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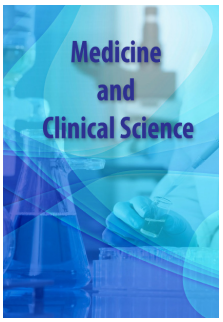

International Reference Pricing in Congressional Bill H.R.3 and Its Potential Impact on the U.S. Biotech Ecosystem

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Abstract

The U.S. Congress has proposed reference pricing for Medicare Part D under Congressional Bill H.R.3 with the objective of benchmarking U.S. drug pricing against an average price basket of 11 countries for the 125 drugs with the greatest net spending in the United States. U.S. drug prices were found to be 3.7 times higher on average.

This study identifies 69 medicines that would be affected by international reference pricing under H.R.3, representing 70% of Medicare Part D spending. We calculate that implementing H.R.3 would lower overall industry revenue by $71.6 billion a year, a reduction of 58% in earnings before interest and taxes (EBIT) revenue.

The industry spends over $60 billion a year investing in partnerships, development agreements, and acquisitions with innovative biotech firms. The revenue reductions caused by H.R.3 would directly impact the free cash flow available for these agreements.

We investigated the historical investments of large pharma companies impacted by H.R.3 into 85 lead assets of biopharma companies in California – that state received the largest share of commercial investments between 2009 and 2019. We show that the total sum of the investments per lead product is a statistically significant predictor of annual product revenue ($p<0.0001$).

We also used a logistic probability model ($p<0.0001$) to test the impact of a 58% reduction in revenue on market entry under H.R.3., finding a greater than 80% reduction in the number of drugs that would be brought to market by California biopharma companies owing to changed investor behavior and reduced firm-level liquidity.

Introduction

Since the election of President Trump and his promise that, "I'm going to bring down drug prices" [1], there have been several U.S. government initiatives aimed at controlling the price of medicines under Medicare Parts B and D. On October 26, 2018, Alex M. Azar II, Secretary of Health and Human Services (HHS), said that the government was to use an international average price for drugs paid by a basket of countries to determine a U.S. average "reference price." That price would be set as a benchmark against which to peg the prices of drugs under Medicare Part B; we calculated and presented the projected impact of that policy in a previous analysis [2].

Following the reference pricing plan of HHS, the U.S. Congress in 2019 proposed its own version of reference pricing for Medicare Part D, known as bill H.R.3: the Lower Drug Costs Now Act of 2019 [3]. Unlike the limited scope of Secretary Azar's plan, which encompasses 21 drugs, H.R.3 targets the 125 drugs for which there was an estimated greatest net spending in the 50 United States, the District of Columbia, and their territories "during the most recent plan year prior to such drug publication date for which data are available." [4] In contrast to the Medicare Part B reference pricing proposal by the HHS, the stated goal of H.R.3 is to reduce pricing throughout the entire U.S. commercial market for the 125 therapies with the highest cost to Medicare Part D.

Specifically, the core objective of H.R.3 is to force U.S. drug prices down to the average of prices paid in a basket of 11 countries, a metric called the Average International Market (AIM) price. The House Ways and Means Committee commissioned research conducted by So-Yeon Kang et al. [5] that compared drug prices in the United States to those in the United Kingdom, Japan, Ontario (Canada), Australia, Portugal, France, the Netherlands, Germany, Denmark, Sweden, and Switzerland to determine the price differences between the markets.

Altering the pricing and revenues of the 125 most sold drugs in the U.S. could have profound effects on the current biopharma ecosystem. One of those effects would be a substantial decrease in free cash flow by $71.6 billion per year available to invest in development agreements, partnerships, and acquisitions with innovative biotech firms. As a case in point, from 2009 to 2019, 25 companies potentially impacted by H.R.3 invested $621 billion in such agreements with U.S.-based biotech firms.

