Skin Cancer
Chapter 4
Burden of Disease
William Gillen, M.D., Brett Coldiron, M.D.

Introduction

Burden of disease is defined as the effects of a disease on the overall health of a population, which is comprised ofdirect treatment costs and indirect costs due to missing work, as well as non-economic costs from decreased quality and duration of life.[1] Among 24 categories of skin diseases, skin cancer is estimated to have the 4th highest medical cost in the United States at about $6.05 billion annually according to the 2017 American Academy of Dermatology Burden of Skin Disease Report, although estimates as high as $8.1 billion have been suggested by the *Surgeon General's Call to Action to Prevent Skin Cancer*.[2,3]

Quality-of-life issues are hard to measure but are especially important for skin diseases, which tend to have a relatively low effect on mortality while having a relatively high effect on economic costs and well-being.[1]

For instance, when considering non-melanoma skin cancer [NMSC], the direct cost of an excision is relatively easy to estimate because those data are routinely available from payers. The indirect cost is more difficult to quantify because productivity lost due to commute time, procedural time and recovery time are not routinely measured and differ significantly based on the scenario (i.e.- anatomic location). The effect on the survival of the patient may be simple to quantify, as a plethora of data regarding mortality due to NMSC are reported. The effect on the patient's well-being, however, is very difficult to quantify because of the abstract nature of the patient's level of anxiety associated with the diagnosis and the physical consequences of and patient's personal feelings toward the appearance of their scar.

There is currently an epidemic of skin cancer sweeping the United States, including both melanoma and NMSC.[4,5] Other countries throughout the world have noted similarly alarming rates of acceleration in the incidence of skin cancer.[6,7] This chapter will discuss the burden of disease of skin cancer in the United States and globally, focusing primarily on economic burdens and secondarily on non-economic burdens.

Non-melanoma Skin Cancer (Keratinocyte Carcinoma)

Epidemiology

NMSC, comprised primarily of basal cell carcinoma [BCC] and squamous cell carcinoma [SCC], is the most common malignancy in the United States, with a higher incidence than all other cancers combined.[4,8] This high incidence is seen in other parts of the world whose populations primarily have light skin.[6,7]It is estimated that in 2012 there were roughly 5.4 million NMSCs occurring on 3.3 million patients. This was a dramatic increase of around 35% from the 2006 figures of 3.3 million NMSCs for 2.46 million patients.[4]In 2013 an estimate derived from a different formula calculates that nearly 3.7

million NMSCs were diagnosed in the United States and 4,376 deaths were attributed to NMSC although the true number is probably much higher because NMSC is not a required-to-report disease.[9]

Direct Costs

Direct medical costs for the treatment of NMSC are estimated at $4.585-$4.8 billion.[2,3]The main sources of direct cost related to skin cancer are 1) treatment (see tables) and 2) diagnosis (see table). In 2008 it was estimated that more than $600 million was paid by Medicare Part B for skin cancer treatments (which includes only destruction, excision and Mohs surgery). This figure did not include charges for repairs, facility fees, pathology and other peripheral costs.[10]

Evaluation and management [E&M] visits contribute to the cost of screening and diagnosing skin cancer. If a suspected skin cancer is noted during a visit, it is biopsied and usually sent for pathologic evaluation, which generates charges for a procedure, preparation of the specimen and histologic evaluation by a dermatopathologist. The estimated sum of the costs for the skin biopsies and associated pathology for the Medicare fee-for-service population in 2015 is about $750 million, which does not include any additional stains or consultations for diagnosis by frozen section(Table 1).[11]

Table 1

Service	CPT code	Number performed	Unit cost	Total cost
Skin Biopsy	11100	3,356,246	$104.55	$350,895,519.30
Additional Biopsy	11101	1,433,790	$33.30	$47,745,207.00
Tissue Exam by Pathologist	88305	4,790,036	$74.11	$354,989,567.96
				$753,630,294.26

***NOTE- this calculation uses actual prices and number of biopsies performed in Medicare fee-for-service population in 2015 and assumes each generated only one 88305

NMSCs make up the vast majority of cutaneous malignancies and are those most commonly treated surgically.[8] For localized tumors, the most common surgical techniques are electrodessication and curettage [ED&C], excision with repair, and Mohs surgery. Each technique offers different cure rates and the costs vary substantially among them.

