Assessing the Potential Benefits of the Melanoma Program

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A recent three-part report in the New York Times (on attempts to find a cure f or melanoma highlights both the complexity of the problem and how important it is to extend life for even one year.[1] When research in Europe indicated that the gene B-RAF a mutation was implicated in about 60% of melanoma cases, a drug company developed a targeted drug to block the protein produced by this defective gene, which would then presumably stopped the growth of tumors.[2] Trials with this drug failed because it also blocked the same protein in healthy cells. Then a small high tech company created PLX_{4032} that only affects the protein produced by this defective gene in cancerous cells. In a phase I trial with seven patients, the experimental drug dramatically reduced tumors in the patients in the trial. However, after about six months, the tumors returned, presumably produced by the production of proteins from other defective genes. Although this treatment did not provide permanent relief, the families involved appreciated the relatively short extension of their loved one's lives.[3] The reporter observed that families would be willing to pay billions for drugs that extend life, especially disease free life for even a year, indicating how important it is to measure the number of months added by specific interventions rather than assigning an economic value to each month or year. It is with the thought of those who are suffering from melanoma, that this report focuses on the benefits provided by the National Cancer Institute in its program in this morbidity. Specifically, we will focus on the gains achieved during the three years of 2006-2008 in projects that had been completed prior to 2009.

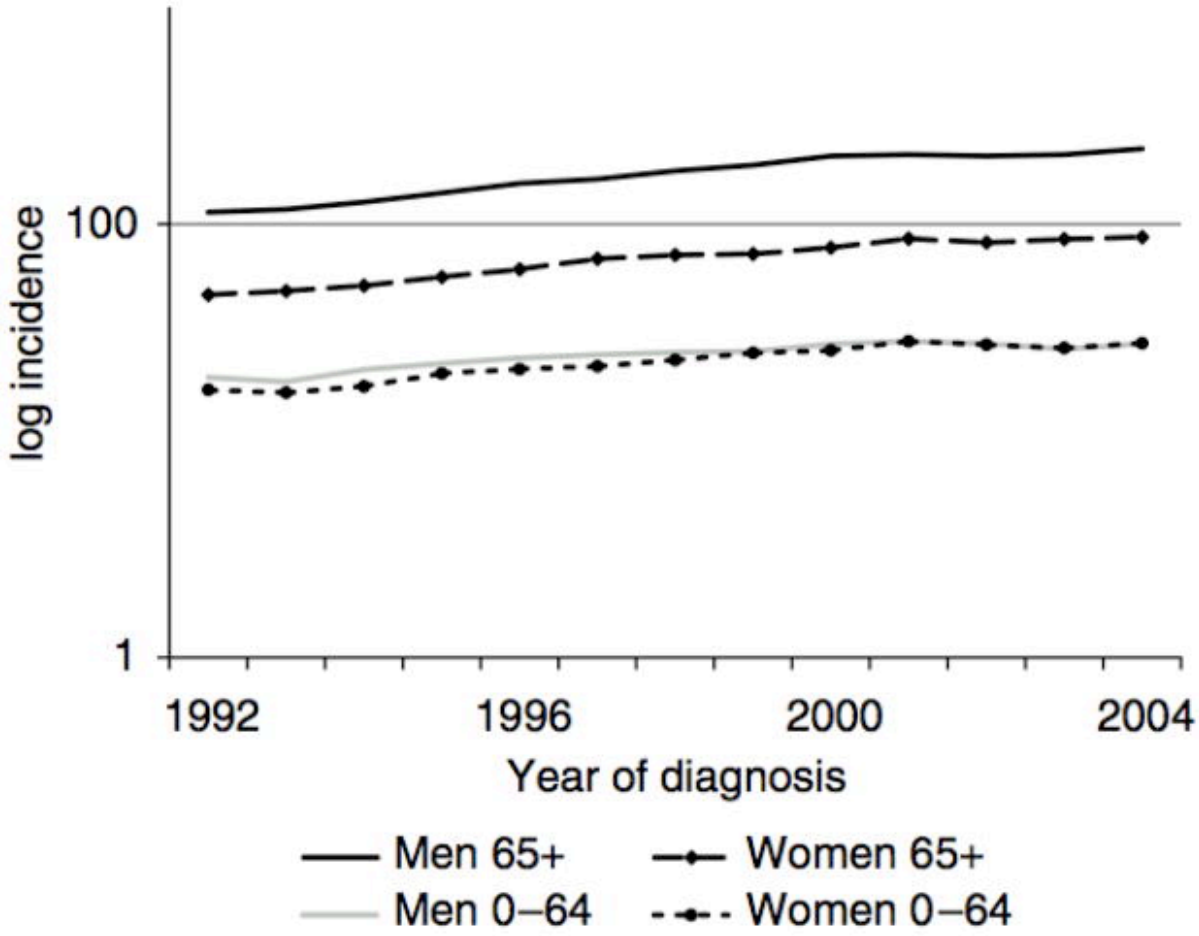
Melanoma is the most deadly of skin cancers but it is relatively rare. It occurs when something goes wrong with melanin producing cells or melanocytes that give color to the skin. Normally, old skin cells are replaced by new and healthy cells on a regular basis. But if some cells develop DNA damage, new cells now begin to grow out of control and form a mass of cancerous cells. What makes melanoma particularly critical is the more or less steady rise in the number of cases. Melanoma is the fastest growing cancer worldwide.[4] In the United States, in the period of 1992-2004, the overall incidence grew by 45% at an annual rate of 3.1%. The incidence rates vary wide by age and gender to say nothing about race or ethnicity. For non-Hispanic whites, the incidence rate went from 18.2 per 100,000 in 1992 to 26.3 per 100,000 in 2004, increasing an average of 3% per year. The greatest increase occurred among men ages 65 and over, increasing from 73.2 new cases per 100,000 in 1992 to 126.1 new cases in 2004 an increase of 4.1% per year. In all the categories of socio-economic status, the incidence rates have largely doubled. While white men had a incidence rate of 29.7 per 100,000 and white women 19.1 on average over the three last years of available seer data (2003-07), the rates per 100,000 all other races and ethnic groups is less than 5.

At he same time, while there have been dramatic increases in the *incidence* of melanoma, the *death rate*s have not raised as sharply, producing a debate in the literature as to why. Between 1992 and 2004, the overall mortality in the United States increased at a much slower rate of 0.4% annually. This same pattern has been repeated in the UK.[5] Over age 65, the mortality rate--consistent with the increases in its incidence in this age

group--grew by annual rate of 1.7% per 100,00. In contrast, for those under age 65, the mortality rates have declined somewhat and remain low (see Figure Two).

