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Dedicated to the memory of my maternal grandfather, who was one of the most inspirational persons in my life.

Never before in history has innovation offered promise of so much to so many in so short a time.

Bill Gates

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ABSTRACT

This dissertation examines several economic elements associated with healthcare innovation and consists of three chapters. The first two chapters focus on the value of healthcare innovation, while the third chapter discusses the pharmaceutical innovation process and the impacts of incentive mechanisms on innovation.

In Chapter 1, I present a model for estimating the value of medical innovation. Contrary to traditional models that only estimate the value of a new treatment to individuals who fall sick ex-post, this model estimates the value of medical innovation from an ex-ante perspective, before susceptible individuals know whether or not they will fall sick. Any risk-averse individual who is susceptible to a disease in the future derives value from the existence of a treatment, because risk-averse individuals prefer to insure against uncertainty in future survival outcomes. The difference between ex-ante and ex-post value is the insurance value of medical innovation due to risk aversion. I show that the percentage of insurance value relative to total value is highest for rare diseases, where afflicted patient populations are small, but vulnerable patient populations are large. I find that for very rare diseases, up to 64 percent of the value of a cure is ex-ante insurance value.

In Chapter 2, I apply the model developed in Chapter 1 to cancer risk and survival data to calculate the full value of cures for cancer. Using a parameterized model and population-level estimates of disease risk for cancer from the National Cancer Institute SEER Database, I find that between 24 and 63 percent of the value of cancer-specific cures is ex-ante insurance value. Estimates vary by the prevalence and mortality risk of each cancer type. Since only sick individuals participate in pharmaceutical market transactions, but a treatment is valued by all susceptible individuals, there will tend to be under-provision of valuable innovation by the private market.

The findings in Chapters 1 and 2 suggest that without external intervention, there will tend to be innovation shortages. Chapter 3 examines various elements of the innovation decision process for pharmaceuticals and discusses methods which can be used to correct

these shortages. I discuss various factors that firms consider when deciding what types of drugs to develop, and the impacts of incentive and subsidies on healthcare innovation. I then discuss several key points about the economics of rare disease drug development, and examine the consequences of the Orphan Drug Act of 1983 on the development of drugs for rare and non-rare diseases.

CHAPTER 1

THE UNACCOUNTED INSURANCE VALUE OF MEDICAL INNOVATION

1.1 Introduction

In this chapter, I propose a new model for valuing medical innovation, that accounts for the ex- ante insurance value associated with the existence of lifesaving treatments. Traditional policy assessments of the value of a medical treatment are carried out ex-post, after it is known which individuals fall sick. These ex-post analyses typically use one of two methods: The first method estimates the value of a new treatment to a newly diagnosed individual by multiplying the estimated number of life years gained from a treatment by the value of one quality adjusted life year, and aggregates this value over all individuals who fall sick. The second measures the maximum amount of lifetime consumption an individual newly diagnosed with a disease would be willing to tradeoff for increased survival, and aggregates this value over all individuals who fall sick. Economic theory suggests that the correct way to determine the value of a new medical innovation is from the present, or ex-ante perspective. A new innovation confers ex-ante value to all susceptible individuals, since these individuals appreciate the existence of a treatment in case they contract the disease in the future. Susceptible individuals are aware that they are at risk for a given disease, but do not know with certainty if they will contract the disease. As such, there is additional insurance value associated with the existence of lifesaving treatments, particularly when individuals are strongly risk-averse. The difference between the ex-ante and ex-post value of a treatment will be the insurance value to susceptible individuals. Since the pool of susceptible individuals is usually large relative to the pool of individuals who do eventually fall sick, the ex-ante value of innovation will usually also be large relative to its ex-post value. I demonstrate that as a percentage of total value, insurance value is proportionally larger for rarer diseases because rare diseases have large susceptible populations but small afflicted

populations.

I begin with a simple example that illustrates the following key points of the model and analysis: First, when individuals are risk-averse, the ex-ante value of a treatment is always greater than its ex-post value and the difference between the ex-ante and ex-post value is the insuranc value of the treatment. Second, the insurance value of a treatment is higher for diseases that are highly deadly without treatment. Third, the ratio of total ex-ante value to total ex-post value is higher for diseases that occur with lower probability (rare diseases). Fourth, the percentage of insurance value decreases with the probability of contracting a disease. In other words, in the presence of risk aversion, the degree of fear individuals have for catching a disease relative to their actual risk is higher for diseases that result in severe health shocks and those that occur with low probability in the population.

I then present a generalized, multi-period, expected-utility model to estimate the ex-ante value of cures. The model estimates the maximum lifetime willingness to avoid the mortality risks associated with a given disease. Previous researchers have argued that willingness to pay for increases in survival are influenced by the (i) substitutability of consumption between time periods and (ii) the value of being alive relative to being dead (Rosen, 1988). Following Becker et. al (2005) and several other papers in the value of life literature, I calibrate the utility function to reflect these two elements. Using a simplified 2-period calibrated model, I estimate the value of treatments for rare diseases that occur with various hypothetical risk probabilities. I find that in the presence of risk aversion, a significant portion of the value of a drug accrues to individuals who never contract the disease. Ex-ante insurance value is high for diseases that are relatively rare but where diagnosis implies severe mortality.

There are several factors that affect the insurance value of a treatment. Firstly, the insurance value of a cure will be higher for diseases that are highly deadly, where survival without treatment is low. For instance, holding all else equal, the insurance value will be higher for a disease where survival without treatment is 1 year compared to a disease where survival without treatment is 5 years. Second, assuming a cure restores expected

survival to that of a healthy individual, controlling for risk profiles, the value of a cure will be higher for younger individuals. For instance, a cure for a deadly disease will be more valuable to a 30 year old than a 70 year old, because a 30 year old has a greater number of years of expected life remaining and has more life to lose if he does contract the disease. Third, the absolute insurance value initially increases with disease probability before declining. However, the percentage of total value that is insurance value monotonically declines with disease probability, holding all else constant. Finally, the timing of risks also impacts insurance value - individuals will be more willing to pay more to insure against imminent risks compared to those that occur far into the future.

The results in this chapter and the next are important from an economic and health policy perspective for several reasons. They show that since only sick individuals participate in pharmaceutical market transactions, but insurance value accrues to all susceptible individuals, there will tend to be under-provision of valuable innovation by the private market. The presence of ex-ante insurance value that cannot be captured by standard, market-based transactions illustrates that medical innovation simultaneously has characteristics of both a public and a private good. Standard market based pricing in the absence of additional subsidies/ market protections will fail to adequately provide the optimal level of medical innovation. Since private entities make decisions based on private benefits and costs, the private equilibrium occurs when marginal private benefits equal marginal private costs. The socially optimal level of provision however, occurs when marginal social benefit equals marginal social cost. If there are benefits accruing to society that are not privately captured, there will be under-provision of public goods (Bergstrom, Blume, and Varian 1986; Roberts 1987; Weisbrod 1964). Since there are ex-ante gains from new medical innovation, marginal cost pricing will fail to compensate for the additional social surplus that results from new medical innovation. As Danzon and Towse (2015) explain, first-best efficiency can rarely be achieved in healthcare markets because producers cannot capture the full social surplus of innovation. My findings provide support for new value-based reimbursement schemes in the spirit of

those proposed by Danzon and Towse (2015) that reward socially valuable innovations

There is a shortage of innovation in certain therapeutic areas, particularly rare diseases. Pharmaceutical companies are highly sensitive to patient population sizes when innovating (Acemoglu and Linn, 2004). It has been posited that the lack of innovation in rare disease areas is due to decreased profitability because of smaller patient populations. According to the National Institutes of Health, there are approximately 6,800 rare diseases that have been identified in the US. A rare disease is defined as one that affects fewer than 200,000 people. As of October 2014, there were only 470 drug approvals to treat rare conditions, which indicates that there still remain more than 6,000 rare diseases without any available treatments. Rare disease drug development is challenging for several reasons. Firstly, the drug development process for any type of drug (for rare diseases or otherwise) is risky to pharmaceutical companies. Previous researchers have documented that only approximately 15% of drugs that are developed make it from the preclinical stages to market approval (DiMasi et. al, 2013). Secondly, drug development is an extremely costly endeavor with the average cost of developing a drug estimated to be more than a billion dollars (Adams and Brantner, 2010). Rare diseases have small patient populations, which likely mean smaller revenues to pharmaceutical companies. Thus, all else being equal, companies will be more reluctant to invest in the development of drugs for rare diseases because small revenue streams will not compensate for large development and clinical trial costs.

While many agree that there are ethical and altruistic reasons to incentivize research into rare diseases, it is generally believed that the overall welfare benefits of rare disease research are small from an economic perspective, given smaller patient populations. The results I present demonstrate that while the total value of cures will still be higher for more prevalent diseases, the percentage of insurance value, relative to total value is in most cases higher for rarer diseases. This finding justifies proportionally higher incentives for rare disease research.

While I demonstrate that the true value of lifesaving treatments is higher than predicted by previous analyses, this finding does not provide justification for higher pharmaceutical

pricing. Drug costs are paid for by patients who are afflicted by a given disease, and their insurance payers. The unaccounted ex-ante value of innovation however largely accrues to individuals who never get sick, and do not participate in the pharmaceutical market. This ex-ante value thus cannot be privately captured through higher pricing. Instead, the findings of this dissertation highlight the public-goods nature of medical innovation and provide justification for subsidies/incentives for valuable medical innovation. Since all susceptible individuals benefit from the existence value of a treatment, placing some of the burden of the cost of innovation on society as a whole through taxation, medical innovation funds etc. might be optimal. For instance, Conti, Glassman and Ratain (2015) argue for new pricing policies that reward the development of novel drugs that deliver significant clinical benefits.

This chapter proceeds as follows. Section II reviews existing literature on the value of lifesaving treatments. Section III provides a simplified example that demonstrates the existence of significant value to individuals who never fall sick and demonstrates that the ratio of this value is higher for rare diseases. Section IV provides a model for calculating the aggregate value of life-saving medical innovation using infra-marginal utilities, Section V illustrates that there is large value associated with rare disease drug development that is unaccounted for in traditional cost- benefit analyses.

1.2 Related Literature

Economists have shown that scientific progress and medical innovation has resulted in huge gains to social welfare over the past century. Murphy and Topel (2006) value improvements to health from 1970 - 2000 and find that the aggregate value of the increase in longevity during this time period surpassed the increased costs of healthcare. They estimate that life expectancy gains over the 20th century were worth more than $1.2 million per person and life expectancy gains conferred from 1970 - 2000 had an economic value about $3.2 million per year to the 2000 U.S. population. Furthermore, the authors find that even a modest 1 percent permanent reduction in cancer mortality would be worth nearly $500 billion to

Americans, while a cure would be worth about $50 trillion. Lakdawalla et. al (2010) quantify the value of cancer survival gains from 1988 to 2000. They find that life expectancy increased by approximately 4 years between 1988 and 2010 and value these survival gains at $322,000 per patient. Overall improvements in cancer survival during this time period were associated with social gains of approximately $1.9 trillion.

There is a small body of literature that explains that ex-ante decisions can results in different outcomes from ex-post ones. Philipson (1995) interprets disease as a random tax that causes individuals to engage in costly preventative activities (e.g. vaccination, less risky sexual behavior etc.) Similar to taxes that impose a burden larger than the revenues associated with the tax if costly tax avoidance occurs, a disease imposes a welfare burden larger than the incidence of the disease. Philipson and Zanjani (2014) argue that current estimates of the value of innovation are understated because they only take into consideration the impacts of new medical innovation on patients that are sick. However, they explain that healthy people also value medical innovation because there is a chance they might fall ill at a later date. For example, the health risks of HIV and breast cancer are much more smoothable than before due to the advent of Highly Active Anti-Retroviral Therapy for HIV and new and effective treatment regimens for breast cancer. They explain that while standard medical insurance enables consumption smoothing, it cannot help with health smoothing if there are no treatments available. Thus, medical innovation is valuable to individuals who are healthy because it offers the ability to insure health. Traditional health insurance on the other hand can only fully insure consumption. Traditional health insurance's ability to insure health is highly dependent on the level of medical technology available for a given illness. Kremer and Snyder (2015) explain that if there is heterogeneity in disease risk, the nature of the demand curve for preventive treatments might affect the ability of firms to extract surplus for these products. They argue that preventives and treatments face different demand curves because the demand for preventives is generated ex-ante, when there is uncertainty in disease risk, whereas the demand for treatments is generated ex-post, when there is no uncertainty in

risk because risk states have been realized. They demonstrate that if there is heterogeneity in disease risk, it is more difficult for firms to extract surplus from consumers for preventives versus treatments.

Pharmaceutical firms are highly responsive to incentives when making innovation decisions. Acemoglu and Linn (2004) examine FDA approvals of new drugs and show that market size is an important driver of innovation. In some cases, market protections can result in distortionary outcomes. Budish, Roin and Williams (2013) demonstrate that differing *effective* patent lengths for cancer drugs can cause firms to under-invest in long term research. They explain that since patents are usually filed before the start of a clinical trial, drugs with shorter clinical trials will tend to have longer effective patent lengths. Using variation in clinical trial length, they find that firms preferred to invest in end of life drugs, which have shorter clinical trials, and longer effective patent length compared to early stage treatments which have longer clinical trials, and shorter effective patent lengths. Haffner(2002) explains that there is a shortage of innovation in rare disease areas because it is more difficult for these drugs to be profitable to pharmaceutical companies unless prices are high enough to compensate for anticipated limited sales volume. There are also several challenges faced during the clinical trial process that may render research and development more risky, including difficulty in recruiting enough patients into randomized clinical trials to meet predefined endpoints at generally accepted statistically significant levels

Baicker, Mullainathan and Schwartzstein (2015) explain that behavioral biases can cause consumers to under-utilize highly effective treatments and over-utilize less effective treatments. For instance, diabetes medications that significantly reduce the risks of diabetes complications such as limb loss and blindness are often underutilized and associated with low adherence levels. On the other hand, antibiotics tend to berisk-averse overused in situations where they are unlikely to be effective. The authors advocate value-based insurance mechanisms that involve higher cost sharing for higher value care in order to correct for these distortions.

1.3 A Simple Example

In order to succinctly demonstrate the main point of this paper, I illustrate the disparity between the ex-ante and ex-post value of treatment using the following highly simplified yet instructive example.

I assume that the entire population starts off healthy and there is only one disease that can be contracted with probability q. I normalize the size of the population to one. Individuals derive utility from consumption and survival. All agents have homogenous preferences and attitudes toward risk and all agents are susceptible to the disease. Utility is strictly increasing and concave in consumption and strictly increasing and weakly concave in survival. For simplicity, I assume there are no savings in the model so lifetime consumption C equals lifetime income Y minus any health expenditures. I also assume no time discounting.

Ex-ante, an individual does not know if he will fall ill but knows that he is susceptible to the disease. If the individual does not suffer any health shock, he enjoys lifetime utility $U(Y, S_H)$ where Y is lifetime income and S_H is the survival of a healthy individual. If he contracts the disease and there is no treatment available, his lifetime utility will be $U(Y, S_D)$ where S_D is expected survival in the diseased state, without treatment. The maximum ex-post willingness to pay for a cure (which restores survival to that of a healthy individual), is then identified by X in equation (1.1). X will be a function of survival in the diseased state without treatment, S_D, survival in the health state, S_H and income, Y. $X = X(S_D, S_H, Y)$.

$$U(Y - X, S_H) = U(Y, S_D) \tag{1.1}$$

Since utility is concave in consumption and survival, the more income an individual has, the greater his willingness to pay for survival improvements. Because of the concavity of utility with respect to survival, we see that the ex-post willingness to pay X depends not only on the number of life years gained, $S_H - S_D$ but how far into the future these survival gains are realized. For instance, the willingness to pay for treatment for a disease where

$S_D = 1$ and $S_H = 2$ will be greater than the willingness to pay when $S_D = 5$ and $S_H = 6$, even though both treatments results in a gain of life of one year.