ED&C has the benefit to the patient of being relatively quick and inexpensive. The downside to ED&C includesa recurrence rate of up to 20% and the usually unattractive, and sometimes hypertrophic,scar.[12-14] ED&C costs $300 to $600.[15]

Treating NMSCs by excision with repair has several permutations that affect the potential cost. NMSC excision is least expensive in the office setting with tissue sent for permanent pathology, followed by the ambulatory surgical center (ASC) and finally in a hospital operating room with tissue being sent intraoperatively for frozen section analysis before repair is performed(see table 2 for costs in each setting).[15]A recent study comparing charge data from case matched outpatient treatment of NMSC and melanoma versus treatment in a hospital operating room found that the average charge for the cases performed in the hospital was $11,589, an average of 6 times more than the $1773 when performed in

the office.[16]The variations of excision share an estimated cure rate of about 90%, although cure rates reported in the literature vary widely.[15]The higher cost incurred in a hospital setting is partially explained by miscellaneous charges that may not initially be apparent, such asanesthesia, intraoperative frozen section analysis, postoperative permanent section analysis, facility fees (which are reimbursed under Medicare Part A and are not currently available for scrutiny), and preoperative workup and medications and supplies such as intravenous setups.

Mohs micrographic surgery is used for NMSC and many rare tumors and accounts for about half of malignant tumor removals based on 2015 Medicare fee-for-service claims data.[11,17-20] Mohs is staged excision of horizontal frozen section yielding 100% histologic margin control. This results in higher cure rates than excision, 95-99% depending on the tumor.[21]

A recent systematic review reports recurrence rates after Mohs surgery of 0-7.1% for primary basal cell carcinoma, 0-10% for recurrent basal cell carcinoma, 2.6-4.5% for primary invasive squamous cell carcinoma and 5.9-23% for recurrent invasive squamous cell carcinoma.[21]When compared to standard surgical excision with repair, Mohs surgery is somewhat more expensive than excision with permanent sections but significantly less expensive than excision with frozen section analysis performed in either an ASC or hospital operating room.[15]

Table 2- Relative estimated costs for treatment of BCC and SCC based on anatomic location.[15]

Estimated costs for treatment of BCC on the cheek by different modalities

Treatment modality	0.6cm	1.1cm	2.1cm	3.1cm	Average
Electrodessication and curettage*	$389	$426	$495	$573	$471
Imiquimod⍰	$929	$942	$950	$1,013	$959
Mohs micrographic surgery‡	$1,122	$1,174	$1,296	$1,460	$1,263
Excision/permanent/immediate repair§	$807	$860	$1,088	$1,270	$1,006
Excision/permanent/delayed repair§	$900	$1,019	$1,232	$1,528	$1,170
Excision/frozen/ASC‖	$2,125	$2,195	$2,349	$2,667	$2,334
Excision/frozen/hospital OR‖	$2,543	$2,856	$3,048	$3,893	$3,085
Radiation therapy (5 Gy fractionation)¶	$2,562	$2,572	$2,598	$2,631	$2,591
Radiation therapy (3.5 Gy fractionation)¶	$3,431	$3,441	$3,467	$3,501	$3,460

Estimated costs for treatment of SCC on the arm by different modalities

Treatment modality	0.6cm	1.1cm	2.1cm	3.1cm	Average
Electrodessication and curettage*	$323	$360	$414	$472	$392
Imiquimod⍰	$896	$903	$939	$985	$931
Mohs micrographic surgery‡	$992	$1,018	$1,163	$1,349	$1,131
Excision/permanent/immediate repair§	$639	$710	$951	$1,326	$907
Excision/permanent/delayed repair§	$729	$794	$1,093	$1,551	$1,041
Excision/frozen/ASC‖	$1,921	$2,028	$2,243	$2,609	$2,200
Excision/frozen/hospital OR‖	$2,166	$2,237	$2,904	$3,413	$2,680
Radiation therapy (5 Gy fractionation)¶	$2,530	$2,538	$2,560	$2,608	$2,559
Radiation therapy (3.5 Gy fractionation)¶	$3,402	$3,410	$3,432	$3,480	$3,431

Legend: *ASC,* ambulatory surgical center; *BCC*, basal cell carcinoma; *permanent*, formalin permanent section margin control; *frozen*, frozen section margin control; *OR*, operating room.

* 20% recurrence rate

⍰ 5% initial incomplete clinical response, 20% recurrence rate

‡ 1% recurrence rate

§ 11% initially positive histologic margins, 10% recurrence rate

‖ 21% initially positive histologic margins, 10% recurrence rate

¶ 7% initial treatment failure, 10% recurrence rate

adapted from: Rogers HW, Coldiron BM. A relative value unit–based cost comparison of treatment modalities for nonmelanoma skin cancer: Effect of the loss of the Mohs multiple surgery reduction exemption. Journal of the American Academy of Dermatology. 2009;61(1):96–103.