Figure One

Incidence Rates Per 100,000 for Men and Women



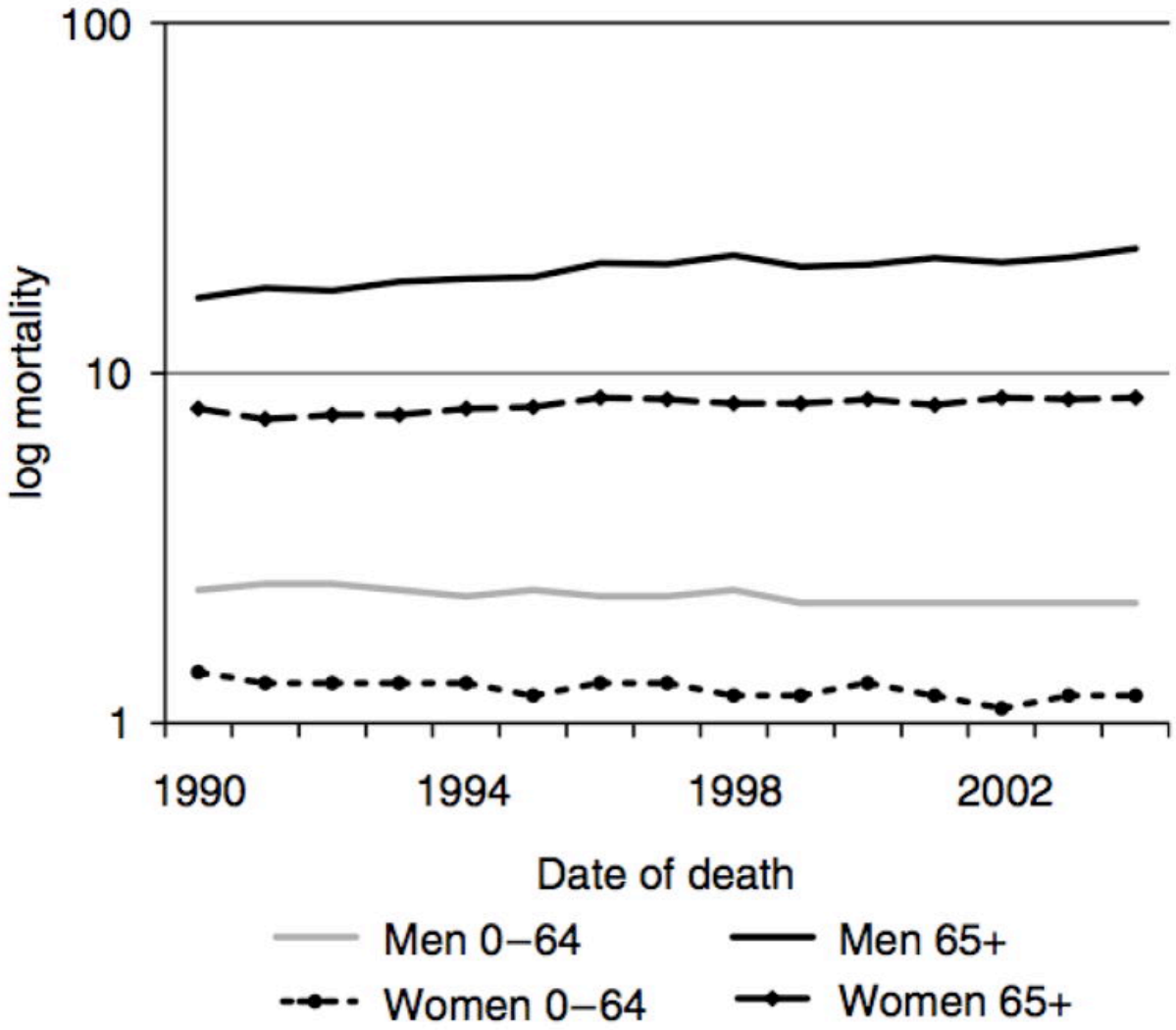
Source: Linos, et al., 2009

Some have argued that the higher incidence rates reflect better knowledge about the dangers of melanoma and more frequent screening. Still others question whether this is correct given the patterns of growth in tumor size at time of diagnosis. The most disturbing statistic is the steady and relentless increases in the tumor size at time of first diagnosis. At indicated below, a major prognostic tool is the thickness of the tumor on the Breslow scale in 1970.[6] The worse prognosis is attached to a thickness of greater than 4 mm., which usually indicates that the melanoma has metastasized to different parts of the body. While the proportions among the four categories (< 1mm, 1.01 mm to 2.00 mm, 2.01 to 4.00 mm, and > 4 mm) have remained largely the same, the growth in the incidence of each category means the number of large tumors is also growing. The incidence of > 4 mm has increased 3.86% per year, 4.10% for men and 3.30% for women) while for men over 65, the annual increase is 5.67%. This suggests that better screening is getting thinner tumors but the thicker ones, which are likely to be

concentrated in the lower socio-economic statuses (SES) are not being screened soon enough. In addition, despite screening improving in low SES areas, the number of large tumors has also increased in them as well.

Figure Two

Mortality Rates per 100,000 for Men and Women



Source: Linos, et al., 2009

Another way of thinking about the role of SES in melanoma is to consider its impact on what has been defined as poor prognosis, that is the ratio between mortality (numerator) and incidence (denominator). The higher this proportion, then, the poorer the prognosis. As one might expect, this is associated with lower education levels, residence in non-white neighbors, and lower income.[7] Of these three attributes, education is by far the most important factor. At the same time, the bottom line is that melanoma has doubled in all SES groups in the last ten years. Also, it is important to

recognize that melanoma is more common among the higher SES groups than those with lower SES even if the prognosis is poorer for these groups.[5]

Etiology of Melanoma

Who is most vulnerable to melanoma? The major implication above is that the most vulnerable group are white non-Hispanic men over age 65. Given this increasing vulnerability, are these men seeing dermatologists on a regular basis? In a random sample of white men and women aged 50 and over interviewed in the National Health Survey, only 16 percent of the men and 13% of the women had seen a dermatologist in the past year.[8] The factors associated with absence of check-up for melanoma are the usual ones: younger age (under 65), lower education level, lack of medical insurance, and lack of another cancer.

As indicated in Table One, there is considerable variability in the life-long risk of getting melanoma for different races with the same age. The lighter the skin, the greater the risk and as can be seen in Table Two, fair skin, blond or red hair, and blue eyes increases the risk considerably, two to three times. In other words, for a fair skin white the life-long risk is as low as 1 in 16. The risk is even greater if the skin does not tan. Red hair is at greater risk than blond hair. But while blacks are much better protected, they can still die of the disease. Bob Marley, the singer, did. The reason is that melanomas in blacks can start on the palms of the hands or the soles of the feet, that is where the skin is lighter. These different patterns of where melanomas start has lead to the differentiation of melanoma into several sub-types and interesting research on the role of pathways.[9]

Table One
Life-Long Risk Before Age 80 by Race

Race	**Life-Long Risk by Age 80**
White	**1 in 50**
Hispanic	**I in 250**
Native American	**I in 350**
Asian	**1 in 800**
Black	**1 in 1,100**

The discussion of fair skin leads naturally into the discussion of risk factors. These can be easily grouped into two, environmental including life style, and genetic. In about 40% of the melanoma cases, no identifiable genetic factor has so far been found.[5] The major life style factor is exposure to ultraviolet (hereafter UV) light at the beach or by frequent use of tanning beds. How this interacts with SES is complex. Presumably, those with higher incomes have more money to take vacations in the summer and to pay the cost of tanning beds. But because they are also better educated, their melanomas are caught in earlier stages.

How UV damages the DNA of skin cells is still not clear but severe sunburn that causes blisters while an adolescent is associated with increased risk of melanoma later in life. For example, in the clinical trial discussed above, one of the patients, Randy Williams, when he was 16 fell asleep at the lake and got such a bad burn on his feet that he could not walk for a week. Twenty years later, the melanoma cancer appeared and spread throughout his body. Multiple sunburns as an adult are also associated with increased risk of melanoma. Furthermore, when individuals are born in geographic areas with high UV concentrations and who spend the first decade in this environment, the chances of having melanoma at any time point in their life increases.[5]

Given the increased knowledge about the role of sunburns, one might ask if this is leading to behavior changes that over the long term might reduce both the incidence and the mortality of melanoma? In other words, the growing death rates among those over 65 reflect their not having the advantage of this knowledge twenty to thirty years earlier. The evidence on this is not encouraging. Between 1998 and 2004 while both the use of sunscreen and three to five behaviors designed to reduce risk increased, other behaviors that increased risk also increased. For example indoor tanning also increased significantly.[10] The prevalence of sunburns changed little despite the use of sunscreen and almost one-half reported summer sunburns with one half of these stating that it was painful (they did not report if it caused blisters). In other words, people are more knowledgeable about what to do but in effect are not changing their behavior that much despite this knowledge.

To obtain some idea about how much risk is attached to sun exposure and to sunburns, a meta-analysis was conducted in a pooled study of 15 case-control studies involving 5,700 melanoma cases and 7,216 controls. The research involved five states in the U.S. including California and Hawaii, four countries in Europe, three regions in Australia and one in Canada. It analyzed the impact of sunbathing activities, total sun recreational sun exposure, occupational sun exposure, and burns in two different age groups on melanomas on different parts of the body. As we shall see, the initial location of primary melanoma is associated with differential death rates reflecting the different pathways in which melanoma can appear. Adjusting the risk for age, sex, hair color and ability to tan and presence of freckles, the risk factor for melanoma is 2.0 on the trunk. The risk factor was lower for other parts of the body with sunbathing activities and it varied by latitude. Total sun exposure for recreational activities in contrast to sunbathing activities was associated with an elevated risk, again controlling for the same variables, of 1.6 for the trunk, 3.2 for the limbs and 3.1 for the head and neck. It is interesting to observe how more important is the measure of total recreational activities that involve exposure. In contrast, the occupational risks were much lower and only affected those in the low latitudes. For sunburns prior to age 15, the risk of a melanoma on the trunk was elevated to 1.5 in the low latitudes but less so for high latitudes and for other parts of the body. However, these studies did not measure whether the sunburn caused blisters or the number of sunburns.

The role of tanning beds has been strongly implicated in a detailed of Minnesota melanoma victims where it was possible to connect those diagnosed with melanoma age 25 to 59 during the years 2004-2007 from the cancer registry with a matched sample selected from the state list of driver's licenses.[11] Both the victims and those in the matched sample were interviewed by telephone. Melanomas were more common with

UVB enhanced and primary UVA emitting devices. Risked increased with years of tanning and the number of hours and of sessions. This provides convincing evidence that when buying sunscreen one needs to protect again both kinds of UV as well as the wisdom of avoiding tanning beds. At the same time, a survey of employees in tanning lounges across many states indicates that 87% require parental consent for minors and 14% require parental accompaniment.[12] State laws requiring parental consent do in fact increase the percentage of sun tanning lounges that are diligent in this regard. But again, given the reported increase in the use of tanning loungers, this public health approach to reducing melanoma does not appear to be very promising. Furthermore, parental consent only applies to those under age 18. Admittedly for reasons that are not completely understood the damage from UV exposure appears to be greater in the young as we have seen above. A study of the influence of both parents and peers on adolescent indoor tanning indicates that parents play a more important role than peer groups.[13] If adolescents perceive that they have their parent's permission to use tanning beds they do. Peer groups also encourage the use of tanning beds but are not as influential.

Table Two
Risk Factors

Risk Factor	**Risk Multiplier**
One atypical mole	**2x**
Red or blond hair, fair skin	**2-3x**
50 or more moles	**2-4x**
Previous other skin cancer	**3-5x**
10 or more atypical moles	**12-14x**

But UV does not cause all melanomas and therefore genetic factors must be taken into consideration. Dysplastic moles or atypical moles are common and many people have several of these. Having one atypical mole increases risk while 10 or mole creates an extremely high probability of developing melanoma. Another kind of skin cancer also increases risk and individuals with one melanoma are likely to have another one, which is why we find that individuals without cancer fail to visit their dermatologist. Interesting enough, a small-scale research project established that each melanoma was in fact an independent event, indicating that the tendency to have multiple melanomas is primarily a genetic predisposition.[14] About 10% of the melanoma patients have one family member with a history of melanoma. Two or more family members with this cancer almost guarantee that the related individual will also have this disease. The above article in the New York Times about attempts to treat melanoma in those patients with a specific genetic origin, mutations in the BRAF gene, indicates that the genetic patterns are still unclear.[15] It is estimated that the specific gene is implicated in about 60% of the tumors and while not permanently successful is the first demonstration of a successful treatment

for a genetic mutation in melanoma. Its benefits are not discussed in the section on the prolongation of life because this trial was funded entirely by the drug company and therefore falls outside the scope of this evaluation. Advances in treatments for melanoma are being made on an annual basis. Recent research has identified the genetic patterns that explain why red hair and freckles are associated with melanoma.[16]

The progression of the disease is as follows. Around a mole, although this is not always the case, damaged skin cells accumulate and change the shape, color, and color intensity of the mole, typically making it irregular. This is one of the diagnostic tests and the size of the mole is used to help in the staging of the disease. As the melanoma grows, it's growth shifts from a spreading to vertical direction when it begins to pierce the epidermis. What makes melanoma so dangerous, is that at this stage it can penetrate both the lymphatic and vascular systems, meaning that cancerous cells can travel in two separate fluid systems in the body. Most typically, it is the lymphatic system where the cancerous cells begin to disseminate, first to the lymph node next to the mole, called the sentinel node, and then after this to the regional nodes. Further metalizes than moves to more remote parts of the lymphatic system. In contrast, penetration of the vascular or blood system leads to even more distant metastasis such as the liver, the lungs or the brain because large quantities of blood are exchanged in these organs. If the original diseased mole is located on the neck or head, then the central nervous system can also be affected.

