following:

$$l(y) = 0.0870885061 \times y - 156.1313443. \quad (8)$$

The contemporary average age of diagnosis with Type 2 Diabetes is 46.01 (Koopman, Mainous, Diaz, Geesey, 2005). Further, Type 2 Diabetes is expected to lower life expectancy by 10 years (Huizen, 2019), thus we have:

$$L(y) = l(y) + 65 - 46.01 - 10. \quad (9)$$

Finally, we can model the cost of therapy during the first phase as:

$$S_{c1}(y) = s_c(y) \times L(y) \times (1 - 0.4). \quad (10)$$

The second phase begins when the first generic version of therapy hits the market, and competition begins to lower price. Cho et al acknowledge this phase of pricing but do not model it. We will assume that the second phase begins in 2039, 20 years after therapy first hit the market in our scenario. This pessimistically accounts for 15 years of patent exclusivity and optimistically assumes 5 years for FDA approval of the first generic. Theoretically, the cost of generic therapy would eventually reduce to its manufacturing cost plus a profit margin. In an extremely efficient production environment, current estimates on the manufacturing cost of comparable cell therapy are $1900 per person (Lopes, Sinclair, Frohlich, 2018). A normal profit margin for drug companies is around 20% (Slovak, 2018), yielding $2280 as the lowest possible cost of therapy per capita. We model the price decrease as an exponential decay, reflecting market inertia, the time to market for more additional generics, and the exponential nature of innovation. The selected τ-value of the decay is 2, as this is slow enough to account for insurance company and FDA inertia yet a fast enough rate for markets to reasonably achieve an equilibrium. Additionally, we must also account for assumption (7). In the first phase, it was accounted for by the increasing reducible costs of current treatment. Letting $y_f = 2038$ be the final year in which no generic therapy is available, we have

$$S_{c2}(y) = 2^{\frac{y-y_f}{13}} \times (1 - 0.4) \times ((S_{c1}(y) - 2280) \times e^{-(y-y_f)/2} + 2280). \quad (11)$$

Since therapy is only applied once per beneficiary while the costs they replace are recurring, we need to model the number of new beneficiaries each year. To do this, we create a model for the mortality rate of FFS patients using historical data from the CMS from 1999 to

2013 (Krumholz, Nuti, Downing, Normand, Wang, 2015). Because a linear regression would yield negative mortality rates before 2100, a non-linear fully-factored exponential decay model was fit in R, using the following model:

```
fit <- nls(rate ~ SSasymp(year, yf, y0, log_alpha))
```

where `rate` and `year` contain the relevant data. The exponential model reflects the nature of innovation combined with the fundamental limitations of contemporary medical practice. This regression yielded $m(y)$, with the mortality rate in 2100 being 3.6% down from 4.7% in 2013.

Thus we can model the number of new therapy recipients yearly:

$$n(y) = b(y) - (b(y-1) \times (1 - m(y))). \quad (12)$$

The exception being the first year therapy is offered, where $n(y) = b(y)$. $n(y)$ is added to the running total of beneficiaries who have received therapy, $N(y)$, while $N(y)$ itself decays yearly based on $m(y)$. However, studies have shown that stem cell therapy tends to be effective in only 70% (Zang, Hao, Liu, Li, Han, Mu, 2017) to 80% ("Stem cell centers," 2018) of treated patients, where "effective" is defined as working or showing condition improvement to some nontrivial degree. We will thus assume a rough average of 75% efficacy, meaning that 75% of the diabetic enrollees in any given year will benefit or be positively affected in some form from the therapy. Given this, we only add a fraction of $n(y)$ to $N(y)$.