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Table 1. *Impact of H.R.3 at the firm level, accounting for a new AIM reference price substituting for 2017 sales; the total impact highlighted is $71.6 billion dollars of net revenue per year.*

Company	Number of Drugs	Reference Discount	US Total Sales 2017 ($US Mil)	Revised Total Sales ($US Mil)	Revised Total Sales Pelosi 1.2 Margin ($US Mil)	Change In Revenue ($US Mil)	Total R&D Spend 2017 ($US Mil)	Reduction as a % of R&D ($US Mil)	Reduction as 20% R&D ratio ($US Mil)
Company S	2	73%	$14,505	$3,965	$4,758	-$9,747	$5,007	-195%	-39%
Company C	5	77%	$8,719	$2,016	$2,419	-$6,300	$3,925	-161%	-32%
Company E	3	83%	$6,479	$1,129	$1,355	-$5,124	$2,254	-227%	-45%
Company F	2	73%	$6,580	$1,801	$2,161	-$4,419	$3,562	-124%	-25%
Company G	6	57%	$9,032	$3,883	$4,659	-$4,373	$3,734	-117%	-23%
Company Q	6	69%	$6,563	$2,025	$2,429	-$4,134	$9,143	-45%	-9%
Company D	2	70%	$6,434	$1,942	$2,331	-$4,103	$3,274	-125%	-25%
Company K	5	78%	$5,518	$1,200	$1,440	-$4,078	$5,357	-76%	-15%
Company H	4	73%	$6,023	$1,654	$1,985	-$4,038	$4,894	-83%	-17%
Company B	4	83%	$4,711	$779	$935	-$3,776	$3,078	-123%	-25%
Company R	3	74%	$4,879	$1,254	$1,505	-$3,374	$7,645	-44%	-9%
CompanyM	4	84%	$3,790	$590	$708	-$3,082	$9,818	-31%	-6%
Company P	3	56%	$5,655	$2,506	$3,008	-$2,647	$14,014	-19%	-4%
Company I	2	79%	$3,400	$708	$850	-$2,550	$4,482	-57%	-11%
Company U	3	76%	$3,448	$844	$1,012	-$2,436	$8,510	-29%	-6%
Company J	4	57%	$4,834	$2,057	$2,468	-$2,366	$5,472	-43%	-9%
Company O	1	65%	$1,331	$470	$564	-$768	$1,957	-39%	-8%
Company L	1	71%	$1,133	$329	$394	-$739	$1,326	-56%	-11%
Company W	1	71%	$1,120	$327	$392	-$728	$2,108	-35%	-7%
Company X	2	78%	$829	$186	$223	-$606	$5,455	-11%	-2%
Company T	2	85%	$733	$109	$130	-$602	$2,930	-21%	-4%
Company N	1	71%	$826	$239	$287	-$538	$1,161	-46%	-9%
Company Y	1	74%	$662	$171	$205	-$457	$10,529	-4%	-1%
Company A	1	71%	$666	$193	$232	-$434	$361	-120%	-24%
Company V	1	71%	$377	$109	$131	-$246	$1,991	-12%	-2%
TOTAL	69	72%	$108,246	$30,484	$36,581	-$71,665	$120,920	-59%	-12%

Materials and methods

In September of 2019 the House Ways and Means Committee published the results of its pricing study, entitled "A Painful Pill to Swallow: U.S. vs. International Prescription Drug Prices" [6]. Its core findings were as follows: "U.S. drug prices were nearly four times higher than average prices compared to similar countries ... individual drug prices in the U.S. ranged from 70 to 4,833 percent higher than the combined mean price in the other 11 countries. On average, U.S. drug prices were 3.7 times higher than the combined average of the other 11 countries in the study" [6].

Based on the House Ways and Means Committee analysis, Vital Transformation identified 69 medicines sold by 25 companies that would be affected by international reference pricing under H.R.3. These 69 medicines account for roughly 70% of 2019 Medicare Part D spending.

Using the 2017 per-dose pricing taken from the Medicare Part D Spending Dashboard [7], we calculated for each of the 25 firms the revised Medicare Part D revenue using the new H.R.3 reference price for their respective medicines. The 2017 U.S. product revenue per firm was extracted from the firms´ audited annual reports, SEC 10-K filings, and the Pharma Intelligence database Medtrack (Table 1).

For example, in Table 1, we observe that Company S, which has two therapies impacted by the AIM index, would see a reduction in its 2017 revenues from $14.5 billion to $4.8 billion—a drop of $9.7 billion per year. As that company currently spends $5 billion a year on R&D, a loss of revenue at this level would have an enormous impact on its future R&D activities. In addition, since the industry historically spends over $60 billion a year investing in partnerships, development agreements, and acquisitions of smaller innovative biotech firms, this revenue reduction would have profound repercussions on how Company S uses its free cash flow to invest in such initiatives. Increasingly, this is how the life sciences sector is moving innovative products quickly from research to market.