The thickness of the diseased mole, as we said above, is associated with prognosis and the staging of the disease (see Table Three). These categories do not precisely fit the terms stages I, II, III, and IV, which are used below.[17] Localized represents both stage I and II. Based on the very large study of the survival patterns of over 17,000 melanoma patients who had been followed for 15 years and reported in 2001, 52.1% were in stage 1, 32.6% in stage II, 8.6% in stage III and 6.6% in stage IV. These figures differ from the more recent data reported in Table Three but represent the best basis on which to compare the progress of various research articles since this early report represents the standard for computing improvements in longevity. Indeed, the small improvements reflect in some undetermined degree measure the beginning fruits of medical research during the past decade, although the differences are small. Regional or stage III declines from 8.6 to 8% and distant or stage IV declines from 6.6 to 4%.

Table Three
Stages and Survival Rate (SEER Data 1999-2006)

Stage	Proportion in Stage	Survival Rate
Localized	**84%**	**98%**
Regional	**8%**	**62%**
Distant	**4%**	**16%**
Unstaged	**4%**	**76%**

The stage system of 2001 used the following variables in addition to thickness:

1) Presence or absence of tumor ulceration for distinctions in stages II and III
2) Number of metastatic lymph nodes involved in stage III

3) Micro vs. macrosopic (the ability to feel the tumor) in stage III
4) Site of distant disease areas (only subcutaneous vs. elsewhere) in stage IV
5) Low Density Lipoprotein (LDH) levels (higher being associated with less survival) in stage IV.

This complex of attributes is simplified in a typology called T (thickness), which becomes local or stages I and II, N (number of nodes involved) which is regional or stage III, and M (metastasized to distant sites), stage IV. The addition of these other attributes create a more nuanced staging system with several different sub-categories in the classification of local, regional, and distant. For example, the presence of ulceration lowers the survival rate for stages II and III. In fact, ulceration is a more powerful risk factor than thickness.[18] As the number of nodes increases in stage III, the survival rate steadily declines. Given these sharp differences in survival rates for various stages, our analysis puts a considerable amount of emphasis on the extension of life relative to the specific stage of the patients involved in the treatment interventions that are reported in this assessment, especially as most of the interventions reviewed in this chapter where for stage III and IV melanoma patients who had not responded to any other kind of treatment.

What makes melanoma particularly difficult and different from many other cancers is that recurrence can occur many years after the original diagnosis. In other words, the rule of the National Cancer Institute of five years without remission as generally being cured from cancer does not apply to melanoma, one reason why the statistics are accumulated over 15 years with the survival rates for each of these categories continuing to decline each year even for stage I.[19] Also, there can be considerable time elapsed between some triggering event such as a blistering sunburn during adolescence and the occurrence of the cancer as we have seen in the case of painful sunburns.

In this discussion, we have not considered the additional complications of the recent research on different types of melanoma (there are now four), nor that there are multiple pathways to melanoma involving different body sites such as the distinctions between trunk and limbs noted above.[20] Current research is trying to relate these distinctions about type and primary site to the different causes such as solar damage and genetic mutations of various kinds and their interactions.[21]

Measuring Potential Benefits

The measurement of the melanoma program potential benefits over three years focuses, as we indicated in the introductory chapter, on two criteria: the reduction in health care costs and the prolongation of life in months and years. In both cases, distinctions must be made by stages. Rather than examine the marginal improvement in the quality of life years, our first objective is to estimate the reduction in the costs of health care minus the costs of the intervention (see Table Four). However, we will compute these findings primarily for prevention, screening and diagnosis techniques and protocols. The treatment studies of experimental drugs are costly and customized efforts, typically occurring in phase I or II trials. In particular, if they are not involved in a clinical trial--and only of the treatment and post-treatment studies that were finished in the years of our research were phase III clinical trials--then it seems unrealistic to compute cost-effectiveness studies. The three treatment studies are in a strict sense *not* cost effective because the interventions themselves are costly experimental treatments,

Interleukin-2 (IL-2) costs $75,955.18, and biochemical therapy is even higher, some $1,535 to 1,800 a day.[22] Therefore, our focus shifts to the prolongation of life whether in years or in months as in the case of the interventions for patients in stage IV who have not responded to any therapy.

The general procedures for estimating how much health care costs can *potentially* be reduced is to estimate the reduction in patients with type II, III, and IV melanomas in the original staging given certain interventions or techniques. We start with the estimated number of new patients, which in 2009 was 68,720. Using the above percentages defined from the largest as yet conducted evaluation of melanoma patients, then 32.6% or 22.403 are expected to be in stage II, 8.7% or 5,979 are in stage III and 6.6% or 4,536 are in stage IV.

The reduction in the cost of their treatments is computed by multiplying the number of individuals who do not advance to a specific stage and the treatment costs of that stage minus the costs of the prior stage. For stage IIB, not including the costs of terminal care, the health care cost for treatment including patient time costs is $54,795, which rises to $160,351 per patient for stage IIIB and $184,806 for stage IV.[22] The major component of costs in each stage is the workup and treatment of metastatic disease followed by the surveillance costs. These estimates have been slightly adjusted by us. Terminal care costs have not been included in stages 11 and III but are included in stage IV. In contrast, the original source left out the costs of surveillance in stage IV, which we have added in and estimated at $25,000 or one half of those in stage IIIB and C. To estimate these costs, we subtracted the costs of therapy in stage II, $55,000 from those in stage III and stage IV. The net costs saved then become $105,000 for each individual who does not advance to stage III and 130,000 for each individual who does not advance to stage IV. Again, the large disparity in costs attached to particular stages of melanoma requires that we consider the impacts of various interventions on the costs per stage.

Following this logic, then:

If 1,000 patients in stage II do not advance to stage III, the saving is 1,000 x $105,000 or 105 million.

If 1,000 patients in stage III do not advance to stage IV, the saving is 1,000 x $130,000 or 130 million.

These savings represent of course only those savings for a single year. Obviously, one continues to use a new technique or treatment in succeeding years. As we indicated in the introduction, we have used five years as the likely period of time before there is some significant change in the treatment or technique. Furthermore, the cost figures for the treatment of melanoma are based on a five year time period. Therefore, in computing the *potential* savings, one would multiply each of these numbers by 5. Given more than 5,000 patients in stage III and 4,500 in stage IV, being able to reduce treatment costs in these stages represents substantial *potential* savings if applied throughout the country.

Of course, *potential* savings are not *actual* savings. In this chapter, we report only the potential savings and in chapter seven we return to the problem of how to estimate the actual savings. But while the numbers generated by only a 1,000 patients in a specific stage after five years appear to be quite large, between 525 to 650 million, they also illustrate what can be done. *Reducing health care costs in the United States means attempting to diffuse these techniques and treatments to reduce the number of melanoma patients in stage II and especially in stages III and IV*. Since there has been a

considerable amount of dialogue about how to reduce health care costs, it is worth focusing on *potential* benefits and then developing public health strategies for realizing a higher percentage of these benefits via better diffusion techniques, an issue that we return to in the last and concluding chapter.

Another reason to make an analytical distinction between stages is the considerable difference in the mortality rates between stages, which were reported above (see Table Three). The same logic would be used in estimating how a specific intervention improves the chances for a long life. If the normal survival rate for stage II on average is 67%, then any increase in survival rates beyond this, would represent prolongation of life. For example for 1,000 patients in stage II, if the survival rate increases from 67% to 77%, then 10% or 100 patients have been saved from death, again recognizing that melanoma can reappear many years later. Over a five-year period, 500 patient life-years would have been saved. Preventing 1000 patients in stage II from advancing to stage III, means approximately a 20% improvement in mortality rate (67%-47% for stage III on average) or 200 patient life-years in one year.

In estimating the gain in months, complications develop when the treatment focuses on those in stage IV similar to the study reported in the New York Times cited above. Not only is the mortality rate extremely high but it varies by the location of the original melanoma as we will indicate in some of the research studies reported below. A good example of both current research and how to estimate the gain in life-months is a research project at the National Cancer Institute under the direction of Dr. Steven Rosenberg that is not part of our study and for two reasons, (1) it is intramural research and not extramural and (2) the paper was published in 2005 before our specific time frame.

The research program explores the impact of vaccines made from one's own tumor. Cancer tumors are removed by surgery and then vaccines are grown in test tubes. Called the adoptive cell transfer (ACT) immunotherapy, it is based on *ex vivo* selection of tumor-reactive lymphocytes and their activation and expansion before reinfusion in the patients and administered along with the vaccine a high dose Interleukin II-2 or cytokines to support the transferred cells because it increases the response of the immune system. Previous studies had indicated that the addition of Interleukin II-2 did increase the response rate of the adoptive cell transfer.[23] Thirty-five patients who had stage IV but had not responded to high dose Interleukin II-2 and whose disease was progressing were enrolled. At the time, their expected life expectancy had to be at least three months. Since survival even in this stage is dependent upon where the original melanoma existed that was being treated (the M in the typology cited above), we have divided the responses into three categories: skin and lymph nodes including colon and rectum, lungs, and liver or brain. Of the 35 patients, 51% achieved a clinical response with 9% having an on-going remission and 43% having at least a 50% reduction in the size of their tumors. When new therapies are developed and especially for cancer, one of the most important indicators of technical progress is clinical response, that is did the treatment actual produce an effect. The next criterion is the extent in the reduction of the tumors.