$$N(y) = 0.75 \times n(y) + (1 - m(y)) \times N(y-1). \quad (13)$$

Tracking $N(y)$ allows us to also account for the cost of the likely necessary anti-rejection medication. Initial 2014 costs were obtained from the literature (Cho, Miranda, Wang, Wong, 2014) and modeled with assumption (7):

$$a_1(y) = 1324.17 \times 2^{(y-2014)/13}, \text{ and} \quad (14)$$

$$a(y) = 371.94 \times 2^{(y-2014)/13}. \quad (15)$$

Thus, we can finally model the total cost of therapy each year:

$$T(y) = n(y) \times (S_c(y) + a_1(y)) + N(y) \times a(y). \quad (16)$$

With that, we can model the inflation-adjusted (assuming 2% inflation year-over-year) savings per year from having employed therapy:

$$B(y) = (b(y) \times s_c(y) - T(y)) \times \frac{1}{1.02^{y-2019}}. \quad (17)$$

and the cumulative savings is calculated by

$$C(y) = \sum_{i=2020}^{y} B(i). \quad (18)$$

The point at which we begin saving money is the point at which

$$B(y) > 0, \quad (19)$$

and the point at which all of the startup costs are made up in savings is the point at which

$$C(y) > 0. \quad (20)$$

With these equations, we now have a model to compare projected total diabetes expenditures given (a) current treatments and (b) the introduction of therapy.

When laid out visually, the model resembles Figure 1.