Now, we look at the ex-ante willingness to pay. If an individual suffers a health shock and there is no treatment available, his lifetime utility will be $U(Y, S_D)$. This state occurs with probability q. Furthermore, $U(Y, S_D) = U(Y - X, S_H)$ from equation (1.1). Expected utility ex-ante is thus given by equation (1.3) below.

$$\begin{aligned} EU &= qU(Y, S_D) + (1 - q)U(Y, S_H) && (1.2) \\ &= qU(Y - X, S_H) + (1 - q)U(Y, S_H) && (1.3) \end{aligned}$$

Traditional methods of calculating the value of a treatment would estimate the ex-post value of a cure to be the value of life gained as a result of the cure, X multiplied by the number of people who fall sick, q.

$$\text{Aggregate value of treatment, ex-post} = qX \tag{1.4}$$

In contrast, an individual's ex-ante value for a cure will be the maximal willingness to pay to avoid the risk of disease, and is given by equation (1.5). An individual would be willing to trade some lifetime income/consumption in exchange for the ability to avoid a health shock in the future. $W(q, S_D, S_H, Y)$ is the ex-ante willingness to pay for a treatment and is a function of the probability of contracting the illness, q, survival without treatment, S_D, survival with treatment, S_H and lifetime income Y.

$$U(Y - W, S_H) = qU(Y - X, S_H) + (1 - q)U(Y, S_H) \tag{1.5}$$

Since the survival term is constant across equation (1.5), we can rewrite equation (1.5) where $\tilde{U}(Y)$ is the one-dimensional set of all points on the utility "surface" U at which

$S = S_H$. $\tilde{U}(Y)$ is increasing and strictly concave in Y.

$$\tilde{U}(Y - W) = q\tilde{U}(Y - X) + (1 - q)\tilde{U}(Y) \tag{1.6}$$

We can solve for W to obtain

$$W(q, S_D, S_H, Y) = Y - \tilde{U}^{-1}\left[q\tilde{U}(Y - X) + (1 - q)\tilde{U}(Y)\right] \tag{1.7}$$

In the ex-ante decision problem, all individuals have willingness to pay W for the existence of a treatment. However, the expected value of life lost due to disease is given by qX. $W - qX$ is thus the insurance value of treatment. I show below that under risk aversion assumptions, the ex-ante willingness to pay is greater than the ex-post willingness to pay.

Remark 1: The ex-ante value, W is greater than the ex-post value, qX when individuals are risk-averse in consumption and $0 < q < 1$

Proof: Since utility is concave in consumption/income, it follows from Jensen's inequality [1] that:

$$U(Y - qX, S_H) > qU(Y - X, S_H) + (1 - q)U(Y, S_H) \tag{1.8}$$

Second, we know that W is defined by the following equation:

$$\begin{aligned} U(Y - W, S_H) &= qU(Y, S_D) + (1 - q)U(Y, S_H) && (1.9) \\ &= qU(Y - X, S_H) + (1 - q)U(Y, S_H) && (1.10) \end{aligned}$$

Substituting back into equation (1.8), we see that

$$U(Y - qX, S_H) > U(Y - W, S_H) \tag{1.11}$$

Since U is an increasing function of consumption, it immediately follows that $W > qX$.

1. Jensen's Inequality: $U[E(K)] > E[U(K)]$ for an increasing, concave (risk-averse) function

Remark 2: The ex-ante value, W is increasing and concave in q for risk-averse individuals.

Proof: The first and second derivatives of W with respect to q are shown below.

$$W_q = -\tilde{U}^{-1'}[q\tilde{U}(Y-X)+(1-q)\tilde{U}(Y)][\tilde{U}(Y-X)-\tilde{U}(Y)] > 0 \quad (1.12)$$

$$W_{qq} = -\tilde{U}^{-1''}[\tilde{U}\tilde{U}(Y-X)+(1-q)\tilde{U}(Y)][\tilde{U}(Y-X)-\tilde{U}(Y)]^2 < 0 \quad (1.13)$$

Since $\tilde{U}(\cdot)$ is increasing and concave, $\tilde{U}^{-1}(\cdot)$ is increasing and convex. Thus, $\tilde{U}'(\cdot) > 0$, $\tilde{U}^{-1'}(\cdot) > 0$ and $\tilde{U}^{-1''}(\cdot) > 0$. Since $\tilde{U}(\cdot)$ is increasing, $\tilde{U}(Y-X)-\tilde{U}(Y) < 0$ and $\tilde{U}'(\cdot) > 0$. The inequality results follow directly.

Remark 3: The ex-ante value, W is higher when survival in the diseased state, S_D is lower and survival in the healthy/cure state, S_H is higher

Proof:

$$\frac{\delta W}{\delta S_D} = \tilde{U}^{-1'}[q\tilde{U}(Y-X)+(1-q)\tilde{U}(Y)]\tilde{U}'(Y-X)\frac{\delta X}{\delta S_D} < 0 \quad (1.14)$$

$$\frac{\delta W}{\delta S_H} = \tilde{U}^{-1'}[q\tilde{U}(Y-X)+(1-q)\tilde{U}(Y)]\tilde{U}'(Y-X)\frac{\delta X}{\delta S_H} > 0 \quad (1.15)$$

Remark 4: The fraction of ex-ante value to ex-post value, $\frac{W}{qX}$ is decreasing in disease probability q.

Proof (informal): Consider two diseases, one with probability q_1 and the other with probability q_2 where $q_1 < q_2$. In order for $\frac{W(q_1,S_D,S_H,Y)}{q_1} > \frac{W(q_2,S_D,S_H,Y)}{q_2}$, we require that the slope connecting the origin to point $(q_1, W(q_1, S_D, S_H, Y))$ be greater than the slope connecting the origin to point $(q_2, W(q_2, S_D, S_H, Y))$ on a graph of W on q. We know that W is increasing and concave in q and that $W = 0$ when $q = 0$. Thus it immediately follows from the concavity of W that $\frac{W(q_1,S_D,S_H,Y)}{q_1} > \frac{W(q_2,S_D,S_H,Y)}{q_2}$.

Remark 5: The fraction of unaccounted value, $\frac{W-qX}{W}$ is decreasing with disease probability q.

Proof: $\frac{W-qX}{W} = 1 - \frac{qX}{W}$. We established in Lemma 1 that $\frac{W}{qX}$ is decreasing in q. Consequently, $\frac{qX}{W}$ is increasing in $q \Rightarrow 1 - \frac{qX}{W}$ is decreasing in q.

Remark 6: The portion of insurance value that accrues to those who will never fall ill (hidden state), decreases with disease probability, q

Proof: The portion of insurance value, as a fraction of total value, that accrues to those who will never fall ill is given by $(1-q)\frac{W-qX}{W}$. Since $1-q$ is decreasing in q and $\frac{W-qX}{W}$ is decreasing in q (Remark 5), it immediately follows that $(1-q)\frac{W-qX}{W}$ is decreasing in q.

1.4 Modeling the Value of New Innovation

The example presented in the previous section was a simplified one-period model that assumed that all agents were homogenous. In this section, I present a multi-period expected utility model where agents have heterogeneous demographic types. Each period is assumed to be one year but the model is easily modified to account for other possibilities. The model estimates both the ex-ante and ex-post value of a cure. The ex-ante value minus the ex-post value is the un-captured insurance value due to risk aversion.

Individuals have a demographic type k and derive utility from consumption, C and survival S. The demographic type k could refer to age, ethnicity, gender etc.[2]. Since there are no savings of bequests, lifetime consumption equals lifetime income, Y_k. The lifetime utility for an individual of type k is given by the value function $V(Y_k, S_k)$ where Y_k denotes consumption/income and S_k denotes survival. Survival without treatment in the diseased state is given by $S_{D,k}$. Survival with a cure available is given by $S_{cure,k}$. We define survival with a cure to be the expected number of years of survival an individual of demographic type k who is healthy would enjoy. Thus, $S_{cure,k} = S_{H,k}$.

2. For the purposes of the empirical analysis in this paper, k to refers to age.

1.4.1 Ex-Post Value

I estimate the ex-post value to a sick individual by estimating the maximum willingness to pay of an individual who has been newly diagnosed with a disease, to go from survival without treatment, S_D to survival with a cure, S_H. The ex-post willingness to pay for an individual of type k is shown in equation (1.16) below. X_k is the amount of consumption/income an individual who knows he is sick would be willing to give up in exchange for increased survival from survival without treatment, S_D to survival with a cure, S_H. The t subscript denotes the time at which the individual is diagnosed.

$$V_t(Y_k - X_k, S_{H,k}) = V_t(Y_k, S_{D,k}) \tag{1.16}$$

Y_k denotes lifetime income starting from the period the individual is diagnosed. If there are no treatments available, we assume that the individual pays nothing for treatment. The total ex-post value is then the value to all individuals in the population that contract the disease over time.

$$\text{Total ex-post value}, X_{agg} = \sum_{t=1}^{T} \sum_{k \in K} N_{k,t} X_{k,t} \tag{1.17}$$

$N_{k,t}$ represents the number of individuals of type k who fall ill in period t. $X_{k,t}$ is the willingness to pay of each individual of type k who falls ill in period t. Total ex-post value is then the sum of individual ex-post valuations aggregated over all types and time periods.

1.4.2 Ex-Ante Value

While the ex-post value measures the willingness to pay of an individual who knows he is sick, the ex-ante value measures the willingness to pay of an individual who is currently healthy, but knows he is susceptible to disease in future time periods. In the initial period, the individual is healthy with probability 1. In every subsequent period, he has a positive

probability of contracting the disease. If he falls sick, his survival will depend on whether or not a treatment exists at the time he contracts the disease. The ex-ante value to an individual of type k, W_k is the maximum amount of lifetime consumption (income) he would be willing to tradeoff for increased expected survival in subsequent periods.

The interpretation of W_k is different from the interpretation of X_k calculated in the previous section. While X_k measures the ex-post willingness to pay for increased survival benefits when the patient is already sick, W_k measures the willingness to pay, decided in the initial period, to be able to enjoy higher expected survival and health-smooth in the future if one happens to fall ill. In other words, it is the willingness to pay to insure against future health shocks and to restore one's survival to the survival of a healthy individual in the event one does fall sick.

If no treatment is available, expected utility is given by equation (1.18). The total lifetime expected utility will be the initial period utility plus the utilities if one were to fall sick in each subsequent period weighted by the probability of falling sick in that period. If a cure never enters the market, the expected utility will be as shown in equation (1.18) where $V_t(Y_k, S_{D,k})$ is the expected lifetime utility, viewed from period 0, if the disease is contracted in period t and no treatments are available. p_t is the probability of falling sick in period t. If the individual never contracts the disease, which occurs with probability p_{never}, he enjoys the usually life expectancy of a healthy individual and a lifetime value function V_{never}.

$$EV_{\text{no cure}} = \sum_{t=1}^{T-1} p_t \cdot V_t(Y_k, S_{D,k}) + p_{never} \cdot V_{never}(Y_k, S_{H,k}) \tag{1.18}$$

$$= \sum_{t=1}^{T} p_t \cdot V_t(Y_k, S_{D,k}) \tag{1.19}$$

where the second equation follows from that fact that if he never contracts the disease, he will live until his expected life expectancy, T. The probability that he never gets the disease, p_{never} is given by 1 - lifetime risk. If a cure is available, his survival is restored to the survival

of an individual without the disease, S_H in the event he does contract the disease. Expected utility is given by equation (1.20).

$$EV_{\text{cure}} = \sum_{t=1}^{T-1} p_t \cdot V_t(Y_k - W_k, S_{H,k}) + p_{never} \cdot V_{never}(Y_k - W_k, S_{H,k}) \quad (1.20)$$

$$= \sum_{t=1}^{T} p_t \cdot V_t(Y_k - W_k, S_{H,k}) \quad (1.21)$$

W_k is identified by setting $EV_{\text{no cure}} = EV_{\text{cure}}$. In other words, the individual, ex-ante value, W_k equalizes expected utility without a cure and expected utility with a cure . The total ex-ante value for the entire population is determined by aggregating individual willingness to pay over all susceptible individuals in the population. N_k denotes the number of individuals of type k in the initial period.

$$\text{Total ex-ante value}, W_{tot} = \sum_{k \in K} N_k W_k \quad (1.22)$$

Finally, the insurance value of a cure is the difference between total ex-ante value and total ex-post value.

$$\text{Insurance value} = W_{tot} - X_{tot} \quad (1.23)$$

$$\text{Percentage Insurance value} = \left(\frac{W_{tot} - X_{tot}}{W_{tot}} \right) \cdot 100\% \quad (1.24)$$

1.4.3 Parameterizing the Model

Following Becker, Philipson and Soares (2005) and several other recent papers that attempt to calculate the value of medical treatments, I parameterize the lifetime value function to have to following form:

$$V(C_k, S_k) = u(c_k) \cdot \tilde{S}_k \quad (1.25)$$

where $u(c_k)$ is annual (yearly) utility from consumption and $\tilde{S}_k$ is discounted survival. $\tilde{S}_k = \sum_{t=0}^{S_k} \beta^t$.

I assume that lifetime income equals lifetime consumption plus healthcare spending. There are no savings, inheritances or bequests in the model. Thus, the lifetime value is given by $V(C_k, S_k)$ below.

$$V(C_k, S_k) = \left(\frac{c_k^{1-1/\gamma}}{1-1/\gamma} + \alpha \right) \cdot \tilde{S}_k = \left(\frac{y_k^{1-1/\gamma}}{1-1/\gamma} + \alpha \right) \cdot \tilde{S}_k \tag{1.26}$$

where γ is the inter-temporal elasticity of substitution and α is a normalization factor that determines the level of consumption at which point utility is zero. In other words, assuming an agent derives 0 utility after death, α determines the level of consumption at which an agent would be indifferent between being alive or dead. I assume that agents are homogenous in their degree of risk aversion. However, the model I present is easily generalizable to account for heterogenous attitudes toward risk.

Following other authors who have researched questions pertaining to the value of life (Becker et. al, 2005; Philipson et. al, 2010; Lakdawalla et. al, 2010), I set $\gamma = 1.25$. We can calculate $\alpha = c^{1-1/\gamma} \left[\frac{1}{\epsilon} - \frac{1}{1-1/\gamma} \right]$ where $\epsilon = \frac{u'(c)c}{u(c)}$ is the elasticity of the utility function with respect to consumption. See footnote for derivation [3]. Following previous authors, I set $\epsilon = 0.346$ [4]. Finally, with these parameters, and setting $c = 26,558$ which corresponds to 2010 median income, I calibrate $\alpha = -16.18$. While Murphy and Topel (2006) fix full income at twice the median income to reflect the value of leisure time, I am intentionally conservative and do not multiply full income by two. Finally, I assume that the value of a year of survival grows at the interest rate $r = 0.03$. I set $\beta = \frac{1}{1+r}$ and thus time discounting effects cancel out.

While the specific ex-ante and ex-post values of cures will be sensitive to the specific

3. $\alpha = c^{1-1/\gamma} \left[\frac{u(c)}{c^{1-1/\gamma}} - \frac{1}{1-1/\gamma} \right] = c^{1-1/\gamma} \left[\frac{1}{\epsilon} - \frac{1}{1-1/\gamma} \right]$

4. See Becker, Philipson, Soares (2005) for detailed justification of these parameters

parameters utilized, the ex-ante value will always be higher than ex-post value regardless of the parameters used as long as there is concavity in the utility function with respect to consumption. Sensitivity analysis for different parameterizations of γ are shown in the Appendix.

1.5 Value of Rare Disease Treatments

While society has long recognized that there is an ethical imperative to incentivize research into rare diseases, the economic justification for incentivizing rare disease research is less obvious. In this section, I demonstrate via a simple simulated model that while the total value of a treatment will still be highest for diseases that affect a large segment of the population, the insurance value, as a fraction of total value is highest for diseases that occur with low probability.

To do so, I simulate the ex-ante, ex-post and insurance values for hypothetical diseases that occur with varying probabilities to a hypothetical cohort of 200 million identical individuals. I also examine how these values change for highly deadly diseases (survival without treatment of one year) and moderately deadly diseases (survival without treatment of 5 and 10 years). I find that the *percentage* of the total value that is insurance value is highest for rare diseases. I also find that insurance value is higher for diseases that are highly deadly. The reasoning for this behavior is that individuals live in more 'fear' of severe health shocks and hence would be willing to pay more to insure against severe health shocks. The reason I use hypothetical probabilities here rather than specific disease risk information is that because rare diseases affect such small populations, there is lack of reliable risk data by age for rare diseases.

This exercise is meant primarily to illustrate that there is higher *proportion* of unaccounted value for rarer diseases. I consider two scenarios. In the first, the risk of contracting the disease is immediate. In the second, the risk occurs in 10 years. These two scenarios are meant to illustrate that the timing of risks can also have an effect on the different between

ex-ante and ex-post value. When the risk is immediate, the amount of time available to make payouts is identical in the ex-ante and ex-post cases. In the case where a cure is available, it is expected to be S_H. When the risk is anticipated to occur in 10 years however, the ex-ante decision problem includes ten additional years where individuals can make payouts to 'insure' against risk.

I assume survival with a cure is the expected life remaining for a healthy individual and is equal to 30 years. I consider three hypothetical diseases that are defined by their survival without treatment. For the first, survival without treatment is 1 year. For the second, survival without treatment is 5 years and for the third, survival without treatment is 10 years. Survival without treatment is 30 years for all three diseases because this is the remaining years of survival a healthy individual would enjoy.