Our conservative estimates of the prolongation of life are as follows:

Location of Primary Site Melanoma and Responses to ACT

Outcome	Skin, nodes	Lungs	Brain, Liver
Expected survival	13 months	8 months	4 months
Present duration	14 months	13 months	9.6 months
Gain in life	1 month	5 months	5.6 months

We do not know the distribution in stage IV between these three forms of metastasis and therefore have simply assumed that each is equal to one third of the case-load.

Since this study, which was published in 2005, Rosenberg has conducted another major test of ACT therapy.[24] Out of 93 patients, 19 or 21% have remained cancer free for three to eight years. And another 32 or 34% had a response to the treatment as indicated by a shrinking of their cancer nodes, one objective measure of quality. As can be seen, this is a considerable improvement over the past decade. The method is to date, quite expensive, $100,000 per patient. Ignoring costs, in part because methods are being developed to make this treatment less expensive, the application of these figures to the expected 4,536 new patients in stage four, produces the following estimates of the prolongation of life:

Responses to ACT

Cancer free, 3 to 8 years .21 x 4,536 = 952 lives x 5 years = 4,762 life years

Again, it should be remembered that the New York Times article documented how much an improvement of six months meant to the family. The success of the ACT therapy approach, which is different from the technique used for patients that had the BRAF gene mutation, is now being tested with other cancers.[24]

In summary we have two sets of procedures for estimating benefits from medical research on melanoma. The first examines the potential benefits of the intervention on the saving of health care costs and the second examines the potential benefits on the prolongation of life.

Reduction in Health Care Costs

In the three-year period of 2006-2009, the treatment studies similar to the one just reported above focused on extending the life of terminally ill melanoma patients. Therefore, their focus was not on reductions in treatment costs as such. These studies will be discussed in the next section.

Prevention

A major risk factor for melanoma is repeated exposure to ultraviolet light. One NCI study, from which several papers were published, focused on this risk factor involved in the use of sun-tanning lounges and in particular relative to young people age 17 and the advantages of requiring parental permission to use a sun-tanning lounge. The World Health Organization recommends banning these sun-tanning lounges for those under the age of 18. We computed the potential savings by eliminating those patients in stages 11, III, and IV age 17 and it could potentially save 8 million a year. But the costs of inspection to ensure the law was obeyed would be enormous. Therefore, there are no real savings to society. Nor did we consider the idea of having more states require parental permission is a very effective technique.

Screening and Diagnosis

The first research project within this group tests in a phase III clinical trial the advantages of a new staining technique over waiting until a diseased lymph node can be

felt or the micro vs. macroscopic approach to diagnosis.[25] As indicated above in our discussion of the progression of the disease, a major diagnostic sign is the thickness of the melanoma but this provides a relatively imprecise diagnosis. Generally surgery involving a wide resection handles most patients with intermediate thickness of the melanoma but in about 15% of the cases as we have noted, the melanoma metastasizes despite this surgical intervention. In particular, some of the patients in stage II could really be in stage III. The objective of this clinical trial was to determine if a staining technique would reduce the number of cases that eventually metastasizes by learning more quickly that the melanoma had started to impact on the sentinel node, that is the lymph node closest to the melanoma. 1327 patients with melanoma's thicknesses between 1.2 and 3.5 mm were enrolled in a eight year evaluation, of which 346 lived in Europe, 221 in North America, and 720 in Australia indicating how much cooperation between various research centers is necessary to obtain large enough numbers for clinical trials. A vital blue dye was developed and used to detect drainage from the melanoma to the sentinel node in the treatment grop, which contained 769 patients. In contrast, the control group in this clinical trial consisted of 500, who were observed and when the sentinel node could be felt, it was excised. The differences between the sum of these two numbers and the original total of 1327, represents withdrawals for various reasons.

In the treatment group (hereafter called the biopsy group), if the stain detected that the melanoma had metastasized to the sentinel, it was surgically removed. In the observation or control group of this clinical trial, biopsies were performed only after the tumor could be felt in the sentinel node. The hypothesis to be tested in the clinical trial is that the staining technique indicates more quickly whether the melanoma has metastasized to the sentinel lymph node and therefore it has to be removed.

The two groups were matched on a number of characteristics including age, sex, location of the original melanoma, Breslow thickness, etc. The overall mortality rate in the two samples was approximately the same, with the following variables explaining differential mortality rates: diseased sentinel node, Breslow thickness, and ulceration, consistent with the recent advances in the criteria of staging. In both groups, approximately 15% were found to have metastasized melanomas, again suggesting that the two groups were essentially the same and corresponding to the figures reported in Table Three. The specific research issue, then, in the clinical trial is: Does earlier detection and removal of a diseased sentinel node improve chances of survival and also reduce the recurrence of melanoma with those that have a melanoma that has spread to the sentinel node. And the answer to both questions is yes.

The five-year survival rate was significantly higher in the biopsy group, that is those who had their sentinel node removed sooner, in comparison to those individuals in the observation group that also had to have their sentinel node removed eventually on the basis of its being detected by touch, that is it becomes macroscopic in terms of the attributes listed above.

Rather than use some subject criterion of quality life year, which then has attached to it some economic value whether $50,000 or 100,000, we prefer to emphasize objective indicators of quality. This evaluation suggestions three: (1) the length of time disease free; (2) the reduction in the number of recurrences that occur within a specific time period; and (3) the side effects of the specific technique or treatment. In this instance, the longer the length of the time disease free, and the fewer the number of

recurrences, the greater the quality of life. The recurrence rate of cancer was significantly lower in the biopsy group. Perhaps the most interesting difference is that in the observation group, on average the recurrence occurred sooner, after 1.33 years. Not only did the recurrence rates differ but so did the number of lymph nodes detected. In the biopsy group, there were on average only 1.4 nodes but 3.3 nodes in the observation group. In other words, allowing the melanoma cancer to go undetected means that it advances and becomes harder to treat. Finally, the third indicator of quality in the treatment group would be the number of false negatives, which was 3.4%, considered normal for this procedure. In considering these findings, it is worth repeating that melanoma can travel not only by the lymphatic system but the vascular or blood system and can continue to reappear after many years.

Since this technique was used only with individuals who had intermediate thicknesses that are from 1.2 to 3.5, we assume that the patients are only in stages II and III. The percentages of the population with melanoma diagnosed in stages IIA, IIB, and IIC are 46%, 36, and 18% respectively. Rather than argue that this staining technique would prevent all those in stage II from advancing to stage III, it is more realistic to suggest that only those in which recurrence occurs would profit from this technique. The most conservative measure of recurrence is 1 – percent who survive. By this measure the respective recurrence rates for these three sub-stages are 33%, 43%, and 60%. Then the number of melanoma patients that would benefit from this procedure is as follows, of the 22,403 patients classified as in stage II on the basis of the 15-year evaluation:

Stage II Sub-categories and Relapse Rates

A .46 x 22,403 = 10,305 patients x .33 = 3,401
B .36 x 22,403 = 8,065 patients x .43 = 3,468
C .18 x 22,403 = 4.033 patients x .60 = 2,420
Total Patients = 9,289

Using the same logic for stage III, produces the following results:

Stage III Sub-categories and Relapse Rates

A .25 x 5,979 = 1,495 patients x .37 = 553
B .36 x 5,979 = 2,152 patients x .54 = 1,162
C .39 x 5,979 = 2,333 patients x .76 = 1,772
Total = 3,488

It might be noted that whereas in stage II, the largest share of the patients are in IIA, in stage III the largest category is in C where the survival rates are quite low. Having an impact on preventing patients in stage IIIC from progressing to stage IV therefore makes a major contribution to improving the survival chances of these patients. Given the number of patients with estimated relapse rates that would be helped by this new staining technique, then the savings to the health care system become enormous.

Reduction in Costs

Stage III 9,289 cases x 105,000 treatment cost = $975 million
Stage IV 3,448 cases x 130,000 treatment cost = $448 million
Total of potential savings of 1.4 billion in one year and 7 billion in five years.

While this number appears to be quite large, it should be remembered that it is *potential* savings, that is savings that only can be realized if in fact this technique diffuses to every dermatologist. Nor is this the net reduction in costs because the technique itself costs about $7,500 for the removal of each sentinel node, which does not include training costs of dermatologists in how to use the staining technique. The annual cost of this staining technique is 212 million for the new 28,382 patients each year diagnosed in stages II and III, which provides a net benefit of 1.2 billion for one year and 5.9 billion over five years, not counting the cost of training. The issue of estimating actual benefits is discussed in chapter seven.

This estimate of potential benefits is at the same time conservative for potential savings because it does not including the following additional savings. For example, this sum does not include the amount of money saved by the reduction in the number of nodes in those individuals who had their sentinel nodes removed immediately, which is probably worth about another $140 million in saved operations depending upon where the nodes are located. This indicator is also much more conservative than the standard cost benefit studies since we have not included the value of a quality life year. In this specific study, we would measure the quality of life by the reduction in the number of nodes that occurred and the amount of time disease free, both of which are greater when the staining technique is employed.

The conclusion of the evaluation is that the clinical trail supports the both the efficacy and efficiency of the use of the staining technique because it suggests that delay in the removal of a diseased sentinel node results in the melanoma becoming more entrenched and aggressive in spreading to other lymph nodes.

The previous study was designed to catch melanomas before they became too large to prevent successful treatment. In contrast, this second research project is designed to prevent melanomas from growing at all, that is to be detected almost immediately after they have become irregular and different in color.[27] This study was also a clinical trial but one much more restricted geographically to Rhode Island and Southeastern Massachusetts. Individuals were recruited from 11 primary practices in this geographic area, 668 into the treatment group, which is designated as the self-examination kit group, and the same number into the control group, which is called the diet group. Rather than just use a matched cohort, the diet group was given the same amount of contact to control for this potential effect. Both received training relative to their particular situation, self-examination for melanoma and diet. Individuals in the treatment group who had previous engaged in self-examination either alone or with a partner were eliminated, reducing the number in the trial to 567. The two groups were well matched on prior-self examination at about 17%, which corresponds to the average noted above.