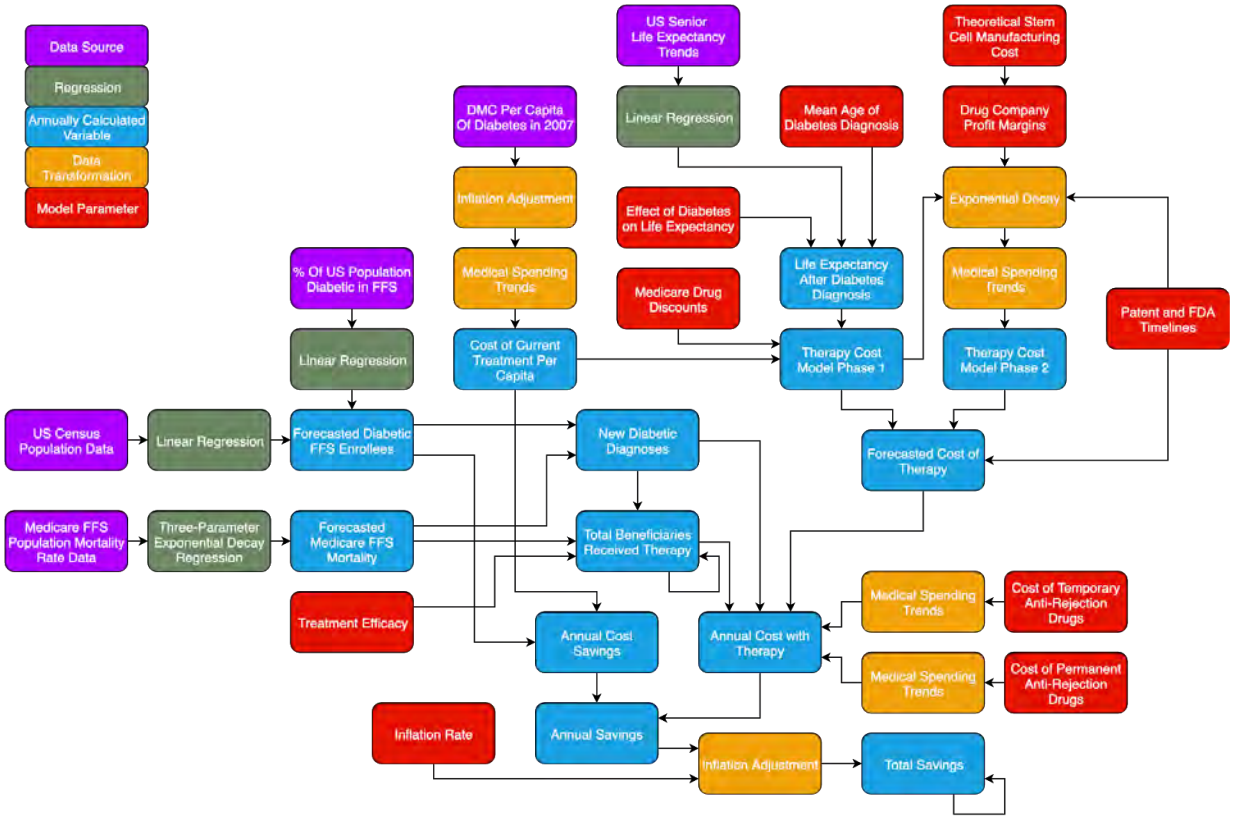

Figure 1. Visual representation of the model.

4 Results & Discussion

4.1 Model Output

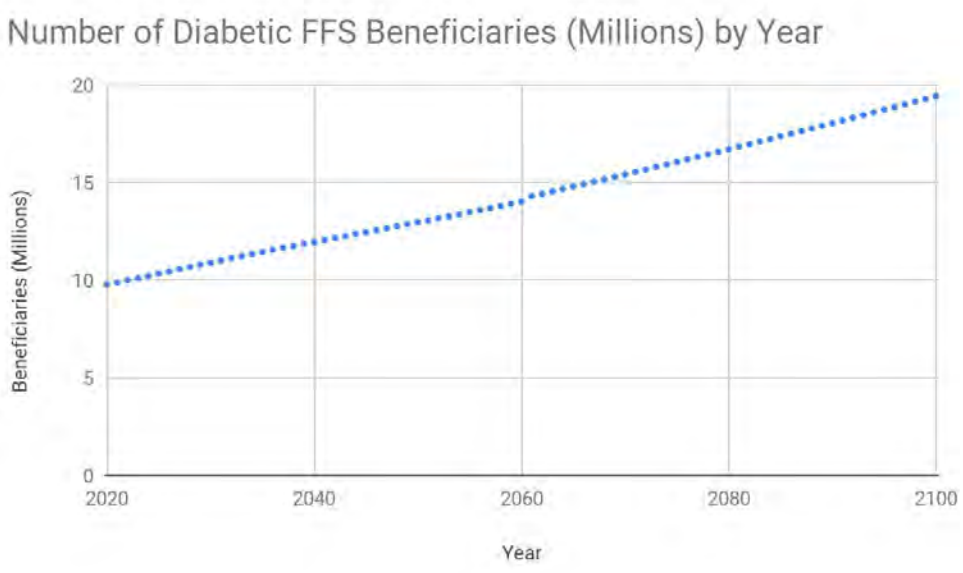

Figure 2. Number of diabetic beneficiaries $b(y)$ by year, 2020 to 2100.