In certain tumors, such as thick malignant melanoma, high-risk squamous cell carcinoma and Merkel cell carcinoma, sentinel lymph node biopsy is considered to evaluate for metastases of the primary tumor to the nodal basin. This is generally performed at the same time as wide local excision and studies suggest that charges generated by this procedure, usually performed in a hospital operating room, average between $10,000 and $15,000 per case.[22,23] It has been suggested that the same procedure can potentially be done under tumescent local anesthesia for 1/9th the cost.[24]

Cost-effectiveness studies suggest annual cost per positive node identified of around $150,000-230,000. Data is not available regarding the number of sentinel lymph node biopsies performed annually that are related to skin cancer, however the value of this procedure is currently a topic of controversy because completion lymphadenectomy for malignant melanoma has recently been shown to not benefit survival.[25]

The Medicare-allowed payment for complete cervical lymphadenectomy is between $900 and $1500, however it is important to remember that this only includes the surgeon's fees and not the hospital and operating room charges where the bulk of the cost resides. Various studies regarding cost effectiveness from the head and neck oncology literature estimate the cost of neck dissection outside of the cost for surgical time at upwards of $25,000, and even more for recurrences .[26,27]

Radiation therapy has long been an option for definitive treatment of NMSC and is available in several forms, each of which entails different costs depending on the treatment modality and setting. The treatments are generally used by dermatologists and radiation oncologists. The cost per lesion treated in the outpatient setting ranges from around $500 for office-based superficial radiation to nearly $8,000 for electronic brachytherapy. Ambulatory treatment in a hospital using orthovoltage radiation costs nearly $4,000 while that for megavoltage electron beam therapy costs around $7,000.[28] Radiation is also used as adjuvant or post-operative therapy in some advanced NMSC, as well as for metastatic disease. Costs for this have been estimated to be significantly higher than those for outpatient treatments and as high as $21,000.[26]

There have been recent developments in systemic therapy for NMSC. Vismodegib and sonidegib are hedgehog pathway inhibitors that are used to treat metastatic or locally advanced BCC that has recurred or is not appropriate for surgery or radiation. They have also been reported as being used off-label in patients with Basal Cell Nevus Syndrome to reduce overall burden of disease.[29] The published data reports relatively low response rates, however for tumors that are otherwise deemed not treatable a small response may be acceptable.

Nivolumab and pembrolizumab are anti-programmed death 1 protein agents that have recently been used in small trials to treat metastatic or locally advanced and unresectable SCC with encouraging results.[30]Their respective prices are outlined below in Table 4.

Indirect Costs

The indirect costs associated with NMSC include opportunity costs (work time lost by patients and caregivers in order to attend visits or undergo treatment) as well as foregone future earnings due to premature death. It is estimated in the 2017 Burden of Skin Disease report from the American Academy of Dermatology that $376 million in productivity costs were generated in 2013 due to work time lost by patients and caregivers in the United States.[9] Although this iteration of the report did not include calculations for productivity lost due to premature death, the prior report from 2004 suggests that this aspect of indirect costs approaches $1 billion.[31]

Non-economic Burden

The non-economic burden of NMSC is generally comprised of quality of life [QoL] detriment that may be caused by the tumor itself (symptoms, appearance), treatment modalities (pain, impairment of daily activities), and psychosocial detriment in the follow-up period due to scarring. Additionally, the tendency to develop additional skin cancers may compound these effects. The QoL effects attributable to NMSC are difficult to quantify due to their abstract nature, reliance on patient questionnaires that may not be designed specifically for NMSC patients, and the relatively small magnitude the effects appear to cause. Overall, most studies report similar QoL scores before and after treatment for NMSC, with the strongest predictors of post-treatment QoL being pre-treatment QoL, mental health status and presence of comorbidities. Additionally, NMSC likely has a smaller impact on QoL than other dermatological pathologies, such as psoriasis or eczema.[32]

Malignant Melanoma

Epidemiology

The rate of diagnosis of both invasive melanoma and melanoma *in situ*has been rising steadily in the United States, as well as worldwide. In addition to increasing incidence of disease, mortality from melanoma has similarly been on the rise. The 2017 Burden of Skin Disease report from the American Academy of Dermatology reports that the prevalence of melanoma in the population is more than 1 million patients (diagnosed) in 2013and 9,394 patients died due to melanoma.[9]Combined incidence of melanoma *in situ* and invasive melanoma in 2016 is estimated to be nearly 145,000.[5]Between 2009 and 2016 the incidence rates of invasive melanoma rose with a 0.9% compound annual growth rate [CAGR], while that of *in situ* melanoma rose with a 3.0% CAGR, yielding a lifetime risk for being diagnosed with invasive or *in situ* melanoma of 1 in 28 Americans. The compound annual growth rate for mortality from melanoma over the same period has been 1.5%.[5]This increase is unlikely due to artifact, better counting methods or changes in histologic diagnosis. Because many melanomas are treated in the outpatient setting and melanoma is not a reportable disease in most states, the rate of increase is likely higher than reported.[33]

Direct Costs

The total medical cost of melanoma in 2013 is estimated to be $1.467 billion, accounting for about 3.2% of overall medical cost for all skin diseases.[2]The services that generate these direct costs

include many of the same E&M and surgical treatments from above, as well as some additional diagnostic modalities and medical therapies that are not used for NMSC.