In total, H.R.3 reduces revenues of 25 companies with impacted Medicare Part D products by $71.6 billion per year. While this finding is significant in and of itself, we see that the impact is even greater on firms that have more than one Medicare Part D product impacted by the AIM price index. As the legislation is based on price assessments at the product level, the more products a firm has, the greater on average will be the reduction in that firm's revenues.

Putting the reduced revenues caused by H.R.3 into context, the global net earnings before income tax (EBIT) of the 25 companies in our analysis that are impacted by H.R.3 were $124.2 billion in 2017.

Table 2. *23 products approved from 2009 - 2019 that received inward or outward California partnership revenue, licensing, or acquisitions from H.R.3-impacted companies, and the total net revenues earned by those products in 2017*

Lead Product Name	Total Invested (million)	2017 Revenue (million)
Sovaldi	$11,000	$4,370
Kyprolis	$10,400	$1,397
Pirfenidone	$8,300	$1,647
Bydureon	$7,000	$1,042
Lokelma***	$2,700	$14
Kybella	$2,100	$106
Suganon	$1,695	$0
Lesinurad	$1,260	$2
Zydelig	$1,200	$149
Inrebic***	$1,200	$11
Blincyto	$1,160	$289
Bevespi Aerosphere	$1,150	$16
Erleada	$1,000	$248
OncoVEX	$1,000	$0
Quillivant XR	$680	$0
Nimotuzumab	$510	$0
Quizartinib	$465	$0
Relovair	$342	$1,269
Parsabiv**	$315	$389
Otiprio	$133	$1
Mepsevii	$75	$0
Laninamivir	$46	$0
Lonhala Magnair	$30	$13

**Revenue taken from 2018
***Revenue taken from 2019

A reduction of $71.6 billion in net revenue represents a loss in net earnings of 58% for the biopharma sector at large. This significant drop in net earnings is in line with the non-partisan Congressional Budget Office's (CBO) estimate of Medicare Part D savings of $336 billion over five years [8].

Further, while the assumption is that H.R.3 prices will only impact Medicare Part D revenues, the reality is that Medicare Part D uses the same pharmaceutical benefit managers (PBMs) as the commercial market to negotiate pricing. It would be impossible to wall off a 70% price reduction in Medicare Part D from the overall commercial market; all prices would fall and the entire commercial market would be impacted.

To understand the wider impact of a 58% drop in net revenue, from October 2009 to 2019, biopharma firms invested a total $621 billion of funding into biopharma partnerships, licensing agreements, and acquisitions in the U.S. Of those investments, California attracted the largest share—approximately 30% ($178 billion), accounting for both inward and outward investments to and from the state. In total, 85 firms received investments into their lead products, of which 23 came to market as a result of these investment partnerships in California.

As we estimate the impact of H.R.3 on free cash flow for investment partnerships and development to be a reduction of 58%, we also aim to determine how accurate the industry is at predicting the future revenue and cash flow of these lead assets. In this way, we

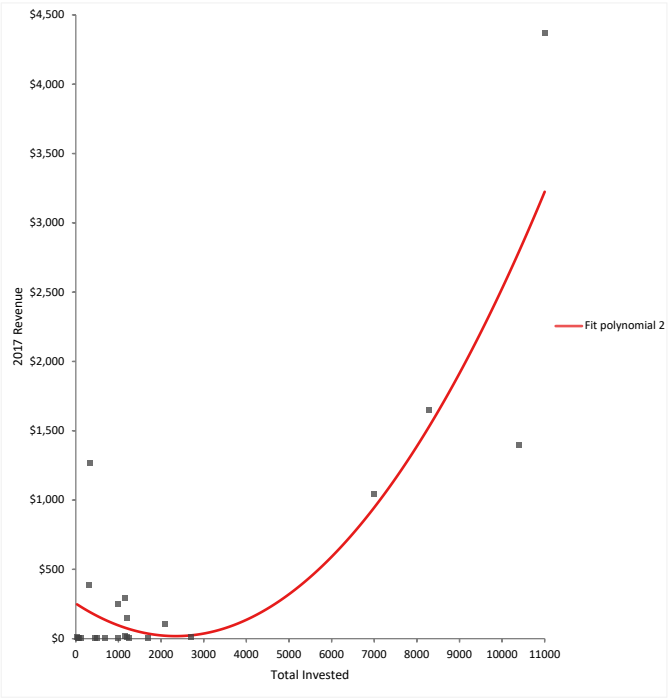

Figure 1. *Regression testing 2017 revenue predicting total investments into 23 marketed assets, p<0.0001.*