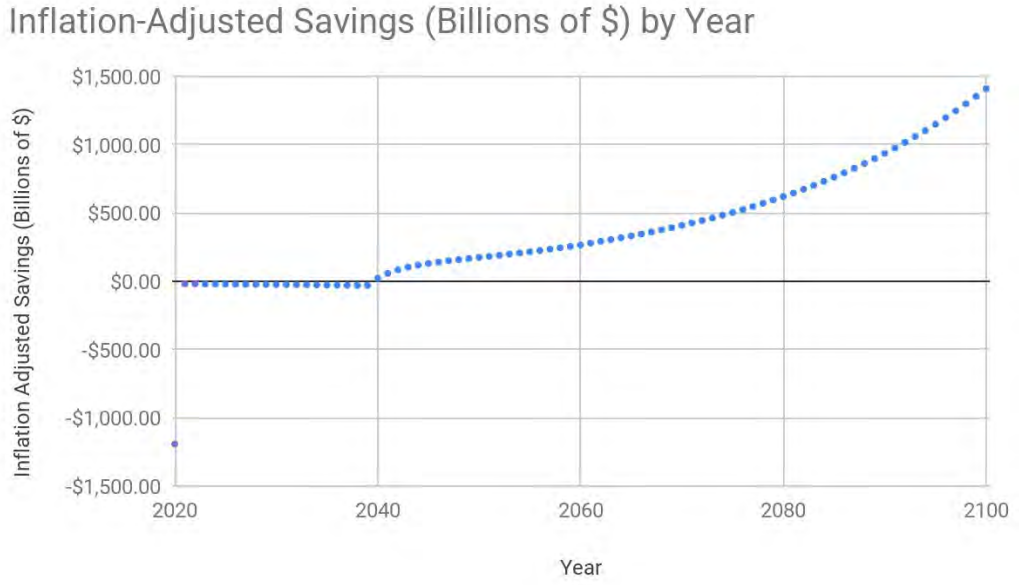

Figure 3. Savings, $B(y)$, by year, 2020-2100. Savings become positive in 2040.

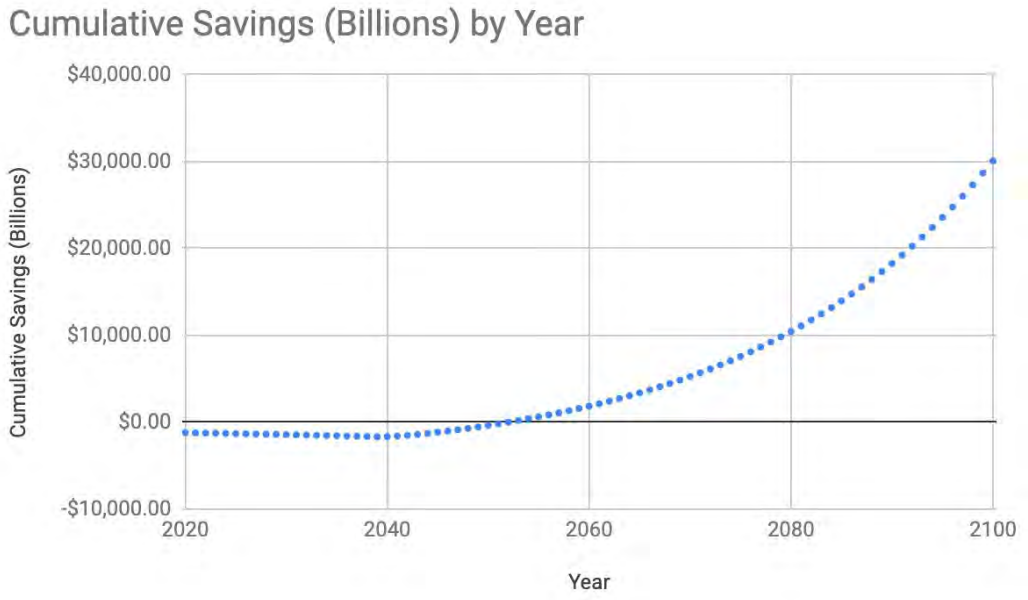

Figure 4. Cumulative savings $C(y)$ by year. Cumulative savings become positive in 2052.

4.2 Quantifying the Change

4.2.1 Severity & Timing

Our model predicts that by 2100, healthcare costs will decrease by **$1.41 trillion** if all Medicare FFS enrollees diagnosed with diabetes receive therapy. If therapy is implemented for

all diagnosed enrollees immediately in 2020, Medicare begins saving money in **2040** when benchmarking against the projected diabetes expenditures with current treatments and saves enough to make up for the startup costs of therapy in **2052**. Cumulatively, we predict that implementing therapy in 2020 will save Medicare **$30.1 trillion by 2100**. All results are in 2019 dollars.