Several molecular technologies such as fluorescence *in situ* hybridization and comparative genomic hybridization are currently emerging and are being studied as both diagnostic and prognostic tests for malignant melanoma. These technologies may allow more accurate staging of melanoma patients, without additional surgery, and cost less than sentinel node biopsy. They cost from around $1,350 to around $7,900.[34,35]

Much of the cost for melanoma is for metastatic disease. In 2009 a cost study in the United States showed that total cost of diagnosis and treatment of a primary *in situ* melanoma with 5 years of follow-upis $4,648.48, while a stage T4b tumor costs $159,808.17.[36]This study found the most expensive line items in the care of melanoma to be adjuvant treatment with interferon-alpha ($75,955.18), which has recently been found to offer no survival benefit.[37]There are also significant costs for palliative care ($14,500), and administration of chemotherapy ($1967.10 for a triple combination of agents). Of note, the model used in this study takes into account the cost of patient time, which is generally considered among indirect costs.[36,38]

New targeted therapies for melanoma (in addition to nivolumab and pembrolizumab above) include primarily ipilimumab, dabrafenib, vemurafenib and trametinib. Their respective costs are outlined in Table 3. While these medications offer improved survival in many patients for whom there was previously no effective treatment, their cost adds significantly to the economic burden placed on the healthcare system by malignant melanoma.[39]

TABLE 3- Relative Pricing of Targeted Therapy

Therapy	Indication	Unit Cost	Cost Per Treatment Course
Vismodegib	BCC (metastatic or unresectable, not appropriate for radiation)	~$15,000 for 30 150mg capsules	$15,000 per month
Sonidegib	BCC (metastatic or unresectable, not appropriate for radiation)	~$10,500 for 30 200mg capsules	$10,500 per month
Nivolumab	Melanoma, SCC (metastatic or unresectable)	~$31,000 for 12 vials (10mL each) at 100mg/10mL	$15,500 per month until disease progression or unacceptable toxicity
Pembrolizumab	Melanoma, SCC (metastatic or unresectable)	~$9,000 for 4 vials of 50mg each	~$12,000 per month
Ipilimumab	Melanoma (metastatic or unresectable)	~$7,000 per 50mg/10mL vial	~$50,000 per month
Dabrafenib	Melanoma (BRAF V600E or V600K mutation)	~$10,000 for 120 75mg capsules	$10,000 per month
Vemurafenib	Melanoma (BRAF V600E mutation)	~$5,500 for 120 240mg tablets	$11,000 per month
Trametinib	Melanoma (BRAF V600E or V600K mutation)	~$11,000 for 30 2mg tablets	$11,000 per month (usually used in combination with dabrafenib)

CITATION GOODRX[40]

Legend: *BCC*, basal cell carcinoma; *SCC*, squamous cell carcinoma

Indirect Costs

Despite the relatively lower incidence of melanoma, the estimated indirect costs are significantly higher than those associated with NMSC.This may be because of its higher mortality rate and its propensity for developing aggressive tumors in young individuals, leading to greater values for loss of future income due to premature death. The American Academy of Dermatology currently estimates that about $88 million is the opportunity cost associated with patient and caregiver time lost due to melanoma in 2013.[9]Although the most recent Burden of Skin Disease report by the American Academy of Dermatology does not include calculations for future income due to premature death, the 2004 edition estimated around $2.8 billion in forgone income.[31]A 2008 study using willingness to pay calculations estimated loss due to premature mortality to be around $15.1 billion in the year 2000 and projected that loss to increase to $21.6 billion in the year 2020.[41] While it is apparent that the method

used to calculate indirect costs of disease can vary widely, it should still be noted that these indirect costs associated with melanoma remain high in any estimation.

Non-economic Burden

The non-economic burden of melanoma consists of the same somewhat abstract concepts as those for NMSC, which makes their quantification quite difficult. These concepts include those of patients' feelings of well-being and their perception of their overall, physical and mental health. Many quantification tools have been designed to measure QoL impacts due to diseases including melanoma, however their application to populations of patients with melanoma appears to frequently provide conflicting results or results that are difficult to interpret.[42,43] As the majority of melanomas are found in their early stage, surgical excision with extended clinical follow-up is frequently the extent of necessary treatment. For patients with localized disease it has been suggested that QOL in those without relapse after two years is comparable to those in the general population but much lower in more significant disease.[44]

Technology Relating to Skin Cancer

Technology has become part of everyday life and is making its way into dermatologic care, including that for skin cancer, in many ways. Of the technological advances with documented impact on skin cancer, the most reported are those associated with teledermatology. Teledermatology exists in two basic forms: store-and-forward and real-time interactive teledermatology. While store-and-forward teledermatology has generally shown to at least be cost-effective, real-time interactive teledermatology studies have conflicting conclusions on its cost-effectiveness, largely based on the study designs.[45,46] Store-and-forward teledermatology has also been shown to provide clinically significant improvement in some skin-specific QoL measures that are not statistically significantly different from those provided by traditional clinic-based consultation.[47] Pre-surgical teledermatology has been reported to decrease both pre-operative evaluation cost as well as time to surgical intervention in a regional hospital setting in Spain.[48]