These individuals then were given a self-examination kit that contained the following three elements:[26]

1) Educational materials (video, brochure of the American Cancer Society, and sample photos of skin cancers);
2) Aids in self-examination (hand mirror, body diagram);
3) Environmental cues (refrigerator magnet, shower card).

At the end of two months, six months, and twelve months, the individuals in the treatment group were telephoned and asked if they had been examining their bodies for skin cancers. At the end of 12 months, the differences between the control group of diet

and the self-examination group was 20%, with the former checking their bodies about 35% of the time and the latter 55%.

In a clinical trial, one would normally subtract the control group's percentage from those in the treatment group on the key dimension. In this instance, because a surprising 35% in the control group visited their dermatologist, suggesting a kind of Hawthorne Effect, that is it is much higher than one might expect, which would limit the advantage to 20%. But because the repeated telephone calls caused heighten awareness, it seems more appropriate to use the initial pre-test percentage of 17%, especially as it was true for both groups and also these individuals were eliminated from the trial. This would mean that the advantage of the self-examination kit was really 38%.

If 38% of the new patients, 68,720, use the self-examination kit for one year and go to their dermatologist when they perceive something suspicious, then 26,098 cases of melanoma would be prevented in the first year. However, if the real figure is only 20% of the 68,720, then there is a dramatic reduction in the benefits of this procedure. The distribution of cases is as follows:

If the difference is 38%:	*If the difference is 20%*
➢ 13,570 in stage one	7,147 in stage one
➢ 8,508 in stage two	4,481 in stage two
➢ 2,271 in stage three	1,196 in stage three
➢ 1,722 in stage four	907 in stage four

Reduction in Costs under Two Different Assumptions

No. of cases	x	Cost of therapy[a]	=	Reduction in health costs	No. of Cases	x	Cost of therapy	=	Reduction in health costs
8,508		$ 54,795	=	$468 million	4,481		$ 54,795		$246 million
2,271		$160,351	=	$363 million	1,196		$160,351		$191 million
1,722		$184,806	=	$318 million	907		$184,806		$167 million
Total potential savings =				***$1.1 billion in first year***					***$604 million in first year***

Under both assumptions, the cost of distributing these kits to the entire population would be large and probably prohibitively expensive. But to indicate why, we provide data on how we arrived at this conclusion. We estimated the target population for the distribution as those individuals between the ages of 20 and 50. Even if we assume that there are about 2.6 persons living in a household, it will take about 51 million kits to handle the estimated 136 million people in this age bracket, which is probably an underestimate because an increasing number of people live alone. The age bracket of 20 to 50 was selected cut-off is age 49, since for age 50 or over, it is recommended that individuals be screened by a dermatologist periodically. Our estimate of $30 per kit is probably an underestimate because the intervention includes telephone calls and some teaching. Given $30 per kit, then assuming one could distribute this to the entire targeted population, then the cost would be a staggering 1.5 billion.

Furthermore, since we are distributing these kits only to those who are under age 50, then the reduction in health care costs has to be reduced by some number given the age distribution of the population that presents itself. Although 60% of the new patients are age 55 and over but because melanoma develops so slowly, we divide by only one-half the benefits of each of these techniques discussed below. This then gives us the

following under each of the restrictive assumptions as to how many would use the kits in the first year:

Total potential savings = $ 650 billion in first year $302 million in first year

The clinical trail lasted one year. Unlike the previous research project, we have a problem in how to estimate the decline in the use of the self-examination kits over the course of five years since we can easily assume fatigue with use. Therefore, we will hypothesize a steep extinction curve of a reduction by 50 percent each year since people we find it tedious. This produces savings of 325 million in the second year, 162 in the third, 81 in the fourth and 40 in the fifth for a total of 1.258 billion. At the end of five years, this intervention would not pay for itself. However, the assumption of only 38% using the kits is perhaps too conservative. If we raise the assumption to 50%, then this technique becomes cost effective at the end of five years.

If the difference is 50%:

- 17,872 in stage one
- 11,201 in stage two
- 2,989 in stage three
- 2,302 in stage four

Reduction in Costs under Assumption of 50%

No. of cases	x	Cost of therapy[a]	=	Reduction in health costs
8,508		$ 54,795	=	$616 million
2,271		$160,351	=	$638 million
1,722		$184,806	=	$426 million

Total potential savings = $1.6 billion in first year divided two = .8 billion

We include these different assumptions to indicate how varied the potential benefits can be depending upon the starting assumptions. Before concluding our discussion of estimating the benefits of the self-examination kit when it is distributed on a mass basis it is useful to know the general improvement in the number of melanomas found. One way of computing this benefit is to indicate how many more melanomas were found at the end of one year. The rate was 2.2/1000 in the trial. The normal rate is 1.5/1000, so it did increase the number of detected melanomas by .7/1000 or close to a 50% increase.

Instead of distributing the kits to everyone, it seems wiser to consider what might be some high-risk patient populations. In the next section, we report a traditional cost-benefit study based on a simulation of year or biannual visits to a dermatologist starting at age 50. The estimate of the cost of a quality benefit year gained is $50,000. As can be seen below, the reduction of costs is dramatic when it is targeted to certain individuals who are high risk (see Table Four). Another source for identifying risk factors and thus more restricted target populations are various behaviors identified in the meta-analysis reported above. Selecting populations that have been had high sun exposure or painful burns during adolescence is another illustration of how we try to combine the research findings from different studies to obtain a better sense of the *programmatic advantages* of research on melanoma. We do not consider a third risk factor, working outdoors, because it appeared to be less involved in the development of melanomas.

The *first risk factor* is high exposure to sun for recreational purposes. No reports were made about the appropriate use of sunscreen. Since the study involves both controls and those who have been diagnosed with melanoma, we assume that the proportion that had high exposure, which is 21% of both the controls and those with melanoma, is the proportion in the general population that have had high exposure for recreational purposes. Certainly, the studies of recreation in the United States, again which were reported above, indicate that there has been little change in behavior. The total number of individuals in both categories in the two studies is 12,600, which is fairly substantial and it is spread across three continents and different latitudes. Of these 21%, about 39% had a melanoma on some part of the body. The differences between latitudes were relatively minor. Given the way in which the control groups were assembled, this might be an overestimate of the proportion of the general population with high exposure. Below we discuss several other assumptions. Relative to new patients, the self-examination could *potentially* reduce the number of new melanoma cases each year by about 5,628 individuals, that is .21 x .39 x 68,720 new cases each year.

Targeting the self-examination kit to this population that is at much higher risk then the general population reduces the costs of the intervention considerable. The number needed was calculated by assuming that 21% of 51 million kits or 10.7 million for the households that have been identified to have one individual who has had high sun exposure. Again, attempting to treat the household appears to be sensible since families tend to spend vacations and leisure time together. This distribution cost would be about 320 million.

The issue is what percentage of these individuals would use the kits in the first year? Since the individuals would be told that they had a 40% chance of getting melanoma cancer, we will assume that in the first year all will use the kits. Therefore,

Reduction in health care costs:

100% of 5,628 cases would be distributed as follows:

Distribution By stage	No. of cases	x	Cost of therapy	=	Reduction in health cost
.326 in stage II	1, 835		$ 54,795	=	$101million
.087 in stage III	490		$160.351	=	$ 98 million.
.066 in stage IV	371		$184,806	=	$ 69million

Total potential savings = $248 million in the first year divided by two = 124 million

Again, using the same quite restrictive extinction curve of 50% per year, then at the end of the five years, the cost of the intervention, 320 million, would not be balanced by the savings in the reduction of health care costs. However, if we assume that the reduction in usage is only one-third per year, then the cost of the intervention would just break-even in the fifth year, with a total savings of 323 million. However, if we assume that only 55% will use the kits, the average in the clinical study reported above after subtracting the 17% who regularly saw examined their bodies, then this procedure is not cost effective and would save only 135 million in the first year. Presumably this population given the facts about the relatively high likelihood of their getting melanoma, 39%, would be highly motivated to do the self-examination in the shower and initial usage would be greater than 55% and at the same time it is unlikely that the extinction curve would be one-half per annum. The cost-benefit ratio for reduction in health costs also changes if

instead of assuming that 21% in the population have high exposure, some smaller number has had such an exposure. Then this obviously reduces the costs of distributing these kits while the reductions in medical costs remain the approximately same because the proportion that develop melanomas is based on a large population base, although admittedly one that is scattered across continents and regions. The benefits also improve if one targets a smaller age bracket, such as 20 through 40. This becomes particularly relevant for the discussion of the second risk factor.

Table Four
Potential Reduction in Health Care Costs

	Reduction in Health Care Costs	**Costs of Intervention**	**Net Benefit Reduction**
Prevention Sun Tanning			
First year			none
Screening/Diagnosis			
Staining[25]			
First year	1.4 billion	212 million	1.18 billion
Five years	7 billion	1.06 billion	5.9 billion
Self-examination Kit[27]			
First year	650 million	1.510 billion	- 960 million
Five years	1.3 billion		- 210 million
First Application of Self-examination Kit to Individuals with High Sun Exposure			
First year	124 million	320 million	- 196 million
Five years	323 million		3 million
Second Application of Self-Examination Kit to Individuals with Painful Sunburns Prior to Age 15			
First year	348 million	750 million	- 402 million
Five years	904 million		154 million

The *second risk factor* is recall of being burned by the sun before age 15, especially the creation of blisters. This risk factor is quite different from the previous one because in this instance, the issue of sunscreen would not appear to apply. People are more likely to recall painful burns and while admittedly the perception of what is painful varies, it seems reasonable to assume that people remember getting blisters from sunburn, this would be an important target group for self-examination on a regular basis. Recall of being sunburned before age 15 is highly associated with sunburn after age 20, indicating a behavioral pattern.