4.2.2 Frequency

Given 75% efficacy, our model predicts that the number of successfully treated beneficiaries varies by year as follows:

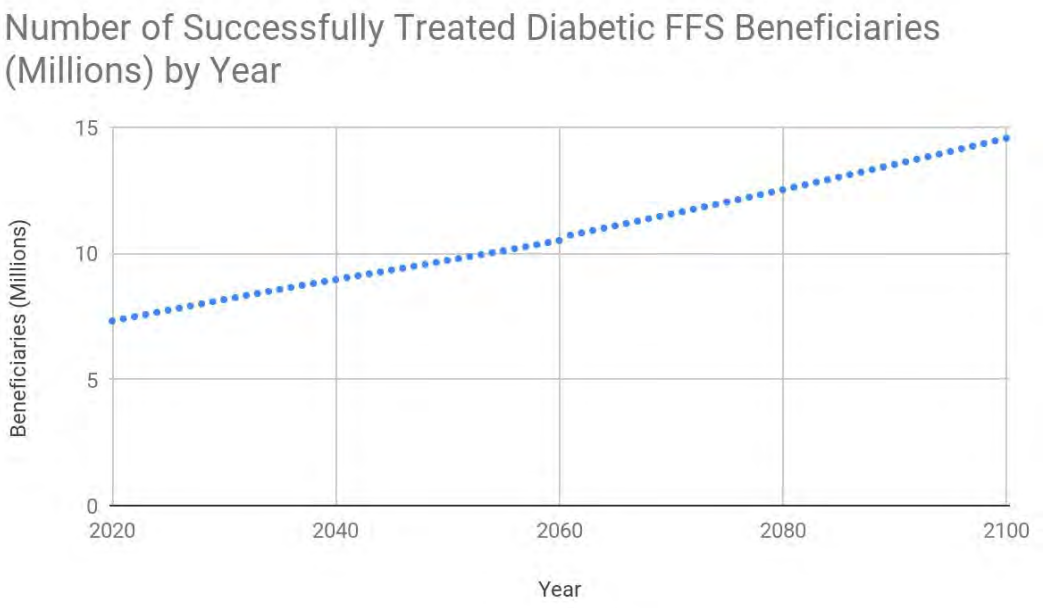

Figure 5. Number of successfully treated beneficiaries by year, 2020 to 2100.

Based on Figure 5, therapy will successfully treat **14.57 million** diabetic Medicare FFS enrollees in 2100. Cumulatively, **62.76 million people** will be successfully treated in the life span of Generation Z.

4.3 Analysis & Discussion

4.3.1 Strengths

1. We considered a decent variety of factors while developing our mathematical model to represent the real world as closely as possible. We did a significant amount of research into multiple human and economic aspects of diabetes and established a fair baseline model for current treatments. We believe we have accounted for the most important factors in calculating cost changes. Our model employs either tried and true regressions or methods found in literature.
2. While solving for the output of our model, we used numbers and statistics from authoritative and trustworthy sources such as the CMS, CDC, US Census Bureau, etc.

Even the statistics that we obtained from 3rd-party sources were from credible, academic studies.

3. We kept our model relatively simple, which makes it easy to understand, verify, and test for sensitivity to assumptions. This also may have helped us avoid faulty assumptions and miscalculations that may have occurred in a more complicated model.