Mobile smartphone apps are also beginning to make their way into skin cancer treatment, although at this time data regarding their merits are somewhat sparse. A mobile teledermoscopy application that forwards dermatoscopic images to dermatologists has shown some promise, however its effect on burden of disease is yet to be explored.[49] Additionally, a tablet-based application designed to assist melanoma patients in keeping up with their skin self-examinations and tracking lesions was well-received by patients in its pilot study, showing potential to improve certain QoL parameters in this population.[50] Applications and devices featuring algorithm-based, computerized diagnosis of melanoma, however, have undergone many studies in the dermatology community with mixed results. Those aiming to improve diagnostic accuracy or biopsy sensitivity when taken in context by practitioners have reported promising results.[51,52]Recommendations in 2015 warned that none "[had] been adequately studied and/or shown to be sufficiently accurate and reliable to recommend."[35]

Outlook and Future Trends

From the preceding discussion of the burden of disease of skin cancer, including both economic and non-economic costs, it is clear that the mounting epidemic of skin cancer, especially keratinocyte carcinomas and melanoma, has the potential to drive costs skyward as the volume of tumors treated annually continues to grow. This leaves the medical community at large with the quandary of how to manage the potential cost explosion associated with the skin cancer epidemic. Through careful examination of the literature and cost data available, strategies for reducing or optimizing expenditures for treatment of skin cancer become apparent.

Prevention and early detection of skin cancer appear to be the best ways to reduce overall output in terms of treatment costs and myriad strategies to facilitate these goals have been proposed, such as high risk clinics and screening guidelines.[36,38,51,53-55]

Although all aspects of skin cancer care generate costs, it is clear from the analysis above that treatment of skin cancer drives the lion's share of cost, regardless of modality.[10] There are, however, several low-hanging fruit in the treatment arena that show potential for improvement in costs. One of these is management of the physical location of skin cancer treatment. Although not every cutaneous tumor is appropriate for surgery in the office setting and not every patient is a good candidate for office-based surgery, many are, and improved patient triage to the most appropriate treatment setting has the potential to drastically reduce costs associated with surgical treatment of skin cancer by shifting a larger proportion of surgeries to the office setting. This shift is further supported by emerging evidence regarding the high safety level of office-based surgery, especially for cutaneous procedures.[56,57]

Additionally, well-tolerated systemic supplements such as nicotinamide have emerging evidence supporting their use in chemoprevention for actinic keratosis, basal cell carcinoma and squamous cell carcinoma. A large randomized controlled trial has shown that development of new basal cell carcinoma and squamous cell carcinoma in the group treated with nicotinamide versus placebo was 20% and 30% lower, respectively. They also showed reduction in actinic keratosis in the treatment group. This supplement is available over the counter and is inexpensive and well-tolerated, making it an interesting target for use in reducing the current economic burden imposed by skin cancer over time.[58,59]

Further evidence supporting or refuting extensive diagnostic and staging measures such as sentinel lymph node biopsy and confocal microscopy, as well as evaluating the efficacy of the many new targeted therapies available may also help to refine how resources are allocated in the treatment of advanced skin cancers. While these procedures and medications are quite expensive, they are used relatively rarely and do not contribute as much to cost as the most commonly used procedures above.[22-24]

Conclusion

Skin cancer incidence is increasing rapidly and economic costs, both direct and indirect, accompany it. Office treatment is much more cost effective than that rendered in a hospital. In terms of cost, destruction is the least expensive (but with the lowest cure rate), followed by excision, Mohs surgery, superficial radiation treatment,ASC surgical excision, and, most expensive of all, treatment in

the hospital outpatient department. New drugs for systemic skin cancer treatment are breathtakingly expensive, and unlikely to become much less so since biosimilars are difficult to manufacture and usually priced closely to the original drug.

Prevention would appear to be the best way to decrease costs across the population, but getting the message out and changing public behavior and misconceptions will incur significant costs of their own. Electronic personal digital media may be a route to reach at-risk populations and tailor a more effective and nuanced message.