Figure (1.1) shows the ex-ante, ex-post and insurance values when survival without treatment, S_D is one year, survival with treatment, S_H is 30 years and disease risk is immediate. We see that total ex-ante and ex-post value are increasing with disease probability, q. The (absolute) insurance value initially increases with disease probability before decreasing. The mathematical reasoning for this behavior is as follows - because of the concavity of the utility function with respect to consumption, the ex-ante willingness to pay is increasing and concave in disease probability. The ex-post willingness to pay however, is linearly increasing in disease probability. Consequently, the difference in ex-ante and ex-post valuations (insurance value) initially increases before decreasing. Figure (1.2) shows the percentage of total value that is insurance value [5] when $S_D = 1, S_D = 5$ and $S_D = 10$. We see that the percentage of value that is insurance value is decreasing with disease probability q. Furthermore, the percentage of insurance value is higher for more deadly diseases ($S_D = 1$) versus less deadly diseases ($S_D = 10$).

For rare diseases where survival without treatment is only one year, more than 60 percent of the value of an innovation is insurance value. The percentage of insurance value decreases

5. Insurance Value = $\frac{\text{Ex-ante value - Ex-post value}}{\text{Ex-ante value}}$

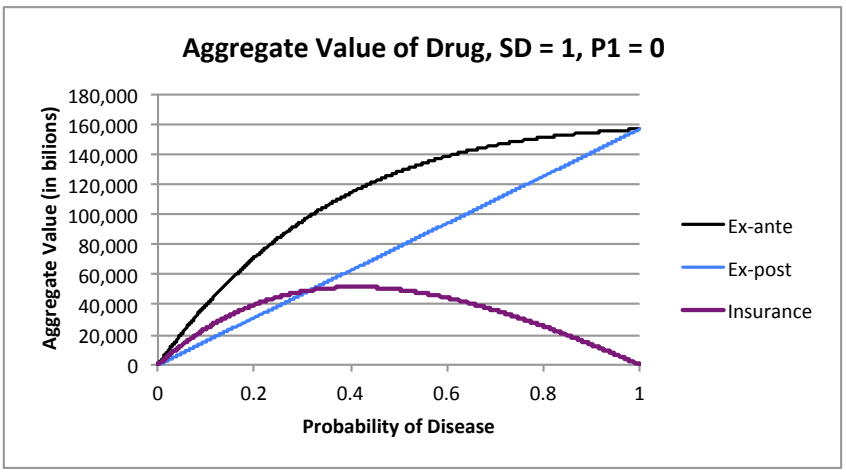

Figure 1.1: Aggregate Value of a Drug (in Billions) by Disease Probability when Risk is Immediate

as the number of years of survival without treatment increases. In other words, people are more afraid of diseases that result in severe mortality risks and are willing to pay more for the insurance value of the existence of a treatment.

Figures (1.3) and (1.4) are analogous to figures (1.1) and (1.2) respectively except that the risk of disease occurs in years rather than immediately. An interesting point to note is that the ex-ante value is greater than the ex-post value even when the probability of disease is 1. This pattern occurs because the ex-ante decision problem is viewed 10 years prior to the occurrence of the risk. Thus, ex-ante, individuals have 10 additional years to make insurance payouts compared to the ex-post scenario. As such, ex-ante value is higher because an individual who knows with certainty that he will contract the disease in 10 years has 10 additional years to 'pay' for the existence of a treatment.

Table 1.1 shows the value of treatments to a hypothetical cohort of 200 million individuals where survival without treatment is 1 year, survival with treatment is 10 years and there is a one time disease risk that occurs in 10 year. The probabilities highlighted in gray roughly correspond to diseases that would qualify as rare diseases under the 200,000 patient (orphan drug) cutoff set by the Food and Drug Administration. We see that under this hypothetical, simulated model, 64 - 65 % of the value of a cure would be insurance value.

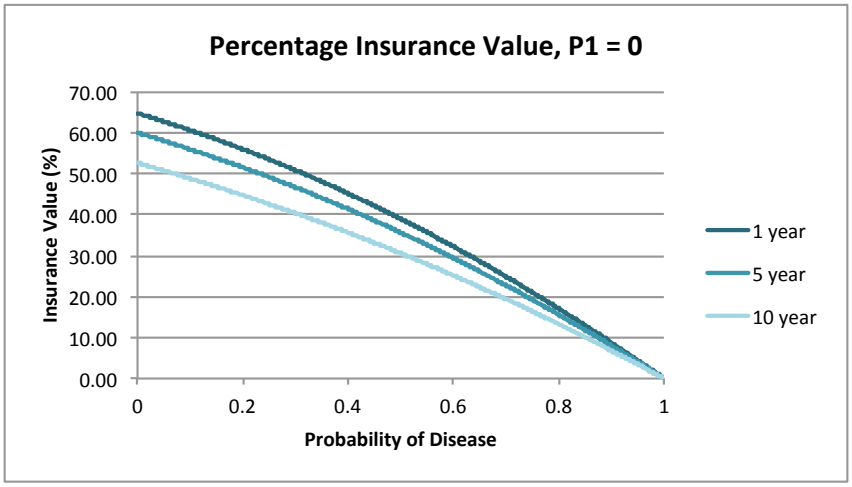

Figure 1.2: Percentage of Value that is Insurance Value when Risk is Immediate and Survival Without Treatment is 1, 5 and 10 years Respectively

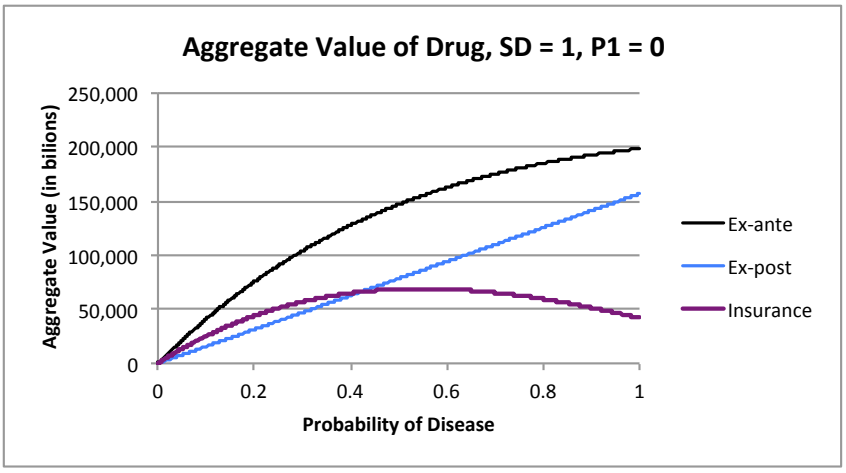

Figure 1.3: Aggregate Value of a Drug (in Billions) by Disease Probability when Risk Occurs in 10 Years

Risk (%)	Sick pop	Ex-ante(ind)	Ex-post (ind)	Ex-ante tot, B	Ex-post tot, B	Insurance, B	Insurance (%)
0.001	2,000	22.26	783,404	4.45	1.57	2.88	64.81
0.002	4,000	44.52	783,404	8.90	3.13	5.77	64.80
0.003	6,000	66.78	783,404	13.36	4.70	8.65	64.80
0.004	8,000	89.03	783,404	17.81	6.27	11.54	64.80
0.005	10,000	111.29	783,404	22.26	7.83	14.42	64.80
0.006	12,000	133.55	783,404	26.71	9.40	17.31	64.80
0.007	14,000	155.80	783,404	31.16	10.97	20.19	64.80
0.008	16,000	178.06	783,404	35.61	12.53	23.08	64.80
0.009	18,000	200.32	783,404	40.06	14.10	25.96	64.80
0.01	20,000	222.57	783,404	44.51	15.67	28.85	64.80
0.02	40,000	445.11	783,404	89.02	31.34	57.69	64.80
0.03	60,000	667.60	783,404	133.52	47.00	86.52	64.80
0.04	80,000	890.06	783,404	178.01	62.67	115.34	64.79
0.05	100,000	1,112.49	783,404	222.50	78.34	144.16	64.79
0.06	120,000	1,334.87	783,404	266.97	94.01	172.97	64.79
0.07	140,000	1,557.22	783,404	311.44	109.68	201.77	64.78
0.08	160,000	1,779.53	783,404	355.91	125.34	230.56	64.78
0.09	180,000	2,001.80	783,404	400.36	141.01	259.35	64.78
0.1	200,000	2,224.04	783,404	444.81	156.68	288.13	64.78
0.2	400,000	4,444.35	783,404	888.87	313.36	575.51	64.75
0.3	600,000	6,660.94	783,404	1,332.19	470.04	862.15	64.72
0.4	800,000	8,873.82	783,404	1,774.76	626.72	1,148.05	64.69
0.5	1,000,000	11,082.98	783,404	2,216.60	783.40	1,433.20	64.66
1	1,200,000	13,288.43	783,404	2,657.69	940.08	1,717.61	64.63
5	1,400,000	15,490.18	783,404	3,098.04	1,096.75	2,001.28	64.60
10	1,600,000	17,688.23	783,404	3,537.65	1,253.43	2,284.21	64.57

Table 1.1: Value of Treatments for Diseases that Occur with Low Probability

Notes: This table shows ex-ante and ex-post valuations for a hypothetical cohort of 200 million Individuals where survival without treatment is 1 year, survival with treatment is 30 years and the disease risk occurs in 10 years. Risk (%) is the risk of disease, faced in 10 years time. Sick pop is the number of individuals that will contract the disease in 10 years, Ex-ante(ind) is the individual willingness to pay for a treatment ex-ante by a susceptible individual, Ex-post (ind) is the individual willingness to pay for a treatment by a newly diagnosed sick individual, Ex-ante tot, B is the total ex-ante value of treatment to the cohort in billions, Ex-post tot, B is the total ex-post value of the treatment to the cohort in billions, Insurance = Ex-ante tot - Ex-post tot is the total insurance value to the cohort. Insurance (%) is the percentage of ex-ante value that is insurance value.

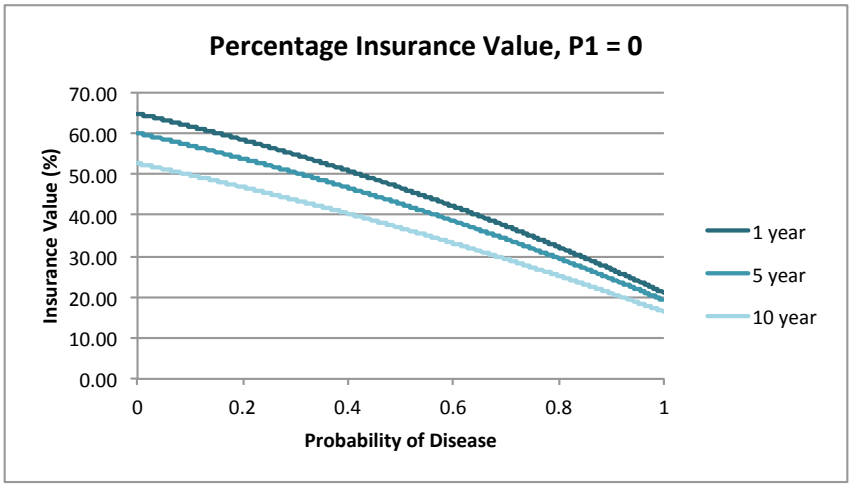

Figure 1.4: Percentage of Value that is Insurance Value when Risk Occurs in 10 Years and Survival Without Treatment is 1, 5 and 10 years Respectively

CHAPTER 2

ESTIMATING THE VALUES OF CURES FOR VARIOUS CANCERS

2.1 Introduction

The model and simulations in Chapter 1 established that there will be significant insurance value associated with the existence of treatments for life threatening diseases. In order to design policies that will correct for innovation shortages, it is important to assess the true magnitude of the value of treatments as well as determine what fraction of the total value of a treatment is insurance value.

In this chapter, I utilize the calibrated model presented in Chapter 1 to estimate the value of cures for various cancer types based on U.S. based population-level disease risk and severity estimates obtained from the National Cancer Institute SEER Database. Specifically, I estimate the value of a hypothetical cure for each cancer site to the 2010 adult population, between the ages of 20 and 80.

2.2 Data and Methods

I employ four datasets for my analysis: (i) Center of Disease Control life expectancy tables 2010, (ii) NCI SEER survival statistics by cancer site (1975 - 2010) , (iii) NCI SEER risk of developing cancer dataset (2009 - 2011) and (iv) 2010 population estimates obtained from the US Census Bureau. The CDC life expectancy tables provide information on the expected number of life years left for each individual conditional on living up to a given age. For instance, the expected life remaining for an individual who is just born is 78.7, which is the average US life expectancy. However, the expected life remaining for an individual who has lived to age 30 is 50 years. The NCI SEER survival statistics provide estimated survival by cancer site by year of diagnosis, and express survival as the proportion of patients alive in

the years subsequent to a cancer diagnosis. For most cancers, survival statistics are provided for up to 20 years after the initial diagnosis. NCI SEER risk of developing cancer dataset lists the 2010 probability of developing cancer in 10, 20 and 30 years as well as the overall lifetime risk of developing cancer for individuals aged 20, 30, 40, 50, 60 and 70.

For most cancers, there is no counterfactual evidence on how patients would have responded without treatment because most cancer clinical trials are not placebo controlled for ethical reasons. Thus, I use NCI SEER survival statistics from the 1975 - 1979 when there were few effective treatments for cancer to proxy for survival without treatment [1]. Using survival statistics for individuals diagnosed in 1975 - 1979, I determined median survival for each cancer, to proxy for median survival without treatment. For less aggressive cancers where more than 50 percent of the population were alive after more than 20 years, I extrapolate the data for up to 30 years in order to estimate median survival.

Since NCI SEER survival statistics are cancer site specific but not age specific, I adjust the median survival for the age of the patient using the CDC life tables, if the number of expected life years left for a patient of a given age group was less than the median years of survival for a given cancer. Thus, I set the survival without a cure $S_{D,k}$ to be the minimum of expected survival years for a particular cancer and the expected life expectancy for a person of a given age. For instance, according to the CDC Life Tables, on average, a 70 year old has 9 years of life left (rounded to closest integer), conditional on having survived to age 70. Thus, if a 70 year old contracts a cancer with a median without treatment of 12 years, I set survival without treatment to 9. Since a cure for a disease is assumed to allow the patient to live aI normal lifespan for his particular age group, I set the years of survival when a cure is available, $S_{H,k}$ to the expected number of life years remaining for an individual of a given age using the CDC Life Tables, rounded to the closest integer. Table 2.1 shows

1. While I realize that this method is not perfect, given that chemotherapy was in existence at the time, the willingness to pay estimates calculated will if at all be under-estimates rather than over-estimates given that the true $\frac{S_D}{S_{cure}}$ will be smaller than our estimate. By using survival in the 1970s to calculate S_D, I amI essentially measuring the value of survival gains relative to survival with treatments in the 1970s.

the median age at which each cancer is diagnosed, the median number of years of survival and the percentage of afflicted individuals surviving 5, 10 and 20 years. For four of the cancer sites listed (Corpus and Uterus, Kaposi Sarcoma, Testis, Thyroid), median survival was more than 30 years. These cancer sites were dropped from this survival-based analysis because these cancers appear to have minimal impacts on patient survival if diagnosed early and managed appropriately.

The NCI SEER risk of developing cancer dataset only provides 10 year, 20 year, 30 year and lifetime cumulative risks of contracting each cancer by age. I set the lifetime cumulative risk ('ever risk') to be the cumulative risk at the expected number of life years remaining for an individual in each age group and assume risk in the initial period is 0. In then linearly interpolated risks for all time periods with missing data. For instance, a 30 year old has a 0.03 % cumulative risk of getting brain cancer in 10 years, a 0.06 % cumulative risk of getting brain cancer in 20 years, a 0.1 % cumulative risk of getting brain cancer in 30 years and a 0.57 % cumulative risk of ever getting brain cancer ('ever risk'). From the CDC life tables, an individual who is alive at age 30 has 50 years of expected life remaining (life expectancy of 80). Thus, I assume that the cumulative risk of contracting the cancer 50 years from the present is the 'ever risk' getting brain cancer. Using this information, I linearly interpolated the cumulative risks of getting brain cancer for a 30 year old at all time periods in where risk data were not available. Furthermore, risk data is only available in 10 year age increments i.e. for individuals aged 20,30,40,50,60,70 and 80. I thus linearly interpolated risks for all age groups with missing risk data.

Then, from this discrete CDF of risks of different cancers over time, I derive the discrete PDF of risks over time by age and cancer type. I also calculate the number of individuals in each age group that will eventually develop cancer, and the age at which they will develop the cancer.