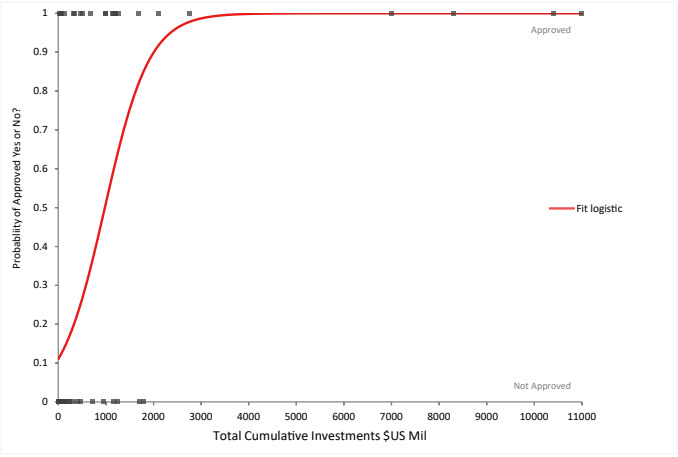

Figure 2. *Logistic probability for a given level of investment from 2009 to 2019 into 81 lead products of emerging Californian biotech firms, 23 products gaining approval for marketing authorization, p<0.0001.*

can calculate the projected impact of reduced revenue on investment behavior and the probability of an asset's market entry.

Investments are made in advance of market entry of a product, often years ahead of its approval. Yet, there appears to be a relationship between the size of the financial commitment made to a product and the annual revenue it generates once the product is authorized. Thus, if the relationship between future revenue and investment size proves to be statistically significant, we can estimate the impact of reduced revenues on partnerships with H.R.3-impacted firms.

An often-heard criticism of the current biopharma development model is that investors backing new and emerging assets are overpaying, thus needlessly driving up costs and taking on unjustifiable risks for a given asset. To assess this critique and to test whether the relationship between investments and revenue is

Table 3. *Impact of reduced revenues on market entry on 23 Californian biotech assets under two U.S. House of Representatives international pricing proposals*

Drug Name	Total Investment ($54 bil) ($USD 000)	Current Probablity	Ways and Means Revised Revenue ($35 bil Available Capital)	H.R. 3 Total Market Impact ($23 bil Available Captial)
Sovaldi/Harvoni	$11,000	100.00%	100.00%	99.96%
Kyprolis	$10,400	100.00%	100.00%	99.93%
Pirfenidone	$8,300	100.00%	99.99%	99.56%
Bydureon	$7,000	100.00%	99.96%	98.58%
Lokelma	$2,755	97.80%	86.15%	59.91%
Kybella	$2,100	91.66%	71.03%	45.25%
Suganon	$1,695	82.22%	57.95%	36.43%
Lesinurad	$1,260	64.61%	42.61%	27.89%
Zydelig	$1,200	61.63%	40.54%	26.81%
Inrebic	$1,200	61.63%	40.54%	26.81%
Blincyto	$1,160	59.59%	39.18%	26.11%
Bevespi Aerosphere	$1,150	59.08%	38.84%	25.93%
Erleada	$1,000	51.17%	33.91%	23.41%
OncoVEX	$1,000	51.17%	33.91%	23.41%
Quillivant XR	$680	34.60%	24.56%	18.63%
Nimotuzumab	$510	26.90%	20.36%	16.41%
Quizartinib	$465	25.05%	19.34%	15.86%
Relovair	$342	20.46%	16.76%	14.43%
Parsabiv	$315	19.52%	16.23%	14.13%
Otiprio	$133	14.13%	13.02%	12.25%
Mepsevii	$75	12.69%	12.10%	11.70%
Laninamivir	$46	12.02%	11.67%	11.43%
Lonhala Magnair	$30	11.66%	11.44%	11.28%
		BRING TO MARKET	DO NOT BRING TO MARKET	

statistically significant, we ran a polynomial regression comparing the annual revenue in 2017 with the total investments made over 10 years (Table 2). The goal of the regression was to assess the model's accuracy in retroactively predicting the total size of those investments based solely upon 2017 revenues (Figure 1, Data table 1 in Appendix).