References

1) Chren M-M, Weinstock MA. Conceptual Issues in Measuring the Burden of Skin Diseases. Journal of Investigative Dermatology Symposium Proceedings. 2004;9(2):97–100.
2) Lim HW, Collins SA, Resneck JS, Bolognia JL, Hodge JA, Rohrer TA, et al. The burden of skin disease in the United States. Journal of the American Academy of Dermatology. 2017;76(5).
3) U.S. Department of Health and Human Services. The Surgeon General's Call to Action to Prevent Skin Cancer. Washington, DC: U.S. Dept of Health and Human Services, Office of the Surgeon General; 2014.
4) Rogers HW, Weinstock MA, Feldman SR, Coldiron BM. Incidence Estimate of Nonmelanoma Skin Cancer (Keratinocyte Carcinomas) in the US Population, 2012. JAMA Dermatology. 2015Jan;151(10):1081.
5) Glazer AM, Winkelmann RR, Farberg AS, Rigel DS. Analysis of Trends in US Melanoma Incidence and Mortality. JAMA Dermatology. 2017Jan;153(2):225.
6) Flohil SC, Seubring I, Rossum MMV, Coebergh J-WW, Vries ED, Nijsten T. Trends in Basal Cell Carcinoma Incidence Rates: A 37-Year Dutch Observational Study. Journal of Investigative Dermatology. 2013;133(4):913–8.
7) Valery PC, Neale R, Williams G, Pandeya N, Siller G, Green A. The Effect of Skin Examination Surveys on the Incidence of Basal Cell Carcinoma in a Queensland Community Sample: A 10-Year Longitudinal Study. Journal of Investigative Dermatology Symposium Proceedings. 2004;9(2):148–51.
8) Karimkhani C, Boyers LN, Dellavalle RP, Weinstock MA. Its time for "keratinocyte carcinoma" to replace the term "nonmelanoma skin cancer". Journal of the American Academy of Dermatology. 2015;72(1):186–7.
9) Burden of Skin Disease briefs [Internet]. American Academy of Dermatology. [cited 2017Jul20]. Available from: https://www.aad.org/about/burden-of-skin-disease/burden-of-skin-disease-briefs
10) Rogers HW, Coldiron BM. Analysis of Skin Cancer Treatment and Costs in the United States Medicare Population, 1996–2008. Dermatologic Surgery. 2013;39(1pt1):35–42.
11) Specialty Society RVS Update Committee Database. Specialty Society RVS Update Committee Database. American Medical Association; 2015.
12) Blixt E, Nelsen D, Stratman E. Recurrence Rates of Aggressive Histologic Types of Basal Cell Carcinoma After Treatment with Electrodesiccation and Curettage Alone. Dermatologic Surgery. 2013;39(5):719–25.
13) Chren M-M, Linos E, Torres JS, Stuart SE, Parvataneni R, Boscardin WJ. Tumor Recurrence 5 Years after Treatment of Cutaneous Basal Cell Carcinoma and Squamous Cell Carcinoma. Journal of Investigative Dermatology. 2013;133(5):1188–96.
14) Rodriguez-Vigil T, Vázquez-López F, Perez-Oliva N. Recurrence rates of primary basal cell carcinoma in facial risk areas treated with curettage and electrodesiccation. Journal of the American Academy of Dermatology. 2007;56(1):91–5.
15) Rogers HW, Coldiron BM. A relative value unit–based cost comparison of treatment modalities for nonmelanoma skin cancer: Effect of the loss of the Mohs multiple surgery reduction exemption. Journal of the American Academy of Dermatology. 2009;61(1):96–103.
16) Johnson RP, Butala N, Alam M, Lawrence N. A Retrospective Case-Matched Cost Comparison of Surgical Treatment of Melanoma and Nonmelanoma Skin Cancer in the Outpatient Versus Operating Room Setting. Dermatologic Surgery. 2017;43(7):897–901.