Using the same logic as above, of 11,688 cases in which there is data, 5,661 or 48% recall having at least one episode of sunburn and of these 48% had a melanoma at some time point. We again are assuming that melanoma has multiple causes and the sunburn is only one of them. Presumably 48% is probably an overestimation. Applying these figures to the number of new patients each year means a potential reduction of

15,833 individuals with melanoma. Again, assuming that the individuals are highly motivated and that 100% would use the kits,

Reduction in health care costs:

100% of 15,833 cases are distributed as follows:

Distribution by stage	No. of cases	x	Cost of therapy[a]	=	Reduction in health costs
.326 in stage II	5,162		$ 54,795	=	$284 million
.087 in stage III	1,377		$160.351	=	$220 million
.066 in stage IV	1,045		$184,806	=	$193 million

Total Potential Savings = $697 million in the first year divided by two = 348 million

In the case, we assume 48% of 135 million people ages 18 to 49 or 65 million would need kits. If these kits are distributed to households, which have 2.6 members, then number needed is 25 million at a cost of 750 million. If we can accept that the idea that 100% would use the kits the first year, and the reduction in usage is only one third per year, then this screening method almost pays for itself at the end the third year. Obviously, as we reduce the percentage, then it would take longer for the distribution of kits to this target population to be cost-effective. But even the more drastic 55% rate of utilization would be efficient at the end of five years even with a large extinction rate each year. A higher usage of the kits, e.g. example moving from 55% to 80% or a less drastic reduction in its use each year, such as 40% rather than 50% makes this intervention quite cost effective.

The logic of this procedure can be fine-tuned to increase its potency. For example enrolling the individuals who are using the kits into Facebook, and reminding them each month to check themselves would considerably increasing the usage rate and would not cost very much. Indeed, it might create a new kind of health social network around the kit, which would also increase its effectiveness in finding melanomas. Another refinement would be rather than provide kits to everyone who has high exposure to sun, reduce it to those individuals who also have sunburns during adolescence. In the latter case, one could restrict distribution of the kits to those individuals who had five or more painful/blistering sunburns during adolescence. Still another issue is the interaction between genetics and sun exposure, where a great deal of current research is concentrated. Another consideration is the genetics of the individuals. Those individuals with the BRAF gene mutation would benefit the most from the self-examination given high sun exposure or multiple sunburns.

Prolongation of Lives

The studies reported above can also be evaluated for their impact on the number of life years saved. Again, it is important to recognize that this reflects an estimation of potential life years and not what would actually occur depending upon the specific kinds of public health practices that are instituted, a topic for chapter seven.

Prevention

As we have indicated in our discussion of cost savings, the attempt to outlaw sun-tanning lounges for those under age 18 is futile. Not only would this law never pass but also the costs of enforcement make it anything but cost effective.

Screening and Diagnosis

As indicated above, the staining technique was a clinical trial. Estimating saved lives requires attempting to interpreted graphs of survival, which is the usual way in which this information is presented in clinical trials. The difference in mortality rates between those with metastasized sentinel nodes that were detected with the staining technique, the treatment group, and those that were located by observation somewhat later is 26.2% vs. 48.7%. But this does not represent a true picture of the number of life years saved per 100 patients especially as we have already indicated melanoma can reappear much latter. Reading the survival graphs admittedly somewhat roughly, for one hundred patients, the number of life years saved between the bioscopy group and the observation groups *in those patients with metastasis in the sentinel nodes* was 57 life years in a five-year time period per 100 patients. Given the number of individuals who might be detected before reaching stages II, III and IV with this technique, there is a potential of 30,945 live years over a five-year period if all new patients received this technique.

But a more effective way of estimating the lives saved from this new technique is to use the same figures that we did previously to estimate the cost savings from preventing someone from moving from stage I to stage II, etc. This was based on the relapse rate that was calculated for each of the patients who do not survive classified by the stage and sub-category that they are initially placed in, as follows:

Stage II Sub-categories and Relapse Rates

A .46 x 22,403 = 10,305 patients x .33 = 3,401
B .36 x 22,403 = 8,065 patients x .43 = 3,468
C .18 x 22,403 = 4.033 patients x .60 = 2,420
Potential Patient Lives in First Year = 9,289

Using the same logic for stage III, produces the following results:

Stage III Sub-categories and Relapse Rates

A .25 x 5,979 = 1,495 patients x .37 = 553
B .36 x 5,979 = 2,152 patients x .54 = 1,162
C .39 x 5,979 = 2,333 patients x .76 = 1,772
Potential Patient Lives in First Year = 3,488
Total Potential Patient Lives in First Year =12,777

A total of 12,777 lives would be saved in the first year and of course after 5 years, this would represent 63,885 lives (12,777 x 5) a substantial benefit to society without having to estimate their annual wages. The number of live-years would be even greater because the first year would have five additional years, the second year four additional years, etc. resulting in a total potential number of life years saved of 191,655. This is a very conservative measure of potential, again recognizing that for this potential to be realized, it requires diffusion throughout the health care system.

If the self-examination kit is distributed on a mass basis to the entire population between the ages of 20 and 50, it would be better to use the more conservative rate of 38%, that is the difference between the 55% that actually used it and the 17% that regularly have their bodies checked for melanoma. If 38% of the new patients, 68,720, use the self-examination kit for one year and go to their dermatologist when they perceive

something suspicious, then 26,098 cases of melanoma would be detected in the first year with the following distribution:

- 13,570 in stage one
- 8,508 in stage two
- 2,271 in stage three
- 1,722 in stage four

Stage II Sub-categories and Relapse Rates (mortality)

A .46 x 8,508 = 3,914 patients x .33 = 1,292
B .36 x 8,508 = 3,063 patients x .43 = 1,317
C .18 x 8,508 = 1,531 patients x .60 = 919
Potential Patient Lives in First Year = **3,528**

Using the same logic for stage III, produces the following results:

Stage III Sub-categories and Relapse Rates (mortality)

A .25 x 5,979 = 1,495 patients x .37 = 553
B .36 x 5,979 = 2,152 patients x .54 = 1,162
C .39 x 5,979 = 2,333 patients x .76 = 1,772
Potential Patient Lives in First Year = **3,488**

Stage IV without sub-categories and Relapse Rate (mortality)

1,722 patients x .84 = 1.446

Total Potential Patient Lives in First Year = 8,462 divided by two = 4,113

Again, the number of life-years at the end of five years would have to be estimated on the basis of some extinction rate. A sharp decline of 50% per annum would produce 34,112 life years saved via a mass distribution of self-examination kits. This calculation is done as follows:

Number of patients	**x**	**Years**	**=**	**Life Years**
8,462		5		42,310
4,231		4		16,924
2,115		3		6,345
1,058		2		2,116
529		1		529

Total Potential Patient Life Years = 68,224 divided by two = 34,112

Besides 34,112 life years, 8,118 lives are saved even with a drop in its usage by one-half each year. But as we have seen the cost of this mass distribution is 1.5 billion and that is probably an underestimate.

In the previous section, we estimated the amount of money saved with a mass distribution of self-examination kits. Another way of thinking about cost-benefits is to estimate the gains in lives saved by the cost of the distribution of these kit. This means an expenditure of about $43,973 per life-year saved. Obviously, if more than 38% utilize the kits, then the cost per life-year starts declining rapidly. A 76% utilization rate would cut the cost in one-half to approximately $ 22,000. A reduction in utilization of less than 50% per year, also reduces the cost per life year accordingly.

But still a third way of thinking about cost-benefits of this mass distribution is to estimate the cost of each life year after deducting the amount of money saved, that is the computation of a *net* cost to obtain a more reliable estimate of the benefit. As indicated in Table Four, the net cost after subtracting the amount of money saved in health care costs is a negative 210 million. Under these circumstances, the net cost is only $6,156 per life year. This procedure indicates the advantages of thinking about cost-benefit analysis in different way. This would suggest quite a definite benefit for the health care system of even a mass distribution of self-examination kits.

At the same time, the cost of 1.5 billion is a large cost and therefore we want to explore the relative benefits of targeting the distribution of these kits to individuals who are much more likely to develop melanomas. Effectiveness in saving lives is more likely to occur when these kits are given to individuals who have high risk and therefore are more strongly motivated to use them, assuming that their risk is carefully explained to them. The *first risk factor* is high exposure to sun for recreational purposes. Our estimates of the number of lives saved, starts with an assumption that the percent of high exposure in the study (both control and treatment groups) is the same as in the general population, i.e. 21%. Of these 39% developed melanoma or the potential reduction in case load is 5,628 cases, that is 68,270 x .21 x .39. These 5,628 would be distributed as follows:

- 1,835 in stage two
- 490 in stage three
- 371 in stage four

As we did when estimating the cost savings, we assume that 100% utilization will occur in a targeted population that has been told it is highly likely to develop melanoma.

Stage II Sub-categories and Relapse Rates (mortality)

A .46 x 1,835 = 844 patients x .33 = 279
B .36 x 1,835 = 661 patients x .43 = 284
C .18 x 1,835 = 330 patients x .60 = 198
Potential Patient Lives in First Year = 761

Using the same logic for stage III, produces the following results:

Stage III Sub-categories and Relapse Rates (morality)

A .25 x 490 = 123 patients x .37 = 45
B .36 x 490 = 176 patients x .54 = 95
C .39 x 490 = 191 patients x .76 = 145
Potential Patient Lives in First Year = 285

Stage IV without sub-categories and Relapse Rate (moratlity)

371 patients x .84 = 312

Total Potential Patient Lives in First Year = 1,358 divided by two = 679

Since the kits are only distributed to the population age 49 or younger, we need to divide the number of lives saved by two to obtain a true estimate.