For this empirical analysis, the individual's type k refers to the age of the individual. Individuals of different ages have different risks of developing each type of cancer. Further-

Cancer Site	5 year (%)	10 year (%)	20 year (%)	Med Age	Med Survival
All	48.9	41.8	35.5	66	5
Brain	23.1	17.7	13.7	58	1
Cervix Uteri	68.3	63.1	56.5	49	26
Colon and Rectum	50.4	45.1	41.3	68	6
Corpus and Uterus	85.8	84.3	83.4	65	$> 30^*$
Esophagus	4.9	2.9	2.1	67	1
Female Breast	74.6	62.4	51.7	61	21
Hodgkin Lymphoma	71.4	61.7	52.1	39	21
Kaposi Sarcoma	76.9	74.7	74.7	46	$> 30^*$
Kidney and Renal Pelvis	50.9	44	36	64	6
Larynx	65.4	54	36.4	65	13
Leukemia	34.6	23.7	16.6	66	3
Liver and Bile Duct	3.4	2.6	2	63	1
Lung and Bronchus	12.5	8.8	5.2	70	1
Mesothelioma	7.9	5.2	4	74	1
Myeloma	25.2	9.9	3.4	69	3
Non-Hodgkin Lymphoma	46.8	34.9	25.1	66	5
Oral Cavity and Pharynx	52.8	42.3	29.9	62	7
Ovary	36.6	32	28.2	63	2
Pancreas	2.5	1.7	1.2	71	1
Prostate	68.7	53.2	37	66	12
Skin	82	76.5	74.3	63	20
Stomach	15.6	12.7	9.2	69	1
Testis	85	83.7	79.3	33	$> 30^*$
Thyroid	92.1	90.5	89.1	50	$> 30^*$
Urinary Bladder	73	63.8	52.8	73	21

Table 2.1: NCI SEER Cancer Survival Estimates Without Treatment

Notes: 5 year (%), 10 year (%), and 20 year (%)shows the percentage of individuals, newly diagnosed with cancer in 1975 - 1979 who survive up to 5 years, 10 years and 20 years respectively. Med age is the median age of onset of each cancer type. Med survival is the median years of survival for each cancer rounded to the closest integer.

more, younger individuals have a larger number of expected life years remaining. As such, a cure will result in a larger number of life years gained for a younger individual than an older individual.

I calculate the expected lifetime utility viewed from the present by calculating the weighted sum of the lifetime utilities if the cancer is contracted in period t, V_t weighted by the probability of developing the cancer in period t , p_t plus the probability of never contracting the cancer, p_{never} times the lifetime utility if one never gets brain cancer, V_{never}. In then determine the willingness to pay in each period, w_k (decided ex-ante), for the increase in expected survival conferred by the existence of a cure. The total ex-ante value of a cure to an individual of type k is given by $W_k = w_k \cdot S_{H,k}$. A detailed example of how the ex-ante value of a cure for brain cancer would be calculated for a 30 year old is given in the Appendix. The aggregate ex-ante value to the 2010 population is found by adding up the individual ex-ante values over the entire (susceptible) adult population aged 20 - 80.

The total ex-post value to an individual of type k is $X_k = w_k \cdot S_{H,k}$. A detailed example of how the ex-post value of a cure for brain cancer would be calculated for a 40 year old is given in the Appendix. The aggregate ex-post value to the 2010 population is found by adding up the individual ex-post values over all individual who will eventually contract the disease.

2.3 Results

Table (2.2) shows the number of individuals from the 2010 adult population that will eventually contract each type of cancer, the average lifetime risk, the average number of life years gained from a cure, and the individual ex-ante and ex-post willingness to pay. Individual ex-post willingness to pay is greater than individual ex-ante willingness to pay because an individual that knows with certainty that he has a disease will be willing to pay significantly more for the existence of a cure. The risks and life years gained showed in this table are averages. A younger individual will have more to gain from a treatment in terms of life

years gained. The risk profile faced also depends on the age of the individual. There are some cancers that tend to affect younger individuals and others that tend to affect older individuals.

Table (2.3) includes the aggregate ex-ante and ex-post values of a cure in billions, the percentage of value of a cure that will be insurance value and the magnitude of ex-ante value relative to ex-post value. An explanation of each column is given in the table notes. We see that brain cancer is associated with the highest percentage insurance value. In general, the percentage insurance value will be highest for cancers that are highly deadly, that affect a small segment of the population. However, in this multi-period analysis, the timing of risks also has an impact on the insurance value. As an example, a 50 year old will have less willingness to pay for a cure for a cancer that typically affects 30 year olds.

2.4 Discussion

In this chapter and the last, I developed a model to estimate the ex-ante insurance value value of new medical innovation and estimated the value of treatments for several rare diseases and cancers. The results presented illustrate that there is large social value from new medical innovation that is not captured within existing valuations of medical innovation. Furthermore, this ex-ante insurance value is not captured by private market transactions because drugs are only purchased by sick individuals and their insurance payers. Thus, the private market will tend to under-provide valuable medical innovation. If the social value of a new innovation is large, there is a case for the government to provide subsidies for the development of that technology.

There are several factors that affect the ex-ante insurance value of a new treatment. First, all else equal, treatments that confer higher life years gained will have higher ex-ante insurance value. Second, the more risk-averse individuals are, the higher the insurance value will be. Third, holding disease risk profiles equal, willingness to pay for a cure will be higher for younger individuals because younger individuals have a higher number of years of

Cancer Site	Sick Pop	Ave. risk (%)	Ave. LYG	Ex-ante (ind)	Ex-post (ind)
Brain	911,477	0.47	35.0	5,527	483,511
Cervix Uteri	441,814	0.44	12.0	1,094	372,031
Colon and Rectum	8,155,904	4.45	30.0	29,952	392,870
Corpus and Uterus, NOS	2,381,505	2.39	16.8	4,139	264,376
Esophagus	913,974	0.49	35.0	4,934	433,360
Female Breast	10,521,425	10.73	15.9	18,106	261,054
Hodgkin Lymphoma	240,752	0.12	15.9	489	268,364
Kaposi Sarcoma	58,896	0.03	16.8	129	289,090
Kidney and Renal Pelvis	2,787,006	1.45	30.0	11,324	422,739
Larynx	638,837	0.33	23.1	1,151	240,735
Leukemia	2,300,192	1.26	33.0	10,821	423,475
Liver and Bile Duct	1,565,615	0.81	35.0	9,048	462,942
Lung and Bronchus	12,346,124	6.64	35.0	62,310	416,380
Mesothelioma	226,034	0.13	35.0	1,112	396,213
Myeloma	1,290,239	0.69	33.0	5,990	418,294
Non-Hodgkin Lymphoma	3,636,420	1.96	31.0	15,037	414,610
Oral Cavity and Pharynx	1,887,386	0.98	29.0	7,415	422,571
Ovary	2,198,046	1.16	34.0	12,250	469,657
Pancreas	2,691,230	1.48	35.0	13,869	416,106
Prostate	14,199,048	14.65	24.1	52,192	505,045
Skin	3,395,876	1.79	16.8	3,157	135,006
Stomach	1,519,118	0.83	35.0	8,105	428,926
Testis	140,960	0.13	16.8	1,450	1,279,878
Thyroid	1,568,364	0.77	16.8	3,151	274,950
Urinary Bladder	4,329,161	2.40	15.9	1,313	49,550

Table 2.2: Average Individual Willingness to Pay for a Cure, Ex-Ante and Ex-Post

Notes: This table shows the average willingness to pay per individual for the existence of a cure ex-ante and ex-post. Sick pop shows the number of individuals in the 2010 adult population that will eventually contract each cancer type. Ave. risk (%) is the average lifetime risk of developing each cancer. Ave. LYG is the average number of life years that will be gained from the existence of a cure if one were to contract the disease. Ex-ante(ind) denotes the average ex-ante willingness to pay of a susceptible individual. Ex-post(ind) denotes the average ex-post willingness to pay of a a sick individual who has been diagnosed with the disease.

Cancer Site	Risk (%)	Ave. LYG	Ex-Ante, B	Ex-Post, B	Insurance (%)	Ratio
Brain	0.47	35.0	1,194.8	440.7	63.1	2.71
Cervix Uteri	0.44	12.0	236.4	164.4	30.5	1.44
Colon and Rectum	4.45	30.0	6,475.1	3,204.2	50.5	2.02
Corpus and Uterus, NOS	2.39	16.8	894.8	629.6	29.6	1.42
Esophagus	0.49	35.0	1,066.7	396.1	62.9	2.69
Female Breast	10.73	15.9	3,914.1	2,746.7	29.8	1.43
Hodgkin Lymphoma	0.12	15.9	105.7	64.6	38.9	1.64
Kaposi Sarcoma	0.03	16.8	27.8	17.0	38.8	1.63
Kidney and Renal Pelvis	1.45	30.0	2,448.1	1,178.2	51.9	2.08
Larynx	0.33	23.1	248.8	153.8	38.2	1.62
Leukemia	1.26	33.0	2,339.3	974.1	58.4	2.40
Liver and Bile Duct	0.81	35.0	1,956.0	724.8	62.9	2.70
Lung and Bronchus	6.64	35.0	13,470.2	5,140.7	61.8	2.62
Mesothelioma	0.13	35.0	240.3	89.6	62.7	2.68
Myeloma	0.69	33.0	1,295.0	539.7	58.3	2.40
Non-Hodgkin Lymphoma	1.96	31.0	3,250.7	1,507.7	53.6	2.16
Oral Cavity and Pharynx	0.98	29.0	1,602.9	797.6	50.2	2.01
Ovary	1.16	34.0	2,648.2	1,032.3	61.0	2.57
Pancreas	1.48	35.0	2,998.1	1,119.8	62.6	2.68
Prostate	14.65	24.1	11,282.8	7,171.2	36.4	1.57
Skin	1.79	16.8	682.6	458.5	32.8	1.49
Stomach	0.83	35.0	1,752.2	651.6	62.8	2.69
Testis	0.13	16.8	313.6	180.4	42.5	1.74
Thyroid	0.77	16.8	681.1	431.2	36.7	1.58
Urinary Bladder	2.40	15.9	283.8	214.5	24.4	1.32

Table 2.3: Aggregate Ex-Ante, Ex-Post and Insurance Value to the 2010 adult population

Notes: This table shows the average willingness to pay per individual for the existence of a cure ex-ante and ex-post. Risk (%) is the average lifetime risk of developing each cancer. Ave. LYG is the average number of life years that will be gained from the existence of a cure if one were to contract the disease. Ex-Ante, B represents the total ex-ante value to the 2010 population, in billions. Ex-Post, B represents the total ex-post value to the 2010 population, in billions. Insurance (%) is the percentage of total value that is insurance value. Ratio = Ex-ante/ex-post shows how large ex-ante value is relative to ex-post value.

expected life ahead of them. Thus, the value of a cure to the sick will generally be higher for diseases that typically afflict younger individuals in contrast to diseases that typically afflict older individuals (an exception is if there are a disproportionately large number of old individuals in a society, in which case, insurance value for treatments for diseases that afflict younger individuals will be diminished).

Analysis of the value of cancer treatments reveals several interesting patterns. Ex-ante insurance value is highest for cancers that are relatively rare but where diagnosis implies severe mortality. For instance, 63.1 percent of the value of a cure for brain cancer, which is relatively rare (0.47 percent average lifetime risk) and highly deadly, will be ex-ante insurance value. In contrast, only 29.8 percent of the value of a cure for breast cancer, which is more common (10.7 percent average lifetime risk) and less deadly is ex-ante insurance value

Furthermore, I find that in many cases, the *percentage* of value accruing to the healthy, and hence will not be transacted in the market, is much larger for rarer diseases. Since rare diseases often comprise large susceptible populations but small afflicted populations, the percentage of the value of a treatment that is ex-ante insurance value is often highest for rare diseases. It is important to note that this is the insurance value *in proportion* to the total value of the drug and not the total monetary value to healthy individuals. This finding suggests that in order to reach the socially optimal level of innovation provision, rare disease research might need to be incentivized more than non-rare disease research. While altruistic and ethical arguments have previously been put forth for providing incentives toward rare disease research, our findings provide some evidence that there is an economic basis for incentive programs that aim to encourage innovation into rare disease treatments.

The findings in this chapter illustrate that cures are highly valuable from societies perspective, both in terms of value to individuals who get sick, but also to those who never fall sick. However, innovation incentive structures currently in place such as the patent system have a tendency to distort innovation away from long term investments and cures (Budish, Roin & Williams, 2013). In light of this behavior, it is important to consider new value-based

incentive and reimbursement systems that reward drugs that are highly innovative and of high value to society.

I parameterize the utility function following the function proposed by Becker, Philipson and Soares (2005). As a sensitivity analysis, I calculate ex-ante and ex-post value for diseases that occur with various hypothetical probabilities using different values of γ (figures shown in Appendix). While the exact values for the ex-ante and ex-post value will depend on the specific parametric assumptions made, the ex-ante value is always greater than ex-post value as long as the lifetime or per-period utility function is concave in consumption/income.

The insurance values for cures obtained for cancer in section VI may sometimes appear somewhat different from those calculated for hypothetical rare diseases with similar probabilities. There are several reasons for this behavior. First, the rare disease calculations assumed a one time risk that occurred either immediately or in 10 years time whereas the cancer empirical analysis accounted for a richer risk profile over time. Second, since the number of life years gained from a cure will depend on the age of an individual, the age distribution of individuals in the 2010 population also has an impact on insurance values. Third, there are time effects at play. A risk that occurs more immediately is likely to be viewed differently from one that occurs far into the future. Thus, results in the two sections should not be directly compared.

One potential limitation of the model simulations and empirical analysis in this dissertation is that only mortality (but not morbidity) is accounted for. While individuals are likely to place more insurance value on a lifesaving treatment, there could also be significant value in treatments that improve the quality of life but not the quantity of life. One example would be treatments for depression that do not impact survival outcomes but do have significant impacts on quality of life. The reason I focus purely on survival is that there is a lack of availability of reliable quality of life data. However, the model presented is easily modifiable to include quality of life parameters. For instance, using a utility function of the form $V(C, S, Q) = u(c) \cdot S \cdot Q$ where Q is a quality of life weighting factor would easily

account for morbidity effects. All other calculations performed would remain the same.

I calculate the value of cures for cancer to the static 2010 adult population from 20 - 80. Since the ex-ante and ex-post values are age specific, population growth dynamics could impact the specific valuations of treatment. Finally, I consider the value of a treatment for each disease in isolation and assume that disease risks are independent. In reality, the risks of developing each type of cancer are likely to be correlated, but there is a lack of information on how risks for different cancers co-vary. The model presented however is easily modified to account for non-independent risks.

The findings in this chapter suggest that the market will fail to provide the socially optimal level of medical innovation, since private payers will only reimburse the ex-post value. There are several ways to correct for this under-provision. One possible method would be for governments to add on a payment to private reimbursements, financed by taxation that is equivalent to the expected insurance value of the drug to society. Another option would be to provide subsidies and tax-credits to firms investing in the search for cures for serious diseases.

One such incentive program was the Orphan Drug Act (ODA) of 1983. The ODA, which awarded manufacturers of rare disease drugs with 50% tax credits on clinical trial costs and 7 years market exclusivity was intended to equalize the risks of rare disease drug development with those of non-rare disease drugs. An orphan drug is defined as a drug for a disease with a US based prevalence smaller than 200,000, or a drug for a larger disease for which the drug will be suitable only for a subset of patients smaller than 200,000, 'an orphan subset'. The ODA was enacted in response to a perceived market failure for the provision of drugs for rare diseases.The ODA is the only healthcare based policy to provide supply side incentives to directly incentivize innovation (Yin, 2008). While many agree that there are ethical and altruistic reasons to incentivize research into rare diseases, it is generally believed that the overall welfare benefits of rare disease research are small from an economic perspective given small patient populations. Our model suggests that the Orphan Drug Act can be optimal

not just from an altruistic perspective but from an economic one too.

Several researchers have found that the Orphan Drug Act has successfully stimulated research into rare conditions. Haffner, Whitley and Moses (2002) and Wellman-Labadie and Zhou (2010) find that since the enactment of the ODA, the number of orphan drugs in the market has increased significantly. Lichtenberg and Waldfogel (2009) find that the ODA increased the incentives for firms to develop drugs for small patient populations relative to larger patient populations. Thus, the ODA decreased sensitivity of drug availability and consequently patient welfare to market size. The authors find sharper growth in drug consumption and larger declines in mortality for low-prevalence diseases relative to higher-prevalence diseases. Lichtenberg and Waldfogel (2009) find that mortality from rare diseases has declined since the enactment of the Act. The benefits of this increased innovation are likely to be very large.

While external incentives are warranted when social benefits of a new innovation are larger than private benefits, it is important to keep in mind that subsidies and market protections could have unintended consequences. For instance, there is evidence that orphan drugs are often priced significantly higher than their non-orphan counterparts. Furthermore, since effort levels of firms are often not observable to regulators, firms might find it profitable to search for disease areas that will enable them to reap the benefits of innovation subsidies while exerting minimal effort. For instance, the ODA awards market exclusivity and tax credits not only for novel innovations (New Molecular Entities and New Therapeutic Biologics) but also for older innovations for a different disease indication that undergo clinical trials for an orphan disease. Since the same level of subsidies and protections are awarded both for novel innovation as well as repurposed innovations, firms might have an incentive to search for older innovations that are applicable to the orphan market. However, for some diseases, the benefits of these older innovations are likely to be lower than those of novel drugs. One solution to alleviate this problem would be to provide higher incentives for drugs that are New Molecular Entities and New Therapeutic Biologics.