17) Boyer JD, Zitelli JA, Brodland DG, Dangelo G. Local control of primary Merkel cell carcinoma: Review of 45 cases treated with Mohs micrographic surgery with and without adjuvant radiation. Journal of the American Academy of Dermatology. 2002;47(6):885–92.
18) Coldiron BM, Goldsmith BA, Robinson JK. Surgical treatment of extramammarypagets disease. A report of six cases and a reexamination of mohs micrographic surgery compared with conventional surgical excision. Cancer. 1991;67(4):933–8.
19) Hou JL, Killian JM, Baum CL, Otley CC, Roenigk RK, Arpey CJ, et al. Characteristics of Sebaceous Carcinoma and Early Outcomes of Treatment Using Mohs Micrographic Surgery Versus Wide Local Excision: An Update of the Mayo Clinic Experience Over the Past 2 Decades. Dermatologic Surgery. 2014;40(3):241–6.
20) Paradisi A, Abeni D, Rusciani A, Cigna E, Wolter M, Scuderi N, et al. Dermatofibrosarcoma protuberans: Wide local excision vs. Mohs micrographic surgery. Cancer Treatment Reviews. 2008;34(8):728–36.
21) Foroozan M, Beauchet A, Funck-Brentano E, Sei J-F, Saiag P. Current evidence on recurrence rate of basal cell and squamous cell carcinomas treated by Mohs micrographic surgery: Systematic review. Journal of the American Academy of Dermatology. 2014;70(5).
22) Agnese DM, Abdessalam SF, Burak WE, Magro CM, Pozderac RV, Walker MJ. Cost-effectiveness of sentinel lymph node biopsy in thin melanomas. Surgery. 2003;134(4):542–7.
23) Martínez-Menchón T, Sánchez-Pedreño P, Martínez-Escribano J, Corbalán-Vélez R, Martínez-Barba E. Cost Analysis of Sentinel Lymph Node Biopsy in Melanoma. ActasDermo-Sifiliográficas (English Edition). 2015;106(3):201–7.
24) Stoffels I, Dissemond J, Körber A, Hillen U, Poeppel T, Schadendorf D, et al. Reliability and cost-effectiveness of sentinel lymph node excision under local anaesthesia versus general anaesthesia for malignant melanoma: a retrospective analysis in 300 patients with malignant melanoma AJCC Stages I and II. Journal of the European Academy of Dermatology and Venereology. 2011Jun;25(3):306–10.
25) Faries MB, Thompson JF, Cochran AJ, Andtbacka RH, Mozzillo N, Zager JS. Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma. The New England Journal of Medicine. 2017Jun8;376(23):2211–22.
26) Acevedo JR, Fero KE, Wilson B, Sacco AG, Mell LK, Coffey CS, et al. Cost-Effectiveness Analysis of Elective Neck Dissection in Patients With Clinically Node-Negative Oral Cavity Cancer. Journal of Clinical Oncology. 2016Oct;34(32):3886–91.
27) Hernando JCA, Villarreal P, Álvarez-Marcos F, García-Consuegra L, Gallego L, Junquera L. Sentinel node biopsy versus elective neck dissection. Which is more cost-effective? A prospective observational study. Journal of Cranio-Maxillofacial Surgery. 2016;44(5):550–6.
28) Wolfe CM, Cognetta AB. Radiation therapy (RT) for nonmelanoma skin cancer (NMSC), a cost comparison: Clarifying misconceptions. Journal of the American Academy of Dermatology. 2016;75(3):654–5.
29) Chang ALS, Arron ST, Migden MR, Solomon JA, Yoo S, Day B-M, et al. Safety and efficacy of vismodegib in patients with basal cell carcinoma nevus syndrome: pooled analysis of two trials. Orphanet Journal of Rare Diseases. 2016Jan;11(1).
30) Beasley GM, Kurtz J, Vandeusen J, Howard JH, Terando A, Agnese D, et al. Immune Checkpoint Inhibitor Therapy as a Novel and Effective Therapy for Aggressive Cutaneous Squamous-cell Carcinoma. Clinical Skin Cancer. 2017;
31) Bickers DR, Lim HW, Margolis D, Weinstock MA, Goodman C, Faulkner E, et al. The burden of skin diseases: 2004. Journal of the American Academy of Dermatology. 2006;55(3):490–500.
32) Gaulin C, Sebaratnam DF, Fernández-Peñas P. Quality of life in non-melanoma skin cancer. Australasian Journal of Dermatology. 2014Aug;56(1):70–6.