4.3.2 Weaknesses

1. We are working with limited data and are extrapolating at a very large scale. Proper time series modeling (and regression in general) is usually stronger with at least 30 data points, so our lack of data might have led to some faulty extrapolation.
2. Our assumption that all claims and cases in the CMS data refer to Type 2 diabetes is inaccurate. While we are unable to calculate the exact percentages of Type 2 and Type 1 cases each year, we may consider finding some data on these percentages given more time.
3. Our model does not consider the downstream costs of diabetes, such as the costs of secondary complications of the disease. The literature indicates this could have a large impact on overall cost reduction (Cho, Miranda, Wang, Wong, 2014). With more research, we may be able to find quantitative figures indicating how much the risk of each complication is reduced by therapy and how much of the cost of each complication is attributable to an initial diagnosis of diabetes.
4. Our model does not evaluate the human-life-cost of diabetes. Given more time and data, we may consider modeling how many lives, if any, would be saved by therapy.
5. Our model does not precisely estimate expenditure changes for nursing facilities, home health agencies, inpatient services, and outpatient services caused by the introduction of therapy. We did not find data that conclusively stated any change in the requirements of these services given the implementation of therapy, so we did not consider any changes in the model. In reality, there may be a marginal increase, at least in the initial few years. We do, however, account for the cost reduction due to these services no longer being necessary in cured beneficiaries.
6. Our model only considers a limited subset of the direct costs of diabetes. For example, we do not consider the cost of lost productivity.
7. We only consider the costs to Medicare. With more data and time, we may expand our model to examine the expenditures of service providers and beneficiaries.

4.3.3 Validation

A study estimates that diabetes costs could “top $336 billion by 2034.” (Radcliffe, 2017) Our model estimates that total reducible spending will be $176,940,840,686 in 2034 if current treatments continue, which is in line with this projection, if conservative.

Our population model showed that a linear fit was the best, and extensive data shows that the world population and the US population have both been growing linearly for the past half century (Boucher, 2018), so linear growth makes intuitive sense.

4.3.4 Sensitivity Analysis

To analyze the sensitivity of our model, we made adjustments to some of our simplifying assumptions made in Section 2.1. Some particularly uncertain parameters include the percentage of diabetes cases that are Type 2 and the efficacy rate of therapy. Thus, we tested the lower bound of the former (90%) and both the upper and lower bounds of the range of the latter. A few other modifications we made include increasing the τ-value of decay (which could occur in real life in the cases of various market inefficiencies), changing the Medicare drug discount (which could happen as a result of a change in legislation), and delaying the introduction of the first generic (which could also occur due to market inefficiencies or delays in clinical trial approval).

Table 2. Raw results of sensitivity analysis.

Modification	**Year When B(y) > 0**	**Year When C(y) > 0**
90% (not 100%) of diabetes cases are Type 2.	2040	2052
Therapy is 80% effective instead of 75%.	2040	2051
Therapy is 70% effective instead of 75%.	2040	2054
τ-value of decay = 4 instead of 2.	2041	2055
Medicare drug discount = .45 instead of .4.	2040	2051
First generic introduced in 2045 instead of 2039.	2046	2057

Table 3. Percent changes in results of model from sensitivity analysis.

Modification	**% Change in Year When B(y) > 0**	**% Change in Year When C(y) > 0**
90% of diabetes cases are Type 2.	0	0
Therapy is 80% effective.	0	-0.04873
Therapy is 70% effective.	0	0.97466
τ-value of decay = 4.	0.049	0.1462
Medicare drug discount = .45.	0	-0.04873
First generic introduced in 2045.	0.2941	0.24366

Based on the results of our analysis in Table 3, the cost model is most sensitive to changes in therapy efficacy and least sensitive to changes in proportions of diabetes cases that are Type 2.

5 Conclusions and Recommendations

5.1 Insulin and Stem Cell Producers

If stem cell therapy is introduced in 2019, we predict that it will positively benefit 62.76 million people by 2100, which is a significant portion of the consumers in the healthcare market. Companies that produce insulin for diabetes patients, such as Eli Lilly, Novo Nordisk, and Sanofi-Aventis will lose tremendous amounts of money once cell therapy is fully developed. Recently, these companies have been under the microscope as they are being investigated for raising prices, often beyond affordability for those who suffer from diabetes. With 90% of the insulin market being held by these top three companies, there is a tremendous lack of competition (Florko, 2018). This has allowed them to continue hiking up prices; as insulin is a life-or-death product, demand is highly inelastic, and consumers cannot do much to combat price changes (Florko, 2018). With the development of a solution with lighter overall costs, diabetes patients will likely drastically reduce their insulin purchases or even stop buying it entirely. As viable alternatives are introduced to the market, these large corporations will lose much of their leverage, losing customers and being forced to reduce prices. Our recommendation for these groups would be to cut insulin prices to be more affordable, thus increasing its appeal as a substitute for or even a supplement for cell therapy. We recommend this strategy because, with prices as high as they are, patients will turn away from insulin when cell therapy is made available.