Incentive schemes such as the ODA could have perverse effects on drug prices. Firms usually have a higher degree of monopoly power in an orphan market because in addition to patent protections they also enjoy ODA market exclusivity which may extend beyond patent expiry. The lack of competition from other firms will lower the elasticity of demand in the orphan segment. ODA exclusivity conditions could thus drive prices even higher than they would have been otherwise. For example, the cancer drug Gleevec (imatinib mesylate) will experience patent expiry in 2015 but its orphan exclusivity for pediatric Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia extends until 2020. Colcrys (colchicine) had been used to treat gout since 1961 but orphan approval of colchicine for Familial Mediterranean Fever in 2009 granted one company exclusive rights to produce colchicine thereby increasing price to $4.50 per tablet - more than 50 times the price prior to orphan approval. High prices may negate some of the welfare benefits of orphan drugs. In other work (Subramaniam, Sharon & Conti, 2016), we show that orphan cancer drugs are on average 75 percent more expensive than their non-orphan counterparts. While the results I present here illustrate that the value of treatments is significantly higher than previously predicted, they do no provide justification for higher drug prices. Since only individuals that fall sick participate in the market for pharmaceuticals, only the ex-post value can be captured by market transactions. New value-based pricing mechanisms and innovation funds might be needed to provide the optimal level of research into cures.

2.5 Conclusion

The value of medical innovation is significantly higher than previously estimated by traditional ex-post valuation methods. Cures confer large insurance value to all individuals susceptible to disease. Since only individuals who fall sick participate in the pharmaceutical market, the market will tend to under-provide valuable medical innovation. When this occurs, incentive mechanisms and subsidies might be needed to equalize private and social benefits and costs.

CHAPTER 3

INCENTIVES FOR VALUABLE HEALTHCARE INNOVATION

Note: Some of the contents of this chapter, especially in, but not limited to Section 3.3.2 and 3.3.4 stem from joint work with Rena Conti and Elad Sharon. Please refer to Subramaniam, Sharon and Conti (2016) for a full description of methodology and results.

3.1 Introduction

There is a significant economic literature, which explains that in many cases, the private sector will tend to underprovide a public good (Bergstrom, Blume, and Varian 1986; Roberts 1987). The reasoning for this behavior is that private entities make decisions based on the benefits that accrue to them individually as well as costs they face to provide the good. In equilibrium, the private entity will produce where private marginal benefits equal private marginal costs. The socially optimal level of provision however occurs when marginal social benefit equals marginal social cost. Since private costs and benefits in general differ from social costs and benefits, the private optimum often differs from the social optimum. If there are benefits accruing to society that are not privately captured by firms, there will be under-provision of a public good.

The social returns to an innovation are measured by the sum of consumer and producer surplus that are generated as a result of the innovation (Griliches 1992). Thus, if social producer and/ or consumer surplus are higher than their private counterparts, economic theory would predict that there would be under-provision in the market. Consequently, innovation shortages could caused by supply (producer) or demand (consumer) side influences.

Supply side disparities in social and private surplus are well documented. The productivity level (and consequently surplus) of a firm will depend not only on the intensity of its own research efforts but also the pool of knowledge that it has access to (Griliches 1979). The discovery of new ideas and technologies will often have impacts on the endeavors of other

innovators inter and intra industry. The R&D of a firm's technological neighbors affects its R&D productivity and consequently profitability (Jaffe 1986).

A less examined facet of innovation is the demand side disparity between private consumer surplus and social consumer surplus. In some instances, the value that accrues to the individuals that directly consume an innovation might be smaller than the total value that accrues to all potential consumers. Demand side disparities in private and social surplus however have been examined less frequently within the innovation literature, perhaps because these demand side effects only happen in select industries, notably those that involve public goods.

The strongest effects are likely to occur in the health industry specifically in the market for new treatments and innovations. The logic is as follows: the number of individuals who care about the existence of a treatment significantly outnumbers the number of actual consumers (patients) of the treatment. Philipson and Zanjani (2014) argue that healthy individuals may appreciate the insurance value of the development of drugs for various diseases in case they were to contract those diseases in the future. For instance, diseases such as HIV are much more treatable now and hence people live in less fear of contracting these diseases. Philipson (1995) views disease incidence as a random tax on individuals and argues that individuals will engage in costly preventative behavior in order to reduce the chance of being exposed to a disease. Thus, similar to a tax that results in deadweight losses, the burden of the disease will be larger than the incidence of the disease itself. Since most diseases tend to have relatively small patient populations but relatively large vulnerable populations, these effects are likely to be large. Furthermore, the process of innovation is associated with the intangible value of hope. Even if a treatment is not approved, for individuals who are critically ill the hope of the possibility that a treatment might be discovered is comforting and welfare enhancing (Conti, Glassman, and Ratain 2015).

In Chapters 1 and 2, I illustrate that the there is large insurance value associated with healthcare innovation. For instance, 24 - 64 % of the full value of cancer cures will be insur-

ance value. However, since only sick individuals purchase drugs, drug developers are unlikely to be able to capture the full social surplus associated with the existence of a lifesaving treatments. As such, the social benefits associated with the existence of an innovation are likely to surpass the private benefits to manufacturers, resulting in market failure. In other words, the observed demand for a treatment (though drug sales etc.) is often very different from the actual demand curve for a drug. Most current measures of consumer welfare only measure the area under the observed demand curve whereas the true value is the area under the actual demand curve. The challenge then is to determine (i) whether to provide incentives to private firms that will equalize private investments with the socially optimal level of investment and (ii) how to design incentive mechanisms that will result in the intended social outcome. Such incentive schemes should target projects where social returns surpass private returns.

Investment in healthcare innovation is different from investment in other areas because innovation is often associated with a large degree uncertainty. Much of the value from new innovation often comes from events that occur with low probability but have very high value outcomes (Popp, Newell, and Jaffe 2010; Scherer, Harhoff, and Kukies 2000). For instance, only approximately 16% of drugs that are developed make it from the preclinical stages to market approval (DiMasi, Feldman, Seckler, & Wilson, 2010).

For these types of high risk innovations, external support might be needed.Governmental support has been found to be particularly important for financing basic R & D because basic R & D is often associated with a high degree of uncertainty and payoffs that only occur in the long term (Popp et al. 2010).

In this chapter, I first discuss the various factors that firms consider when making innovation decisions. I then provide an overview of policy levers that can be used to increase innovation to socially optimal levels, before focusing on the Orphan Drug Act, which aimed to increase investment into rare disease drug development. I explain that while incentive mechanisms can increase innovation, they are often associated with unintended consequences.

3.2 Private Versus Social Consumer Demand

In chapters 1 and 2 of this dissertation, I demonstrate that the full value of lifesaving innovations accrues not only to patients that contract the disease, but also to anyone that fears that they might contract the disease in the future. As such, the total "demand" for the existence of lifesaving innovations, is larger than the population of patients that will eventually use those innovations. However, if pharmaceutical firms only observe demand from patients, then the market equilibrium quantity of innovations will likely be lower than the socially optimal equilibrium.

Let's suppose a firm is deciding whether to invest in an innovation in a given area. The firm's decision will depend on several factors including the cost of the investment, the probability of successfully getting an innovation to market, and the anticipated revenues if the product is market-approved. Let's assume that there are perfect capital markets, and firms will invest in innovation areas where anticipated profit is positive.

Next, lets assume for simplicity that we have a homogeneous population which contracts a given disease with probability q. Furthermore, let's suppose that survival without treatment is S_D, survival with treatment is S_H and income is Y. Then, the ex-post willingness to pay of a newly diagnosed individual is $X(Y, S_D, S_H)$ whereas the ex-ante willingness to pay for all individuals at risk is $W(q, Y, S_D, S_H)$. From the example in Chapter 1, Section 1.3, we know that $W > qX$.

Now, if firms can only charge patients for the innovation, the maximum price that can be charged per patient is X because X is the maximum willingness to pay per newly diagnosed individual. Assuming we normalize the size of the population to 1, the the maximum revenue that pharmaceutical firms can obtain is $qP = qX$ (since the disease is contracted with probability q).

However, if firms can extract surplus from the entire population that values the innovation, they will be able to charge a maximum price of $W > qX$ per individual at risk. Consequently, the probability that a firm invests in an innovation is lower if they can only

recoup ex-post value as shown below whereΠ is anticipated profit, c is marginal cost, K is fixed costs and γ is the probability that an innovation successfully makes it to market.

If only ex-post value can be extracted:

$$\Pr(\Pi > 0) = \Pr(\gamma(qX - c) - K > 0) \tag{3.1}$$

If ex-ante value can be extracted:

$$\Pr(\Pi > 0) = \Pr(\gamma(W - c) - K > 0) \tag{3.2}$$

However, we know that

$$\Pr(\gamma(W - c) - K > 0) > \Pr(\gamma(qX - c) - K > 0) \tag{3.3}$$

In other words, if firms are only reimbursed ex-post value, they will be less likely to invest into the development of a drug than if they can capture ex-ante value. Consequently, there will be a lower level of investment into lifesaving innovation if firms can only recoup ex-post value while society at large gains from the existence of an innovation.

3.3 Commonly Used Incentive Mechanisms

There are several policy levers that have been proposed to increase private R & D to socially optimal levels. Tax credits are often cited as a useful policy tool for increasing innovation because they boost private efforts by reducing costs to private firms while internalizing the innovation decision and reducing the inefficiencies of large bureaucracies. Tax credits act by indirectly reducing R & D costs. By examining fiscal incentives in a panel of nine OECD countries from 1979 - 1997, Bloom, Griffith and Van Reenen (2002) estimate that a 10 percent fall in R & D costs results in just over a 10 percent increase in long run R & D but the increase in short run R & D was limited to 1 percent. Studies of the US R & D and

Experimentation Credit have found elasticities of R & D of approximately 1 percent. (Hall 1993, Mamuneas and Nadiri , 1996).

In addition to tax credits, economists have long studied the impacts of market protections such as patents on innovations e.g. Nordhaus (1969). These analyses weighed the benefits of increased innovation against the higher prices and deadweight losses that would result as a consequence of these market protections. Older analyses of the impacts of market protections on innovation tended to view innovations as isolated events. However, a more recent body of research has shown that new innovation builds upon older innovations and ideas. This idea has been central to several macroeconomic models of innovation and growth (Acemoglu and Akcigit 2012; Aghion and Howitt 1992) . Furthermore, the possibility that innovation spillovers will stimulate future innovation is often used to justify public policies that award innovation.

While protectionary incentive mechanisms such as patents and intellectual property rights are aimed to stimulate innovation, there are instances where these mechanisms can prevent follow-on innovation (Heller and Eisenberg 1998). For instance, protections put in place can make it difficult for future innovators to develop new treatments without navigating complicated and costly licensing hurdles. Furthermore, earlier scientific discoveries are often inputs into future innovation. Galasso and Schankerman (2014) found that patent invalidation by U.S. courts had large effects on future innovation. A patent invalidation was associated with a 50 percent increase in citations for the focal patent. Using evidence from intellectual property rights for human genes, Williams (2013) found that intellectual property rights granted to the private firm Celera reduced follow on innovation relating to those protected genes. The assumption that patents might diminish follow-on innovation and constrain valuable public knowledge has in several cases caused the US Supreme Court to restrict the set of discoveries (e.g. genes) that are patentable (Kesselheim et al. 2013).

Intellectual property rights might also distort the types of drugs that are developed by pharmaceutical firms. For instance, using evidence from cancer clinical trials, Budish,

Roin, and Williams (2014) find that patent length affected pharmaceutical firms' decisions regarding the type of drug development they pursued. Firms were more likely to launch clinical trials into treatments for terminal cancers as these treatments typically had shorter clinical trials and hence longer effective patent lengths. However, this pattern was not observed for trials that were based on surrogate endpoints that were shorter by design.

While incentives in general are believed to improve intensity of research efforts, information asymmetries may result in the lack of alignment between the goals of policymakers and private entities. Since private firms will focus on areas of highest profit while policymakers are often interested in areas of greatest need, care needs to be taken to ensure that there are no moral hazard issues or unintended consequences when providing incentives for innovation especially in the presence of information asymmetries and monitoring constraints (Hall and Lerner 2010). The pharmaceutical industry is highly regulated but firms have private information on the costs of technological advancement that is not observable to regulators. Cadot and Sinclair-Desgagne (1996) consider a similar problem but in the context of pollution control. They suggest that the problems of asymmetric information can be reduced with government issued threats of regulation.

A notable area where innovation shortages are likely to have occurred is rare disease drug development. In the next section, I describe the history of rare disease drug development in the United States as well as the Orphan Drug Act which was enacted in 1983 to increase investment into rare disease drug development.

3.4 Rare Disease Drug Development

Rare disease drug development is challenging for several reasons. Firstly, the drug development process for any type of drug (for rare diseases or otherwise) is risky to pharmaceutical companies (DiMasi et. al, 2013). Secondly, drug development is an extremely costly endeavor with the average cost of developing a drug estimated to be more than a billion dollars (Adams and Brantner, 2010). Rare diseases have small patient populations, which likely

mean smaller revenues to pharmaceutical companies. Thus, all else being equal, companies will be more reluctant to invest in the development of drugs for rare diseases because small revenue streams will not compensate for large development and clinical trial costs.

3.4.1 Background On The Orphan Drug Act (ODA) of 1983

In order to encourage research into rare diseases and improve the lives of suffering patients, the US Orphan Drug Act (ODA) was enacted in 1983. The ODA provided both push and pull incentives to increase investments into the development of rare disease therapies. ODA provisions award a 50 percent tax credit on clinical trial costs and seven years of market exclusivity to pharmaceutical firms engaged in the development of orphan drugs. An orphan drug is a drug intended to disease with a US prevalence of less than 200,000 or, a drug for a subset smaller than 200,000 of a larger disease whereby the drug would only be suitable for that subset. Examples of orphan subset drugs include drugs that are prescribed based on certain genetic biomarkers and drugs that are prescribed only when other treatments have been unsuccessful.

Figure 3.1 shows the number of orphan designations granted by the FDA from 1983 - 2013. Figure 3.2 shows the number of orphan market approvals granted by the FDA from 1983 - 2013. We see that since the enactment of the ODA, the number of orphan drugs in the market has increased significantly. It has also been documented that mortality from rare diseases has declined (Lichtenberg and Waldfogel 2003) . However, it is unclear to what extent this increase is due to the ODA. For instance, changing patient demographics and the ability to charge premium pricing for niche drugs are also likely to have contributed to the increase in drugs to treat rare diseases. Furthermore, since new innovation often builds on previous innovations and scientific knowledge, it is possible that there could be two (or more) innovation steady states: one with a very low level of innovation since there is no wealth of knowledge to build upon and another with a higher level of innovation after certain discovery thresholds have been surpassed.

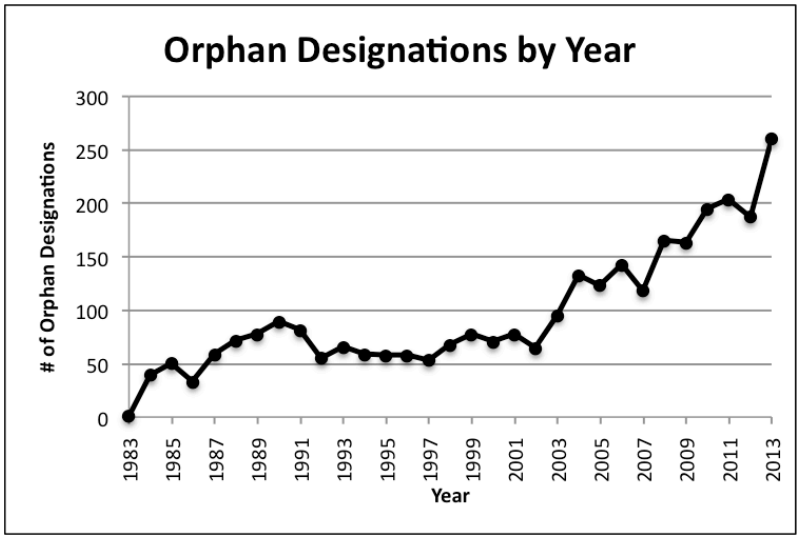

Figure 3.1: Orphan Designations from 1983 - 2013

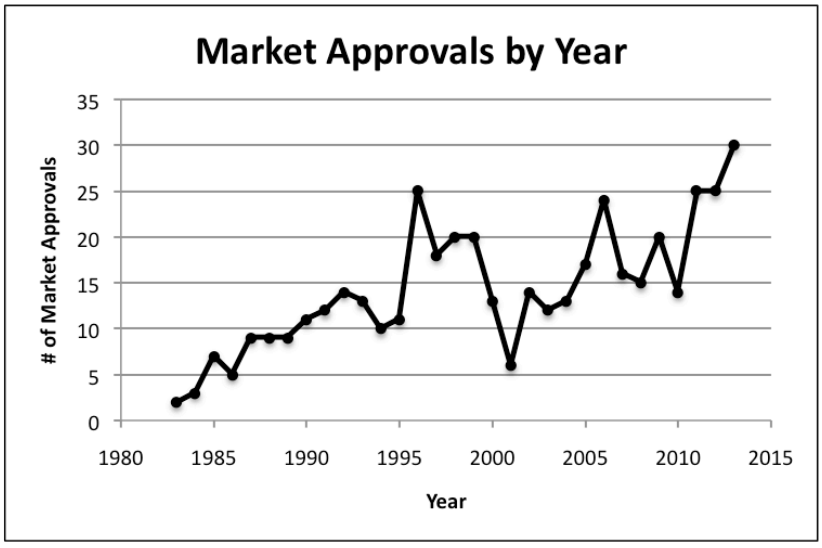

Figure 3.2: Orphan Approvals from 1983 - 2013

To my knowledge, the only counterfactual analysis of the ODA has been by Yin (2008). Yin uses diseases with patient populations slightly higher than the 200,000 ODA patient population cutoff as a control group since these diseases are likely to yield similar profits to those right below the cutoff (absent ODA incentives) but do not qualify for ODA incentives. Using a difference-in-difference approach and comparing the number of clinical trials for diseases slightly above and below the 200,000 ODA cutoff, Yin finds that the ODA mainly stimulated investment into larger orphan diseases i.e. diseases qualifying for ODA provisions closer to the 200,000 ODA patient population cutoff. In a follow up paper (Yin 2009), Yin finds that the ODA caused pharmaceutical companies to develop drugs for ODA qualifying subsets of larger diseases.