Rather than assume a 50% reduction in self-examination, here we will assume that only one-third stop using the kit each year:

Number of patients	**x Years**	**=**	**Life Years**
1,358	5		6,790
905	4		3,620
604	3		1,812
403	2		806
268	1		268
Total Potential Patient Life-Years			***= 13,298 divided by two = 6,649***

In this instance, 1,769 lives are saved as well as 6,649 life years.

Above we computed the amount of money saved in health care costs with the distribution of these kits under various assumptions. Since we know the cost of the distribution, assuming that our estimate of $30 per kit is correct, we can compute the cost of each life-year saved by dividing 320 million by 6,649, which is $48,127 per life year. But given that under certain assumptions the cost of the distribution pays for itself at the end of five years, the cost of each life year saved is actually zero, *that is free*. From the perspective of *net* cost-benefit analysis then this intervention is highly desirable.

Obviously, if one reduces the percentage that use the kits from 100% to another figure, the saving in patient lives accordingly diminishes. Above, in the discussion of the advantages of this technique for reducing costs in treating melanoma, we mentioned a number of refinements. One additional consideration is how often should individuals check their body for melanoma. If this is reduced to once a month, which seems probably, without adverse effects, compliance via systems such as Facebook can probably be improved beyond 67%.

The *second risk factor* is recall of being burned by the sun before age 15. Again, the use of sunscreen would not appear to apply. People are more likely to recall painful burns and while admittedly the perception of what is painful varies, this would be an important target group for self-examination on a regular basis. As we have already observed, individuals with sunburn prior to age 15, appear to keep getting sunburns. Using the same reasoning as we did above, there are 15,833 new cases that one can assume are likely to have had a significant sunburn prior to age 15. The added survival benefits are distributed as follows:

- 5,162 in stage two
- 1,377 in stage three
- 1,045 in stage four

As we did above, we assume that 100% utilization will occur.

Stage II Sub-categories and Relapse Rates (morality)

A	.46 x	5,162 =	2,374 patients	x	.33	=	784
B	.36 x	5,162 =	1.858 patients	x	.43	=	799
C	.18 x	5,162 =	929 patients	x	.60	=	557

Potential Patient Lives in First Year = 2,140

Using the same logic for stage III, produces the following results:

Stage III Sub-categories and Relapse Rates (mortality)

A	.25 x	1,377 =	344 patients	x	.37	=	127
B	.36 x	1,377 =	496 patients	x	.54	=	268
C	.39 x	1,377 =	537 patients	x	.76	=	408

Potential Patient Lives in First Year = 803

Stage IV without sub-categories and Relapse Rate (morality)

1,045 patients x .84 = 878

Total Potential Patient Lives in First Year = 3,821

Again, let us assume that the drop-off rate is only one-third.

Number of patients	**x**	**Years**	**=**	**Life Years**
3,821		5		19,105
2,547		4		10,189
1,698		3		5,094
1,130		2		2,260
753		1		753

Total Potential Patient Live Years = 37, 401 divided by two = 18,700

At the end of five years, almost 5,000 (5,974) individuals are saved and a total of 18,700 life years assuming the rate of decline is only one-third from the initial usage of 100%. The cost per life year is a little less than the one above, about $40,106 per life year. In this more targeted approach, now only does the distribution save the health care system some 150 million, again depending upon the assumptions, but from the perspective of net benefits, it saves 5,000 lives at no cost. In the discussion of how to improve the potency of this method in the previous section, the same logic would be applied here. In particular, distributing the kits to those with multiple painful sun-burns would considerably reduce the cost of the distribution and improve the net benefits evens more.

The last study was a cost-effectiveness simulation supported by the NCI. Since the cost of a large clinical trial to test for the effectiveness of melanoma screening starting at age 50 is so high, mainly because the relative rate of melanoma per 100,000 populat ion is small (1.5/100,000), this study used simulation to test for improvement in cost-effectiveness given different frequencies and risk factors. The logic of their procedure is quite different from what we have been doing. In the simulation they attempt to determine the marginal increase of cost for each quality life year gained by increasing the frequency of surveillance. One visit to the dermatologist at age 50 costs 10,000 for each QALY year gained in the population. But biannual visits raise the cost to 81,000 for each year while annual visits raise the marginal cost to 587,000, an enormous increase. In cost-effectiveness studies, there is little agreement about what is an acceptable increase in cost to save one life. Some use the estimate of $50.000 and others $100,000.

As one would expect from what has been reported above, a more targeted focus on siblings of patients with melanoma, costs only $4,000 for each year of life gain with a single visit at age 50. Again, the marginal costs increase for biannual and annual visits but not as rapidly to 36,000 and 258,000 respectively. An even more targeted focus on high-risk siblings becomes much more cost effective. Each year gained costs only $900 and the biannual and annual marginal costs are 15,000 and 100,000 respectively.

Rather than visits to the dermatologist, it might be better to use the self-examination kit as one way of reducing the large costs of visits to the dermatologist in the population at large. As indicated above, this does become more cost effective provided it is focused on various high risk groups in the age brackets of 50 and older.

Treatment Studies

The first treatment study[28] is another example of the movement towards much more complex treatment protocols and especially for melanoma. This research project, in the spirit of AIDS therapy, compares two vaccines, one made with 4 peptides and one made with 12. Both the four and twelve peptide vaccines were administered with a tetanous toxide peptide. In this trial both the treatment and control groups are actual therapies, differing only in their complexity. We will refer to the four-peptide therapy as the control group and the twelve-peptide therapy as the treatment group. The two major objectives of the trial were to determine if the more complex vaccine produced a better immune response and if its toxicity was tolerable. The initial results, the study is still on going, are encouraging. No grade 4 toxicities were reported. Grade 3 toxicity was slightly higher in the treatment group rather than the control group (40% vs 35%).

Since separate results were not reported by the two groups even though this a phase II clinical trial with random assignment, we have to make some heroic assumptions to estimate the impact of the treatment of twelve peptides on survival. But in the spirit of attempting to estimate potential benefits given the problem of major cuts in research funding, let us indicate how we attempt to solve this problem.

The patients that were recruited in the study ranged from stage IIB through Stage IV with equal numbers for both the control and the treatment groups. While we are told the number of patients in stage II, III, and IV, we are not given any of the sub-categories. Therefore, our first heroic assumption is that the distribution among them is the same as would it appear in the general population. In practice, neither the four or twelve peptides would be given to all patients because of the toxicities of these treatments. Only fairly health people can tolerate them. To account for this after making the estimates of how the combination of the two treatments would impact on the prolongation of life, we multiply by .60 because 40.8% of the population that are diagnosed with melanoma according to SEER are ages 65 and over. Eliminating this large a proportion, over one-third, may represent an over estimate of how many are not strong enough physical to support these treatments.

At the end of an average of 2.6 years, using standard techniques to estimate the numbers that would still be alive after five years for stage II, four years for stage III, and two years for stage IV, the combined results of the two treatments were also encourage. None of the stage II patients had yet experienced mortality, and the expected mortality for stage III was 42% at the end of four years and 29% expected mortality in two years for stage IV. We subtract the observed mortality from the expected mortality for each of the sub-categories. This means for that stage IIIA the observed mortality is higher than the expected and therefore we compute this as a "loss of life" to obtain a net benefit for stage III patients since we do not know the distribution of these patients among the three sub-categories.

Stage II Sub-categories, Expected - Observed Relapse Rates

B .36 x 22,403 = 8,065 patients x (.43 - .00) = 3,468
C .18 x 22,403 = 4.033 patients x (.60 - .00) = 2,420
Potential Patient Lives over Five Years = 5,888

Using the same logic for stage III, produces the following results:

Stage III Sub-categories, Expected – Observed Relapse Rates

A .25 x 5,979 = 1,495 patients x (.37 - .42) = - 76
B .36 x 5,979 = 2,152 patients x (.54 - .42) = 258
C .39 x 5,979 = 2,333 patients x (.76 - .42) = 793

Potential Patient Lives over Four Years = 975

Stage IV Expected – Observed Relapse Rates at the End of Two Years

4,536 patients x (.75 - .29) = 2,087

Total Potential Patient Lives = 8,950

This total has to be adjusted in several ways. *First*, the total needs to be corrected for the expected age distributions. Again, we assume that the patients in this phase II clinical trial have the same distribution as those in the general population that are diagnosed as having melanoma. This means that we would multiply the 8,950 by .60 on the assumption that anyone age 65 and over would not be able to tolerate the toxicity of these treatments, that is 5,370 lives. It is difficult to know whether this is a pessimistic or optimistic assumption. *Second*, since these results represent the combined prolongation of life to two different treatments, some attempt should be made to apportion them among the two. To do this we rely on upon the much stronger T-cell responses, *and therefore likely survival*, of those patients that received the twelve peptides. But except to argue that probably the individuals in the treatment group are surviving longer than those who were in the control group, we cannot estimate the proportions since there is no available data.

Above, we reported that the toxicity of the two treatments and we have suggested that is an objective measure of the quality of life. On the positive side, there is another measure of quality that we have suggested at the beginning of this chapter and that is the period disease free. The New York Times series clearly indicates how important it is getting an extension of six months in this phase one trial. In this phase II clinical trial, the disease free period for both stage IIB and C and stage III patients as on average been 35 months or 76% the first year, 59% for two years, and 47% for three years. We believe that most individuals would accept the toxicity of the treatment to have these kinds of odds of remaining disease free even if they realize that it is not a permanent solution. The research project of O'Day, Atkins, Boasberg, et al.[29] involved the use of a maintenance biotherapy after induction into a biochemotherapy trial study. Although biochemotherapy provides enhanced objective responses in the tumors, it so far has not had much impact on the survival rates of stage IV patients. The objective of this trial was to determine if by providing a maintenance regimen after the initial dosage, one could begin to impact on the standard measures of treatment success.