33) Rigel DS. Trends in Dermatology: Melanoma Incidence. Archives of Dermatology. 2010Jan;146(3).
34) Ferris LK, Farberg AS, Middlebrook B, Johnson CE, Lassen N, Oelschlager KM, et al. Identification of high-risk cutaneous melanoma tumors is improved when combining the online American Joint Committee on Cancer Individualized Melanoma Patient Outcome Prediction Tool with a 31-gene expression profile–based classification. Journal of the American Academy of Dermatology. 2017;76(5).
35) March J, Hand M, Grossman D. Practical application of new technologies for melanoma diagnosis. Journal of the American Academy of Dermatology. 2015;72(6):929–41.
36) Alexandrescu DT. Melanoma costs: A dynamic model comparing estimated overall costs of various clinical stages [Internet]. Dermatology Online Journal. 2009 [cited 2017Jul20]. Available from: http://escholarship.org/uc/item/53f8q915?query=melanoma costs dynamic model
37) Mcmasters KM, Egger ME, Edwards MJ, Ross MI, Reintgen DS, Noyes RD, et al. Final Results of the Sunbelt Melanoma Trial: A Multi-Institutional Prospective Randomized Phase III Study Evaluating the Role of Adjuvant High-Dose Interferon Alfa-2b and Completion Lymph Node Dissection for Patients Staged by Sentinel Lymph Node Biopsy. Journal of Clinical Oncology. 2016;34(10):1079–86.
38) Serra-Arbeloa P, Rabines-Juárez Á, Álvarez-Ruiz M, Guillén-Grima F. Cost of Cutaneous Melanoma by Tumor Stage: A descriptive analysis. ActasDermo-Sifiliográficas (English Edition). 2017;108(3):229–36.
39) Amann V, Ramelyte E, Thurneysen S, Pitocco R, Bentele-Jaberg N, Goldinger S, et al. Developments in targeted therapy in melanoma. European Journal of Surgical Oncology (EJSO). 2017;43(3):581–93.
40) Prescription Prices, Coupons & Pharmacy Information - GoodRx [Internet]. Prescription Prices, Coupons & Pharmacy Information - GoodRx. [cited 2017Jul27]. Available from: http://www.goodrx.com/
41) Yabroff KR, Bradley CJ, Mariotto AB, Brown ML, Feuer EJ. Estimates and Projections of Value of Life Lost From Cancer Deaths in the United States. JNCI: Journal of the National Cancer Institute. 2008;100(24):1755–62.
42) Cornish D, Holterhues C, Poll-Franse LVVD, Coebergh JW, Nijsten T. A systematic review of health-related quality of life in cutaneous melanoma. Annals of Oncology. 2009;20(suppl 6):vi51–vi58.
43) Hamel J-F, Pe M, Coens C, Martinelli F, Eggermont AM, Brandberg Y, et al. A systematic review examining factors influencing health related quality of life among melanoma cancer survivors. European Journal of Cancer. 2016;69:189–98.
44) Schlesinger-Raab A, Schubert-Fritschle G, Hein R, Stolz W, Volkenandt M, Holzel D, et al. Quality of life in localised malignant melanoma. Annals of Oncology. 2010;21(12):2428–35.
45) Snoswell C, Finnane A, Janda M, Soyer HP, Whitty JA. Cost-effectiveness of Store-and-Forward Teledermatology. JAMA Dermatology. 2016Jan;152(6):702.
46) Whited JD. Economic Analysis of Telemedicine and the Teledermatology Paradigm. Telemedicine and e-Health. 2010;16(2):223–8.
47) Whited JD, Warshaw EM, Edison KE, Kapur K, Thottapurathu L, Raju S, et al. Effect of Store and Forward Teledermatology on Quality of Life. JAMA Dermatology. 2013Jan;149(5):584.
48) Ferrándiz L, Moreno-Ramírez D, Ruiz-De-Casas A, Nieto-García A, Moreno-Álvarez P, Galdeano R, et al. An Economic Analysis of PresurgicalTeledermatology in Patients with Nonmelanoma Skin Cancer. ActasDermo-Sifiliográficas (English Edition). 2008;99(10):795–802.
49) Börve A, Terstappen K, Sandberg C, Paoli J. Mobile teledermoscopy—there's an app for that! Dermatology Practical & Conceptual. 2013;3(2).

50) Dennis M, Masthoff J, Smith KA, Murchie P, Hall S. Designing a Tablet-based Intervention to Support Self-checking for Melanoma. Proceedings of the 5th International Conference on Digital Health 2015 - DH 15. 2015;
51) Rigel DS, Russak J, Friedman R. The Evolution of Melanoma Diagnosis: 25 Years Beyond the ABCDs. CA: A Cancer Journal for Clinicians. 2010;60(5):301–16.
52) Yoo J, Tucker N, White R, Rigel D. The impact of probability of melanoma information provided by a multispectral digital skin lesion analysis device (MSDSLA) on resident dermatologists' decisions to biopsy clinical atypical lesions. Journal of the American Academy of Dermatology. 2015;72(5).
53) Pil L, Hoorens I, Vossaert K, Kruse V, Tromme I, Speybroeck N, et al. Cost-effectiveness and Budget Effect Analysis of a Population-Based Skin Cancer Screening. JAMA Dermatology. 2017Jan;153(2):147.
54) Robinson JK, Halpern AC. Cost-effective Melanoma Screening. JAMA Dermatology. 2016Jan;152(1):19.
55) Watts CG, Cust AE, Menzies SW, Coates E, Mann GJ, Morton RL. Specialized Surveillance for Individuals at High Risk for Melanoma. JAMA Dermatology. 2015Jan;151(2):178.
56) Starling J, Coldiron BM. Outcome of 6 years of protocol use for preventing wrong site office surgery. Journal of the American Academy of Dermatology. 2011;65(4):807–10.
57) Starling J, Thosani MK, Coldiron BM. Determining the Safety of Office-Based Surgery: What 10 Years of Florida Data and 6 Years of Alabama Data Reveal. Dermatologic Surgery. 2012;38(2 Part 1):171–7.
58) Chen A, Martin A, Dalziell R, Mckenzie C, Lowe P, Eris J, et al. A phase II randomized controlled trial of nicotinamide for skin cancer chemoprevention in renal transplant recipients. British Journal of Dermatology. 2016Oct;175(5):1073–5.
59) Chen AC, Martin AJ, Choy B, Fernández-Peñas P, Dalziell RA, Mckenzie CA, et al. A Phase 3 Randomized Trial of Nicotinamide for Skin-Cancer Chemoprevention. New England Journal of Medicine. 2015;373(17):1618–26.