Yin's analysis however does not account for innovation "spillovers" between orphan and non-orphan drug categories. Using diseases with prevalence slightly above 200,000 as a control group implicitly assumes that there are no "spillover" effects between larger ODA qualifying diseases and smaller non-ODA qualifying diseases. However, the entry of drugs for diseases with patient populations slightly above 200,000 should not be considered independent of the entry of drugs below the ODA cutoff for a couple of reasons. First, it is well documented that "spillovers" are common when subsidies to R & D are provided (Griliches 1992) and are often a desired outcome by public agencies providing R & D incentives.

Second, an examination of recent orphan approvals by Subramaniam, Sharon and Conti (2016) revealed that innovation "spillovers" are common between orphan and non-orphan drugs. Twenty-nine percent of orphan drugs approvals from 2009 - 2012 had additional approvals in non-orphan diseases, six percent had additional approvals in orphan indications, and approximately eight percent had approvals in both orphan and non-orphan indications. Multiple approvals were most common for drugs treating cancer. The presence of these "spillovers" will tend to distort results obtained from using a difference-in-difference approach.

While it is clear that there has been an increase in the number of orphan drug approvals,

it is unclear if the increase is purely due to the ODA. For instance, changes in patient demographics, patient epidemiology or market pricing dynamics could have caused orphan drug manufacture to be more attractive to pharmaceutical firms. Furthermore, ODA incentives could cause firms to search for areas of maximum profit. In some cases, this behavior might result in behavior that is suboptimal from the perspective of consumers. In the next section, I describe some potential unintended consequences that can occur as a result of ODA incentives.

3.4.2 Intended and Unintended Consequences of the ODA

While external incentives such as the ODA are warranted when social benefits of a new innovation are larger than private benefits, it is important to keep in mind that subsidies and market protections could have unintended consequences. For instance, there is evidence that orphan drugs are often priced significantly higher than their non-orphan counterparts. Furthermore, since effort levels of firms are often not observable to regulators, firms might find it profitable to search for disease areas that will enable them to reap the benefits of innovation subsidies while exerting minimal effort. For instance, the ODA awards market exclusivity and tax credits not only for novel innovations (New Molecular Entities and New Therapeutic Biologics) but also for older innovations for a different disease indication that undergo clinical trials for an orphan disease. Since the same level of subsidies and protections are awarded both for novel innovation as well as repurposed innovations, firms might have an incentive to search for older innovations that are applicable to the orphan market. However, for some diseases, the benefits of these older innovations are likely to be lower than those of novel drugs. One solution to alleviate this problem would be to provide higher incentives for drugs that are New Molecular Entities and New Therapeutic Biologics.

Incentive schemes such as the ODA could have perverse effects on drug prices. Firms usually have a higher degree of monopoly power in an orphan market because in addition to patent protections they also enjoy ODA market exclusivity which may extend beyond

patent expiry. The lack of competition from other firms will lower the elasticity of demand in the orphan segment. ODA exclusivity conditions could thus drive prices even higher than they would have been otherwise. Furthermore, firms could use ODA exclusivity incentives to extend their monopoly power for a longer period of time. For example, the cancer drug Gleevec (imatinib mesylate) will experience patent expiry in 2015 but its orphan exclusivity for pediatric Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia extends until 2020.Such exclusivity rights will likely delay the entry of more affordable generic drugs. Colcrys (colchicine) had been used to treat gout since 1961 but orphan approval of colchicine for Familial Mediterranean Fever in 2009 granted one company exclusive rights to produce colchicine thereby increasing price to $4.50 per tablet - more than 50 times the price prior to orphan approval. High prices may negate some of the welfare benefits of orphan drugs. The same manufacturer also secured an orphan approval for Quinine sulfate for the treatment of malaria effectively creating a monopoly for a drug that had been freely used for many years.

A recent US Government Accountability Office report examined Medicare Part B expenditures in 2010. Their results suggest twenty-one of the fifty-five drugs with the highest Medicare expenditures have orphan approval for at least one indication, including four (Epoetin alfa, rituximab, bevacizumab, infliximab) of the top five highest Medicare Part B expenditure drugs. In 2010 alone, Medicare spending amounted to 2 billion for Epoetin alfa, 1.302 billion for rituximab, 1.13 billion for bevacizumab and 900 million for infliximab. These numbers suggest that in some cases (i) orphan drug manufacture can be lot more profitable than previously anticipated and (ii) additional incentives may not be warranted for all "orphan" drugs. In the next section, I provide a simple example that shows that when a drug is approved for more than one therapeutic area, the presence of a highly price inelastic orphan market can drive prices higher than they would have been otherwise. These effects can be further accentuated by subsidies and market protections provided under the ODA.

3.4.3 Impacts of the ODA on Pharmaceutical Pricing

In this section, I provide a simple example that illustrates how for drugs that are approved for multiple conditions, the presence of a highly price inelastic market can drive up drug prices. The presence of spillovers does not only affect innovation decisions but also has important consequences on drug prices. While pharmaceutical pricing is highly complex and influenced by many factors, prices must on some level still adhere to the assumptions of standard price theory (Berndt, McGuire, and Newhouse 2011). We would thus expect that prices are highly dependent on the willingness to pay and elasticity of demand of patients.

The willingness to pay for a drug depends on several factors. First, patients who have few alternative treatments available will be highly price inelastic. Second, the more effective a drug is at improving the quantity and quality of life, the more patients will be willing to pay for it. Thus, the willingness to pay and elasticity of demand for a drug will depend on the disease afflicting the patient and the availability of alternative treatments.

When a drug is approved for two or more patient populations (as is common for many drugs), manufacturers are faced with two or more markets segments with differing elasticities of demand. However, manufacturers cannot price discriminate based on the type of illness a patient has. In other words, if a single drug is approved for multiple diseases, manufacturers cannot charge different prices based on the disease. They will then choose a single price that maximizes current and future expected profit streams. When a drug is approved for both an orphan and non-orphan populations, manufacturers will price in a way that maximizes combined profits from both segments. It is still possible however that manufacturers might be able to price discriminate based on the type of payer, hospital etc.

Patients without alternative treatments to choose from will tend to be more price inelastic. Furthermore, the higher the efficacy of a drug, the more inelastic demand will be. Consequently, orphan patients will in general have more inelastic demand than non-orphan patients since patients with rare diseases often have fewer treatments available to them. For drugs with both orphan and non-orphan approvals, the presence of a highly inelastic orphan

market might drive prices up if orphan and non-orphan patients must be charged the same price. This could have adverse consequences for non-orphan patients who will now have to pay higher prices than they would have in the absence of an orphan approval.

For simplicity, I initially assume a model with two markets for a given drug with differing elasticities of demand and market sizes. The first market has elasticity ϵ_1 and market size n_1. The first market has elasticity ϵ_2 and market size n_2. Suppose a firm has developed a drug that is an effective treatment for both markets and must price the drug optimally. For simplicity we assume a linear demand curve. $q_i = a_i - b_i p, \ \forall i = 1, 2.$

We initially assume the firm has monopoly power in the market. If the firm were to price individually in each market, then $p_1 = \frac{MC}{1-1/|\epsilon_1|}$ and $p_2 = \frac{MC}{1-1/|\epsilon_2|}$. However, the firm cannot price discriminate between markets and must thus set a common price for both market segments. The market elasticity will be sum of the individual elasticities weighted by the market share of each individual market. [1]

$$\epsilon_{tot} = \epsilon_1 \frac{q_1(P)}{Q(P)} + \epsilon_2 \frac{q_2(P)}{Q(P)} \tag{3.4}$$

In the presence of two distinct patient populations (markets), firms will set prices such that $P = \frac{MC}{1-1/|\epsilon_{tot}|}$. The presence of more than one patient population then has important impacts on prices faced by the other patient population. If $\epsilon_1 \neq \epsilon_2$ The total market elasticity will be in between the two individual elasticities. If $\epsilon_1 < \epsilon_2$, then $\epsilon_1 < \epsilon_{tot} < \epsilon_2$. [2]

When the total market elasticity is higher than the elasticity for one of the individual segments (as will be the case if $\epsilon_1 \neq \epsilon_2$, the segment that had a higher initial elasticity will be made worse off by the presence of the less inelastic market segment. In other words,

1. Market elasticity is weighted sum of individual elasticities:

$$\epsilon_{tot} = Q'(P) \cdot \frac{P}{Q(P)} = q_1'(P)\frac{P}{Q(P)} + q_2'(P)\frac{P}{Q(P)} = \epsilon_1 \frac{q_1(P)}{Q(P)} + \epsilon_2 \frac{q_2(P)}{Q(P)}$$

2. If $\epsilon_1 \frac{q_1(P)}{Q(P)} + \epsilon_2 \frac{q_2(P)}{Q(P)} > \epsilon_1 \Rightarrow \epsilon_1 \left(1 - \frac{q_1(P)}{Q(P)}\right) < \epsilon_2 \frac{q_2(P)}{Q(P)}$. But we know $1 - \frac{q_1(P)}{Q(P)} = \frac{q_2(P)}{Q(P)}$. Thus result immediately follows if $\epsilon_1 < \epsilon_2$

when there is an inelastic orphan patient population, more price elastic non-orphan patients might now face higher prices than they would have if the drug had been marketed only to non-orphan patients. Conversely, the existence of the non-orphan patient population can drive down drug prices for the orphan population.

ODA incentives can further accentuate these pricing dynamics. ODA incentives act in two ways. Firstly, the tax credit reduces fixed costs in the orphan segment by approximately 50 percent. Fixed costs should not impact a firm's pricing decision but will impact whether or not a firm chooses to enter into a particular market. If fixed costs are too high relative to anticipated revenue streams, a firm will simply not enter into a particular area. $FC_{ODA} = 0.5FC$. Thus, due to ODA tax credits, firms will enter orphan therapeutic areas that they would not have entered before. Thus, there will be an increased availability of drugs to treat rare conditions.

ODA market exclusivity makes demand even more inelastic in the orphan segment by reducing the availability of other medications to treat the same condition. $|\epsilon_{1,ODA}| < |\epsilon_1|$. Thus, the total market elasticity in the presence of the ODA will be lower than the total market elasticity in the absence of the ODA as shown in equation 3.5. Consequently, prices will be higher in *both* orphan and non-orphan markets under the presence of ODA exclusivity since $P_{ODA} = \frac{MC}{1-1/|\epsilon_{tot,ODA}|} \geq \frac{MC}{1-1/|\epsilon_{tot}|} = P$.

$$\epsilon_{tot,ODA} = \epsilon_{1,ODA}\frac{q_1(P)}{Q(P)} + \epsilon_2\frac{q_2(P)}{Q(P)} \leq \epsilon_1\frac{q_1(P)}{Q(P)} + \epsilon_2\frac{q_2(P)}{Q(P)} = \epsilon_{tot} \tag{3.5}$$

The above example is intended to be an illustration of how ODA incentives can drive prices higher than they would have been otherwise, both for patients with orphan diseases, as well as patients with non-orphan diseases that are using a drug that has been approved for an orphan patient population. In reality, there are a multitude of factors that enter into pharmaceutical pricing decisions so it is difficult to accurately predict prices.

Then, intuitively, given that firms prefer to invest in connected nodes than unconnected ones (assume everything else is equal), ODA incentives might push firms to start developing new therapies within the orphan drug landscape before expanding use to non-orphan populations. What we would expect to see in approvals and sales data is that an increasing proportion of new molecular entities enter into the orphan landscape before enjoying expanded use in non-orphan areas.

3.4.4 Characteristics of Orphan Drug Approvals from 2009 - 2012

Note: The results in this section are based on joint work with Rena Conti and Elad Sharon in the paper "The Unexpected Benefits of Being an Orphan (Drug)". Please refer to the original paper for a full description of results and methodology used.

Subramaniam, Sharon and Conti (2016) perform a descriptive analysis of pricing for cancer drugs demonstrates that cancer drugs that are launched with orphan status enjoy higher pricing than their non-orphan counterparts. We analyzed launch prices for cancer drugs that entered the market between 2009 and 2012 and compared the prices of cancer drugs that were launched with orphan status, and those that were launched without orphan status. We found that annual prices were significantly higher for cancer drugs with only orphan approvals ($87,399, 95% CI [$56,184, $118,613]) when compared to cancer drugs with only non-orphan approvals ($50,013, 95% CI [$38,486, $61,539]). This result was significant at the 5-percent level (p-value=0.024).

On average, drugs with only orphan approvals conferred significantly higher life-extension benefits (0.51 years, 95% CI [0.26, 0.75]) for the first indication for which they were approved than drugs with only non-orphan approvals (0.28 years, 95% CI [0.15, 0.40]). Results were significant at the 10-percent level (p-value=0.064). Inflation-adjusted price per life-year gained was $223,903 for drugs with only orphan approvals compared to $263,761 for drugs with only non-orphan approvals. However, we could not reject the null hypothesis that the two means were the same at the 10-percent level.

3.5 Similarities Between Orphan Diseases and Neglected Tropical Diseases

There are many similarities between the issue of scarcity of certain rare disease treatments in the US and the scarcity of access to effective medications to treat neglected tropical diseases. Since the anticipated profit streams of pharmaceutical manufacturers guide drug development, it follows that there is a scarcity of treatments available to treat diseases that primarily afflict poorer countries, which have lesser ability to pay price premiums for treatments. While these diseases are not rare per se, they are often neglected because of smaller anticipated revenue streams to pharmaceutical corporations.

Kremer (2001) argues that there is little incentive to develop vaccines for diseases such as malaria, tuberculosis and strains of HIV common in Africa, which annually kill more than 5 million people. In addition to not being able to pay high enough prices for treatments, there are serious market failures for vaccines and treatments for malaria, tuberculosis and HIV. He explains that regulators sometimes use their powers to force prices to a level lower than would have been achieved in the free market. Furthermore, individual countries have little incentive to pay high prices to drug manufacturers because they realize that the treatment will have spillover benefits to other countries facing similar health problems. He estimates that in the case of vaccine development, social benefits can sometimes be about ten times as large as private benefits resulting in a level of medical innovation that is much lower than optimal.

One can make a similar argument for why access to HIV/AIDS treatment in Africa is so poor despite the existence of highly effective therapies in the US. Inability to pay high prices and market failures are likely to have impeded access to lifesaving drugs. While there is no cure for AIDS, patients with HIV that are properly treated can have life expectancies that are quite close to normal. Furthermore, being on an appropriate anti-retroviral regimen reduces the virulence of the disease and reduces the risk of transmission. While Highly Active

Antiretroviral Therapy has been utilized in the US since 1997, treatment of HIV/AIDS in many developing countries is extremely poor. There are important social benefits to improved access to medication but it is unlikely to be adequately provided privately.

The issue of investing in medical treatments becomes even more serious when the disease in question is contagious. We have observed several instances of diseases that caused severe fatalities because of the inadequacy of medical response and treatment. Oftentimes, medical response needs to be almost immediate in order to curtail an outbreak. However, the grim reality is that proper intervention often comes too late, resulting in a high number of casualties.

When a disease is contagious, the larger the number of individuals afflicted, the faster the spread of the disease because there is a higher chance of an infected individual coming in contact with an uninfected individual. In this regard, if a significant fraction of the population is vaccinated against a disease, even the unvaccinated have a lower chance of contracting the disease. In fact, if a large enough fraction of the population is vaccinated, a disease cannot take hold and will quickly die out. For these reasons, contagious diseases are highly social and impacted by various cultural and network related factors.