The result indicates that the relationship between investments and future annual revenues is statistically significant ($p<0.0001$). As well, the estimated relationship explained by the regression between investments and revenues accounts for 77% of the model's variability ($R^2=0.773$).

In essence, what the model shows is that investors are sensitive to the revenue potential of new therapies and dedicate the most capital to those assets with the greatest probability of generating liquidity. In consequence, a potential future 58% cut in net revenues from free cash flow due to H.R.3 would have substantial implications for their willingness to invest in higher-risk, lower margin products.

The key question then is how many assets would not be brought to market as they would be no longer economically viable under H.R.3 revenue reductions?

To answer that question, we used a logistic regression to model the probability of market entry for 81* products invested through Californian biotech partnerships from 2009 to 2019, based on the total investment they received (Figure 2, Data table 2 in Appendix). The result shows that the total amount invested in a firm is a statistically significant predictor of successful market entry, and the point at which a firm has a 50/50 probability of market entry is at an investment of roughly $1 billion.

Results

Given that our logistic regression represents a probability model for market entry for a given level of investments, we can use the probability logit function equation to test the impact of revised revenues on the likelihood of an asset's market entry as a function of the decision to invest. We modeled two scenarios: the impact of the House Ways and Means Committee's proposal on Medicare Part D, and the full AIM impact on the commercial market – including a 20% "fair price" margin allowed under H.R.3 (Table 3).

*For the purpose of this analysis, we have removed the classes of ophthalmology and dermatology investments to keep the analysis focused on innovative treatments for areas of high unmet medical needs.

Investors will still need to invest in clinical research to understand the revenue potential of a given asset, and the threshold for that investment as determined by our logistic regression model (Figure 2) is roughly $1 billion for a 50/50 probability of market entry. This will continue to be a fixed cost per asset, as none of the provisions under H.R. 3 target regulatory reform.

The average rate of market entry in biopharma for new assets is a 9% success/91% failure ratio [9]. Under H.R.3, competition for the most promising assets would likely not reduce the cost of acquisitions, and productivity in pharmaceutical R&D also continues to decline [10] as development costs continue to increase. Given these facts, it is axiomatic that any reduction in revenue caused by H.R.3 would lead to fewer assets receiving investments. As the failure rates of clinical research are above 90%, this impact will be nonlinear.

When modeling the full impact of H.R.3, which reduces the available investment capital in the Californian biopharma market from $54 to $23 billion, we find the market entry for new products similarly shrinks from 23 to 5, all things being equal and assuming only those assets with a positive probability will remain investable. Under the revised scenario, no longer approved would be treatments for cancer, non-insulin-dependent diabetes, chronic obstructive pulmonary disease (COPD), and novel treatments for gout, bronchitis, and emphysema.

Also concerning is the fact that our cohort would lose orphan drugs for rare conditions with no other treatment options, including therapies for pediatric hyperparathyroidism, Sly syndrome, and bone cancer.

Discussion

H.R.3 specifies that the AIM price, that is the international average price, can be raised to what is called a "fair price," which "shall not exceed 120 percent of the AIM price applicable to such drug with respect to such year" [11]. Yet, the average AIM discount in our cohort of 69 drugs is a 72% reduction from the current price; a 20% "fair" margin added back to the AIM price would yield only an additional 6% in revenue when compared with the unadjusted 2017 price. In other words, the revenue reduction in the AIM price of 72% is so large that a 20% increase from the new reduced base would be negligible.

What H.R.3 ignores are several key facts about the way our

biopharma system actually works. Mainly, the way the bill is drafted seems to assume that biopharma innovation occurs internally in a closed R&D environment. This is not the case.

Increasingly, the pharmaceutical industry specializes in partnering with innovative small, emerging biotech firms and carrying their most promising new assets over the phase III finish line for commercialization internationally. Both undertakings are very demanding in terms of human and material resources, time, and costs. As small biotech firms are not staffed and built to commercialize assets, the barriers under the current regulatory structures are far too onerous for them to manage alone.