A phase II trial of 133 patients who had not received chemotherapy but had metastatic melanoma (but that had not spread to the central nervous system) were recruited into the trial. Most of the patients (68%) were in MIc, that their metastasis involved other sites than lungs or is their melanoma given a regime of bio-chemotherapy. Then maintenance doses were given to those that did not have disease progression over 12 months. Of the 133 patients, only 79 patients finally received the maintenance doses because of attrition of either because of rapid progression of the disease or unwillingness to participate in the study. However, of these 79 patients, 44% achieved a clinical response with 8% having an on-going remission and 36% a partial response (at least a

50% reduction in the size of the tumors). Unlike the previous treatment study that includes stage IIB through stage IV, this study largely focuses on only stage IV, therefore the number of lives saved for a certain time period is correspondingly reduced. The article reported the bench-marks of other studies, which are reported below.

Outcome	Previous Experience	Study Results	Improvement
Objective Response	10-20%	45%	25%
Disease Free Survival	2 to 4 months	9 months	6 months
Median Survival	8 to 9 months	13.5 months	5 months

Table Five
Potential Lives Saved

Prevention	First Year Lives	Five Years: Lives	Life years
Sun Tanning	not applicable		
Screening/Diagnosis			
Staining	12,777	63,885	191,655
Self-examination Kit	8,462[a]	16,399[b]	68,224
High Sun Exposure	1,358[c]	3,806[d]	13,298
Sunburn Prior Age 15	3,821[c]	9,949[d]	37,401
Treatment			
12 vs. 4 peptides		5,370[e]	
Maintenance biotherapy		543[f]	
ACT with IL-2		707[g]	

a. Assumes that the utilization rate is only 38% will be use the kit in the first year
b. Assumes that the drop-off rate 50% per year
c. Assumes that the utilization rate if 100%
d. Assumes that the drop-off rate is 33 and 1/3% per year
e. This represents the combination of five years for stage II, four years for stage III, and two years for stage IV as well as the combination of the two different treatments.
f. This represents the number of individuals with stage IV alive at the end of two years.
g. Adjusts the figure in f. by 30% on the basis of the longer survival.

Another way in which to measure the benefit of this maintenance regimen is to translate the number of lives saved for a two period, 45% when the expectation is only 25%, as follows:

Stage IV Expected – Observed Relapse Rates at the End of Two Years

4,536 patients x (.75 - .55) = 907 lives

But just as above we had to correct our estimates for the problem of toxicity, the same would be true in this case. We can only assume that about 60% of the population would

be healthy enough to tolerate grade 3 or 4 toxicity. In this study, both 3 and in a few cases 4 level toxicity was experienced by the patients. Using 60% as an estimate of the relative segment of the population for which this treatment can be administered provides a conservative estimate of 543 lives potentially could be saved for a duration of two years. However, in this regard it is interesting to observe that while the median age was 50, the range was 18 to 76, indicating that some individuals over the age of 64 can tolerate these treatments. Therefore, this is a serious underestimate of the number of months or lives saved for a certain time period. Since melanoma can return after very long time periods, it is important to keep emphasizing this latter point, the number alive at the end of two years. But on the positive side, as we have already noted, the value to the individuals and their families involved of some extension in live is priceless. Furthermore, this is an on-going study with 20% remaining alive at the end of 30 months and 9% remaining in complete remission.

Despite these quite promising results, a very large number of patients (39%) developed metastasis of their melanoma to the central nervous system, a very discouraging result. The authors believe that this is because the patients are being kept alive longer, the disease now has a change to attack another part of the body and this particular regimen does work as effectively against this kind of metastasis. At the same time, this study also demonstrated that the different vaccines did not compete with each other, suggesting that even more complex cocktails might be developed.

The third treatment study is a follow-up on a much smaller phase I study conducted by Rosenberg, 1999 on only 31 patients that demonstrated that the combination of IL-2 with ACT considerably increased the potency of the latter.[30] Since this was a phase III clinical trial the relative efficiency of two different treatment protocols can be easily compared. The 185 patients recruited into the trial either were classified as stage IV or were locally advanced stage III. The first arm or control group received a high dose of IL-2 alone, a standard treatment in melanoma cases, while the second or treatment group were given :209-217 (210) peptide + Montanide ISA followed by a high dose of IL-2. The toxicities were consistent with the experience of using IL-2.

Outcome	**Only IL-2**	**ACT IL-2**	**Improvement**
Objective Response	10%	22%	12%
Disease Free Survival	1.6 months	2.9 months	1.3 months
Median Survival	12.8 months	17.6 months	4.8 months

We do not have access to the entire article, only the abstract, and therefore, do not know what percent of the individuals in the treatment group (ACT plus IL-2) were alive at the end of two years. However, we can observe that the median survival was improved by 30% and therefore can use this to estimate the number of lives saved for two years by taking the above figure, which has been corrected for the problem of the number of patients that can tolerate the toxicity and multiply it by 30% to obtain the estimated number of lives, as follows:

Stage IV Expected – Observed Relapse Rates at the End of Two Years

4,536 patients x (.75 - .55) = 907 lives x 1.30 = 1,179 lives

Again, multiplying this figure by .60 gives us the estimate that 707 lives would be saved for a period of two years. Since we do not have a copy of the article, we do not know if this particular intervention is more effective than the previous one in preventing the progression to the central nervous system.

Since we began this chapter with a report from the New York Times on the success and failure of a treatment of melanoma among patients with a defective BRAF gene, we might place the results of this phase I trial, which focused on the different dosages of PLX4032 that needed to be administered and yet could still be treated. Of the seven patients with this defective gene in this phase I trial, five of the patients had shrinkage of up to 83% in their tumors while two others had a wild type of this gene and did not respond. Two of four other patients with unknown genetic type had a positive response of at least 50% in tumor regression. Of these seven patients that responded to this new treatment, they remained disease free from about four to 14 months but on average, the disease returned after six months.

The patient mixes within stage IV are not necessarily the same in these two last treatment studies and as we would argued, the probability is that these approaches may work with quite different groups of patients depending upon their age, genetic profile, gender and race. The key point about this last three research projects is that the patients were dying and therefore the extension of life has been seen in that context. These treatment research projects indicate how complex is the problem of developing treatments for melanoma patients and especially when they have reached stage IV. But they are also a testimony to the vitality of the research being conducted in this area and the ingenuity and creativity of these researchers.

The Assessment

One of our foci of interest has been the reduction in health care costs after the cost of an intervention has been subtracted. As can be seen in Table Four, the staining technique and providing kits to high risk populations defined by their exposure to the sun can reduce health care costs by the end of the fifth year, depending upon the particular assumptions that are made. Even with quite conservative estimates the staining technique can save considerable treatment costs over the course of five years. In contrast, the three estimations of the advantages of using a self-examination kit that is provided on a mass basis are highly sensitive to the assumptions about the cost of the kit. We have tried to be conservative and estimated its cost at $30 per kit. We also assumed a conservative utilization rate for mass distribution but a generous one for targeted populations. Examples of different rates of decline in the utilization to illustrate how sensitive these assumptions are for demonstrating whether the intervention can pay for itself in the reduction of health care costs without considering the gains in patient lives.

It would be simple if we could just add the estimated actual savings in the right hand column of Table Four given various assumptions but we cannot because each of these studies overlaps and thus involves the same population. To avoid double counting, again we are forced to make certain assumptions to reduce the margin of error. We start with the problem of how to combine the benefit of the staining technique for those who have already developed melanoma and the benefit of the self-examination kit to help people detect diseased moles before they become dangerous. In one sense, these are quite different interventions. The staining technique is used with individuals who already have melanomas to determine if they are metastasized and its benefits reflect preventing

individuals from moving into stages III and IV. In contrast, the self-examination kits are designed to help individuals discover that they have melanomas and get them to visit a dermatologist sooner.

Above, we somewhat arbitrarily divided the benefits of the self-examination kits by one-half since they were being given only to people under age 50. The logic of this procedure would be to divided the benefits of the staining technique into one half and then add the benefits of each procedure together. For example, the staining technique would then only provide 2.4 billion of savings to count against the loss of -210 million, which we do not reduce by one-half because once we divided the benefits of the staining technique in half, we are accounting for the fact that it is only being used for those age 55 and older.

In the two-targeted distributions, the problem becomes more complicated. The more difficult task is to estimate how to add together the two different targeted populations to which self-examination kits would be distributed. Absence of any data, we will assume that 50% of those with high sun exposure overlap with those who have had sunburn. If so, then the combined benefit at the end of five years would be one-half of the five year benefit of the former (1.5 million) plus one-half of the benefit of the latter (77 million) or 78 million. These would be added together with one-half of the staining technique for a total benefit of about 2.5 billion.

The three years covered in the study, NIH allocated approximately a little over $300 million to its research program in melanoma. As can be seen, the research findings and with quite conservative estimates not only has produced actual benefits of several billions of dollars saved in health care costs in addition to paying for the costs of the various interventions. However, it is important to recognize that all of these research projects have been generally been funded across many years, not just three, and in many instances by multiple countries as well as more than just the National Cancer Institute.

But the main benefit of medical research programs is in lives saved. To avoid double counting we can employ the same corrections that used above, specifically: The combination of one-half the lives saved with the staining technique and the lives saved with the mass distribution is 31,942 + 16,399 = 48,341 lives saved. The combination of one-half the lives saved with the staining technique and the lives saved in the combination of the two targeted distributions are 31,942 + (1,903 + 4,974) = 38,819 lives saved. *In both cases, the lives saved are cost-free because the interventions reduce the health care costs and considerably so.* No assumptions have to be made about the value of life.

When we shift to studies of the various treatments for those patients who already have metastasized melanoma, then the opposite is true. The interventions are quite expensive. So far the treatments prolong life at best for about two years and then for only about one-half the patients. It is up to policy makers to evaluate whether or not these sums of money should be spent on large numbers of patients who are in stage III or IV. But at the same time, these are real benefits that mean a great deal to the individuals involved and therefore justify the continuation of research on melanoma with the hope that more effective and less costly treatments can be found.

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