Evaluating private versus social benefits is of increased significance in the study of contagious diseases. Interventions need to start early in order to be more effective. One recent example was the (2014) Ebola outbreak in Africa. Ebola is not a new disease. As of 2014, it had been present for thirty-eight years. However, there were no vaccines or treatments available. One explanation for the absence of a vaccine for Ebola is the smaller patient populations of earlier outbreaks and the poverty of the nations primarily affected (DRC and Uganda) made private benefits of developing a treatment small. The Center of Disease Control reported that as of April 2016, there had been 28,657 suspected cases, and 11,325 deaths. As of April 2016, there are several vaccines in development, but none have been market approved.

The Ebola story illustrates several key points. Firstly, the epidemiology of a disease

evolves over time. Thus, estimated benefits of developing a treatment when a disease first emerges might be very different from the value later on. There is a potential public benefit to developing treatments for newly emerging diseases even though they may not initially seem very prevalent. Secondly, it illustrates that there are considerable externalities in the development of treatments for contagious diseases.

3.6 Conclusion

ODA incentives act in two ways. They push orphan innovation by reducing the costs of clinical trials in orphan markets. They pull orphan innovation by promising market exclusivity for orphan approved indications. ODA incentives affect the relative attractiveness of marketing to orphan and/or non-orphan patient populations to firms and are likely to impact the mix of orphan and non-orphan products in the market.

At the same time, ODA incentives reinforce monopoly power for firms in orphan markets thereby enabling high pricing among orphan drug developers. Another less considered fact is that when a drug is approved for both orphan and non-orphan patient populations, the increased monopoly power due to ODA incentives can translate to higher prices for non-orphan consumers of the same drug. In other words, ODA incentives reinforce premium pricing in both orphan and non-orphan markets. In some cases, this might result in reduced patient welfare especially to non-orphan patients.

At the same time, there are many lifesaving drugs that have entered the market as orphan drugs and gone on to help non-orphan patients. Thus, non-orphan patients also reap benefits of orphan drug development. It is also likely that the ODA spurred the innovation of many personalized medicines that are prescribed to patients based on certain genetic biomarkers.

Because of the possibility of spillovers between several similar diseases, the ODA might have encouraged pharmaceutical companies to engage in strategic behavior in the timing of orphan and non-orphan approvals. For instance, manufacturers might initiate an orphan approval before expanding drug use to other patient populations or search for and secure

multiple orphan and non-orphan approvals for the same molecular/biologic entity.

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APPENDIX A

EX-ANTE AND EX-POST VALUE CALCULATION EXAMPLES

A.1 Example: Calculating the Ex-Ante Value of a Treatment for Brain Cancer to a 30 year old

From the CDC life tables, an individual who is alive at the age of 30 has 50 expected life years remaining. From the NCI SEER risk of developing cancer data, a 30 year old has a 0.03 % cumulative risk of getting brain cancer in 10 years, a 0.06 % cumulative risk of getting brain cancer in 20 years, a 0.1 % cumulative risk of getting brain cancer in 30 years and a 0.57 % cumulative risk of ever getting brain cancer (*ever risk*). From the CDC life tables, an individual who is alive at age 30 has 50 years of expected life remaining (life expectancy of 80). Thus, I assume that the cumulative risk of contracting the cancer 50 years from the present is the *ever risk* of getting brain cancer. Finally, I assume the risk of getting the cancer in the initial period is 0. Using this information, I linearly interpolated the cumulative risks of getting brain cancer at all time periods in where risk data were not available (using the stata ipolate function) [1]. Then, from this discrete CDF of risks over time, I derive the discrete PDF of risks over time for a 30 year old. Using this cancer risk data, I calculate the number of individuals in each age group that would eventually develop cancer, and the age at which they would develop the cancer.

For most cancers, there is no counterfactual evidence on how patients would have responded without treatment, because most cancer clinical trials are not placebo controlled for ethical reasons. Thus, I use NCI SEER survival statistics from the 1975 - 1979, when there were few effective treatments for cancer, to proxy for survival without treatment. [2]

1. ipolate does not draw a line of best fit but instead linearly fills in missing values in between non-missing values

2. While I realize that this method is not perfect, given that chemotherapy was in existence at the time,

From NCI SEER Survival Statistics, the median survival without treatment for brain cancer is 1 year. One limitation of NCI SEER survival data is that it is not age specific.

I assume lifetime utility takes on the following form. Lifetime utility is per period utility from consumption, $u(y)$ multiplied by discounted years of survival, S. I set $\beta = 0.97$.

$$V(Y,S) = u(y)S = u(y)\sum_{t=0}^{S}\beta^t \tag{A.1}$$

Without treatment, if a 30 year old gets cancer when he is 31 (one year from the present) and there is no treatment, he will live for one year. Thus, he lives for 2 years total (including the current year) and his discounted total lifetime utility viewed from the present is $V_1 = u(y)\sum_{t=0}^{1}\beta^t$. If he does not get it in when he is 31, he could get it when he is 32, but then he would live for 3 years total, viewed from the present. Thus, total discounted lifetime utility is $V_2 = u(y)\sum_{t=0}^{2}\beta^t$. If he does not get it when he is 32, he could get it when he is 33, and so on. I assume that this problem continues in each period until he either contracts the cancer, or dies. If he never contracts the cancer, I assume he will live until the average life expectancy for a 30 year old. I weight the lifetime utility if he were to develop the cancer in time period t by the probability of developing the cancer in time period t. If he never contracts brain cancer, his expected survival is 50 years. This occurs with probability (1 - *ever risk*). If a cure is available, I assume that this individual will enjoy survival of 50 years regardless of whether he contracts brain cancer or not.

Using this information, I calculate the expected lifetime utility by calculating the weighted sum of the lifetime utilities if the cancer is contracted in period t, V_t weighted by the probability of developing the cancer in period t , p_t plus the probability of never contracting the cancer, p_{never} times the lifetime utility if one never gets brain cancer, V_{never}.

With this information, I calculate the maximum lifetime income an individual would agree

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the willingness to pay estimates calculated will if at all, be under-estimates rather than over-estimates given that the true $\frac{S_D}{S_{cure}}$ will be smaller than our estimate. By using survival in the 1970s to calculate S_D, I am essentially measuring the value of survival gains relative to survival with treatments in the 1970s.

to give up ex-ante to avoid the mortality risk of brain cancer. To avoid credit constraint issues in the initial period, I assume that perfect credit markets and that the individual commits to paying w in *each period* he is alive to avoid the mortality risk of brain cancer. The total ex-ante willingness to pay is then $W = w \cdot S_H$ where S_H is the discounted expected survival of a healthy individual (since a cure restores survival to healthy survival levels).

A.2 Example: Calculating the Ex-Post Value of a Treatment for Brain Cancer for a 40 year old

From the CDC life tables, an individual who is alive at the age of 40 has 41 expected life years remaining (rounded to closest integer). A 40 year old who contracts brain cancer will live on average 1 year without treatment. A healthy 40 year old will live on average 41 years more (conditional life expectancy of 81) without treatment. Then, the ex-post willingness to pay is calculated as follows:

$$\sum_{t=0}^{41} \beta^t u(y - w_I) = u(y) \tag{A.2}$$

w_I is the ex-post willingness to pay per period. The lifetime willingness to pay is then $W_I = w_I \cdot S_H$

APPENDIX B

SENSITIVITY ANALYSIS

B.1 Value of Cancer Cures for Different Inter-temporal Elasticity of Substitution Parameters

Table B.1 shows the percentage insurance value for difference values of γ.

Cancer Site	Insurance			
	$\gamma = 0.8$	$\gamma = 1.1$	$\gamma = 1.25$	$\gamma = 1.5$
Brain	67.03	64.00	63.11	62.43
Cervix Uteri	38.29	32.64	30.47	27.52
Colon and Rectum	56.53	52.13	50.51	48.47
Corpus and Uterus, NOS	37.24	31.73	29.63	26.78
Esophagus	66.84	63.77	62.86	62.15
Female Breast	37.30	31.89	29.82	27.00
Hodgkin Lymphoma	46.40	40.95	38.85	35.98
Kaposi Sarcoma	46.43	40.92	38.79	35.87
Kidney and Renal Pelvis	57.89	53.48	51.87	49.87
Larynx	45.77	40.29	38.18	35.32
Leukemia	63.23	59.58	58.35	57.06
Liver and Intrahepatic Bile Duct	66.86	63.83	62.94	62.26
Lung and Bronchus	65.46	62.65	61.83	61.25
Mesothelioma	66.77	63.66	62.73	61.98
Myeloma	63.25	59.56	58.32	57.00
Non-Hodgkin Lymphoma	59.33	55.12	53.61	51.79
Oral Cavity and Pharynx	56.51	51.93	50.24	48.10
Ovary	65.32	62.04	61.01	60.08
Pancreas	66.58	63.54	62.64	61.94
Prostate	43.55	38.42	36.44	33.73
Skin	40.40	34.92	32.83	29.97
Stomach	66.76	63.71	62.81	62.10
Testis	49.87	44.52	42.46	39.65
Thyroid	44.29	38.80	36.68	33.80
Urinary Bladder	31.72	26.41	24.42	21.73

Table B.1: Sensitivity Analysis: Insurance Percentage for Different Values γ

Notes: This table shows the percentage insurance value for different values of the elasticity of the elasticity of inter-temporal substitution γ

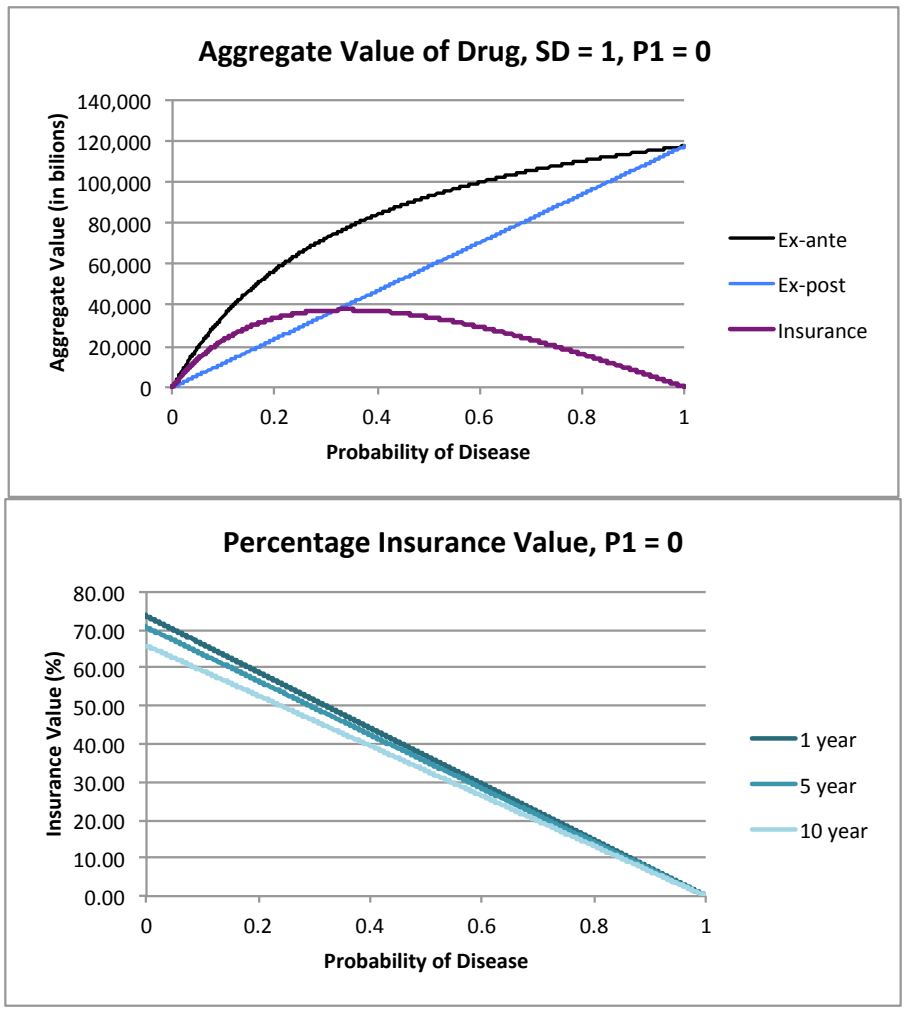

Figure B.1: Insurance Value when $\gamma = 0.5$

B.2 Value of Rare Disease Treatments for Different Inter-temporal Elasticity of Substitution Parameters

Figures (B.1), (B.2), (B.3) and (B.4) illustrate ex-post, ex-ante and insurance value when $\gamma = 0.5, \gamma = 1.1, \gamma = 1.5$ and $\gamma = 2$ respectively. I assume a hypothetical cohort of 200 million individuals. The top panel of each figure shows ex-ante, ex-post and insurance value when survival without treatment is 1 year, survival with treatment is 30 years and the disease risk is immediate. The bottom panel of each figure shows percentage insurance value when survival without treatment is either 1,5 or 10 years, survival with treatment is 30 years and the disease risk is immediate.