In the view of Ithai Stern, professor of strategy at the Kellogg Business School, "For these tiny biotech firms, forming partnerships is everything. Their success depends heavily on their ability to build relationships with established companies—and in many cases, the earlier, the better" [12]. Indeed, the optimum solution for small biotech firms is often to partner with a bigger pharmaceutical company and license assets for commercialization or eventual acquisition.

Conclusions

H.R.3 is one of several legislative proposals related to drug pricing. As mentioned earlier, HHS is also promoting the International Pricing Initiative for Medicare Part B, which alone would reduce net revenue by $15 billion a year, amounting to a total annual reduction of $87 billion for the industry for both proposals. The combined impact of these bills would be catastrophic to the U.S. innovative biotech sector, which has been a growth engine for the U.S. economy. For example, California doubled employment in biotech R&D from 21,000 to 44,000 people over the ten-year period of our cohort analysis [13].

According to HHS Secretary Alex M. Azar II, "[Reference pricing assumes] that companies cannot drive somewhat higher prices in Europe and Japan, which they almost certainly can do" [14]. In fact, most companies operating in the EU are under severe pressure to lower their current pricing, and have been facing increasing threats that governments will confiscate their IP under the World Trade Organization allowances for compulsory licensing [15].

A far more likely scenario is that companies with exposure to H.R.3 would simply "slow-walk" any new drug approval in Europe, or even avoid releasing the therapy in any country where they are AIM benchmarked at all, rather than risk their U.S. profit margin. This means that those in need of new treatments in Europe would likely not gain access until a generic treatment becomes available.

In 2015, Vital Transformation held an international conference with 200 thought leaders in the U.S. capital, co-sponsored by 21st Century Cures, where we discussed adaptive licensing and adaptive reimbursement for new medicines [16]. An adaptive pathway harnessing real world evidence could theoretically reduce the time to market by half, radically impacting the capital requirements for drug discovery while stimulating the market to increase competition, thus lowering costs.

Perhaps it is time to have another look at adaptive licensing and reimbursement. Punitive measures such as H.R.3 would either devastate available cash flow by over 50% and radically impact pipelines or leave Europeans with untreated medical conditions without access to effective innovative medicines.

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Appendix

Data table 1 – Regression values underlying the model in Figure 1

Fit

N	23
Mean of Y	476.698696

Equation: 2017 Revenue = 253.7 - 0.2007 Total Invested + 4.28e-05 Total Invested^2

R^2	0.773
R^2 adjusted	0.750
RMSE	494.546152

Parameter	Estimate	95% CI		SE	t	p-value
Constant	253.7	-99.53	to 606.9	169.33	1.50	0.1497
Total Invested	-0.2007	-0.5107	to 0.1093	0.14860	-1.35	0.1920
Total Invested^2	4.280E-05	1.350E-05	to 7.210E-05	1.4046E-05	3.05	0.0064

H0: $\beta = 0$
The parameter is equal to 0.
H1: $\beta \neq 0$
The parameter is not equal to 0.

Effect of Model

Source	SS	DF	MS	F	p-value
Difference	16669699.6	2	8334849.81	34.08	<0.0001
Error	4891517.93	20	244575.897		
Null model	21561217.6	22	980055.343		

H0: $E(Y|X=x) = \mu$
The model is no better than a null model Y=μ.
H1: $E(Y|X=x) = \beta_0 + \beta_1 x + \beta_2 x^2$
The model is better than the null model.

Data table 2 - Logistic Regression values underlying the model in Figure 2

Fit

N	81

Parameter	Estimate	95% CI		SE
Constant	-2.089	-2.894	to -1.285	0.41051
Total	0.002136	0.001017	to 0.003255	5.7095E-04

$\beta = \log \Phi_1$

Effect of Model

Source	Log-likelihood	DF	G^2 statistic	p
Difference	15.127	1	30.25	<0.0001
Fitted model	33.202	79		
Null model	48.328	80		

H0: $g(x) = \beta_0$
The model is no better than a null model Y=π.
H1: $g(x) = \beta_0 + \beta x$
The model is better than the null model.

The data set used in this analysis is available at the following link:
https://1drv.ms/x/s!AlGuTWbx7xz9yAHMUzdpSRfmSNFm?e=4GVpRf