Although stem cell therapy is a game-changing technology, the scientific community holds a few reservations regarding its usage due to ethical concerns. As outlined in the Technology Overview, there are a few different types of stem cells. Two types that are currently causing a lot of controversy are human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs). The issue regarding human embryonic stem cells is their acquisition — a cluster of these cells can be extracted from an embryo during the early stages of its development (Volarevic, Markovic, Gazdic, Volarevic, Jovicic, Arsenijevic, Stojkovic, 2018), resulting in the embryo being destroyed (Volarevic, Markovic, Gazdic, Volarevic, Jovicic, Arsenijevic, Stojkovic, 2018). Much like abortion, this process has raised concerns over the ethics of destroying potential life and calls into question the moral status of an embryo. Therefore, we recommend that producers strive to use human embryonic cells as sparingly as possible and that they carefully consider these ethical concerns when they must use them.

However, embryonic stem cells are far from the only option for fighting diabetes. The development of induced pluripotent stem cells provides an alternative method for generating insulin-producing cells. By reprogramming certain somatic cells (non-reproductive cells), iPSCs avoid the ethical concerns that arise with using cells from human embryos (Volarevic, Markovic, Gazdic, Volarevic, Jovicic, Arsenijevic, Stojkovic, 2018). However, while iPSCs avoid the principal ethical issue surrounding the treatment of diabetes with human cells, they come with their own ethical issue. Because of their ability to be programmed to differentiate into an extremely wide variety of cell types, they could potentially be used for human cloning and the creation of human embryos in a lab (Volarevic, Markovic, Gazdic, Volarevic, Jovicic, Arsenijevic, Stojkovic, 2018). To avoid legal entanglements of this nature, we recommend that

companies in the diabetes healthcare industry only use iPSCs for the direct curative purpose they were designed for. In addition, companies should publish annual reports detailing the exact use cases of their stem cell technology in order to be as transparent as possible.

The final issue revolves around a safety concern. The Technology Overview discussed the potential applications of mesenchymal stem cells (MSCs), a type of stem cell originating from bone marrow. MSCs, which have broad uses that range from generating new bone cells to curing cardiac and liver diseases, can solve a variety of medical problems (Volarevic, Markovic, Gazdic, Volarevic, Jovicic, Arsenijevic, Stojkovic, 2018). However, they have shown to increase the risk of tumor formation and metastasis (the development of secondary malignant growths) in individuals who undergo transplants using these cells (Volarevic, Markovic, Gazdic, Volarevic, Jovicic, Arsenijevic, Stojkovic, 2018). In light of this, we recommend that companies release annual safety reports on their technology that include statistics on complication development rates. This way, consumers can be fully informed about the products they buy, and this transparency will be conducive to greater consumer trust in these companies.

5.2 Diabetes Patients

First and foremost, the development of cell therapy to cure diabetes would tremendously benefit those with diabetes, especially Type 2 diabetes. Currently, we sorely lack a permanent treatment to this condition. By losing weight, eating healthily, exercising, monitoring blood sugar, and taking certain types of medication, people can return blood sugar content to a normal amount (“Type 2 Diabetes,” 2019). However, these are temporary measures that do not address the core issue. With the introduction of stem cells to produce insulin and reduce insulin resistance in cells, patients would be provided with an adequate long-term solution. This would allow them to live a more normal lifestyle as well as potentially cut a variety of expenses related to their diabetes, such as hospital care, prescription medication, and other supplies (“The Cost of Diabetes,” 2018). Additionally, they would be able to compensate for the indirect costs of diabetes, including lost productivity and early mortality. Our recommendation for this group would be to adopt cell therapy treatment as it is developed.