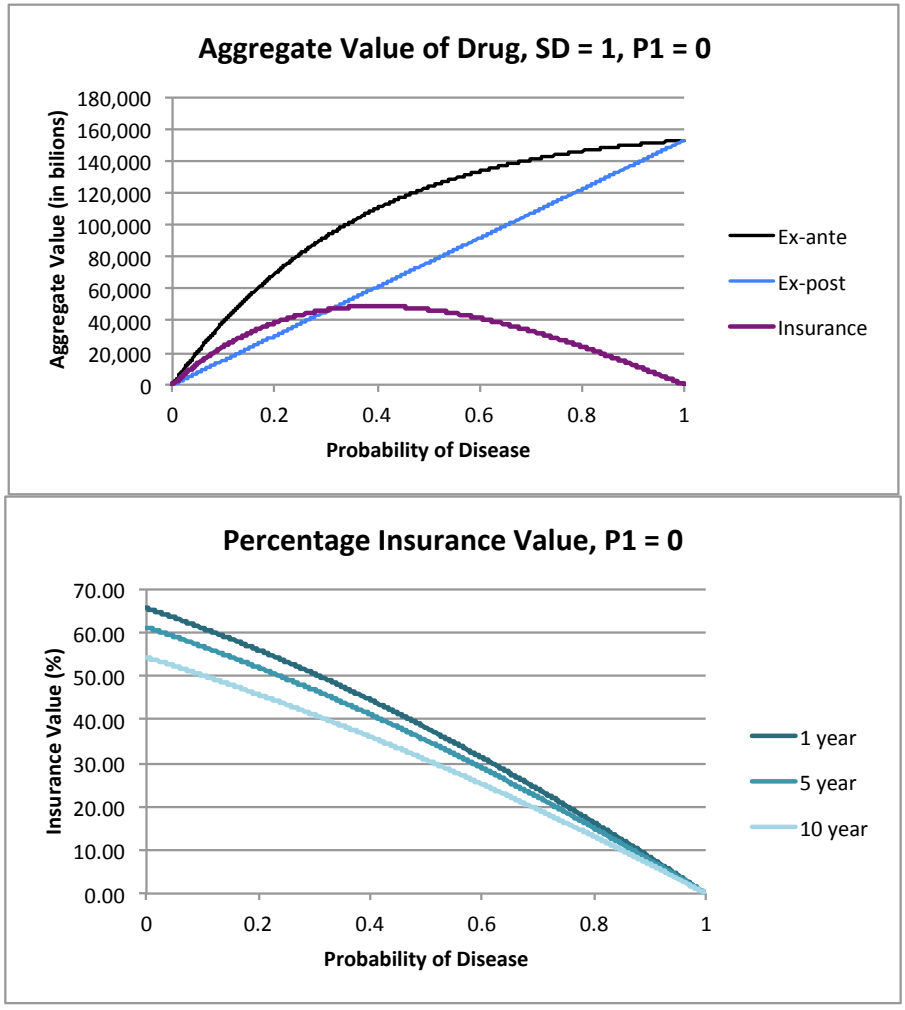

Figure B.2: Insurance Value when $\gamma = 1.1$

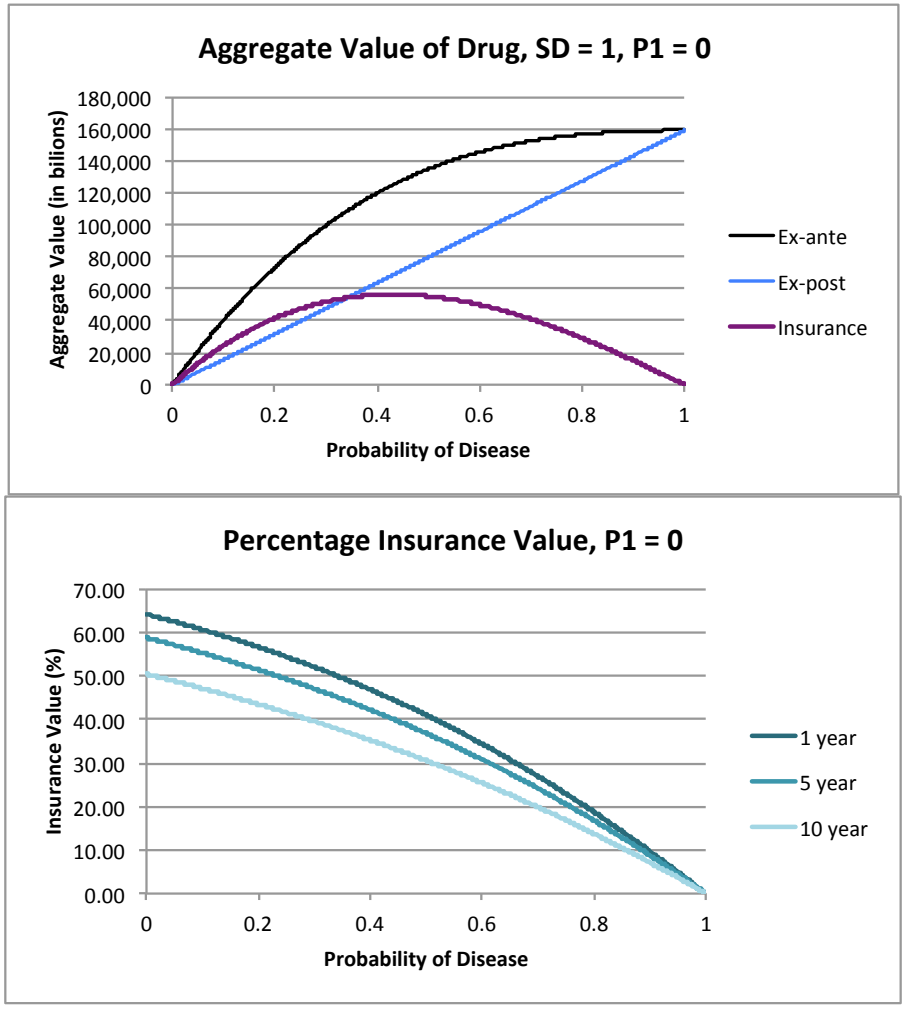

Figure B.3: Insurance Value when $\gamma = 1.5$

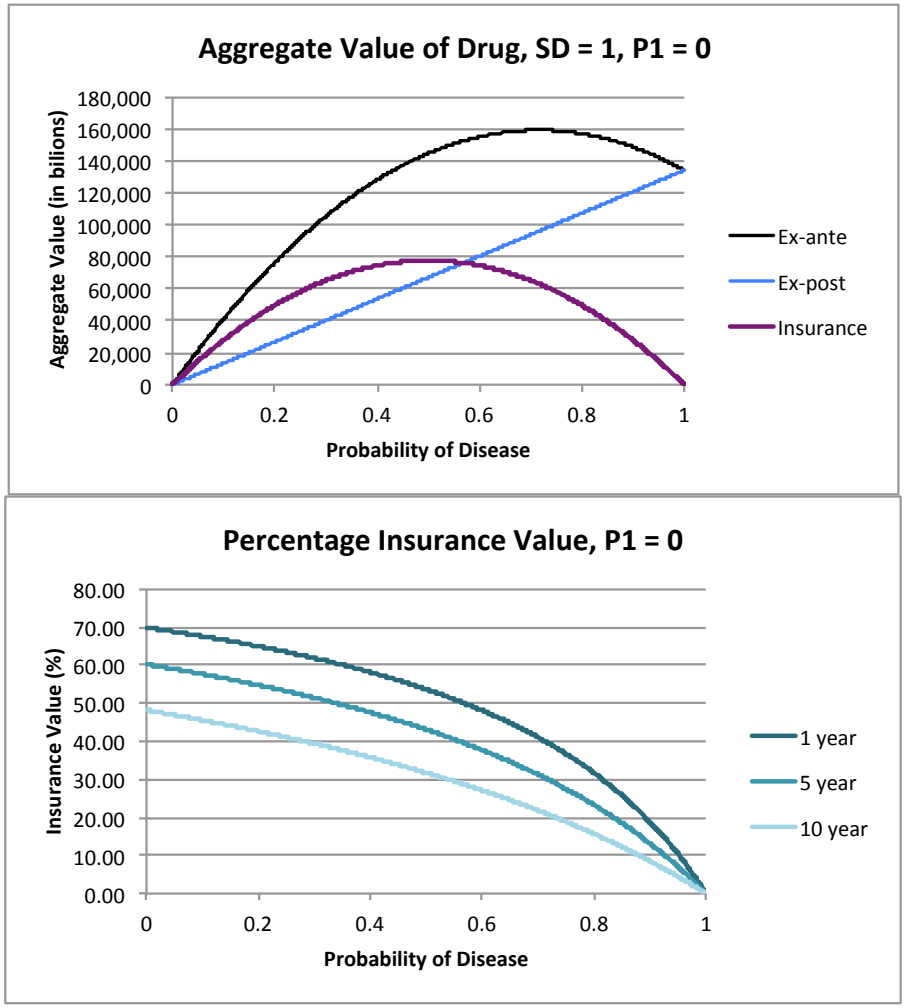

Figure B.4: Insurance Value when $\gamma = 2$

APPENDIX C

CANCER RISK PROFILES BY AGE AND CANCER SITE

Table C.1: Risk of Developing Various Cancers by Age

Site	Age	10 Year Risk	20 Year Risk	30 Year Risk	Ever Risk	Risk of Dying
All	20	0.46	1.52	4.13	40.73	21.13
All	30	1.08	3.72	9.64	40.77	21.26
All	40	2.7	8.75	19.44	40.55	21.38
All	50	6.35	17.56	29.97	39.69	21.35
All	60	12.47	26.28	34.85	37.1	20.69
All	70	17.16	27.81		30.61	18.53
Brain	20	0.02	0.06	0.1	0.57	0.45
Brain	30	0.03	0.08	0.16	0.55	0.44
Brain	40	0.05	0.13	0.26	0.52	0.44
Brain	50	0.08	0.22	0.36	0.48	0.42
Brain	60	0.14	0.3	0.4	0.42	0.38
Brain	70	0.18	0.29		0.32	0.29
Cervix Uteri	20	0.03	0.15	0.28	0.65	0.23
Cervix Uteri	30	0.11	0.25	0.36	0.62	0.23
Cervix Uteri	40	0.14	0.25	0.37	0.52	0.21
Cervix Uteri	50	0.12	0.23	0.32	0.39	0.18
Cervix Uteri	60	0.12	0.21	0.26	0.28	0.14
Cervix Uteri	70	0.1	0.16		0.18	0.1
Colon and Rectum	20	0.02	0.09	0.32	4.72	1.97
Colon and Rectum	30	0.07	0.31	0.88	4.75	1.98
Colon and Rectum	40	0.24	0.82	1.8	4.74	1.99
Colon and Rectum	50	0.6	1.6	3.02	4.62	1.98
Colon and Rectum	60	1.07	2.58	3.88	4.28	1.93
Colon and Rectum	70	1.73	3.21		3.67	1.79
Corpus and Uterus	20	0.01	0.08	0.28	2.77	0.58
Corpus and Uterus	30	0.07	0.26	0.83	2.77	0.58

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Table C.1 – *Continued from previous page*

Site	Age	10 Year Risk	20 Year Risk	30 Year Risk	Ever Risk	Risk of Dying
Corpus and Uterus	40	0.2	0.77	1.63	2.73	0.58
Corpus and Uterus	50	0.59	1.46	2.15	2.58	0.58
Corpus and Uterus	60	0.92	1.65	2.01	2.1	0.54
Corpus and Uterus	70	0.81	1.22		1.31	0.44
Esophagus	20	0	0	0.02	0.51	0.5
Esophagus	30	0	0.02	0.08	0.52	0.5
Esophagus	40	0.02	0.08	0.22	0.52	0.51
Esophagus	50	0.07	0.21	0.37	0.52	0.5
Esophagus	60	0.15	0.33	0.45	0.48	0.47
Esophagus	70	0.2	0.34		0.37	0.38
Female Breast	20	0.06	0.5	1.92	12.48	2.76
Female Breast	30	0.44	1.88	4.07	12.49	2.77
Female Breast	40	1.45	3.67	6.83	12.2	2.74
Female Breast	50	2.29	5.56	8.76	11.1	2.63
Female Breast	60	3.48	6.89	8.9	9.39	2.38
Female Breast	70	3.88	6.16		6.72	1.99
Hodgkin Lymphoma	20	0.04	0.07	0.1	0.2	0.04
Hodgkin Lymphoma	30	0.03	0.06	0.08	0.16	0.04
Hodgkin Lymphoma	40	0.03	0.05	0.08	0.13	0.04
Hodgkin Lymphoma	50	0.02	0.05	0.08	0.11	0.03
Hodgkin Lymphoma	60	0.03	0.06	0.08	0.09	0.03
Hodgkin Lymphoma	70	0.04	0.06		0.07	0.03
Kaposi Sarcoma	20	0	0.01	0.02	0.05	0
Kaposi Sarcoma	30	0.01	0.02	0.02	0.04	0
Kaposi Sarcoma	40	0.01	0.01	0.02	0.03	0
Kaposi Sarcoma	50	0.01	0.01	0.02	0.03	0
Kaposi Sarcoma	60	0.01	0.01	0.02	0.02	0
Kaposi Sarcoma	70	0.01	0.02		0.02	0
Kidney and Renal Pelvis	20	0.01	0.05	0.16	1.61	0.48
Kidney and Renal Pelvis	30	0.04	0.15	0.4	1.62	0.48

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Table C.1 – *Continued from previous page*

Site	Age	10 Year Risk	20 Year Risk	30 Year Risk	Ever Risk	Risk of Dying
Kidney and Renal Pelvis	40	0.12	0.36	0.79	1.6	0.49
Kidney and Renal Pelvis	50	0.26	0.7	1.18	1.52	0.48
Kidney and Renal Pelvis	60	0.47	0.98	1.28	1.35	0.46
Kidney and Renal Pelvis	70	0.59	0.93		1	0.4
Larynx	20	0	0	0.02	0.36	0.13
Larynx	30	0	0.02	0.08	0.36	0.13
Larynx	40	0.02	0.08	0.18	0.36	0.13
Larynx	50	0.06	0.17	0.29	0.36	0.13
Larynx	60	0.12	0.24	0.3	0.31	0.12
Larynx	70	0.14	0.21		0.22	0.09
Leukemia	20	0.03	0.06	0.13	1.36	0.86
Leukemia	30	0.04	0.1	0.23	1.35	0.86
Leukemia	40	0.06	0.2	0.46	1.32	0.86
Leukemia	50	0.13	0.41	0.82	1.29	0.86
Leukemia	60	0.29	0.73	1.11	1.23	0.86
Leukemia	70	0.5	0.93		1.07	0.83
Liver and Bile Duct	20	0	0.01	0.05	0.9	0.69
Liver and Bile Duct	30	0.01	0.05	0.23	0.9	0.69
Liver and Bile Duct	40	0.04	0.22	0.47	0.9	0.7
Liver and Bile Duct	50	0.19	0.44	0.69	0.89	0.69
Liver and Bile Duct	60	0.27	0.53	0.7	0.74	0.62
Liver and Bile Duct	70	0.3	0.49		0.54	0.51
Lung and Bronchus	20	0.01	0.03	0.18	6.85	5.75
Lung and Bronchus	30	0.02	0.18	0.8	6.9	5.8
Lung and Bronchus	40	0.16	0.78	2.43	6.96	5.87
Lung and Bronchus	50	0.64	2.33	4.94	6.99	5.91
Lung and Bronchus	60	1.79	4.56	6.39	6.74	5.74
Lung and Bronchus	70	3.15	5.23		5.63	4.93
Mesothelioma	20	0	0	0	0.13	0.1
Mesothelioma	30	0	0	0.01	0.13	0.1

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Table C.1 – *Continued from previous page*

Site	Age	10 Year Risk	20 Year Risk	30 Year Risk	Ever Risk	Risk of Dying
Mesothelioma	40	0	0.01	0.03	0.13	0.1
Mesothelioma	50	0.01	0.03	0.08	0.13	0.1
Mesothelioma	60	0.03	0.07	0.12	0.13	0.11
Mesothelioma	70	0.05	0.11		0.12	0.1
Myeloma	20	0	0.01	0.04	0.73	0.42
Myeloma	30	0.01	0.03	0.11	0.73	0.43
Myeloma	40	0.03	0.11	0.28	0.74	0.43
Myeloma	50	0.08	0.26	0.51	0.73	0.44
Myeloma	60	0.18	0.45	0.64	0.68	0.44
Myeloma	70	0.31	0.52		0.56	0.4
Non-Hodgkin Lymphoma	20	0.03	0.09	0.21	2.13	0.79
Non-Hodgkin Lymphoma	30	0.06	0.18	0.42	2.12	0.79
Non-Hodgkin Lymphoma	40	0.12	0.36	0.82	2.09	0.79
Non-Hodgkin Lymphoma	50	0.25	0.72	1.38	2.02	0.8
Non-Hodgkin Lymphoma	60	0.5	1.2	1.75	1.88	0.8
Non-Hodgkin Lymphoma	70	0.8	1.42		1.57	0.76
Oral Cavity and Pharynx	20	0.01	0.03	0.12	1.11	0.29
Oral Cavity and Pharynx	30	0.03	0.11	0.33	1.11	0.29
Oral Cavity and Pharynx	40	0.09	0.3	0.6	1.1	0.29
Oral Cavity and Pharynx	50	0.22	0.53	0.81	1.04	0.28
Oral Cavity and Pharynx	60	0.32	0.62	0.81	0.87	0.26
Oral Cavity and Pharynx	70	0.34	0.56		0.62	0.21
Ovary	20	0.02	0.06	0.18	1.33	0.99
Ovary	30	0.04	0.16	0.37	1.32	1
Ovary	40	0.12	0.33	0.63	1.29	1
Ovary	50	0.22	0.52	0.87	1.2	0.98
Ovary	60	0.32	0.69	0.95	1.02	0.91
Ovary	70	0.4	0.69		0.78	0.76
Pancreas	20	0	0.01	0.05	1.53	1.36
Pancreas	30	0.01	0.05	0.19	1.54	1.37

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Table C.1 – *Continued from previous page*

Site	Age	10 Year Risk	20 Year Risk	30 Year Risk	Ever Risk	Risk of Dying
Pancreas	40	0.04	0.18	0.51	1.55	1.38
Pancreas	50	0.15	0.48	0.99	1.54	1.39
Pancreas	60	0.35	0.89	1.35	1.48	1.35
Pancreas	70	0.61	1.13		1.28	1.2
Prostate	20	0	0.01	0.33	15.27	2.71
Prostate	30	0.01	0.34	2.49	15.46	2.75
Prostate	40	0.33	2.52	8.04	15.69	2.8
Prostate	50	2.26	7.98	13.47	15.91	2.88
Prostate	60	6.29	12.34	14.57	15.02	3.05
Prostate	70	7.52	10.3		10.86	3.23
Skin	20	0.05	0.15	0.33	2.07	0.32
Skin	30	0.1	0.28	0.58	2.04	0.32
Skin	40	0.18	0.48	0.94	1.96	0.32
Skin	50	0.31	0.78	1.32	1.83	0.31
Skin	60	0.5	1.08	1.51	1.62	0.29
Skin	70	0.66	1.15		1.27	0.26
Stomach	20	0	0.02	0.06	0.88	0.41
Stomach	30	0.02	0.05	0.14	0.88	0.41
Stomach	40	0.04	0.13	0.31	0.88	0.41
Stomach	50	0.09	0.28	0.56	0.86	0.41
Stomach	60	0.2	0.49	0.74	0.81	0.39
Stomach	70	0.33	0.61		0.7	0.36
Testis	20	0.12	0.23	0.3	0.36	0.02
Testis	30	0.12	0.19	0.22	0.25	0.02
Testis	40	0.07	0.11	0.12	0.13	0.01
Testis	50	0.03	0.05	0.06	0.06	0.01
Testis	60	0.02	0.03	0.03	0.03	0.01
Testis	70	0.01	0.02		0.02	0.01
Thyroid	20	0.08	0.23	0.44	1.12	0.06
Thyroid	30	0.16	0.37	0.59	1.06	0.06

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Table C.1 – *Continued from previous page*

Site	Age	10 Year Risk	20 Year Risk	30 Year Risk	Ever Risk	Risk of Dying
Thyroid	40	0.21	0.44	0.66	0.91	0.07
Thyroid	50	0.24	0.46	0.64	0.72	0.07
Thyroid	60	0.24	0.43	0.5	0.51	0.06
Thyroid	70	0.21	0.29		0.31	0.06
Urinary Bladder	20	0	0.01	0.06	2.44	0.61
Urinary Bladder	30	0.01	0.06	0.24	2.46	0.62
Urinary Bladder	40	0.05	0.23	0.73	2.47	0.62
Urinary Bladder	50	0.18	0.7	1.56	2.49	0.63
Urinary Bladder	60	0.55	1.46	2.24	2.45	0.65
Urinary Bladder	70	1.04	1.92		2.16	0.64