Much like insulin producers, diabetes patients should be aware of the ethical and safety concerns. They should become educated on the moral question of whether an embryo is alive and carefully consider their answer to this question in deciding whether or not to use stem cell therapy. If they have qualms about the gathering of hESCs, it would be advisable to err on the side of caution, using treatments involving hESCs less or waiting for a more ethical alternative. Additionally, given that companies do release safety reports, it would be best for patients to assess the negative side-effects of stem cell therapy. Only once the reported possibility for medical consequences becomes acceptable, by the patient’s judgment, should the treatment be taken. However, if patients are firmly of the opinion that the acquisition of hESCs is acceptable after adequate thought and are convinced they will be safe, we would highly recommend stem cell therapy. Currently, the costs related to diabetes are too high and a long-term solution through cell therapy would be able to drastically reduce them. Because of the potential for a permanent change in the patient’s body, we believe that cell therapy will be well worth taking advantage of.

5.3 The Government

Implementing stem cell therapy could save the government $30.1 trillion by 2100, which is a significant amount. Due to the promising results from our model, we recommend that the government continue to loosen legislation regarding stem cell research and provide more funding for researchers to speed up the process of the discovery of such innovations.

Currently, a number of states have opposed embryonic stem cell research, including Arkansas, Michigan, and Virginia, among others ("Stem cell laws", 2019). Because of the enormous benefits that will come with successful stem cell therapy for diabetes patients, we believe it is necessary to lift bans and restrictions on such research. However, as with any ethical issue, deregulation should be done deliberately and with adequate caution and respect for opposing perspectives. Rather than eliminating all regulations immediately, we would suggest a gradual reduction as more research is done in this area and as the technology matures.

However, given that the current administration has recently elected to ban research using human fetal tissue from elective abortions (Goodnough, 2019), it is unlikely that they will pass legislation allowing for more research on embryonic stem cells. In view of this, we further encourage the government to focus their efforts on deregulating iPSC and MSC research. Specifically, we recommend that the Food and Drug Administration give stem cell therapy priority review status and/or breakthrough therapy status to expedite the execution and approval of clinical trials ("Fast Track," 2018).

We acknowledge the ethical issues of (1) the moral status of the embryo with human embryonic cell use, (2) the potential for human cloning and other nonessential activities with iPSCs, and (3) the safety risks of MSCs. To allow for research while accounting for these issues, we recommend that the government impose a tax on embryonic stem cell research and development. The more potent differentiability of embryonic cells makes a hard ban too extreme, but the financial deterrent should play a role in encouraging more ethical development with iPSCs and MSCs than embryonic cells. Regarding iPSCs, the government should place a ban on the use of these cells for anything other than the specific purpose of curing chronic conditions (i.e. human cloning and any other similarly unethical practices that arise should be banned). In addition, the government should require companies to publish annual technology usage reports detailing their specific use cases for stem cells, where non-compliance is punishable by fines and imprisonment. These reports would help ensure transparency and improve public trust in the new technology. Regarding MSCs, the government should also require companies to publish annual reports on the complication risks of their technologies (i.e. percentages of patients who develop tumors or other complications). This would also help ensure transparency and allow consumers to make more informed decisions about their healthcare.

In short, the government should gradually lift restrictions on stem cell research and financially encourage the development of iPSCs and MSCs.

5.4 Concluding Remarks

Overall, implementing stem cell therapy is a favorable option in the long run, both from economic and human perspectives. In view of these favorable outcomes, we urge the federal government to invest more into stem cell research and lift restrictions on this research to the

extent that it is ethically sound. Therapy may even have benefits beyond those considered in our model. For these and numerous other reasons, we recommend that stem cell therapy be introduced to the diabetes healthcare market as a primary choice of treatment as soon as possible.

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